



**HAL**  
open science

# Synthese enantioselective d'alcools et d'aminoalcools par transfert d'hydrogene asymetrique catalyse par le rhodium et le ruthenium

Longsheng Zheng

► **To cite this version:**

Longsheng Zheng. Synthese enantioselective d'alcools et d'aminoalcools par transfert d'hydrogene asymetrique catalyse par le rhodium et le ruthenium. Autre. Université Paris sciences et lettres, 2018. Français. NNT : 2018PSLECO15 . tel-03510254

**HAL Id: tel-03510254**

**<https://pastel.hal.science/tel-03510254>**

Submitted on 4 Jan 2022

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

# THÈSE DE DOCTORAT

de l'Université de recherche Paris Sciences et Lettres  
PSL Research University

Préparée à Chimie ParisTech

Enantioselective synthesis of alcohols and aminoalcohols via rhodium-  
and ruthenium-mediated asymmetric transfer hydrogenation

Synthèse énantiosélective d'alcools et d'aminoalcools par transfert  
d'hydrogène asymétrique catalysé par le rhodium et le ruthénium

Ecole doctorale n°406

Chimie moléculaire Paris Centre

**Spécialité** Chimie Moléculaire

Soutenue par Longsheng **ZHENG**

le 25 Octobre 2018

Dirigée par Virginie **VIDAL**

Phannarath **PHANSAVATH**



## COMPOSITION DU JURY :

**Mme. PRUNET Joëlle (DR)**  
University of Glasgow, Rapporteur  
et Président

**M. BRUNEAU Christian (IR)**  
Université de Rennes 1, Rapporteur

**Mme. COSSY Janine (Prof.)**  
ESPCI Paris, Examineur

**Mme. VIDAL Virginie (DR)**  
Chimie ParisTech, Directrice de Thèse



*“We keep moving forward, opening new doors,  
and doing new things, because we're curious and  
curiosity keeps leading us down new paths.”*

**Walt Disney**



# Acknowledgements

This thesis was conducted at Chimie ParisTech - PSL University, at l'Institut de Recherche de Chimie Paris under the supervision of Dr **Virginie VIDAL**, CNRS Research Director and Dr **Phannarath PHANSAVATH**, Associate Professor.

My sincere thanks to Dr **Jo ãle PRUNET**, Senior Lecturer at the University of Glasgow, and Dr. **Christian BRUNEAU**, CNRS Researcher Engineer at the Institut des Sciences Chimiques de Rennes, for having accepted to be rapporteurs for my thesis. I also thank Prof. **Janine COSSY** at ESCPI Paris and Prof. **Max MALACRIA** at Sorbonne Universit é (Pierre and Marie Curie University) for having taken the time to review this thesis work.

I thank very warmly my two supervisors **Virginie** and **Pocki** for the trust and freedom that they have granted me in my work and to have helped me to acquire the necessary skills in chemistry. Thank you for all the rewarding discussions that we had during the working meetings. I am full of gratefulness for the corrections on my reports and oral presentations. More personally, I would like to deeply thank **Virginie** for her guidance and decisions during every scientific discussions on each projects, and her availability, the many re-readings of this manuscript and also its way of mothering the lab and students (you are a little the "lab mum"! ). Thank you for taking care when I was sick one time and provided your help. In addition, I would like to thank you for giving me opportunity to attend the international BOSS<sup>XVI</sup> conference, which is a high level organic synthesis symposium in Europe. Furthermore, you were also highly concerned and helped me a lot for my future career. A huge thank you to **Pocki** for listening and availability all the time and for all the corrections of the manuscript. Thank you for your good mood and your kindness even sometimes when the chemistry was changeable and I needed reassurance. Thank you for your many tips and for your calm and your instructions in problem analysis. Besides, I obviously remember when we were trying together to model the transition state for understanding the mechanism. That's amazing! Thank you for your greetings and encouragement after work when leaving. Recently, thank you also for your film tickets.

Thank you Virginie and Pocki from the bottom of the heart!

I would like to thank all the members of the laboratory that I have been able to meet during these three years. I will first thank my lab mate, **Quentin**. My Chinese colleagues and I like to

call him “钢蛋”. I still remember that under his guidance, I started to be familiar with other colleagues and finish my first year’s registration. These two years have been very great with you in the lab. Thank you for your kindness and your help during my experiments. Besides, thank you for driving me during every personal activities.

I want to thank dear **Charlene**, “Chacha” for the 2 years working together. Thanks for her very valuable help and her seriousness. Thank you also for all the things she has done for the group. Now, she got an administrative position. I hope everything goes well for her.

Besides, I would like to thank little **Maxime**, who is very gentlemanlike and talented. He always had an elegant gesture and let me pass first, when we were face to face across the aisle. He has a solid theoretical background in chemistry. Next, I want to thank **Benjamin**, who is the “King of battery” and “King of forest”, as well as “Brother of snake” ;-). He is good at sports, like basketball, bowling, Ping-Pong ... Thank you for inviting us to your home and organizing a lot of activities.

Of course, many thanks must be delivered to **Fei**, who is one of my best friend such as my brother. We got our Master’s education from the same lab in Hangzhou Normal University in China. We had already been working together for 5 years and I really enjoyed all the time that we worked and spent together. He is very brilliant and hardworking student, and always very dynamic. I hope he will enjoy the post-doctoral experience in Germany and will publish papers such as “JACS, ACIE, Nature or Science ☺ etc.” Meanwhile, I hope he will find a new “hot” girlfriend to enjoy the life.

Thanks also to **Charlotte**, “Panda sister”, who enjoyed learning Chinese and Chinese food. She also taught me French, “ça marche” and helped me a lot in the lab and in translating some documents. I also enjoyed the time we were jogging together in the Luxembourg garden.

I also would like to thank the former PhD students. **Marc**, he helped me a lot when I needed to fill in some administrative documents. **Fabien**, thanks for his good humor and jokes. Pierre-Georges, **PG**, his thesis was wonderful and helped me a lot.

Next, I would like to thank all the former Post-docs and ATER. **Eder**, thanks for teaching me how to use the software of viewing crystal structure, that’s amazing. I wish him to have a good

future in academic research. **Sudipta**, thanks for his kindness and his delicious Indian food. Forgive me when I made a joke when we were in a party, “you will never be drunk with red face”. He is the well-known hardworking guy in our lab. I believe he will have a bright future. **Aur die**, she is highly motivated in chemistry and always very nice to help me. Congratulations for her permanent position in ICSN and best wishes to her in academic research. **Clément**, thanks to him, when I need to borrow some staffs, he was always available and warm-hearted. **Fatma**, thanks for her greetings when we went to the CROUS for lunch and her hometown’s food. Besides, thanks to **Christine**, ATER, I enjoyed her London’s accent and her humor. Thanks to her mother’s cooked nems.

I next want to thank the present PhD students. **Yue**, he is a talented, knowledgeable PhD student. He loves music and chemistry. I learn from him that chemistry could be wonderful if combined with other things. Many thanks to help a lot when he was in the lab. Besides, thanks to his guidance when I had vacations last summer to visit Nice. **Bin**, he is very funny guy. Thanks to his humor and his distilled petroleum ether. Besides, thanks for waiting me to go home together. **Yantao**, thanks to him for teaching me how to use the GC. Thanks also to him and his wife for preparing delicious Sushi. **Deyang**, he is a good mood guy and always with a big smile. Thanks also for the GC. **Ayman**, I enjoyed his joke when I went to ask him borrow some staffs (I can’t count how much money I owe you. \*^©^\*). Many thanks for giving me help in the lab. He is also highly enthusiastic, motivated and hardworking student. **Johanne**, she is an excellent PhD student. “Bon courage!” also to you to finish your PhD. Thanks for maintaining the solvent system. Thanks to her elaborately prepared Christmas Day’s meal. **Anne**, thanks to her good mood and kindness as my lab mate. Thanks to bring delicious cakes several times.

Furthermore, for all the permanent members in our lab, first, I’d like to give my thanks to “big” **Maxime**, who is described as a “Swiss knife”. He has strong various skills on computer as well as for analysis instruments. A special thanks for maintaining SFC and HPLC for all the lab, which enabled me to test my samples. Thanks also to his special humor. Thanks to **Tahar**, his humor gives us a lot of fun. Thanks to **Sylvain**, he has a good mood and his laugh makes us full of happiness. **Mansour**, a “young” guy for all of us, we all enjoyed his humor... I knew a lot of funny things from **Fei**. His bowling skills is comparable to Benjamin. **Véronique**, she was helpful, when I needed some staffs in her office.

I also want to thank all the permanents working in the platforms of Chimie ParisTech.

Particularly, I would like to thank **Marie-Noële** for her hard work in NMR management lab.

Thanks to **Cédine** and **Claudine** for their incredible work in mass spectrometry. Thanks to **Frédéric** for some measurements of melting points. Thanks to **David** for his good mood and greetings. Thanks to **Franck** for preparing everyday all the experimental consumables and solvents. Thanks also to **Suzanne** and **Marjorie** for the administrative work.

I would like also to thank **Lise-Marie Chamoreau** and **Geoffrey Gontard** for the X-ray analysis. I also want to thank my tutors of "Comité de suivi de thèse", Dr **Muriel Amatore** and Dr **Didier Buisson**, for their comments and advices on my work during my PhD.

Many thanks to all my friends in France and China who helped and supported me. A special thankfulness to my friend and roommate **Tao**, he helped me a lot during these three years.

I deeply thank my beloved family, my parents and my relatives, for their thorough concern and great confidence in me all over these years.

Finally, I would like to give a special acknowledgement to **China Scholarship Council** for a three years' fellowship in Paris.

# Table of Contents

|   |           |
|---|-----------|
| <b>Abbreviation .....</b>   | <b>6</b>  |
| <b>R ésum é.....</b>  | <b>11</b> |
| <b>General introduction.....</b>  | <b>33</b> |
| <b>Part A: Recent developments on transition metal-catalyzed asymmetric transfer hydrogenation (ATH) of ketones .....</b> | <b>37</b> |
| <b>1. Theoretical background on asymmetric transfer hydrogenation.....</b>  | <b>37</b> |
| 1.1 Introduction to asymmetric transfer hydrogenation.....  | 37        |
| 1.1.1 Mechanisms .....  | 39        |
| 1.1.2 Ligands.....  | 41        |
| 1.1.3 Noyori's bifunctional catalysts .....   | 42        |
| 1.1.4 General mechanism .....   | 43        |
| 1.1.5 Origins of enantioselectivity.....  | 46        |
| 1.1.6 Other catalysts for asymmetric transfer hydrogenation .....   | 48        |
| 1.1.7 The various hydrogen sources .....  | 51        |
| <b>2. Reaction scope: catalysts and chiral ligands.....</b>   | <b>58</b> |
| 2.1 Ruthenium catalysts .....   | 58        |
| 2.1.1 Aminoalcohols as ligands .....  | 58        |
| 2.1.2 Diamines as ligands .....   | 59        |
| 2.1.3 Phosphorus containing ligands .....   | 64        |
| 2.1.4 Sugar containing ligands .....  | 66        |
| 2.1.5 Sulfur containing ligands .....   | 67        |
| 2.1.6 Heterocyclic ligands.....   | 67        |
| 2.1.7 Other type of chiral Ru complexes.....  | 68        |
| 2.2 Tandem reactions using Ruthenium catalysts .....  | 69        |
| 2.3 ATH of functionalized ketone derivatives with Ruthenium catalysts .....   | 71        |
| 2.4 Rhodium catalysts .....   | 74        |
| 2.5 Iridium catalysts .....   | 75        |

|  |            |
|--|------------|
| 2.6 Iron catalysts .....   | 80         |
| 2.7 Manganese catalysts .....  | 82         |
| 2.8 Osmium catalyst .....  | 83         |
| <b>3. Applications in total synthesis .....</b>  | <b>84</b>  |
| <b>4. Immobilized catalysts.....</b>   | <b>87</b>  |
| <b>5. Conclusions .....</b>  | <b>89</b>  |
| <b>Part B: ATH of (hetero)aryl ketones and <math>\alpha,\alpha</math>-dihalogeno <math>\beta</math>-Ketoesters.....</b>  | <b>91</b>  |
| <b>1. ATH of (hetero)aryl ketones catalyzed with tethered rhodium complexes .....</b>  | <b>91</b>  |
| 1.1 Introduction .....   | 91         |
| 1.2 Results and discussion.....  | 93         |
| 1.2.1 Synthesis of novel complexes <b>(<i>R,R</i>)-C85-C87</b> .....   | 93         |
| 1.2.2 Optimisation of the reaction conditions for the ATH of acetophenone with complex <b>(<i>R,R</i>)-C84</b> .....   | 95         |
| 1.2.3 ATH of aryl ketones mediated by complexes <b>(<i>R,R</i>)-C23, C84-C87</b> .....   | 96         |
| 1.2.4 ATH of heteroaryl and alkyl ketones mediated by complexes <b>(<i>R,R</i>)-C23, C84-C87</b> .....   | 99         |
| 1.2.5 ATH of unsymmetrical benzophenones mediated by complexes <b>(<i>R,R</i>)-C23, C84</b> .....  | 100        |
| 1.2.6 ATH of 1,4-diaryl diketone mediated by complexes <b>(<i>R,R</i>)-C23, C84</b> .....  | 101        |
| 1.2.7 Proposed mechanism of ATH of ketones with tethered Rh(III) complex .....   | 102        |
| 1.3 Conclusion .....   | 103        |
| <b>2. Synthesis of enantioenriched <math>\alpha,\alpha</math>-dichloro and <math>\alpha,\alpha</math>-difluoro <math>\beta</math>-hydroxy esters and amides via ruthenium-catalyzed asymmetric transfer hydrogenation.....</b> | <b>105</b> |
| 2.1 Introduction.....  | 105        |
| 2.2 Different routes to access $\alpha,\alpha$ -dihalogeno $\beta$ -hydroxyester derivatives .....   | 106        |
| 2.3 Results and discussion.....  | 108        |
| 2.3.1 Synthesis of $\alpha,\alpha$ -dihalogeno $\beta$ -ketoesters .....   | 108        |
| 2.3.2 ATH of $\alpha,\alpha$ -dichloro $\beta$ -ketoesters - optimisation of the reaction conditions .....   |            |

|   |            |
|---|------------|
| .....   | 111        |
| 2.3.3 Substrate scope .....   | 114        |
| 2.4 Scale up experiment and post-functionalization reaction.....  | 117        |
| 2.5 Proposed rationale for the stereochemical outcome of the ATH.....   | 118        |
| 2.6 Conclusion .....  | 119        |
| <b>Part C: ATH of ketone derivatives via dynamic kinetic resolution.....</b>  | <b>121</b> |
| <b>1. Short overview on ATH-DKR of ketones.....</b>   | <b>121</b> |
| 1.1 Resolution methods .....  | 121        |
| 1.1.1 Kinetic resolution (KR).....  | 121        |
| 1.1.2 Dynamic kinetic resolution (DKR).....   | 123        |
| 1.2 Examples of DKR/ATH of ketone derivatives .....   | 124        |
| 1.2.1 DKR/ATH of 1,2-diketones.....   | 124        |
| 1.2.2 DKR/ATH of 1,3-diketones.....   | 125        |
| 1.2.3 DKR/ATH of linear $\alpha$ -substituted $\beta$ -keto derivatives .....   | 127        |
| 1.2.3.4 DKR/ATH of $\alpha$ -alkoxy (or siloxy) $\beta$ -keto esters (or phosphonates) .....  | 132        |
| 1.2.4 DKR/ATH of $\alpha$ -substituted cyclic ketone derivatives .....  | 134        |
| 1.2.5 DKR/ATH of $\beta$ -substituted $\alpha$ -keto esters and phosphonates .....  | 140        |
| 1.3 DKR/ATH of $\alpha$ -amino $\beta$ -keto derivatives.....   | 143        |
| 1.3.1 DKR/ATH of $\alpha$ -amino $\beta$ -ketones to access chiral 1,2-amino alcohols.....  | 143        |
| 1.3.2 DKR/ATH of $\alpha$ -amino $\beta$ -keto esters to access <i>anti</i> $\beta$ -hydroxy $\alpha$ -amino esters .....                                   | 144        |
| 1.3.3 DKR/ATH of $\alpha$ -amino $\beta$ -keto esters to access <i>syn</i> $\beta$ -hydroxy- $\alpha$ -amino esters .....                                   | 147        |
| <b>2. Rhodium-mediated ATH: a diastereo- and enantioselective synthesis of <i>syn</i>-<math>\alpha</math>-amido <math>\beta</math>-hydroxy esters .....</b> | <b>151</b> |
| 2.1 Interest of <i>syn</i> - $\alpha$ -amino $\beta$ -hydroxy derivatives.....  | 151        |
| 2.2 Results and discussion.....   | 153        |
| 2.2.1 Preparation of $\alpha$ -amido $\beta$ -ketoesters <b>24a-z</b> .....   | 153        |
| 2.2.2 Optimisation of the reaction conditions .....   | 156        |

|   |            |
|---|------------|
| 2.3.3 Substrate scope .....   | 161        |
| 2.3.4 Determination of the absolute configuration .....   | 166        |
| 2.3 Conclusion .....  | 167        |
| <b>3. Novel rhodium-mediated ATH: a diastereo- and enantioselective synthesis of <i>syn</i>-<math>\alpha</math>-alkoxy <math>\beta</math>-hydroxy esters .....</b>                | <b>168</b> |
| 3.1 Introduction.....   | 168        |
| 3.1.1 Biological interest of <i>syn</i> diols derivatives .....   | 168        |
| 3.1.2 Different synthetic pathways for 1,2-diols derivatives .....  | 169        |
| 3.2 Results and discussion.....   | 171        |
| 3.2.1 Synthesis of aryl $\alpha$ -methoxy $\beta$ -keto esters.....   | 171        |
| 3.2.2 Synthesis of a new Rh(III)-TsDPEN-based tethered complex.....   | 174        |
| 3.2.3 Optimisation of the reaction conditions .....   | 175        |
| 3.2.4 Substrate scope .....   | 178        |
| 3.3 Conclusion .....  | 181        |
| <b>4. Ruthenium-catalyzed dynamic kinetic asymmetric transfer hydrogenation: stereoselective access to <i>syn</i> 2-(1,2,3,4-tetrahydro-1-isoquinolyl)ethanol derivatives....</b> | <b>182</b> |
| 4.1 Introduction.....   | 182        |
| 4.1.1 Biological interest of chiral 1,3-amino alcohol derivatives .....   | 182        |
| 4.1.2 Methods to access chiral 1,3-amino alcohol derivatives .....  | 182        |
| 4.1.3 DKR/ATH of $\beta$ -substituted ketone derivatives to access the corresponding alcohols bearing 1,3-diastereocenters.....   | 183        |
| 4.2 Results and discussion.....   | 187        |
| 4.2.1 Synthesis of THIQ-based $\beta$ -amino ketones .....  | 187        |
| 4.2.2 Optimisation of the reaction parameters .....   | 190        |
| 4.2.3 Substrate scope .....   | 194        |
| 4.2.4 Post-functionalization .....  | 198        |
| 4.3 Conclusion .....  | 199        |
| <b>General conclusion .....</b>   | <b>201</b> |
| <b>Experimental part .....</b>  | <b>205</b> |

|   |     |
|---|-----|
| 1. General informations .....                                     | 205 |
| 2. Description of the synthesized products .....                  | 207 |
| 2.1 Index of synthesized products .....                           | 207 |
| 2.2 Description of the synthesis processes and detailed data..... | 230 |

## Abbreviation

|          |              |  |
|----------|--------------|--|
|          | Ac           | Acetate  |
|          | AIBN         | 2,2'-Azobis(2-methylpropionitrile)               |
|          | ALK          | Anaplastic lymphoma kinase                       |
| <b>A</b> | Ar           | Aromatic   |
|          | ATH          | Asymmetric transfer hydrogenation                |
|          | atm          | Atmosphere                                       |
|          | [ $\alpha$ ] | Specific rotation                                |
|          | $\beta$ -LG  | Beta-lactoglobulin                               |
|          | BMS          | Bristol-Myers Squibb                             |
| <b>B</b> | Bn           | Benzyl   |
|          | Boc          | <i>Tert</i> -butoxycarbonyl                      |
|          | Bu           | Butyl  |
|          | Bz           | Benzoyl  |
|          | Cat.         | Catalyst   |
|          | Cbz          | Carboxybenzyl                                    |
|          | °C           | Celsius degree                                   |
|          | CDC          | Cross-dehydrogenative coupling                   |
| <b>C</b> | CDI          | 1,1'-Carbonyldiimidazole                         |
|          | CIL          | Chiral ionic liquids                             |
|          | Cod          | Cycloocta-1,5-diene                              |
|          | Cp           | Cyclopentadienyl                                 |
|          | Cp*          | Pentamethylcyclopentadienyl                      |
|          | Cy           | Cyclohexyl                                       |
|          | DABCO        | 1,4-Diazabicyclo[2.2.2]octane                    |
|          | DCC          | Dicyclohexylcarbodiimide                         |
| <b>D</b> | DCD          | D édoublément cin étique dynamique               |
|          | DCE          | 1,2-Dichloroethane                               |
|          | DDQ          | 2,3-Dichloro-5,6-dicyano- <i>p</i> -benzoquinone |

|          |        |   |
|----------|--------|---|
|          | de     | Diastereomeric excess   |
|          | DHPD   | 5,6-Dihydrophenanthridine   |
|          | DIPA   | Diisopropylamine  |
|          | DKR    | Dynamic kinetic resolution  |
|          | DMAP   | 4-Dimethylaminopyridine   |
|          | DMAPA  | Dimethyl aminopropyl acrylamide   |
|          | DMC    | Dimethylcarbonate   |
|          | DMF    | <i>N,N</i> -Dimethylformamide   |
|          | DMP    | Dess-Martin periodinane   |
|          | DMSO   | Dimethyl sulfoxide  |
|          | DPEN   | 1,2-Diphenylethylenediamine   |
|          | dr     | Diastereomeric ratio  |
|          | DIODMA | <i>N<sup>4</sup>,N<sup>4</sup>,N<sup>5</sup>,N<sup>5</sup></i> ,2,2-hexamethyl-4,5-bis-(aminomethylene)-1,3-dioxolane |
|          | δ      | Chemical shift  |
|          | ee     | Enantiomeric excess   |
| <b>E</b> | equiv  | Equivalent  |
|          | Et     | Ethyl   |
| <b>F</b> | FDA    | US Food and Drugs Administration  |
|          | g      | Gramme  |
| <b>G</b> | gem    | Geminal   |
|          | GPR    | G-protein coupled receptor  |
|          | h      | Hour  |
|          | IBX    | 2-Iodobenzoic acid  |
|          | HIV    | Human immunodeficiency virus  |
| <b>H</b> | HMDS   | Hexamethyldisilazane  |
|          | HMSN   | Hollow mesoporous silica nanospheres  |
|          | HPLC   | High performance liquid chromatography  |
|          | HRMS   | High resolution mass spectra  |

|          |                  |   |
|----------|------------------|---|
|          | IC <sub>50</sub> | Half maximal inhibitory concentration             |
| <b>I</b> | <i>i</i> Bu      | <i>Iso</i> -butyl                                 |
|          | <i>i</i> Pr      | <i>Iso</i> -propyl                                |
|          | IPA              | <i>Iso</i> -Propanol                              |
|          | IR               | Infrared radiation                                |
|          | IUPAC            | International Union of Pure and Applied Chemistry |
| <b>K</b> | k                | Rate constant                                     |
|          | KR               | Kinetic resolution                                |
| <b>L</b> | L*               | Chiral ligand                                     |
|          | LDA              | Lithium diisopropylamide                          |
|          | Lit.             | Literature  |
| <b>M</b> | MW               | Molecular weight                                  |
|          | MCM              | Mobil composition of matter                       |
|          | Me               | Methyl  |
|          | 2-MeTHF          | 2-Methyltetrahydrofuran                           |
|          | min              | Minute  |
|          | MMP              | Macromolecular polymers                           |
|          | m.p.             | Melting point                                     |
|          | Ms               | Methylsulfonyl                                    |
|          | NMDA             | <i>N</i> -methyl-D-aspartate                      |
|          |                  | Nuclear magnetic resonance                        |
|          |                  | <i>J</i> : coupling constant                      |
|          |                  | <i>s</i> : singlet                                |
|          | NMR              | <i>d</i> : doublet                                |
|          |                  | <i>t</i> : triplet                                |
|          |                  | <i>q</i> : quadruplet                             |
|          |                  | <i>quint</i> = quintuplet,                        |

|          |                                 |  |
|----------|---------------------------------|--|
|          |                                 | <i>sext</i> = sextuplet,   |
|          |                                 | <i>hept</i> = heptuplet,   |
|          |                                 | <i>m</i> : multiplet   |
|          |                                 | <i>br</i> : broad  |
|          | NADH                            | Dihyronicotinamide adenine dinucleotide  |
|          | NADPH                           | Dihyronicotinamide-adenine dinucleotide phosphate                                |
|          | Pd/C                            | Palladium on activated charcoal  |
|          | PEG                             | Polyethylene glycol  |
|          | Ph                              | Phenyl   |
|          | pH                              | Hydrogen ion concentration   |
| <b>P</b> | PHOX                            | Phosphinooxazolines  |
|          | P*P                             | Chiral diphosphine   |
|          | ppm                             | Parts per million  |
|          | Pr                              | Propyl   |
|          | P <sub>R</sub> , P <sub>S</sub> | Product enantiomers  |
|          | PTSA                            | <i>para</i> -Toluenesulfonic acid  |
|          |                                 |  |
| <b>Q</b> | Quant.                          | Quantitative   |
|          |                                 |  |
|          | rt                              | Room temperature   |
| <b>R</b> | R <sub>f</sub>                  | Retention factor   |
|          | rac                             | Racemic  |
|          | ROS1                            | a receptor tyrosine kinase   |
|          |                                 |  |
|          | SFC                             | Supercritical Fluid Chromatography   |
|          | Selectfluor™ FTEDA-             | 1-(chloromethyl)-4-fluoro-1,4-   |
|          | BF <sub>4</sub>                 | Diazoniabicyclo[2.2.2]octane ditetrafluoroborate                                 |
| <b>S</b> | SpiroPAP                        | Spiro pyridine aminophosphine  |
|          | Synphos                         | 6,6'-Bis(diphenylphosphino)-2,2',3,3'-tetrahydro-5,5'-<br>Bibenzo[b][1,4]dioxine |
|          | S <sub>R</sub> , S <sub>S</sub> | Substrate enantiomers  |

|          |             |  |
|----------|-------------|--|
|          | T           | Temperature                            |
|          | t           | Time                                   |
|          | TAPS        | Tetraarylphosphonium salts             |
|          | TBS         | <i>tert</i> -Butyldimethylsilyl        |
|          | TCCA        | Trichloroisocyanuric acids             |
|          | <i>t</i> Bu | <i>tert</i> -Butyl                     |
|          | TEOS        | Tetraethoxysilane                      |
|          | Tf          | Triflate                               |
| <b>T</b> | TH          | Transfer hydrogenation                 |
|          | THA         | Transfert d'hydrogène asymétrique      |
|          | THF         | Tetrahydrofuran                        |
|          | THIQ        | Tetrahydroisoquinoline                 |
|          | TLC         | Thin layer chromatography              |
|          | TMS         | Trimethylsilyl                         |
|          | TIPS        | Triisopropylsilyl                      |
|          | TOF         | Turnover frequency                     |
|          | Ts          | Toluenesulfonyl                        |
|          |             | $t_R$                                  |
| <b>U</b> | UV          | Ultraviolet                            |
|          |             |  |
| <b>V</b> | VMAT-2      | Vesicular monoamine transporter type 2 |
|          | VCD         | Vibrational Circular Dichroism         |
| <b>W</b> | wt%         | Percentage by weight                   |





# RÉSUMÉ



## Résumé

### Partie A: Développements récents sur le transfert d'hydrogène asymétrique de cétones catalysé par des métaux de transition.

Ce chapitre présente un rappel sur le transfert d'hydrogène asymétrique (THA) de composés insaturés catalysé par des complexes de métaux de transition (Schéma 1).

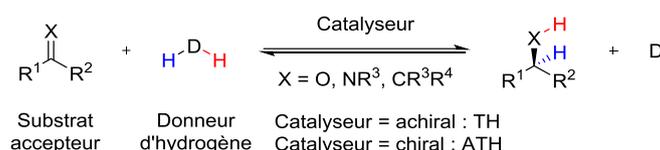


Schéma 1

Les différents complexes utilisés dans ce type de réactions sont présentés, ainsi que les différentes sources d'hydrogène et le mécanisme général est discuté. De nombreux exemples de réactions de transfert d'hydrogène asymétrique de cétones illustrent cette partie.

### Partie B: Transfert d'hydrogène asymétrique d'(hétéro)arylcétones et de $\alpha,\alpha$ -dihalogéno- $\beta$ -cétoesters

#### 1. Transfert d'hydrogène asymétrique d'(hétéro)arylcétones catalysé par des complexes de rhodium.

Une série de nouveaux complexes Rh(III)/Cp\* **C85-C87** contenant le ligand *N*-(p-tolylsulfonyl)-1,2-diphényléthylène-1,2-diamine ont été préparés et caractérisés (Schéma 2).

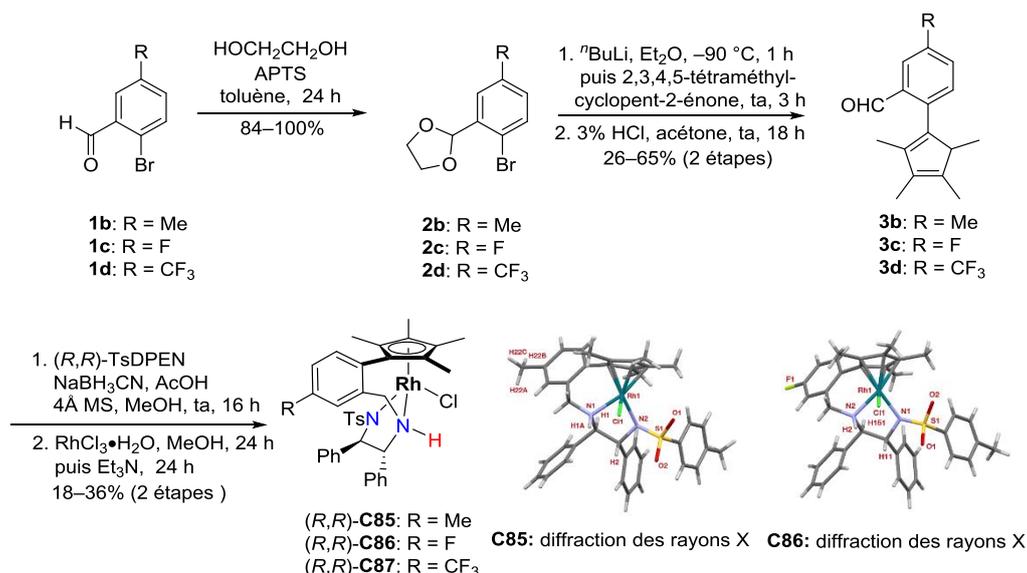


Schéma 2

Ces complexes ont ensuite été évalués, conjointement avec le complexe de Wills **C23** (R = H) et le complexe **C84** (R =  $\text{OCH}_3$ ) préparé précédemment au laboratoire, dans le THA

d'une large gamme d'hydroarylcétones. La réaction a été réalisée en utilisant les complexes **C23**, **C84-C87** comme pré-catalyseurs dans des conditions douces avec le système acide formique/triéthylamine (5:2) comme source d'hydrogène et, dans la plupart des cas, a fourni des alcools énantioenrichis avec de bons rendements et des énantiosélectivités élevées à excellentes (94→99% ee). Cependant, de faibles discriminations énantiofaciales ont été observées pour les arylcétones possédant un substituant en *ortho* comme pour la 2-bromoacétophène **4h** (64-71% ee) et la 1-acétonaphtone **4j** (78-85% ee). En outre, une montée en échelle du THA de la 4-chromanone **4o** à l'échelle du gramme a fourni quantitativement le produit réduit avec une excellente énantiosélectivité démontrant l'utilité potentielle de ces nouveaux complexes (Schéma 3)

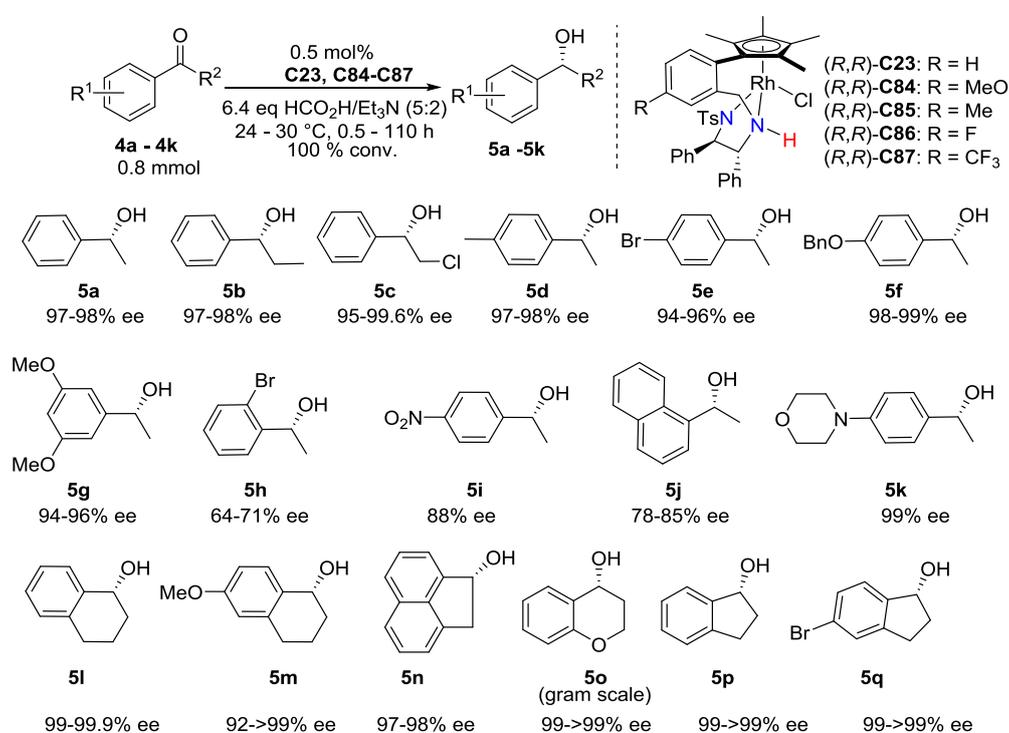


Schéma 3

Bien que la nature des substituants présents sur le lien benzyle ne modifie pas le cours stéréochimique de la réaction, les complexes portant des groupements électro-donneurs présentent une activité catalytique plus élevée que ceux ayant des groupes électro-attracteurs, comme le montre la Figure 1.

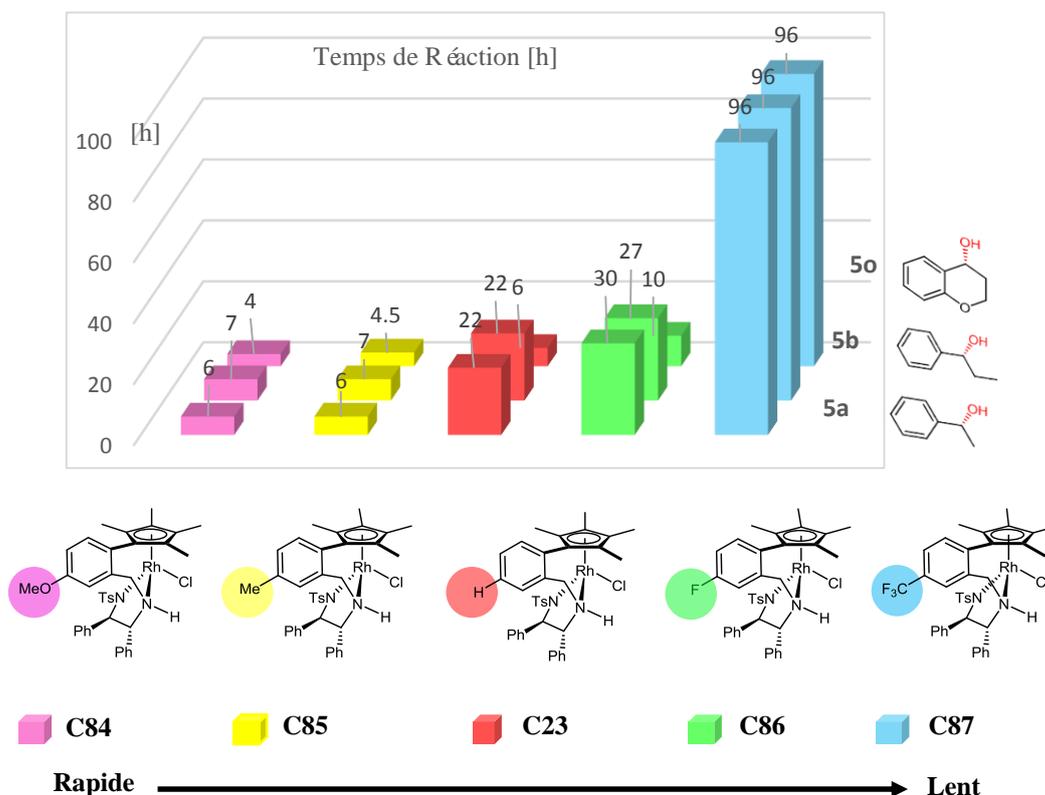


Figure 1

L'étude des substrats a été étendue aux hétéroaryles **6a-6d** et alkylcétones **6e-6f**. Le THA des premiers composés conduit à de bons rendements et les composés **7a-7d** sont obtenus avec des inductions asymétriques élevées pour tous les complexes Rh(III)/Cp\* examinés. En ce qui concerne les cétones non aromatiques, la téralone **6e** a donné des ee modérés (80 à 83 %), tandis que des stéréosélectivités élevées ont été obtenues pour le THA de l'acétalcyclohexane **6f** (93 à 95 % ee) (Figure 2).

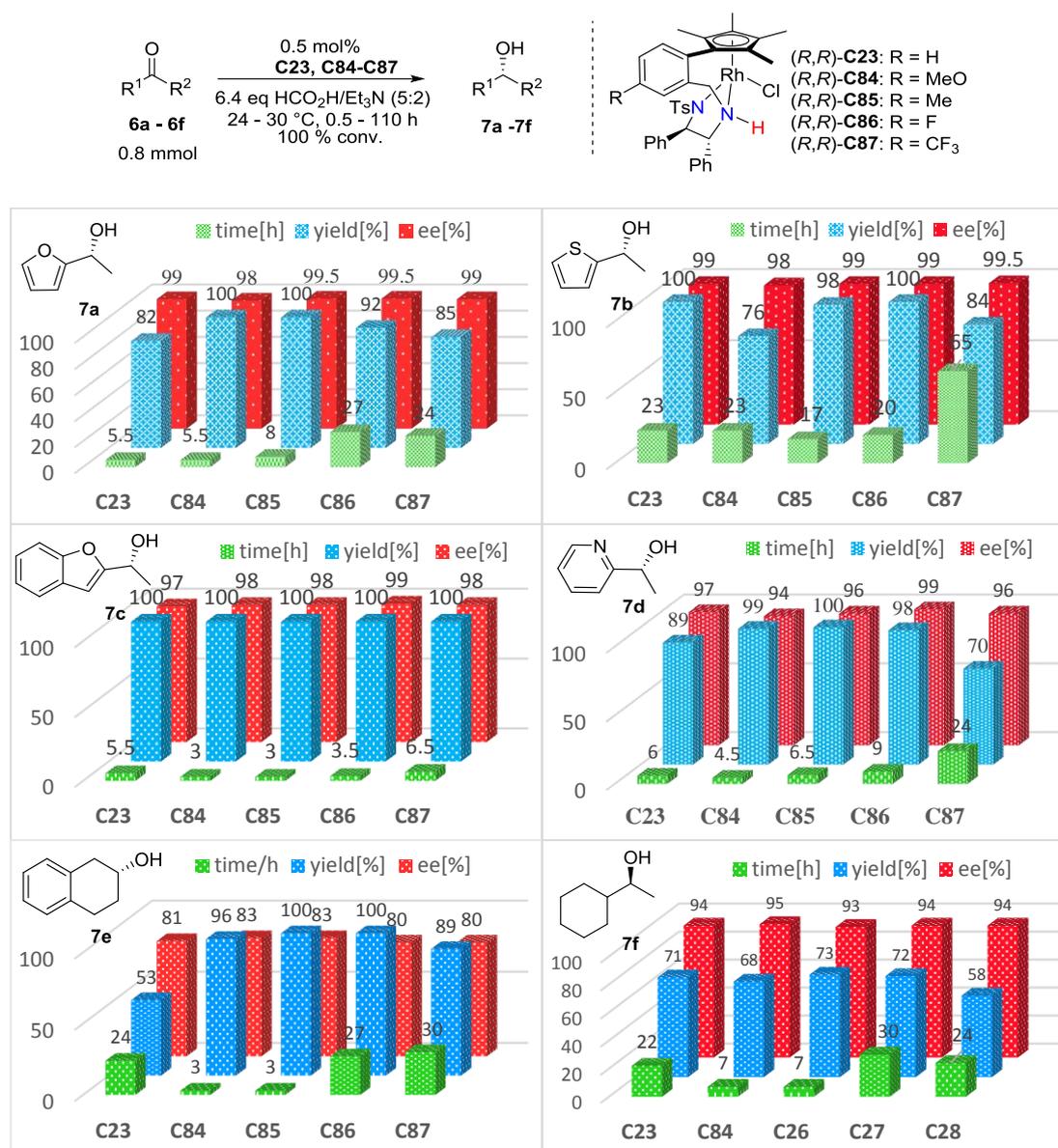


Figure 2

Les performances catalytiques de nos nouveaux complexes ont également été testées dans le THA de substrats diarylcétoniques. Il est intéressant de noter que lors de l'utilisation du complexe Rh-TsDPEN (*R,R*)-C84 dans les conditions de réaction standard, la 4'-nitrobenzophénone donne un excès énantiomérique satisfaisant de 83% tandis que des énantioinductions faibles sont observées pour la 4'-chlorobenzophénone et la 4'-méthoxybenzophénone. La stéréosélectivité la plus élevée est observée avec le substrat *ortho*-substitué la 2'-méthylbenzophénone, qui est convertie en alcool correspondant à 99% ee (Schéma 4).

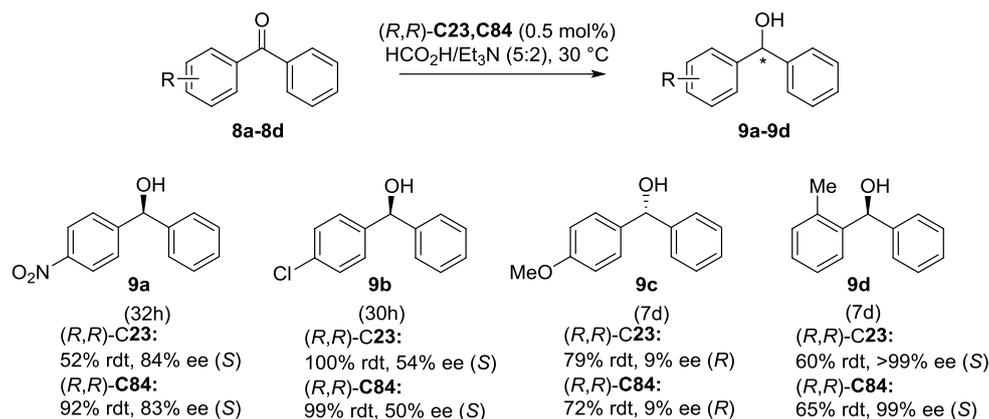
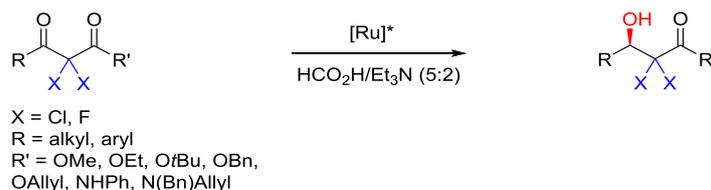


Schéma 4

## 2. Synthèse de $\alpha,\alpha$ -dichloro et $\alpha,\alpha$ -difluoro $\beta$ -hydroxy esters et amides par transfert d'hydrogène asymétrique catalysé au ruthénium.

Le transfert d'hydrogène asymétrique catalysé au ruthénium de  $\alpha,\alpha$ -dichloro et  $\alpha,\alpha$ -difluoro  $\beta$ -cétosters et amides a été étudié et conduit efficacement aux alcools dihalogénés correspondants avec de très bons rendements et d'excellentes énantiosélectivités (Schéma 5).



Scheme 5

Pour cette étude, une gamme d'aryl et alkyl  $\beta$ -cétosters  $\alpha,\alpha$ -dichloro- et  $\alpha,\alpha$ -difluoro-substitués **13a-13r** a été synthétisée soit par chloration électrophile directe de  $\beta$ -cétosters soit par oxydation des dérivés  $\alpha,\alpha$ -dichloro- et  $\alpha,\alpha$ -difluoro  $\beta$ -hydroxyesters (Schéma 6).

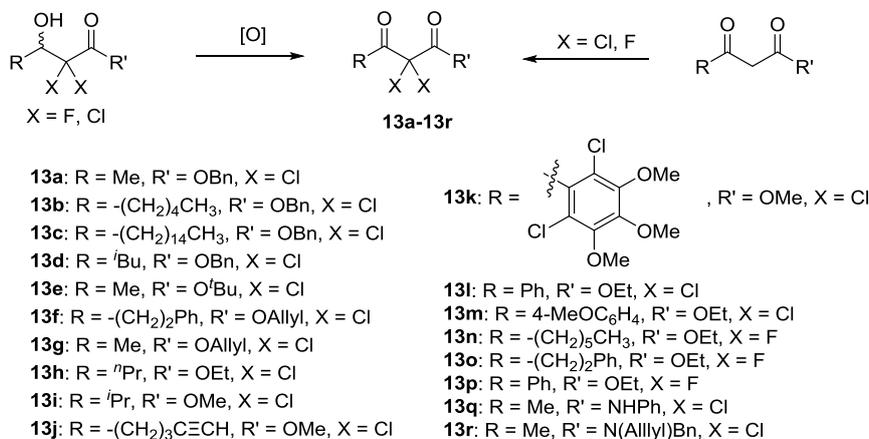
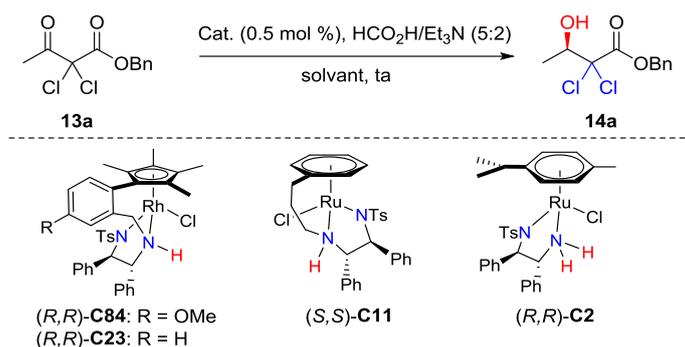


Schéma 6

Le 2,2-dichloro-3-oxobutanoate de benzyle **13a** a été choisi comme substrat modèle

pour l'étude des différents paramètres (tels que la température, le solvant et la concentration) de la réaction de transfert d'hydrogène asymétrique en utilisant différents complexes de rhodium et ruthénium, en présence du mélange azéotropique HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) comme source d'hydrogène. Les conditions optimales retenues sont: (*R,R*)-**C2** (0.5 mol %) comme pré-catalyseur, HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) (2.0 équiv.), CH<sub>2</sub>Cl<sub>2</sub> (0.2 M) à 30 °C.

**Tableau 1. Optimisation des conditions de réaction du THA du 2,2-dichloro-3-oxobutanoate de benzyle (13a).<sup>a</sup>**



| Entrée           | cat.                      | solvant                         | Temps (h) | rendement <sup>b</sup> (%) | ee <sup>c</sup> (%) |
|------------------|---------------------------|---------------------------------|-----------|----------------------------|---------------------|
| 1                | <b>C84</b>                | CH <sub>2</sub> Cl <sub>2</sub> | 4         | 77                         | 98                  |
| 2                | <b>C23</b>                | CH <sub>2</sub> Cl <sub>2</sub> | 5         | 84                         | 98                  |
| 3 <sup>e</sup>   | <i>(S,S)</i> - <b>C11</b> | CH <sub>2</sub> Cl <sub>2</sub> | 20        | 91                         | -99                 |
| 4                | <i>(R,R)</i> - <b>C2</b>  | CH <sub>2</sub> Cl <sub>2</sub> | 20        | 92                         | >99                 |
| 5 <sup>d</sup>   | <i>(R,R)</i> - <b>C2</b>  | CH <sub>2</sub> Cl <sub>2</sub> | 5         | 91                         | >99                 |
| 6 <sup>d,e</sup> | <i>(R,R)</i> - <b>C2</b>  | CH <sub>2</sub> Cl <sub>2</sub> | 3         | 87                         | >99                 |
| 7 <sup>d,f</sup> | <i>(R,R)</i> - <b>C2</b>  | CH <sub>2</sub> Cl <sub>2</sub> | 3         | 83                         | >99                 |
| 8 <sup>d</sup>   | <i>(R,R)</i> - <b>C2</b>  | EtOAc                           | 17        | 64                         | >99                 |
| 9 <sup>d</sup>   | <i>(R,R)</i> - <b>C2</b>  | THF                             | 17        | 67 <sup>g</sup>            | >99                 |
| 10 <sup>d</sup>  | <i>(R,R)</i> - <b>C2</b>  | <sup>i</sup> Pr <sub>2</sub> O  | 3         | 86                         | >99                 |
| 11 <sup>d</sup>  | <i>(R,R)</i> - <b>C2</b>  | <sup>i</sup> PrOH               | 5         | 81                         | >99                 |
| 12 <sup>h</sup>  | <i>(R,R)</i> - <b>C2</b>  | CH <sub>2</sub> Cl <sub>2</sub> | 7         | 96                         | >99                 |

<sup>a</sup> Conditions générales: **13a** (0.6 mmol), catalyseur (0.006 mmol), HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) (101 μL), CH<sub>2</sub>Cl<sub>2</sub> (3.0 mL)

<sup>b</sup> Rendement isolé, conversion complète, sauf lorsque indiqué <sup>c</sup> Déterminé par SFC. <sup>d</sup> Réaction effectuée à 40 °C.

<sup>e</sup> [0.4 M]: CH<sub>2</sub>Cl<sub>2</sub> (1.5 mL). <sup>f</sup> [0.6 M]: CH<sub>2</sub>Cl<sub>2</sub> (1.0 mL). <sup>g</sup> Conversion 92%. <sup>h</sup> Réaction effectuée à 30 °C.

Avec ces conditions optimisées en main, nous avons ensuite étudié l'étendue de la

réaction avec une série de composés dichloro et difluoro **13b-13r** (Schéma 7). Le THA des composés **13b-13k**, **13n-13o** portant des substituants benzyl-, *tert*-butyl-, allyl-, éthyl-, et méthyl-ester et une alcylcétone, ainsi que les composés **14q-14r** portant un amide et une alcylcétone, conduit aux alcools correspondants avec des rendements modérés à élevés (26%-99%) et d'excellentes énantiosélectivités (98->99% ee), excepté pour le composé **14j**. Cependant, les composés **13l-13m** et **13p** portant une arylcétone donnent les produits de réduction **14l-14m** et **14p** avec des énantiosélectivités modérées à bonnes (56-71% ee). Une montée en échelle réalisée sur le composé **13a** (0.91 g, 3.48 mmol) en utilisant une charge catalytique plus faible (0.5 mol%) conduit aux mêmes rendements et ee que sur une échelle de 0,6 mmol. La configuration absolue (*R*) de l'alcool **14q** a été attribuée sans ambiguïté par analyse cristallographique par diffraction des rayons X. Par analogie, nous supposons que les autres produits réduits suivent la même tendance.

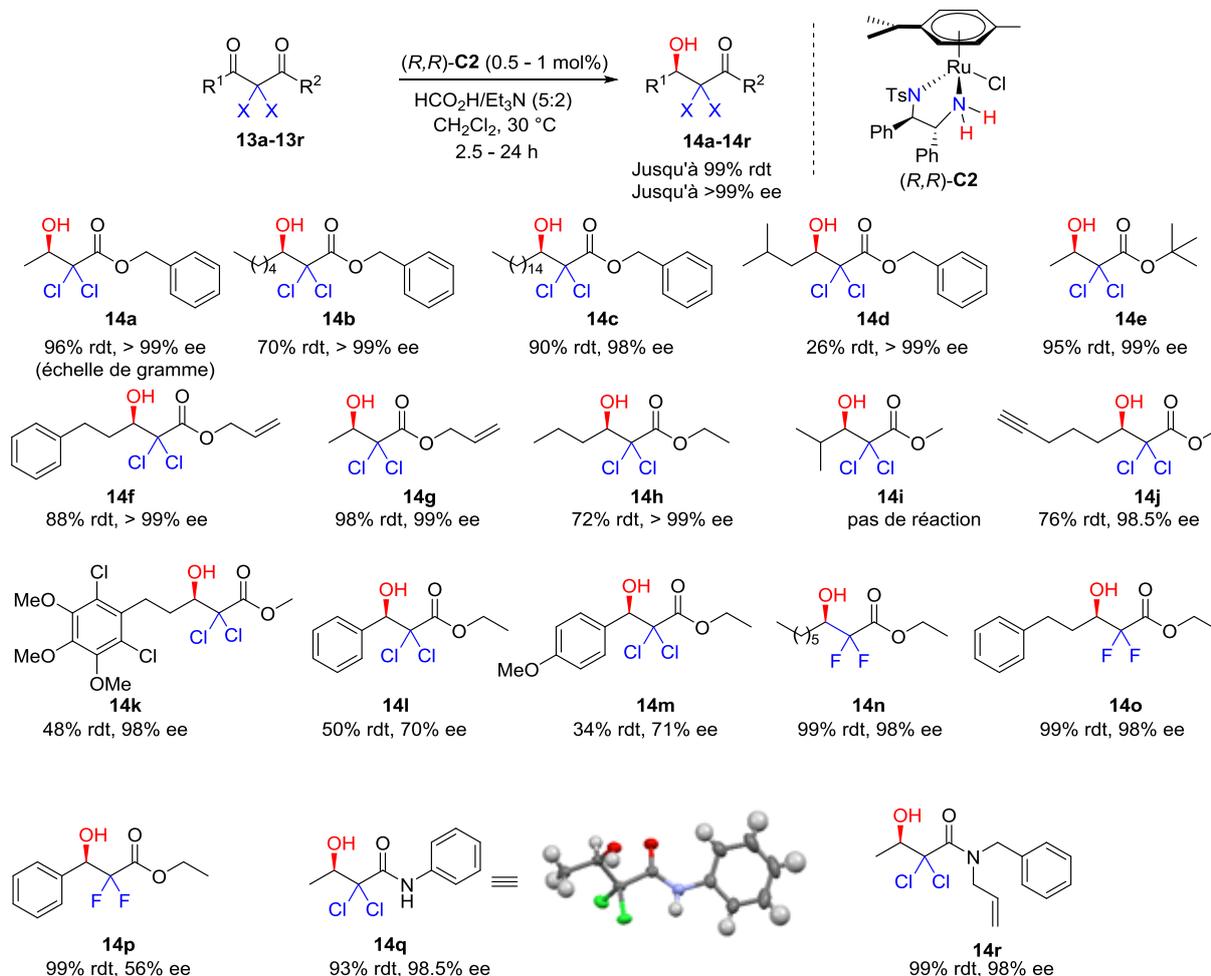


Schéma 7

De plus, la post-fonctionnalisation de **14f** et **14h** a été étudiée. Ainsi, une méthylation

croisé entre le (*R*)-2,2-dichloro-3-hydroxy-5-butanoate d'allyle **14f** et le 1-octène en présence du catalyseur de Grubbs II permet la formation de l'alcène **20** obtenu sous la forme d'un mélange *E/Z* (5.8:1) avec un rendement de 67%. D'autre part, le (*R*)-2,2-dichloro-3-hydroxyhexanoate d'éthyle **14h** est facilement converti en l'amide de Weinreb **21** correspondant avec un rendement de 85%, puis transformé en phénylcétone **22** par traitement avec le chlorure de phénylmagnésium (Schéma 8).

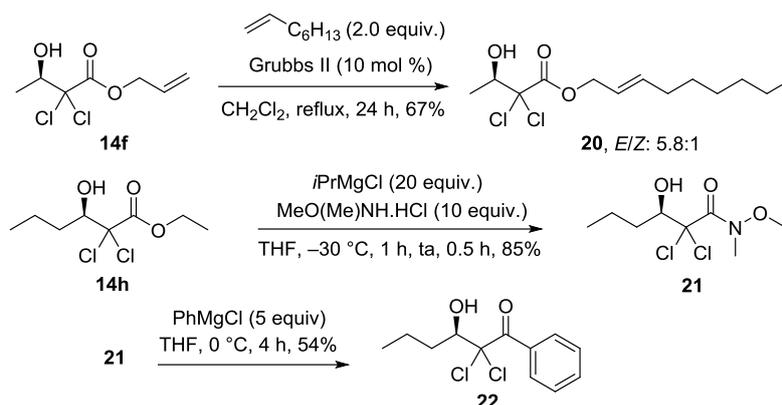


Schéma 8

## Partie C : Transfert d'hydrogène asymétrique de dérivés cétoniques par doublement cinétique dynamique.

### 1. Principe du THA-DCD et examen du THA-DCD de dérivés de cétones catalysés par des métaux de transition.

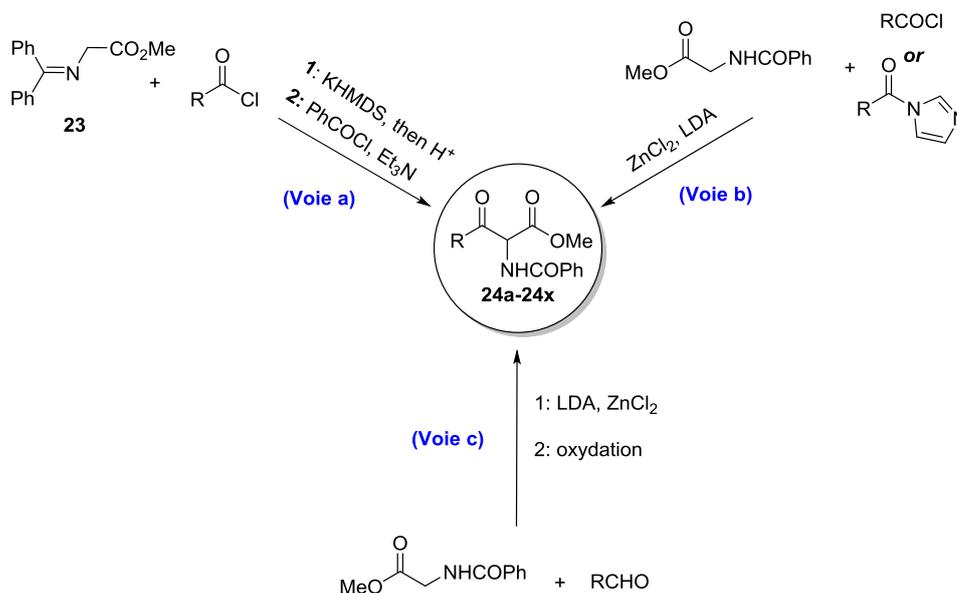
Dans cette partie est présenté le doublement cinétique dynamique (DCD), qui est une combinaison entre un doublement cinétique et un processus de racémisation dynamique. L'étape de doublement cinétique assure la transformation efficace du substrat en un énantiomère du produit (énantioinduction) et l'épimérisation rapide entre les deux énantiomères du mélange racémique de départ permettent ainsi d'avoir un rendement théorique de 100%.

Les travaux publiés entre 2015 et août 2018 portant sur le THA-DCD de dérivés cétoniques catalysés par des métaux de transition, sont ainsi détaillés dans ce chapitre.

### 2. Transfert d'hydrogène asymétrique catalysé par le rhodium : synthèse diastéreo- et énantioselective de *syn*- $\alpha$ -amido $\beta$ -hydroxy esters

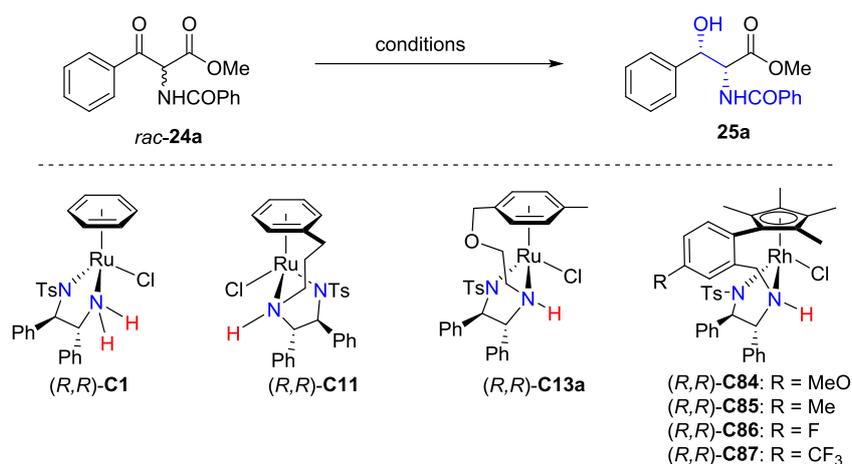
Les dérivés d'alcools  $\beta$ -aminés énantio-purs, portant deux stéréocentres contigus, sont des motifs importants présents dans de nombreux produits naturels et pharmaceutiques, et peuvent également être utilisés comme ligands en catalyse asymétrique. Nous avons choisi d'étudier le THA-DCD de  $\alpha$ -amido  $\beta$ -cétoesters racémiques pour accéder efficacement à ces motifs.

Pour cette étude, une gamme de  $\alpha$ -amido  $\beta$ -c étoesters, portant soit des aryl- soit des alkyl-c étones a d'abord é épr épar ée selon diff érentes voies indiqu ées sur le Sch éma 9.



Sch éma 9

Le 2-benzoylamino-3-oxo-3-ph énylpropanoate de m éthyle a é échoisi comme substrat standard pour cette étude (Tableau 2). Les premi ères exp ériences de THA ont é é r éalis ées dans le CH<sub>2</sub>Cl<sub>2</sub> à 30 °C en utilisant les complexes de ruth éni um (*R,R*)-**C1**, (*S,S*)-**C11** et (*R,R*)-**C13** en présence d'un m élange az éotrope HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) comme source d'hydrog ène, et conduisent majoritairement aux alcools *anti* correspondants avec de faibles exc ès énantiom ériques (Tableau 2, entr ées 1-3). Étonnamment, un bon rapport diast é r éom érique (86:14) en faveur de l'isomère *syn* est observ é pour l'alcool avec un bon rendement et un excellent ee en passant du complexe de ruth éni um au complexe de rhodium (*R,R*)-**C84** dans les m êmes conditions (Tableau 2, entr ée 4). Divers catalyseurs au rhodium et diff érents solvants ont é é étudi és pour essayer d'augmenter la diast é r éos électivit é mais n'ont pas permis d'apporter d'am éli oration (Tableau 2, entr ées 5-11). Par ailleurs, la charge catalytique, la concentration et la temp érat ure (Tableau 2, entr ées 12-13) ont é également é évalu ées et les conditions de r éaction optimis ées ont é é d éfinies comme suit: 0,5 mol% de (*R,R*)-**C84**, HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) comme source d'hydrog ène, CH<sub>2</sub>Cl<sub>2</sub> comme solvant (0.5 M), et une temp érat ure de r éaction de 0 °C.

Tableau 2. Criblage des catalyseurs <sup>a</sup>

| Entrée            | Catalyseur        | Solvant                                      | Temps (h) | rendement (%) | dr ( <i>syn/anti</i> ) <sup>b</sup> | ee <sub>syn</sub> <sup>c</sup> (%) |
|-------------------|-------------------|--|-----------|---------------|-------------------------------------|------------------------------------|
| 1                 | <b>C1</b>         | CH <sub>2</sub> Cl <sub>2</sub>              | 96        | 96            | 15 : 85                             | 28 <sup>d</sup>                    |
| 2                 | (S,S)- <b>C11</b> | CH <sub>2</sub> Cl <sub>2</sub> <sup>e</sup> | 7         | 95            | 10 : 90                             | 36 <sup>d</sup>                    |
| 3                 | (R,R)- <b>C13</b> | CH <sub>2</sub> Cl <sub>2</sub> <sup>e</sup> | 9         | 94            | 8 : 92                              | 25 <sup>d</sup>                    |
| 4                 | (R,R)- <b>C84</b> | CH <sub>2</sub> Cl <sub>2</sub>              | 5         | 90            | 86 : 14                             | > 99                               |
| 5                 | (R,R)- <b>C84</b> | CH <sub>3</sub> CN                           | 4.5       | 86            | 87 : 13                             | > 99                               |
| 6                 | (R,R)- <b>C84</b> | THF  | 23        | 89            | 87 : 13                             | > 99                               |
| 7                 | (R,R)- <b>C84</b> | <i>i</i> PrOH                                | 28        | 88            | 83 : 17                             | > 99                               |
| 8 <sup>e</sup>    | (R,R)- <b>C84</b> | —  | 4         | 87            | 86 : 14                             | > 99                               |
| 9                 | (R,R)- <b>C85</b> | CH <sub>2</sub> Cl <sub>2</sub>              | 7         | 89            | 86 : 14                             | > 99                               |
| 10                | (R,R)- <b>C87</b> | CH <sub>2</sub> Cl <sub>2</sub>              | 7         | 88            | 86 : 14                             | > 99                               |
| 11 <sup>e</sup>   | (R,R)- <b>C86</b> | —  | 20        | 89            | 84 : 16                             | > 99                               |
| 12 <sup>f</sup>   | (R,R)- <b>C84</b> | CH <sub>2</sub> Cl <sub>2</sub>              | 47        | 93            | 92 : 8                              | >99                                |
| 13 <sup>f,g</sup> | (R,R)- <b>C84</b> | CH <sub>2</sub> Cl <sub>2</sub>              | 28        | 93            | 92 : 8                              | >99                                |

<sup>a</sup> Conditions: 0.8 mmol de **24a**, 0.5 mol% de pré-catalyseur, 134  $\mu$ L of HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) dans 4 mL de solvant à 30 °C. Conversions complètes dans tous les cas. <sup>b</sup> D déterminé par RMN <sup>1</sup>H du produit brut. <sup>c</sup> D déterminé par analyse SFC. <sup>d</sup> ee du composé *anti*. <sup>e</sup> Réaction sans solvant. <sup>f</sup> Température de réaction de 0 °C. <sup>g</sup> 1.6 mL de solvant utilisé

Nous avons ensuite étudié l'étendue de la réaction de THA dans les conditions de réaction optimisées, avec une série de  $\beta$ -cétosters  $\alpha$ -benzoylamino diversement substitués. Les composés portant des groupes phényle substitués sur la cétone donnent généralement les produits réduits *syn* correspondants **25a-25i** avec des rendements et des diastéreo-inductions

devés ainsi que d'excellentes énantiosélectivités, indépendamment du caractère électrodonneur ou électroattracteur des substituants. Une exception à cette tendance est observée pour **24j** ayant un substituant *ortho*-tolyle sur la cétone, qui donne avec un rendement modéré le composé *anti* majoritairement (*syn/anti*: 13:87), mais avec un excès énantiomérique modéré (52% ee), alors que l'isomère *syn* est obtenu avec un ee >99% (Schéma 10).

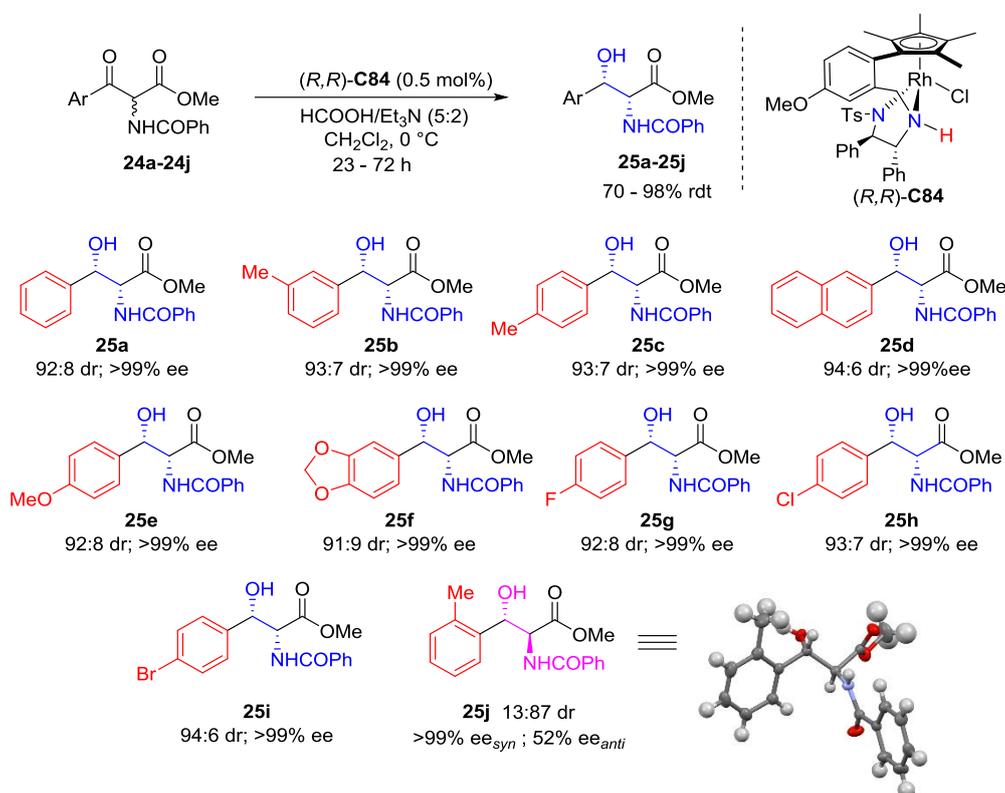


Schéma 10

D'autre part, les hétéroarylcétones conduisent à d'excellents niveaux de diasté- et énantio-inductions et les composés réduits sont obtenus avec de très bons rendements, à l'exception du composé **24l**, qui donne **25l** avec un dr de 87:13 et un ee de 96% et du composé **24p** contenant un substituant *N*-méthylpyrrole sur la cétone qui n'est pas réduit dans les conditions standard. Il est intéressant de noter que, pour l'amido ester **24o** portant un substituant thiényle sur la cétone, la réaction peut être effectuée à 30 °C en seulement 1 h sans aucune altération des dr ou ee. Le champ d'application des substrats a ensuite été étendu aux  $\alpha$ -amido  $\beta$ -cétosters contenant une alkylcétone. Pour ces composés, les produits réduits *syn* sont obtenus avec des dr plus faibles tandis que les ee restent élevés (>99%). De la même manière que pour le substrat stériquement encombré **24j**, une inversion de la diastéosélectivité est également observée pour l'amido ester **24s** ayant un substituant *isopropyle* sur la cétone. Dans ce cas, l'isomère *anti* est formé avec un niveau très élevé de diasté- et énantioinductions, bien qu'après un temps de réaction plus long (10 jours), qui peut être réduit à 92 h en travaillant

à 30 °C sans perte de stéréosélectivité. Enfin, le THA du substrat **24t** ayant un résidu alcyne se réalise avec des diastéreo- et énantiosélectivités quasi parfaites en 10 jours à 0 °C ou en seulement 24 h à 30 °C (Schéma 11).

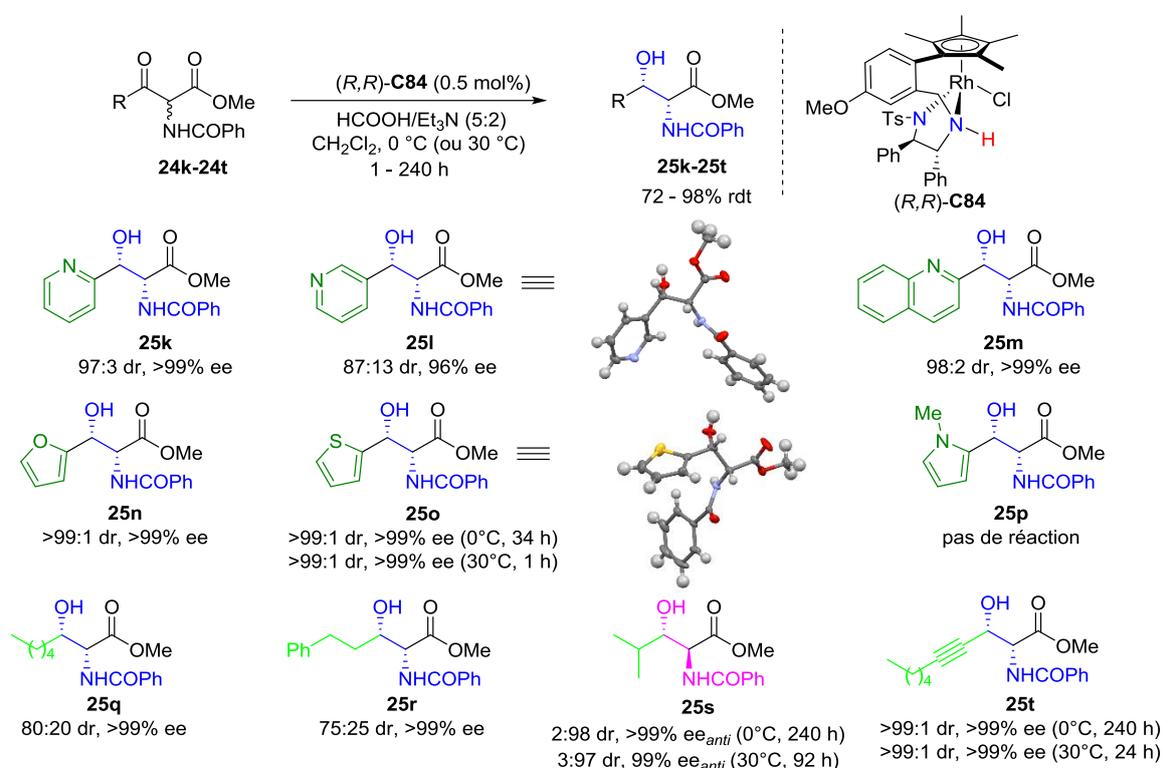


Schéma 11

### 3. Transfert d'hydrogène asymétrique catalysé par le rhodium: synthèse diastéreo- et énantiosélective de *syn*-α-alkoxy β-hydroxy esters

Les diols-1,2 chiraux sont des motifs structuraux importants présents dans un certain nombre de molécules naturelles et biologiquement actives, et trouvent de nombreuses applications en synthèse organique en tant que ligands chiraux ou auxiliaires. Par conséquent, le développement de nouvelles méthodologies catalytiques diastéreo- et énantiosélectives pour accéder à des diols-1,2 monodifférenciés énantiomériquement purs avec une stéréosélectivité élevée et avec une économie d'atomes maximale est primordial. Suite aux résultats obtenus précédemment dans l'équipe sur le THA/DCD catalysé au Ru de α-alkoxy β-céto esters, nous avons étudié cette réaction en utilisant des complexes Rh et plus particulièrement un nouveau complexe possédant une agrafe carbonée, pour évaluer leurs performances catalytiques (Schéma 12).

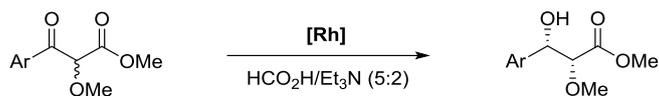


Schéma 12

Pour cette étude, nous avons d'abord préparé une série de β-cétoesters **26a-26m** selon les méthodes A ou B données ci-dessous (Schéma 13).

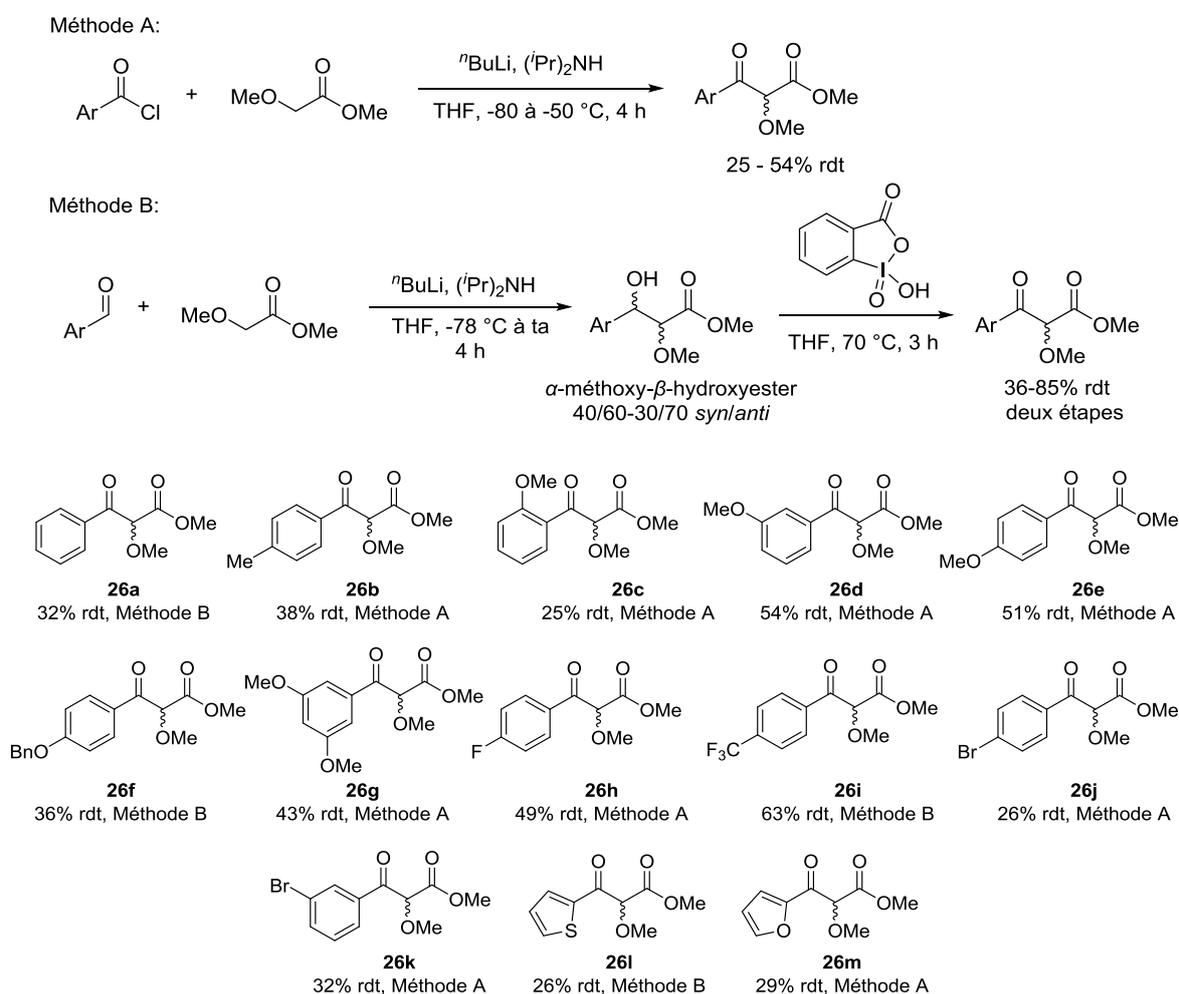


Schéma 13

Par ailleurs, un nouveau complexe de rhodium **C90** a été préparé à partir du 2-(2,3,4,5-tétraméthylcyclopenta-1,3-diène-1-yl)benzaldéhyde selon la séquence réactionnelle suivante (Schéma 14):

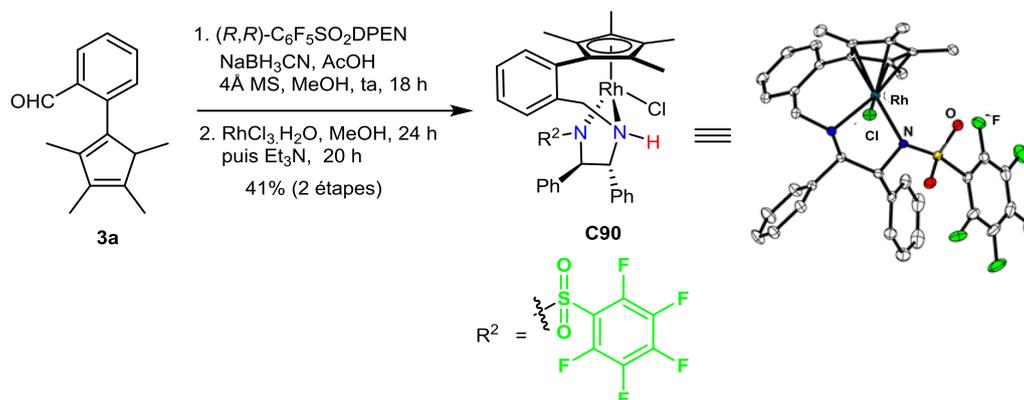
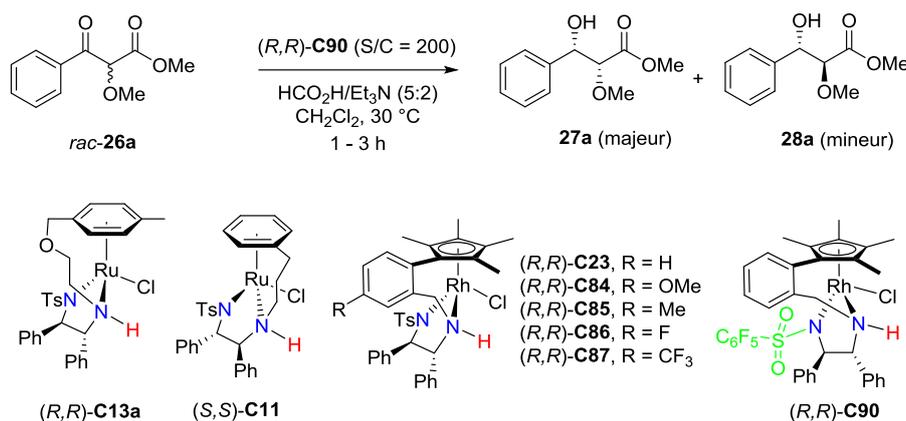


Schéma 14

Pour l'étude de la réaction de THA/DCD, le composé **26a** a été choisi comme substrat modèle et différents complexes de ruthénium ou de rhodium ont été testés en présence de HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) comme source d'hydrogène dans le dichlorométhane à 30 °C. D'après les résultats regroupés dans le Tableau 3, les meilleurs résultats en termes de diastéreo- et énantioselectivités (93:7 dr, 99% ee) sont obtenus avec le complexe de rhodium **C90** précédemment synthétisé (Tableau 3)

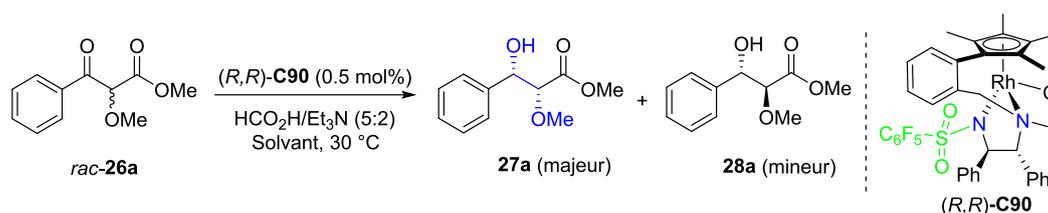
Tableau 3. Influence des pré-catalyseurs



| Entrée         | Catalyseur | Temps (h) | Rendement (%) | dr (27a:28a) <sup>c</sup> | ee <sub>syn</sub> (%) <sup>d</sup> |
|----------------|------------|-----------|---------------|---------------------------|------------------------------------|
| 1              | (R,R)-C13a | 20        | 85            | 85:15                     | 99                                 |
| 2 <sup>e</sup> | (S,S)-C11  | 14        | 85            | 70:30                     | -97                                |
| 3              | (R,R)-C84  | 1         | 91            | 91:9                      | 99                                 |
| 4 <sup>f</sup> | (R,R)-C84  | 22        | 90            | 88:12                     | 99                                 |
| 5              | (R,R)-C85  | 1         | 89            | 91:9                      | 99                                 |
| 6              | (R,R)-C86  | 3         | 89            | 91:9                      | 99                                 |
| 7              | (R,R)-C87  | 3         | 92            | 89:11                     | 99                                 |
| 8              | (R,R)-C90  | 3         | 94            | 93:7                      | 99                                 |
| 9              | (R,R)-C23  | 1         | 89            | 91:9                      | 99                                 |

<sup>a</sup> Conditions: **26a** (0.8 mmol), [Rh] ou [Ru] (0.5 mol%), HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) (2.0 équiv.), CH<sub>2</sub>Cl<sub>2</sub> (4.0 mL, 0.2 M), 30 °C, conversion complète. <sup>b</sup> Rendement isolé pour **27a** et **28a**. <sup>c</sup> Déterminé par RMN <sup>1</sup>H du produit brut. <sup>d</sup> Déterminé par analyse HPLC ou SFC. <sup>e</sup> Enantiomère *ent-27a* majoritaire. <sup>f</sup> Réaction effectuée à 0 °C.

L'influence du solvant a ensuite été étudiée, et compte tenu des résultats observés, nous avons privilégié l'utilisation du 2-MeTHF comme solvant vert pour le reste de cette étude (Tableau 4). Les conditions de réaction optimisées ont été fixées comme suit: **26a** (0.8 mmol), complexe (R,R)-C90 (0.5 mol%), HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) (2.0 équiv.), 2-MeTHF (4.0 mL), 30 °C.

Tableau 4. Influence du solvant <sup>a</sup>

| Entrée | Solvant                         | Temps (h) | Conv. (%) <sup>b</sup> | Rendement (%) <sup>c</sup> | dr ( <b>27a</b> : <b>28a</b> ) <sup>b</sup> | ee <sub>syn</sub> (%) <sup>d</sup> |
|--------|---------------------------------|-----------|------------------------|----------------------------|---|------------------------------------|
| 1      | CH <sub>2</sub> Cl <sub>2</sub> | 3         | 100                    | 94                         | 93:7  | 99                                 |
| 2      | CH <sub>3</sub> CN              | 72        | 46.5                   | 42                         | 94:6  | 99                                 |
| 3      | Toluene                         | 6         | 100                    | 88                         | 95:5  | 99                                 |
| 4      | <i>i</i> PrOH                   | 6         | 100                    | 87                         | 94:6  | 99                                 |
| 5      | <i>i</i> Pr <sub>2</sub> O      | 22        | 75                     | 68                         | 86:14                                       | 99                                 |
| 6      | EtOAc                           | 3         | 100                    | 93                         | 96:4  | 99                                 |
| 7      | THF                             | 10        | 100                    | 95                         | 97:3  | 99                                 |
| 8      | THF                             | 5         | 100                    | 95                         | 95:5  | 99                                 |
| 9      | 2-MeTHF                         | 5         | 100                    | 93                         | 97:3  | 99                                 |
| 10     | DMC <sup>e</sup>                | 3         | 100                    | 92                         | 95:5  | 99                                 |
| 11     | neat                            | 6         | 100                    | 93                         | 81:19                                       | 99                                 |

<sup>a</sup> Conditions: **26a** (0.8 mmol), **(R,R)-C90** (0.5 mol%), HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) (2.0 équiv.), solvant (4.0 mL, 0.2 M), 30 °C, réaction suivie par CCM. <sup>b</sup> Déterminé par RMN <sup>1</sup>H du produit brut. <sup>c</sup> Rendement isolé pour **27a** et **28a**. <sup>d</sup> Déterminé par analyse HPLC ou SFC. <sup>e</sup>DMC = Dimethyl carbonate.

L'étendue de la réaction de THA/DCD de β-methoxy β-cétoesters catalysée par le complexe **(R,R)-C90** a ensuite été étudiée pour une série d'aryl cétones différemment substitués **26a-26k** portant des substituants électrodonneurs ou électroaccepteurs sur le cycle aromatique. De très bonnes diastéreo- et énantio-sélectivités sont généralement observées avec des rendements de bons à élevés. Cependant, le THA de la cétone **26c** stériquement plus encombrée par un substituant méthoxy en position *ortho*, s'effectue avec un temps de réaction plus long et conduit à une inversion de la diastérosélectivité en faveur du produit *anti* (*syn/anti* 4:96) bien que l'isomère majoritaire soit obtenu avec un ee plus faible (88%). Il est intéressant de noter que les substrats hétéroaromatiques **26l-26m** conduisent à des diastérosélectivités quasi parfaites (99:1 dr) et à d'excellentes énantiosélectivités (Schéma 15).

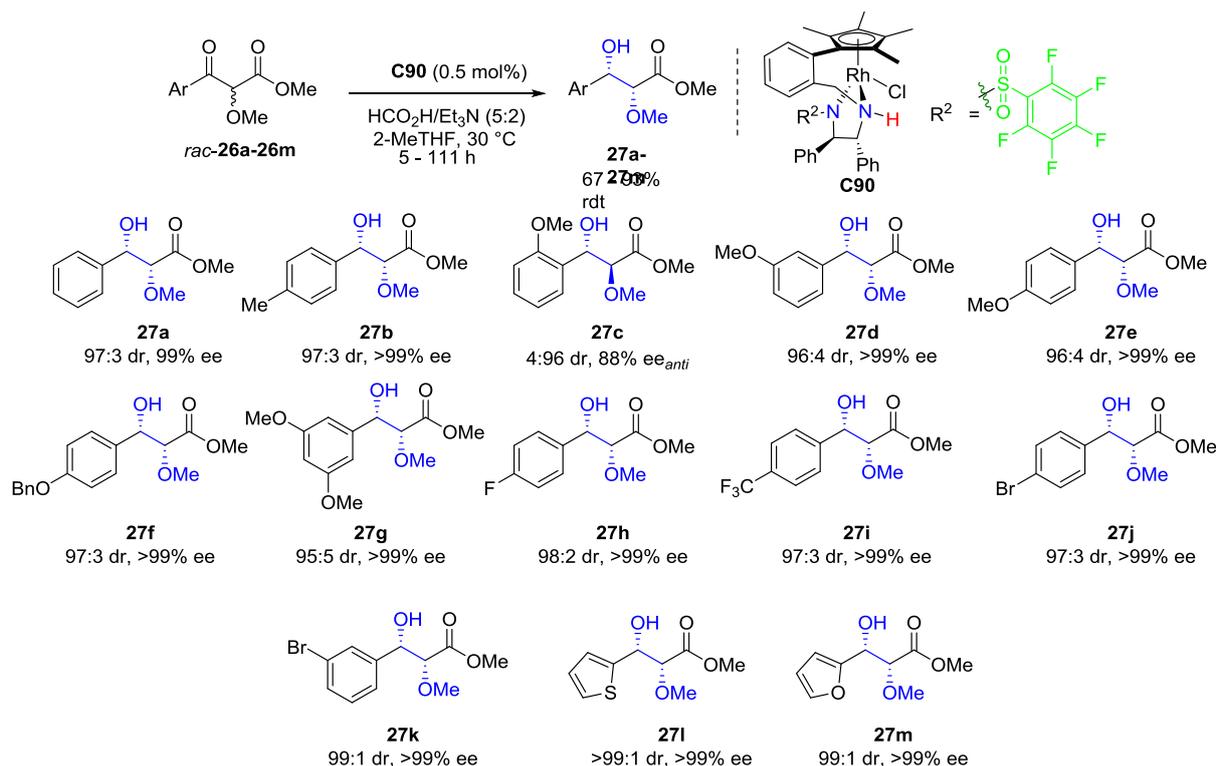


Schéma 15

En conclusion, un nouveau complexe de Rh comportant un ligand pentafluorobenzènesulfonyl-DPEN a été développé et s'est révélé très efficace pour la réaction de THA/DKR d' $\alpha$ -alkoxy  $\beta$ -cétosters donnant les dérivés diols-1,2 *syn* correspondants avec de très bons rendements (jusqu'à 98%) ainsi que des diasté- et énantio-sélectivités très élevées (jusqu'à >99:1 dr; jusqu'à >99% ee).

#### 4. Transfert d'hydrogène asymétrique catalysé au ruthénium/doublement cinétique dynamique: accès stéréosélectif aux dérivés 2-(1,2,3,3,4-tétrahydro-1-isoquinolyl)éthanol *syn*

Le motif aminoalcool-1,3 *syn* ou *anti* est un motif important présent dans une vaste gamme de molécules bioactives et de médicaments. C'est pourquoi de nombreuses approches ont été développées pour accéder à ces amino alcools-1,3. Toutes impliquent l'introduction du premier stéréocentre par des réactions d'aldolisation ou de Mannich, suivies d'une réduction des fonctions cétone ou imine résultantes, respectivement. La réduction asymétrique de cétones racémiques  $\alpha$ - ou  $\beta$ -substituées associée à un processus de doublement cinétique dynamique (DCD) constitue un moyen efficace pour la création de plusieurs stéréocentres en une seule étape. Dans ce domaine, le THA/DCD de cétones substituées en  $\alpha$ , catalysé par des métaux de transition, a fait l'objet de nombreuses études, tandis que les exemples impliquant des cétones substituées en  $\beta$  sont plus rares.

Pour cette étude, une série de  $\beta$ -amino-cétones **29a-j** et **29l-q** ont d'abord été préparés par une réaction de Mannich redox (Schéma 16).

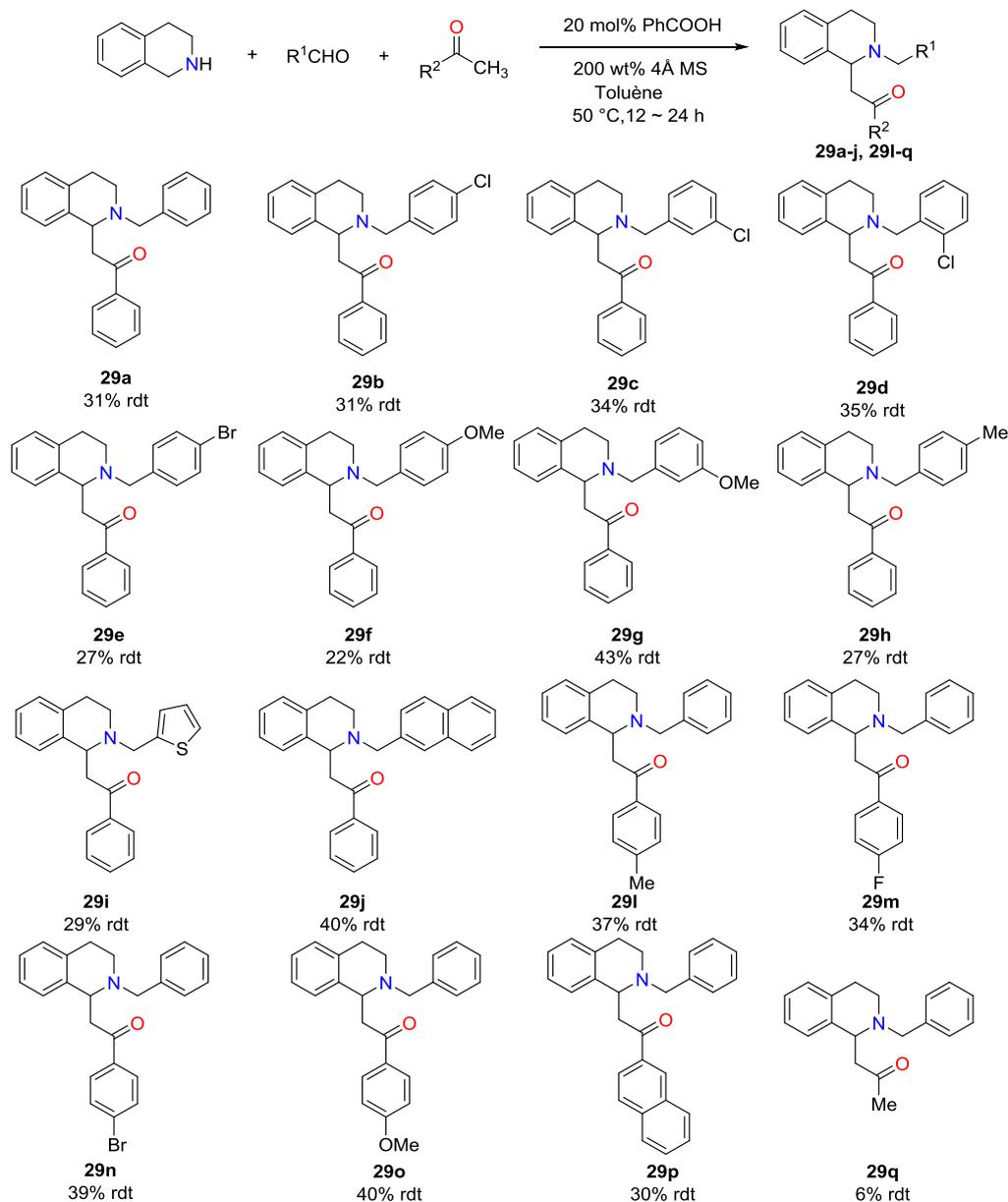
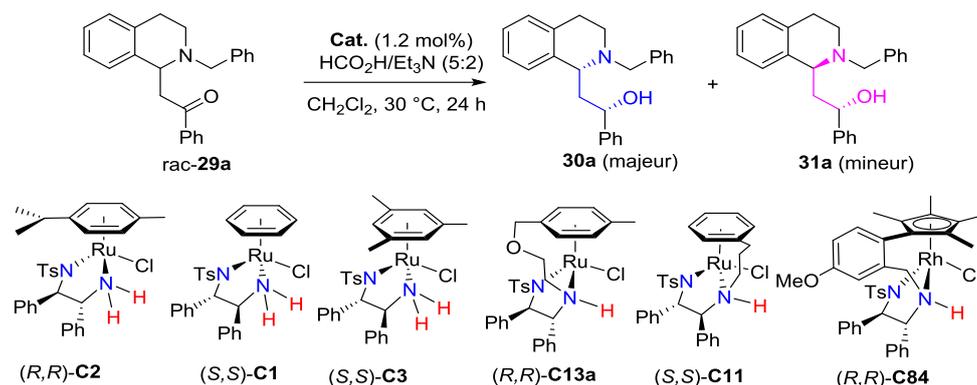


Schéma 16

Le substrat  $\beta$ -amino cétone **29a** a été choisi comme substrat standard pour l'étude des paramètres de la réaction de THA/DCD. Les premiers essais sont réalisés à 30 °C dans le dichlorométhane, en utilisant 1.2 mol% de complexe de Ru(II) (*R,R*)-**C2**, (*S,S*)-**C1**, (*S,S*)-**C3**, (*S,S*)-**C11**, (*R,R*)-**C13** ou de Rh(III) (*R,R*)-**C84** en présence de HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) comme source d'hydrogène. En termes de conversion et de rendement, ainsi que de diastéréosélectivité et d'énantiosélectivité le pré-catalyseur (*S,S*)-**C1** est celui qui conduit aux meilleurs résultats (Tableau 5).

Tableau 5. Screening du THA/DCD de **29a** avec différents pré-catalyseurs.<sup>a</sup>

| Entrée         | Catalyseur                  | Conv. (%) <sup>b</sup> | Rendement (%) <sup>c</sup> | dr ( <b>30a:31a</b> ) <sup>b</sup> | ee <b>30a/31a</b> (%) <sup>d</sup> |
|----------------|-----------------------------|------------------------|----------------------------|------------------------------------|------------------------------------|
| 1              | ( <i>R,R</i> )- <b>C2</b>   | 47                     | –                          | 76:24                              | 96 (–)/98 (–)                      |
| 2 <sup>e</sup> | ( <i>R,R</i> )- <b>C2</b>   | 64                     | –                          | 73:27                              | 99 (–)/99 (–)                      |
| 3              | ( <i>S,S</i> )- <b>C1</b>   | 97                     | 76                         | 68:32                              | 98 (+)/99 (+)                      |
| 4              | ( <i>S,S</i> )- <b>C3</b>   | 88                     | 68                         | 67:33                              | 99 (+)/99 (+)                      |
| 5              | ( <i>R,R</i> )- <b>C13a</b> | 96                     | 68                         | 52:48                              | 97 (–)/96 (–)                      |
| 6              | ( <i>S,S</i> )- <b>C11</b>  | 96                     | –                          | 49:51                              | 99 (+)/99 (+)                      |
| 7              | ( <i>R,R</i> )- <b>C84</b>  | 100                    | –                          | 47:53                              | 96 (–)/98 (–)                      |

<sup>a</sup> Conditions: **29a** (0.42 mmol), **Cat.** (1.2 mol%), HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) (2.75 équiv.), CH<sub>2</sub>Cl<sub>2</sub> (1.3 mL), 30 °C, 24 h. <sup>b</sup> Déterminé par RMN <sup>1</sup>H du produit brut. <sup>c</sup> Rendement isolé pour **30a:31a**. Dans le cas de conversions et/ou de dr insuffisants, les produits réduits n'ont pas été isolés. <sup>d</sup> Déterminé par analyse HPLC. <sup>e</sup> 11.0 équiv. de HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) utilisés, temps de réaction de 40 h.

L'influence du solvant, de la source d'hydrogène, de la température et de la concentration a ensuite été examinée en présence du complexe (*S,S*)-**C1** et les conditions réactionnelles optimales ont été établies comme suit: **29a** (0.42 mmol), (*S,S*)-**C1** (1.2 mol%), HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) (2.75 équiv.), dichlorométhane (1.3 mL, 0.32 mol·L<sup>-1</sup>) à 30 °C pendant 24 h. Puis l'étendue de la réaction du THA/DCD de β-amino cétones a été étudiée avec les substrats **29a-j** et **29l-q** préalablement préparés. Les composés portant des substituants électro-attracteurs ou électro-donneurs sur le noyau phényle du lien *N*-benzyle sont réduits avec de bons rendements et d'excellentes énantiosélectivités ainsi qu'un dr acceptable, du même ordre que celui observé pour le composé **29a**, à l'exception du substrat **29d** ayant un substituant *o*-chlorobenzène plus encombrant. La réaction est également compatible avec des substrats possédant des substituants thiényle et naphtyle (**30h**, **30i**) à la place du noyau benzénique. Cependant, la réduction de la cétone **29k** portant un substituant *p*-MeO-benzène sur l'atome d'azote au lieu d'un dérivé

benzylique ne conduit qu'à des sous-produits et le composé attendu **30k** n'a pas été isolé (Schéma 17).

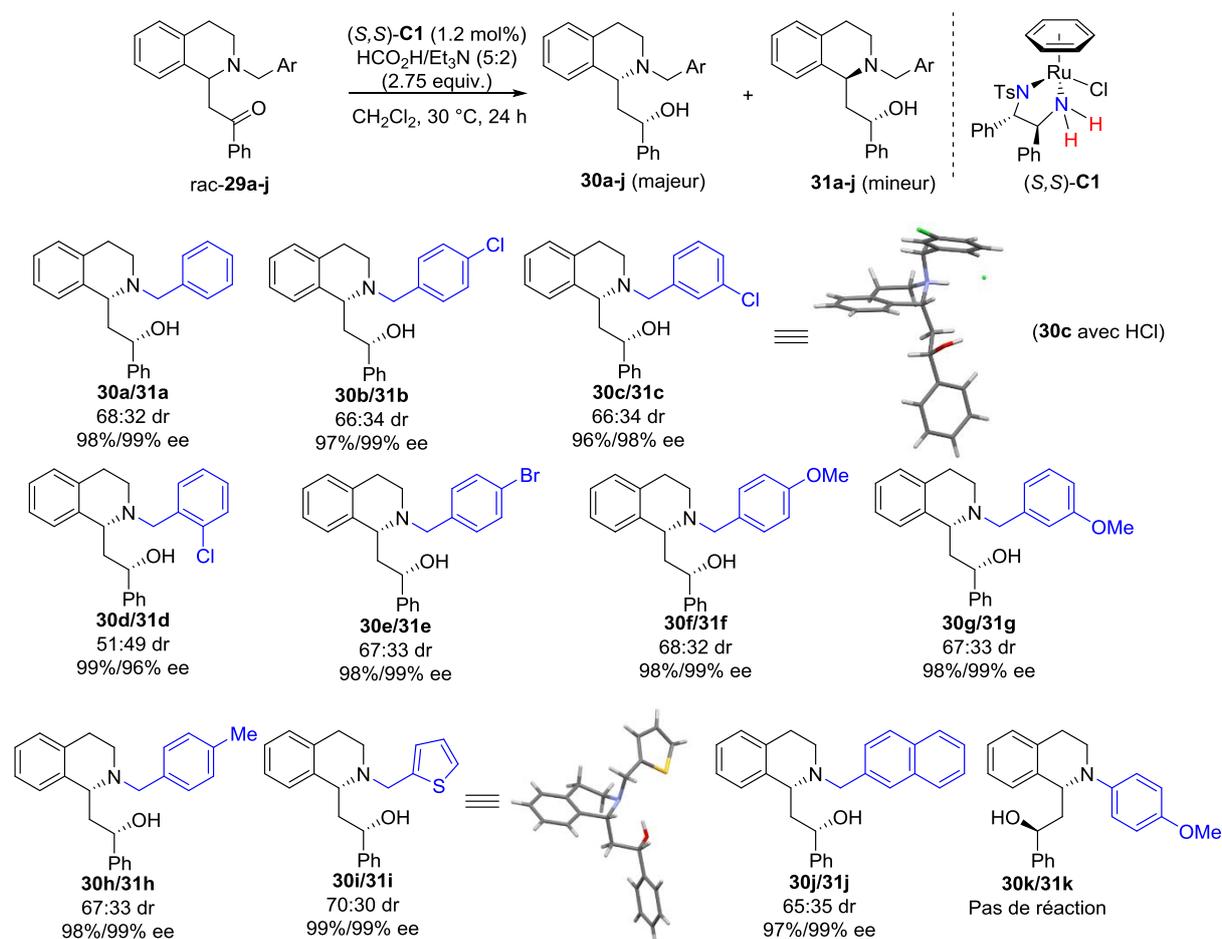


Schéma 17

La substitution sur la fonction cétone (substrats **29l-q**) a également été étudiée et a montré que les groupes électro-donneurs (méthyle, méthoxy) ou électro-attracteurs (fluor, brome) sur le noyau phényle étaient bien tolérés. La présence d'un groupe naphthyle sur la cétone n'apporte pas d'effet significatif sur le résultat de la réaction, tandis qu'un substituant non aromatique tel qu'un groupe méthyle conduit à un excès énantiomérique plus faible (Schéma 18).

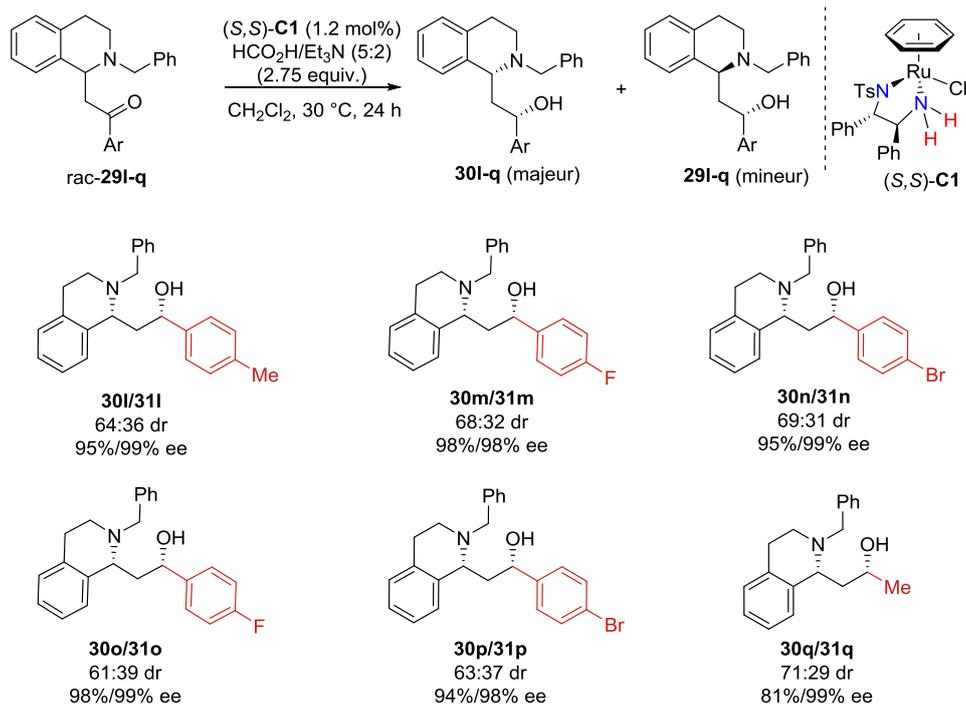


Schéma 18

Pour évaluer l'application pratique de cette méthode, la réduction de **29a** a été effectuée sur l'échelle du gramme et a permis d'obtenir efficacement le produit attendu (1,04 g, 76% de rendement, 69 :31 dr, 98% ee pour le produit *syn*) (Schéma 19).

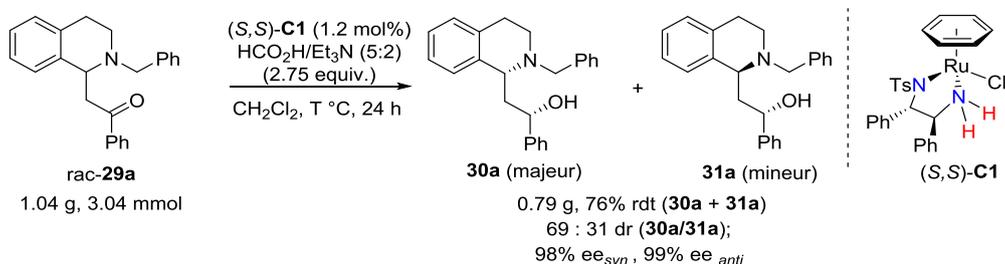


Schéma 19

En conclusion, un accès stéréosélectif efficace vers les dérivés du 2-(1,2,3,4-tétrahydro-1-isoquinolyl)éthanol par le THA de β-amino-cétones a été émis au point. La réaction s'effectue dans des conditions douces en présence de RuCl[(*S,S*)-TsDPEN](benzène) et HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) comme source d'hydrogène, fournissant une variété de dérivés 2-(1,2,3,4-tétrahydro-1-isoquinolyl)éthanol *syn* avec une excellente énantiosélectivité (jusqu'à 99% ee) et des rapports diastéréomériques jusqu'à 71:29.



# **General Introduction**

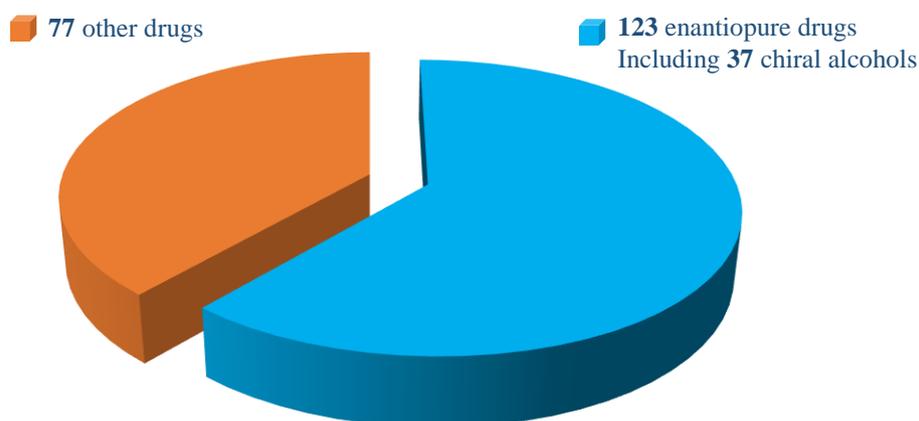


## General introduction

Chirality is now one major topic in academic research as well as in pharmaceutical development. Accounting for their significant work in chiral separation, the 2001 Nobel Prize in Chemistry has been awarded to three scientists: W. S. Knowles, K. B. Sharpless and R. Noyori, for their development of asymmetric synthesis using chiral catalysts in the production of single enantiomer drugs or chemicals. Thanks to a wide range of new technologies for chiral separation, US Food and Drug Administration (FDA) recommends the assessments of each enantiomer activity for racemic drugs in body and promotes the development of new chiral drugs as single enantiomers.<sup>1</sup>

Because the use of enantiomerically pure drugs has numerous advantages, such as: (i) an improvement of the therapeutic index through increased potency and selectivity and decreased side-effects; (ii) a faster onset of action; (iii) a reduced propensity for drug-drug interactions, and (iv) the exposition of the patient to a lower dosage, 15 racemate drugs have been successfully switched to the single-enantiomer version from 1994 to 2011.<sup>2</sup>

It is worth noting that among the top 200 pharmaceutical products by prescriptions in 2010, the major part (60%) are chiral molecules under their enantiomerically pure form with 30% of latter having alcohol moieties.



### Top 200 Pharmaceutical Products by Prescriptions in 2010<sup>3</sup>

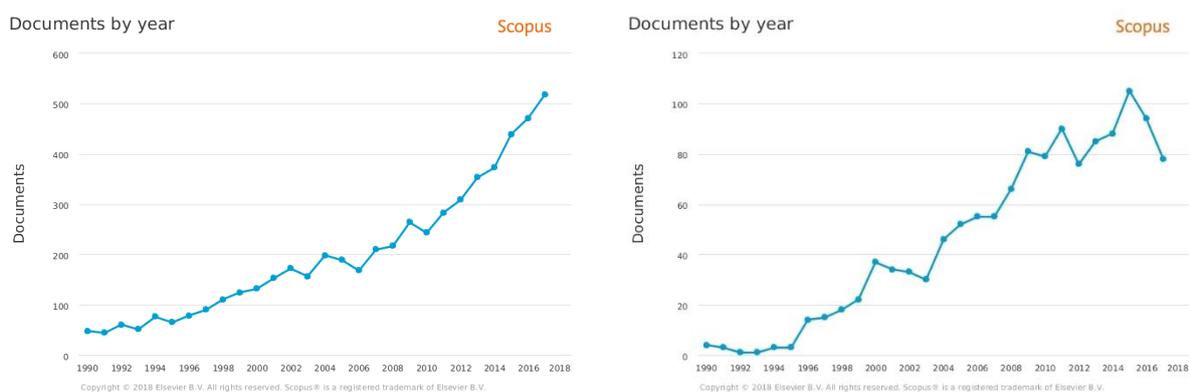
Therefore, the development of efficient synthetic approaches to access these optically

<sup>1</sup> Nguyen, L. A.; He, H.; Pham-Huy, C. *J Biomed Sci* **2006**, *2*, 85.

<sup>2</sup> Calcaterra, A.; D'Acquarica, I. *J. Pharm. Biomed. Anal.* **2018**, *147*, 323.

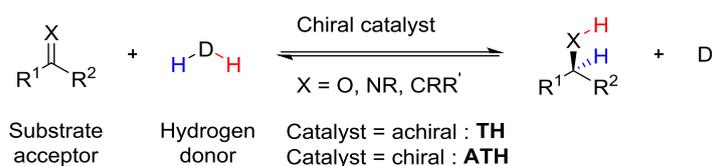
<sup>3</sup> McGrath, N. A.; Brichacek, M.; Njardarson, J. T. *J. Chem. Educ.* **2010**, *87*, 1348.

active alcohols is highly desired. To this end, one of the most direct methods relies on asymmetric reduction of carbonyl compounds to prepare secondary chiral alcohols and in this field, asymmetric hydrogenation (AH) and asymmetric transfer hydrogenation (ATH) appear as powerful tools. By searching the topic “transfer hydrogenation” and “asymmetric transfer hydrogenation” from 1990 to 2017 in Scopus, we can see the trend of yearly publications for both TH and ATH is generally increasing.



(left: TH; right: ATH)

In this manuscript, we will more particularly focus on ATH. Transfer hydrogenation (TH) can be described as the reduction of an unsaturated acceptor substrate (such as ketone, imine or alkene) with the aid of a hydrogen donor  $DH_2$  in the presence of a catalyst. The hydrogen donor  $DH_2$  is then converted into a dehydrogenated by-product  $D$ . When chirality is introduced during the reaction by using a chiral catalyst, this process is called asymmetric transfer hydrogenation (ATH).



A broad range of hydrogen donors, typically alcohols, formic acid and its salt can be used, thus avoiding handling of molecular hydrogen. Therefore, asymmetric transfer hydrogenation has received considerable attention because this technology is considered as one of the most powerful, practical, and versatile tools especially to access chiral alcohols and amines in organic synthesis.

Although a number of catalysts have been developed for ATH, the development of more efficient catalysts and new applications using known catalysts are still ongoing.

One aim of this thesis work was to develop new catalysts for the ATH of ketones. Thus,

the preparation and evaluation of a new family of phenyl tethered rhodium complexes will be described. Additionally, because enantiomerically pure  $\alpha,\alpha$ -dichloro- or  $\alpha,\alpha$ -difluorosubstituted secondary alcohols are found in a number of biologically relevant molecules, the ATH of  $\alpha,\alpha$ -dichloro- or  $\alpha,\alpha$ -difluoro-substituted ketone derivatives catalyzed by a new tethered Rh complex will be investigated to access the target compounds.

Chiral alcohols or amines bearing multiple stereocenters are important building blocks in pharmaceuticals and natural products. In this manuscript, we will study the ATH reaction combined with a dynamic kinetic resolution (DKR) process of racemic  $\alpha$ -benzoylamino  $\beta$ -ketoesters and  $\alpha$ -alkoxy  $\beta$ -ketoesters to access enantiomerically enriched aminoalcohol and diol derivatives.

In addition, the same method will be applied to tetrahydroisoquinolyl (THIQ)-based  $\beta$ -amino ketones to prepare chiral  $\beta$ -aminoalcohols.



**PART A:**

**Recent developments on transition  
metal-catalyzed ATH of ketones**

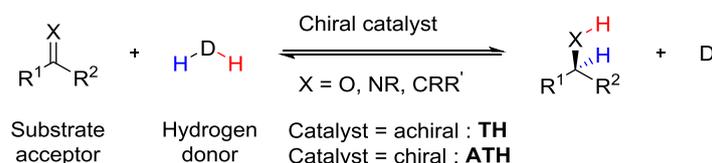


## Part A: Recent developments on transition metal-catalyzed asymmetric transfer hydrogenation (ATH) of ketones

### 1. Theoretical background on asymmetric transfer hydrogenation

#### 1.1 Introduction to asymmetric transfer hydrogenation

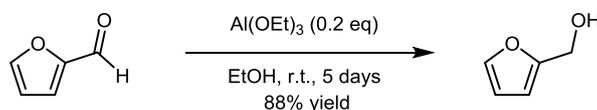
Transfer hydrogenation (TH) can be described as the transfer of a hydride ion and a proton from a hydrogen donor to an unsaturated acceptor substrate. The hydrogen donor  $DH_2$  is then converted into a dehydrogenated by-product  $D$ . The reaction is facilitated by a catalyst that will promote the hydride transfer. When a chiral catalyst is used, the reaction is named asymmetric transfer hydrogenation (ATH) (Scheme 1).<sup>4</sup>



**Scheme 1**

This technology has many advantages over traditional hydrogenation reactions. Indeed, it does not require the use of hydrogen gas and high pressure equipment, thus limiting the risks in terms of safety and also in terms of cost.

Historically, the first homogeneous hydrogen transfer reaction was described in 1925, when Meerwein and Schmidt reported the reduction of furfural using an aluminum alkoxide as Lewis acid and ethanol as the hydrogen source (Scheme 2).<sup>5</sup>



**Scheme 2**

This reaction, later known as the Meerwein-Ponndorf-Verley (MPV) reduction, saw its scope broadened thanks to the work of Verley,<sup>6a</sup> Ponndorf<sup>3b</sup> and Lund.<sup>3c</sup> In 1937, Oppenauer

<sup>4</sup> (a) Andersson, P. G.; Munslow, I. J. *Modern Reduction Methods*, Wiley, **2008**, p135. (b) De Vries, J. G.; Elsevier, C. J. *Handbook of Homogeneous Hydrogenation*, Wiley, **2007**, p.585 and p.1215.

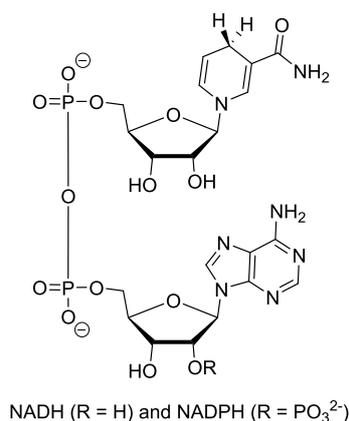
<sup>5</sup> Meerwein, H.; Schmidt, R. *Justus Liebigs Ann. Chem.* **1925**, *444*, 221.

<sup>6</sup> (a) Verley, A. *Bull. Soc. Chim. Fr.* **1925**, *37*, 537. (b) Ponndorf, W. *Angew. Chem.* **1926**, *39*, 138. (c) Lund, H. *Ber. Dtsch. Chem. Ges.* **1937**, *70*, 1520.

studied the reverse reaction, *i.e.* the oxidation reaction.<sup>7</sup> These reactions were subsequently improved with the use of other types of alkoxymetals.<sup>8</sup> The main disadvantage of these two reactions lies in the low catalytic activity obtained with these Lewis acids. Therefore, the introduction of transition metal catalysts for this type of reaction has emerged as a major advantage in ATH.

Mitchell *et al.* reported, in 1964, the reduction of cyclohexanone using the hexachloroiridic acid catalyst  $\text{H}_2\text{IrCl}_6$  in an isopropanol/water solution.<sup>9</sup> The introduction of the Wilkinson catalyst  $[\text{RhCl}(\text{PPh}_3)_3]$  for hydrogen transfer reactions in 1966 also contributed to these advances. Although designed for hydrogenation in the presence of molecular hydrogen, this catalyst has been used extensively in hydrogen transfer catalyzed reactions.<sup>10</sup>

In nature, hydrogen transfer occurs when metabolites are reduced within biological systems. The catalysts responsible for hydrogen transfer are called enzymatic dehydrogenases and are assisted by cofactors that facilitate the transfer of electrons, such as NADH or NADPH (Scheme 3).



**Scheme 3**

The following bibliographical part will cover the transition metal-catalyzed ATH of ketones.<sup>11</sup>

<sup>7</sup> Oppenauer, R. V. *Recl. Trav. Chim. Pays-Bas* **1937**, *56*, 137.

<sup>8</sup> (a) Namy, J. L.; Soupe, J.; Collin, J.; Kagan, H. B. *J. Org. Chem.* **1984**, *49*, 2045. (b) Okano, T.; Matsuoka, M.; Konishi, H.; Kiji, J. *Chem. Lett.* **1987**, 181. (c) Campbell, E. J.; Zhou, H.; Nguyen, S. T. *Org. Lett.* **2001**, *3*, 2391. (d) Ooi, T.; Miura, T.; Itagaki, Y.; Ichikawa, H.; Maruoka, K. *Synthesis* **2002**, 279. (e) Liu, Y.-C.; Ko, B.-T.; Huang, B.-H.; Lin, C.-C. *Organometallics* **2002**, *21*, 2066.

<sup>9</sup> Haddad, Y. M. Y.; Henbest, H. B.; Husbands, J.; Mitchell, T. R. B. *Proc. Chem. Soc.* **1964**, 361.

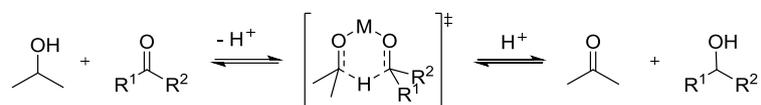
<sup>10</sup> Osborn, J. A.; Jardine, F. H.; Young, J. F.; Wilkinson, G. *J. Chem. Soc. A* **1966**, 1711.

<sup>11</sup> (a) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97. (b) Palmer, M. J.; Wills, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2045. (c) Everaere, K.; Mortreux, A.; Carpentier, J.-F. *Adv. Synth. Catal.* **2003**, *345*, 67. (d) Gladiali, S.; Alberico, E. *Chem. Soc. Rev.* **2006**, *35*, 226. (e) Ikariya, T.; Blacker, A. J. *Acc. Chem. Res.* **2007**, *40*, 1300. (f)

### 1.1.1 Mechanisms

Hydrogen transfer can be carried out according to two type of mechanisms<sup>12</sup> depending on the nature of the metal and ligands:

- *Direct transfer mechanism*: this proceeds via a complex in which the donor and the acceptor are linked to the metal. By coordinating with the metal, the hydride acceptor will be activated and thus the nucleophilic attack of the hydride is facilitated. The spatial proximity of the two entities will also facilitate a concerted mechanism via a six-centered transition state without involving a metal-hydride intermediate. This mechanism is not limited to transition metals since this mechanism is proposed for the Meerwein-Ponndorf-Verley reduction (Scheme 4).

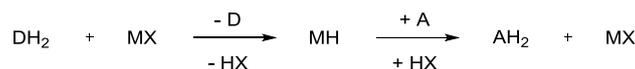


**Scheme 4**

- *Indirect transfer mechanism (hydride pathway)*: this mechanism first involves the transfer of a hydride from a donating molecule to the metal catalyst, leading to the formation of a metal hydride. The hydride is then transferred from the metal centre to the accepting substrate. Thus, the privileged precatalysts with a metal center bearing a strong affinity to hydride, such as ruthenium, rhodium and iridium, follow this type of mechanism. The Lewis acidity of these metals is too weak to sufficiently activate direct hydrogen transfer catalysis and, conversely, the affinity of aluminium (III) to hydride anion is too low to catalyse indirect hydrogen transfer. For this type of mechanism, a monohydride and a dihydride pathway are possible (Scheme 5).

Slagbrand, T.; Lundberg, H.; Adolfsson, H. *Chem. Eur. J.* **2014**, *20*, 16102. (g) Štefane, B.; Požgan, F. *Catal. Rev.* **2014**, *56*, 82. (h) Foubelo, F.; Nájera, C.; Yus, M. *Tetrahedron: Asymmetry* **2015**, *26*, 769. (i) Wang, D.; Astruc, D. *Chem. Rev.* **2015**, *115*, 6621. (j) G. Nedden, H.; Zanolli-Gerosa, A.; Wills, M. *Chem. Rec.* **2016**, *16*, 2623. (k) Ayad, T.; Phansavath, P.; Ratovelomanana-Vidal, V. *Chem. Rec.* **2016**, *16*, 2754 and references therein.  
<sup>12</sup> (a) Bäckvall, J.-E. *J. Organomet. Chem.* **2002**, *652*, 105. (b) Clapham, S. E.; Hadzovic, A.; Morris, R. H. *Coord. Chem. Rev.* **2004**, *248*, 2201. (c) Samec, J. S. M.; Bäckvall, J.-E.; Andersson, P. G.; Brandt, P. *Chem. Soc. Rev.* **2006**, *35*, 237.

*monohydride route :*

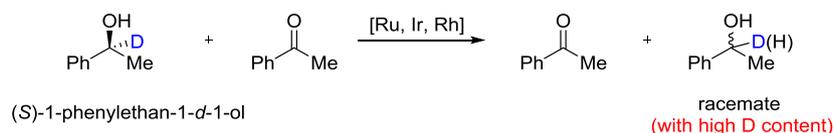


*dihydride route :*

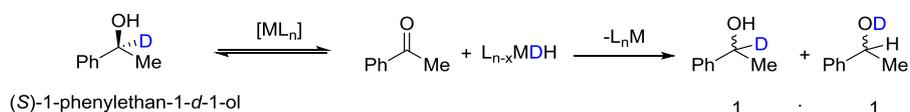


### Scheme 5

To well-understand the mono- or dihydride mechanisms for metal-catalyzed transfer reactions, Bäckvall *et al.* have designed an experiment for metal-catalyzed hydrogen transfer reactions.<sup>13</sup> To demonstrate the monohydride mechanism, first, they utilized enantiomerically pure  $\alpha$ -deuterated (*S*)-phenylethanol in the presence of acetophenone with an achiral metal complex as a catalyst precursor. By monitoring and analyzing the deuterium level in the  $\alpha$  position of racemized phenylethanol, they observed that using most of metal catalysts, such as iridium, rhodium and ruthenium complexes, resulted in high deuterium content during the racemized reaction. The results revealed that the nature of the metal as well as that of the ligands were important for the type of mechanism, which could be classified as a monohydride mechanism (Scheme 6). In addition, another experiment has been performed to investigate the dihydride mechanism, which is to racemize an optically active  $\alpha$ -deuterated (*S*) - phenylethanol (Scheme 7). If the catalysts follow the dihydride mechanism, the deuterium will be equally distributed between carbon and oxygen (C–D : O–D = 1 : 1).



### Scheme 6

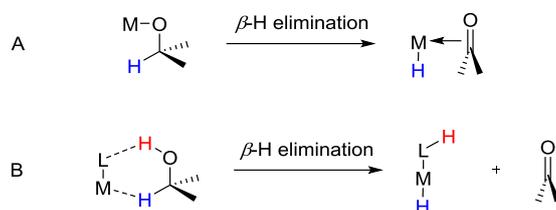


### Scheme 7

In addition, there are two types of catalysts operating according to a monohydride mechanism: those for which the transfer of hydride takes place in the inner sphere of the metal, *i.e.* there will be a direct interaction between the hydrogen donor and the metal during the formation of the hydride metal (Scheme 8, **A**) and those for which the transfer takes place

<sup>13</sup> (a) Laxmi, Y. R. S.; Bäckvall, J.-E. *Chem. Commun.* **2000**, 611. (b) Pàmies, O.; Bäckvall, J. E. *Chem. Eur. J.* **2001**, 7, 5052.

outside the internal sphere of the metal, *i.e.* there will be no direct coordination of the donor on the metal (Scheme 8, **B**).<sup>12c</sup>



**Scheme 8**

After this short description of the different possible mechanisms for asymmetric transfer hydrogenation, we will focus on the ligands that can be used with transition metals, and will pay a particular attention to the bifunctional ligands developed by the Noyori's group.

### 1.1.2 Ligands

Numerous ligands can be used for ATH, associated with transition metals such as iridium, rhodium or ruthenium. Their structures are quite diverse, such as bidentate, tridentate or tetradentate. The following section is a non-exhaustive description of selected ligands used for ATH of acetophenone as a point of comparison (Scheme 9).<sup>11b</sup>

Generally, chiral diphosphines such as DIOP<sup>14</sup> **L1** led to moderate conversions and enantioselectivities under high temperature conditions.<sup>15</sup> Phenanthroline-derived ligands such as **L2** showed low to moderate enantioselectivities for transfer hydrogen of acetophenone.<sup>16</sup> The introduction of the tetrahydro-bis(oxazole) **L3** ligand by Pfaltz and co-workers<sup>17</sup> allowed moderate to good enantioselectivities for different aromatic ketones. Tridentate ligands *P,N,P* **L7**<sup>18</sup>, *N,N,N* **L8**<sup>19</sup> or *N,P,N* **L9**<sup>20</sup> were used by Zhang's group leading to weak to excellent enantioselectivities. Tetradentate ligands such as **L10** and **L11** have been developed.<sup>21</sup> These

<sup>14</sup> (a) Dang, T. P.; Kagan, H. B. *J. Chem. Soc. D* **1971**, 7, 481. (b) Kagan, H. B.; Dang, T. P. US3798241, **1974**.

<sup>15</sup> (a) Bianchi, M.; Matteoli, U.; Menchi, G.; Frediani, P.; Pratesi, S.; Piacenti, F.; Botteghi, C. *J. Organomet. Chem.* **1980**, 198, 73. (b) Krause, H. W.; Bhatnagar, A. K. *J. Organomet. Chem.* **1986**, 302, 265. (c) Spogliarich, R.; Kašpar, J.; Graziani, M.; Morandini, F. *J. Organomet. Chem.* **1986**, 306, 407. (d) Genêt, J.-P.; Ratovelomanana-Vidal, V.; Pinel, C. *Synlett* **1993**, 478. (e) Khai, B. T.; Arcelli, A. *Tetrahedron Lett.* **1996**, 37, 6599. (f) Barbaro, P.; Bianchini, C.; Togni, A. *Organometallics* **1997**, 16, 3004.

<sup>16</sup> (a) Botteghi, C.; Chelucci, C.; Chessa, G.; Delogu, G.; Gladiali, S.; Soccolini, F. *J. Organomet. Chem.* **1986**, 304, 217. (b) Gladiali, S.; Pinna, L.; Delogu, G.; De Martin, S.; Zassinovich, G.; Mestroni, G. *Tetrahedron: Asymmetry* **1990**, 1, 635.

<sup>17</sup> Müller, D.; Umbricht, G.; Weber, B.; Pfaltz, A. *Helv. Chim. Acta* **1991**, 74, 232.

<sup>18</sup> Jiang, Q.; Van Plew, D.; Murtuza, S.; Zhang, X. *Tetrahedron Lett.* **1996**, 37, 797.

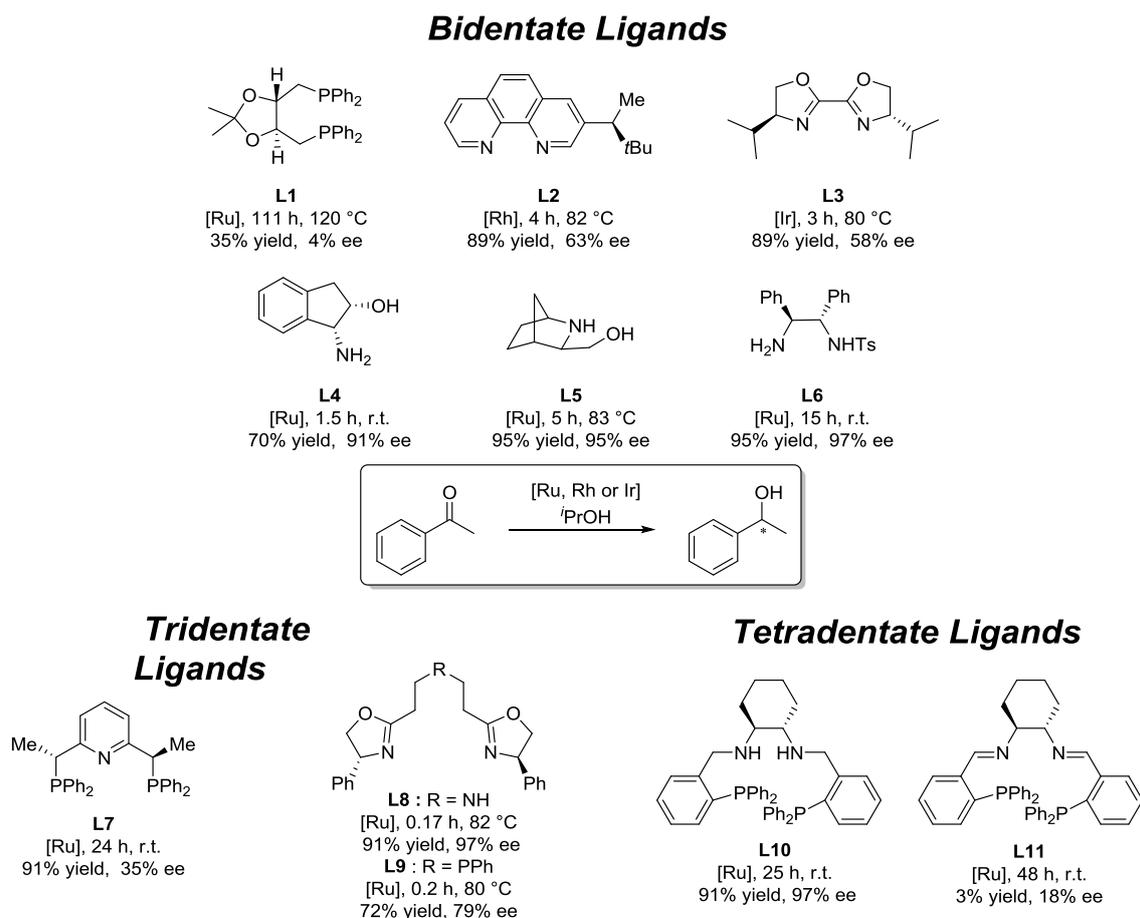
<sup>19</sup> Jiang, Y.; Jiang, Q.; Zhang, X. *J. Am. Chem. Soc.* **1998**, 120, 3817.

<sup>20</sup> Jiang, Y.; Jiang, Q.; Zhu, G.; Zhang, X. *Tetrahedron Lett.* **1997**, 38, 215.

<sup>21</sup> Gao, J.; Ikariya, T.; Noyori, R. *Organometallics* **1996**, 15, 1087.

examples of tridentate or tetradentate ligands have demonstrated the crucial role of the NH group on the reactivity and stereoselectivity.<sup>22</sup> Indeed, ligands with an NH group such as **L8** or **L10** showed an acceleration effect in reactivity as well as better stereoselectivities as compared to ligands without an NH group such as **L9** or **L11** (Scheme 9).

Among all ligands, the most effective in terms of catalytic performance and substrate compatibility are 1,2-aminoalcohols<sup>23</sup> such as **L4**,<sup>24</sup> **L5**,<sup>25</sup> and the monotosylated diamine **L6** developed by Noyori's group<sup>26</sup> (Scheme 9).



Scheme 9

### 1.1.3 Noyori's bifunctional catalysts

The importance of the basic NH group on the ligand led Noyori's group to develop

<sup>22</sup> Zhao, B.; Han, Z.; Ding, K. *Angew. Chem. Int. Ed.* **2013**, *52*, 4744.

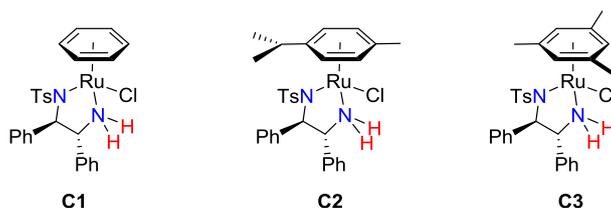
<sup>23</sup> Takehara, J.; Hashiguchi, S.; Fujii, A.; Inoue, S.; Ikariya, T.; Noyori, R. *Chem. Commun.* **1996**, 233.

<sup>24</sup> Palmer, M.; Walsgrove, T.; Wills, M. *J. Org. Chem.* **1997**, *62*, 5226.

<sup>25</sup> Alonso, D. A.; Guijarro, D.; Pinho, P.; Temme, O.; Andersson, P. G. *J. Org. Chem.* **1998**, *63*, 2749.

<sup>26</sup> Hashiguchi, S.; Fujii, A.; Takehara, J.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 7562.

bifunctional metal-ligand catalysts **C1–C3** (Scheme 10).<sup>11a,27</sup>



**Scheme 10**

### 1.1.4 General mechanism

The proposed mechanism for the ATH of ketone derivatives catalyzed by the complexes developed by Noyori and Ikariya involves a concerted transfer of the proton and hydride from the catalytic species mono-hydride [RuH ( $\eta^6$ -arene) ((*R,R*)-TsDPEN)] **A** to the substrate via a cyclic six-center transition state **B** to release the desired alcohol, and the 16-electron Ru (II) intermediate [Ru ( $\eta^6$ -arene) ((*R,R*)-TsDPEN)] **C** (Scheme 11).

The NH unit forms a hydrogen bond with the oxygen atom of the carbonyl group which stabilizes the transition state **B**. Therefore, the presence of the NH group within the ligand core is of great importance for obtaining good bifunctional catalytic performances. Indeed, the use of *N,N*-dimethyl ligands led to ruthenium complexes which proved to be totally inactive as catalysts.<sup>11a</sup>

The proton and hydride originating from isopropanol are then delivered to the complex **C**, via a six-center cyclic transition state **D**, respectively to the amine and the metal, to release acetone and regenerate the initial catalytic Ru (II) species [RuH ( $\eta^6$ -arene) ((*R,R*)-TsDPEN)] **A** mono-hydride (Scheme 11).

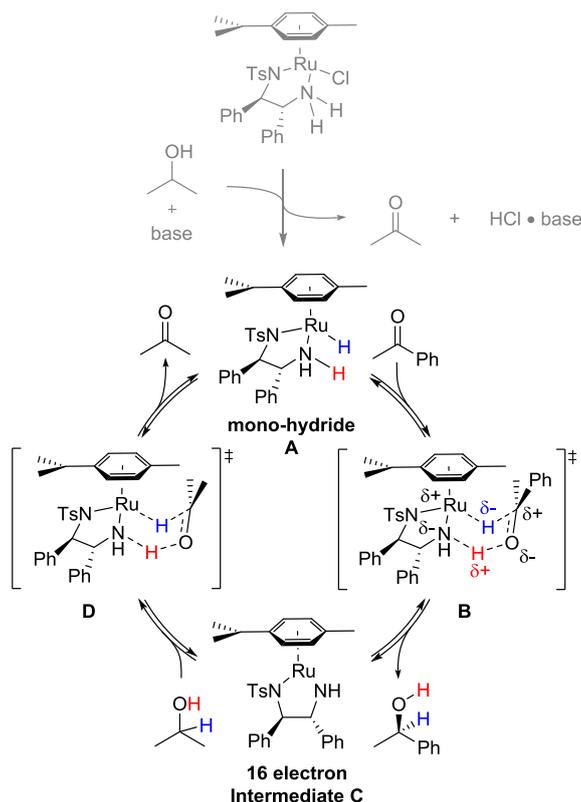
This mechanism has been confirmed by numerous studies (chemical, theoretical and kinetic). Indeed, complexes **A** and **C** have been isolated, characterized and successfully tested in catalysis.<sup>27b</sup> Several theoretical studies<sup>27f,28</sup> confirmed that the 6-center transition state was

<sup>27</sup> (a) Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 2521. (b) Haack, K.-J.; Hashiguchi, S.; Fujii, A.; Ikariya, T.; Noyori, R. *Angew. Chem. Int. Ed.* **1997**, *36*, 285. (c) Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738. (d) Noyori, R.; Ohkuma, T. *Angew. Chem. Int. Ed.* **2001**, *40*, 40. (e) Noyori, R.; Yamakawa, M.; Hashiguchi, S. *J. Org. Chem.* **2001**, *66*, 7931. (f) Noyori, R. *Angew. Chem. Int. Ed.* **2002**, *41*, 2008. (g) Ikariya, T.; Murata, K.; Noyori, R. *Org. Biomol. Chem.* **2006**, *4*, 393

<sup>28</sup> (a) Alonso, D. A.; Brandt, P.; Nordin, S. J. M.; Andersson, P. G. *J. Am. Chem. Soc.* **1999**, *121*, 9580. (b) Yamakawa, M.; Ito, H.; Noyori, R. *J. Am. Chem. Soc.* **2000**, *122*, 1466. (c) Petra, D.; Reek, J.; Handgraaf, J.; Meijer, E.; Dierkes, P.; Kamer, P.; Brussee, J.; Schoemaker, H.; van Leeuwen P. W. N. M. *Chem. Eur. J.* **2000**, *6*, 2818. (d) Dub, P. A.; Ikariya, T. *J. Am. Chem. Soc.* **2013**, *135*, 2604.

the lowest energy transition state.

Detailed structural analyzes of the catalyst and reaction intermediates showed that the effective catalytic species was the 16-electron complex  $[\text{Ru}(\eta^6\text{-arene})((R, R)\text{-TsDPEN})]$  **C**. In particular, it shows a Ru-N bond length comprised between a single bond and a triple bond.<sup>27b</sup> Because of the nature of this Ru-N bond, this electron-deficient complex readily dehydrogenates isopropanol to deliver the ruthenium monohydride complex  $[\text{RuH}(\eta^6\text{-arene})((R, R)\text{-TsDPEN})]$  **A** as a single diastereoisomer.



**Scheme 11**

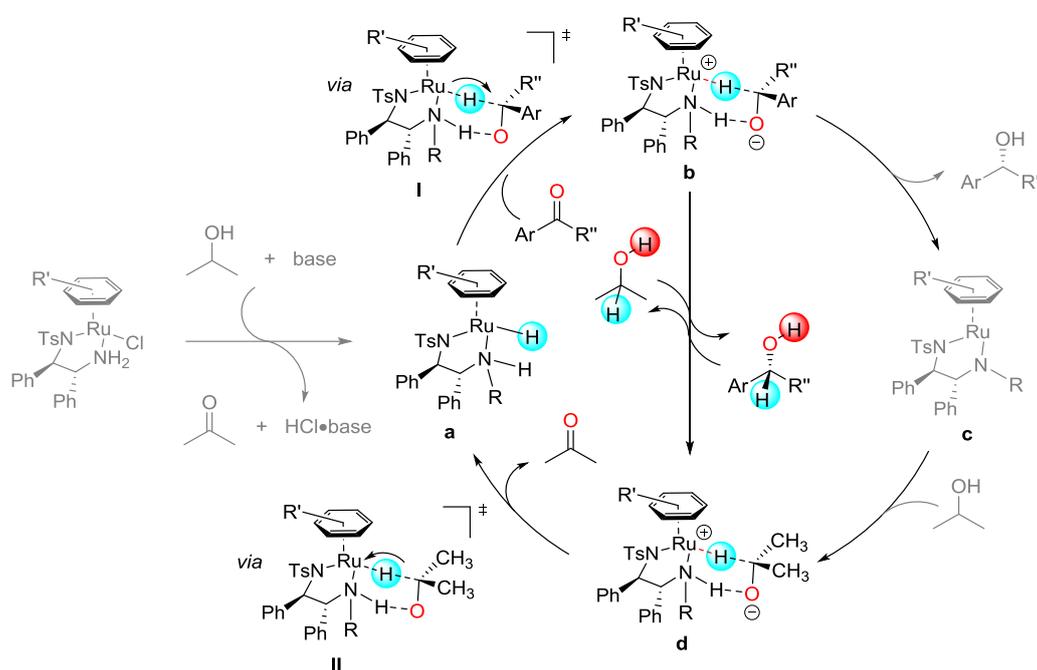
Throughout the catalytic process, the stereochemistry on the metal center is thus preserved and the carbonyl compound is activated without interacting directly with the metal center. It is therefore a hydrogen transfer mechanism named as "outer sphere" because the ketone substrate and the hydride donor remain outside the coordination sphere of the metal.

In 2003, the Casey's group studied the kinetic isotopic effect of the dehydrogenation of isopropanol by the Ru (II) catalytic intermediate of  $[\text{Ru}(\eta^6\text{-}p\text{-cymene})((S, S)\text{-TsDPEN})]$  and found that both hydride transfer and proton transfer occur simultaneously and reversibly,<sup>29</sup> which is consistent with the bifunctional concerted mechanism *via* a six-center transition state

<sup>29</sup> Casey, C. P.; Johnson, J. B. *J. Org. Chem.* **2003**, *68*, 1998.

suggested by Noyori and co-workers.

However, Dub and Gordon's group proposed in 2016 a revised catalytic cycle for the ATH of aromatic ketones in propan-2-ol using the Noyori–Ikariya (pre)catalyst. First, as proposed in early studies, the oxidation state of the metal does not change during the catalytic reaction and the ketone derivatives are indeed reduced within the outer sphere, *i.e.* without initial coordination of the substrate to the metal. However, this reduction proceeds *via* a one-bond type hydride ( $\text{H}^-$ ) transfer to generate the ion-pair intermediate (complex **b**, Scheme 12). The corresponding transition state ( $\text{TS}_d$ ) has been found to be the enantio- and typically rate-determining step (Scheme 12).<sup>28d,30</sup>



**Scheme 12**

For the transfer hydrogenation process with the Noyori–Ikariya's catalyst in isopropanol, there are two pathways to neutralize the anion of the ion-pair product **b** (“starting” branching point) and regenerate the catalyst. The latter proceeds *via* a one-bond type C–H proton plus two electron transfer from the isopropoxide anion to the cation within the ion-pair of type **d** (“closing” branching point), Scheme 12. In this process, the hydrogen atom is repolarized as follows  $\text{H}^+ \rightarrow \text{H}^-$ . In one pathway, the source of the proton that neutralizes the anion in **b** is the ligand, thus the N–H ligand is chemically non-innocent. This mechanism for ketone reduction can be denoted as a step-wise metal–ligand bifunctional in order to explain the difference with

<sup>30</sup> Dub, P. A.; Gordon, J. C. *Dalton Trans.* **2016**, 45, 6756.

the conventional mechanism, which is concerted and realized only in the gas-phase. In the second path, the source of the proton used to neutralize the anion in **b** is propan-2-ol, therefore the N–H ligand is chemically innocent in this case. This is the same type of H<sup>-</sup>/H<sup>+</sup> outer-sphere hydrogenation, except that the source of the proton used to neutralize the anion is now a protic solvent molecule. The crossover of these two reaction pathways is possible and likely takes place in all transfer hydrogenation processes catalyzed by bifunctional catalysts. Although the relative contribution of each mechanism is computationally intractable,<sup>28d</sup> the neutralization of the anion within ion-pair **b** by a protic solvent seems to be more probable, especially with increasing reaction medium polarity, *e.g.*, if the reaction is carried out in more polar formic acid or water.<sup>28d</sup> In fact, Car–Parrinello molecular dynamics studies of Meijer<sup>31</sup> suggest that the catalytic reaction in water<sup>32,33</sup> proceeds exclusively or largely through, what we call here a H<sup>-</sup>/H<sup>+</sup> outer-sphere hydrogenation mechanism.

### 1.1.5 Origins of enantioselectivity

The enantioselectivity of ATH for aromatic ketones catalyzed by the Noyori-Ikariya complex originates from the stabilization of the favorable transition state through multiple C–H $\cdots\pi$  electrostatic interactions<sup>28d,34</sup> between the electron-deficient proton of the arene attracted by the ruthenium metal center and the electron-enriched carbons of the aromatic ring of the substrate, as well as from the destabilization of the unfavorable diastereomeric transition state via lone pair(s)– $\pi$  repulsion<sup>35</sup> between the SO<sub>2</sub> group and the  $\pi$ -cloud of the approaching aromatic ketone as shown in Scheme 13.

---

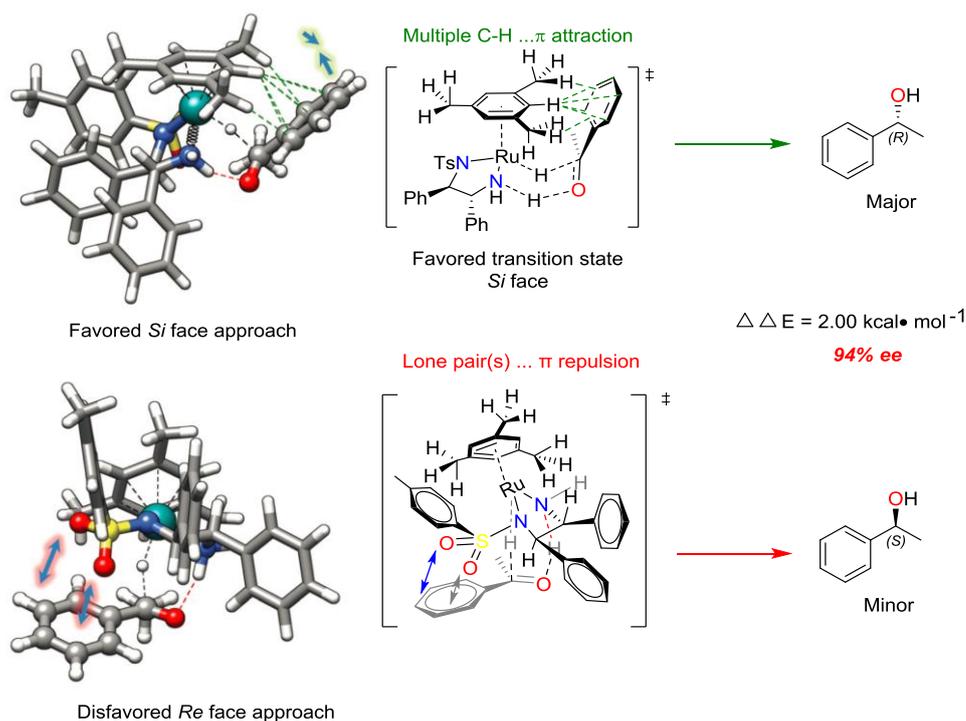
<sup>31</sup> Pavlova, A.; Meijer, E. J. *ChemPhysChem* **2012**, *13*, 3492.

<sup>32</sup> Wu, X.; Liu, J.; Di Tommaso, D.; Iggo, J. A.; Catlow, C. R. A.; Bacsa, J.; Xiao, J. *Chem. Eur. J.* **2008**, *14*, 7699.

<sup>33</sup> Tanis, S. P.; Evans, B. R.; Nieman, J. A.; Parker, T. T.; Taylor, W. D.; Heasley, S. E.; Herrinton, P. M.; Perrault, W. R.; Hohler, R. A.; Dolak, L. A.; Hesterf, M. R.; Seest, E. P. *Tetrahedron: Asymmetry* **2006**, *17*, 2154.

<sup>34</sup> Matsuoka, A.; Sandoval, C. A.; Uchiyama, M.; Noyori, R.; Naka, H. *Chem. Asian J.* **2015**, *10*, 112.

<sup>35</sup> Mooibroek, T. J.; Gamez, P.; Reedijk, J. *CrystEngComm* **2008**, *10*, 1501.

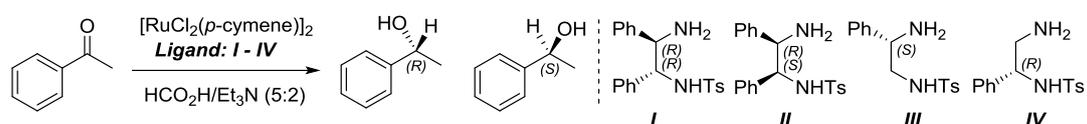


Wills group undertook a comparative study<sup>36</sup> to understand the importance of the following parameters:

- The *anti* diamine configuration of the diamine
- The disubstitution of the diamine
- Which stereogenic center is involved in the asymmetric induction?

The results are gathered in the table below (Table 1).

**Table 1.** Ru-catalyzed ATH of acetophenone



| Entry | Ligand     | Time    | Conv./ % | Ee/%            |
|-------|------------|---------|----------|-----------------|
| 1     | <b>I</b>   | 22 h    | 100      | 98 ( <i>R</i> ) |
| 2     | <b>II</b>  | 220 h   | 32       | 70 ( <i>S</i> ) |
| 3     | <b>III</b> | 48 h    | 95       | 69 ( <i>S</i> ) |
| 4     | <b>IV</b>  | 13 days | 46       | 33 ( <i>R</i> ) |

Based on experimental results, better stereoselectivities are obtained when the diamine

<sup>36</sup> Hayes, A.; Clarkson, G.; Wills, M. *Tetrahedron: Asymmetry* **2004**, *15*, 2079.

is disubstituted (Entries 1 and 2 vs. entries 3 and 4). When the ligand **II** presents a (*R,S*)-configuration, a reversed configuration for 1-phenyl-ethanol is observed (Entries 1 and 2). If the ligand has only one stereogenic center, the alcohol will have the same configuration as the ligand (Entries 3 and 4). However, when the ligand has two stereogenic centers, the alcohol will follow the stereochemistry of the stereocenter bearing the tosylated amine (Entries 1 and 2). Therefore, the chirality of the final product seems to be determined by the absolute configuration of the tosylated amine.

### 1.1.6 Other catalysts for asymmetric transfer hydrogenation

The excellent performances of the Noyori-Ikariya ruthenium(II) precatalysts **C1-C3** have prompted other research groups to develop different types of ruthenium complexes (Scheme 14, selected examples), as well as rhodium and iridium precatalysts containing an NH group (Scheme 15, selected examples).

In 2002, Zhou's group described the **C4** complex with a chiral tetrahydroquinolinyl-oxazoline ligand for ATH of aromatic ketones with moderate enantioselectivities (46–83%).<sup>37</sup>

Since 2004, Wills *et al.* introduced various ruthenium complexes (**C28**,<sup>38</sup> **C11**,<sup>38</sup> **C5**,<sup>39</sup> **C14**<sup>40</sup> and **C12**<sup>41</sup>), as well as rhodium precatalysts (**C30**,<sup>42a</sup> **C23**,<sup>42b</sup> **C31**<sup>43</sup>) in which the aminoalcohol or diamine unit is linked to the arene with an alkyl or a benzyl tether. These diamine containing complexes are more stable thanks to a three-point anchorage to the metal constraining the free rotation of the arene ring and allowing control of the spatial positions of the substituents on the complex. For example, the tethered complex **C11** gave excellent conversions and enantioselectivities, with shorter reaction time than the untethered Noyori's complex **C3** in the ATH of ketones.<sup>44</sup>

In 2011, Ikariya's group demonstrated the effectiveness of ruthenium catalysts (**C13a**

---

<sup>37</sup> Zhou, Y.-B.; Tang, F.-Y.; Xu, H.-D.; Wu, X.-Y.; Ma, J.-A.; Zhou, Q.-L. *Tetrahedron: Asymmetry* **2002**, *13*, 469.

<sup>38</sup> (a) Hannedouche, J.; Clarkson, G. J.; Wills, M. *J. Am. Chem. Soc.* **2004**, *126*, 986. (b) Cheung, F. K. K.; Hayes, A. M.; Hannedouche, J.; Yim, A. S. Y.; Wills, M. *J. Org. Chem.* **2005**, *70*, 3188.

<sup>39</sup> Hayes, A. M.; Morris, D. J.; Clarkson, G. J.; Wills, M. *J. Am. Chem. Soc.* **2005**, *127*, 7318.

<sup>40</sup> (a) Cheung, F. K.; Lin, C.; Minissi, F.; Crivillé, A. L.; Graham, M. A.; Fox, D. J.; Wills, M. *Org. Lett.* **2007**, *9*, 4659. (b) Cheung, F. K.; Hayes, A. M.; Morris, D. J.; Wills, M. *Org. Biomol. Chem.* **2007**, *5*, 1093. (c) Soni, R.; Jolley, K. E.; Clarkson, G. J.; Wills, M. *Org. Lett.* **2013**, *15*, 5110.

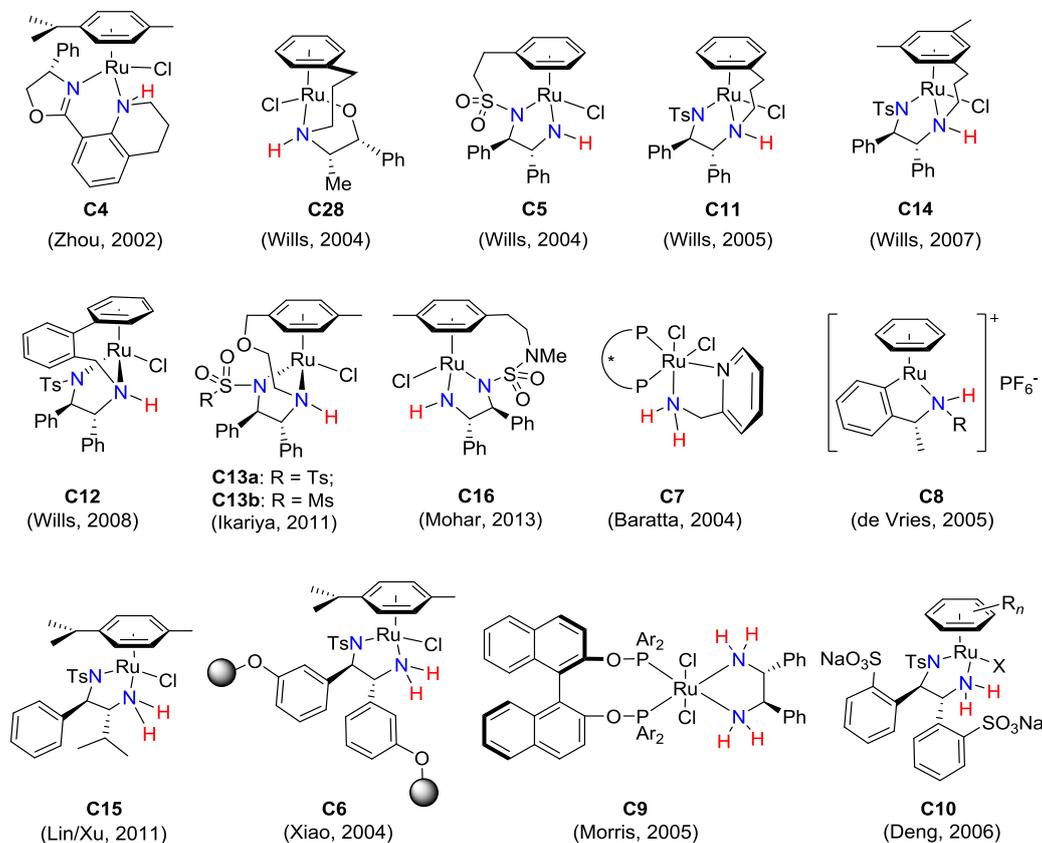
<sup>41</sup> Martins, J. E. D.; Morris, D. J.; Tripathi, B.; Wills, M. *J. Organomet. Chem.* **2008**, *693*, 3527.

<sup>42</sup> (a) Cross, D. J.; Houson, I.; Kawamoto, A. M.; Wills, M. *Tetrahedron Lett.* **2004**, *45*, 843. (b) Matharu, D. S.; Morris, D. J.; Kawamoto, A. M.; Clarkson, G. J.; Wills, M. *Org. Lett.* **2005**, *7*, 5489.

<sup>43</sup> (a) Matharu, D. S.; Morris, D. J.; Clarkson, G. J.; Wills, M. *Chem. Commun.* **2006**, 3232. (b) Matharu, D. S.; Martins, J. E. D.; Wills, M. *Chem. Asian J.* **2008**, *3*, 1374.

<sup>44</sup> Morris, D. J.; Hayes, A. M.; Wills, M. *J. Org. Chem.* **2006**, *71*, 7035.

and **C13b**) bearing an ether tether for the ATH of various aromatic ketones with 84–99% ee.<sup>45</sup> In 2013, Mohar's group reported a series of sulfonamide tethered ruthenium complexes,<sup>46</sup> such as **C16**, which has been demonstrated to be active in the ATH of aromatic ketones with high yields and enantioselectivities.



Scheme 14

To fulfill the principles of green chemistry,<sup>47</sup> an immobilized version of the ruthenium(II) precatalyst (**C6**) has been synthesized.<sup>48</sup> Similarly, water-soluble ruthenium (**C10**, Scheme 14) and iridium (**C20**, Scheme 15) catalysts have been prepared by Deng's<sup>49</sup> and Carreira's<sup>50</sup> groups, enabling the reduction of  $\alpha$ -functionalized acetophenones, and  $\beta$ -

<sup>45</sup> (a) Touge, T.; Hakamata, T.; Nara, H.; Kobayashi, T.; Sayo, N.; Saito, T.; Kayaki, Y.; Ikariya, T. *J. Am. Chem. Soc.* **2011**, *133*, 14960. (b) Ikariya, T. *Bull. Chem. Soc. Jpn.* **2011**, *84*, 1. (c) Parekh, V.; Ramsden, J. A.; Wills, M. *Catal. Sci. Technol.* **2012**, *2*, 406.

<sup>46</sup> (a) Kišić, A.; Stephan, M.; Mohar, B. *Org. Lett.* **2013**, *15*, 1614. (b) Kišić, A.; Stephan, M.; Mohar, B. *Adv. Synth. Catal.* **2014**, *356*, 3193.

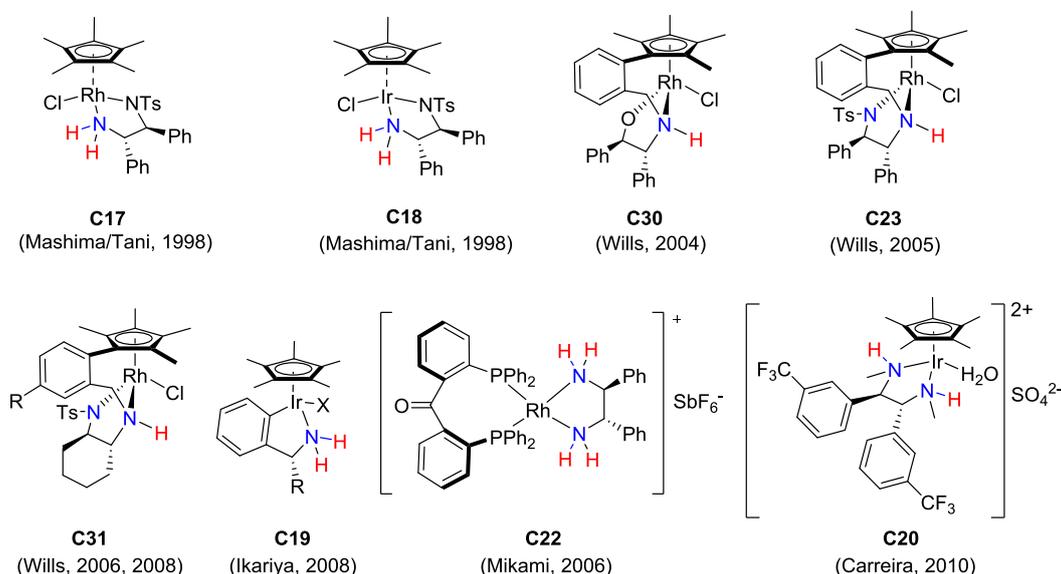
<sup>47</sup> Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*, Oxford University Press: New York, **1998**, p.30.

<sup>48</sup> (a) Li, X.; Wu, X.; Chen, W.; Hancock, F. E.; King, F.; Xiao, J. *Org. Lett.* **2004**, *6*, 3321. (b) Li, X.; Chen, W.; Hems, W.; King, F.; Xiao, J. *Tetrahedron Lett.* **2004**, *45*, 951.

<sup>49</sup> Wu, J.; Wang, F.; Ma, Y.; Cui, X.; Cun, L.; Zhu, J.; Deng, J.; Yu, B. *Chem. Commun.* **2006**, 1766.

<sup>50</sup> (a) Soltani, O.; Ariger, M. A.; Vázquez-Villa, H.; Carreira, E. M. *Org. Lett.* **2010**, *12*, 2893. (b) Vázquez-Villa, H.; Reber, S.; Ariger, M. A.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2011**, *50*, 8979. (c) Ariger, M. A.; Carreira, E. M.

ketoesters in the presence of sodium formate and/or formic acid in water with excellent enantioselectivities up to 99%. In most cases, the stereoselectivities observed in water were better than those obtained using formic acid/triethylamine azeotropic mixture in an organic solvent.



Scheme 15

Ruthenium and rhodium precatalysts with a diamino-phosphine ligand have been successfully used by the Baratta's (**C7**),<sup>51</sup> Morris's (**C9**)<sup>52</sup> and Mikami's (**C22**, Scheme 15)<sup>53</sup> groups for the ATH of various ketones.

Metallacycles such as **C8**<sup>54</sup> or **C19**<sup>55</sup> (Scheme 15) were shown to be active and enantioselective for the reduction of prochiral ketones.

The rhodium (**C17**) and iridium (**C18**) analogues of the Noyori's ruthenium catalyst also displayed excellent activities for ATH of aromatic ketones (84–99% ee) (Scheme 15).<sup>56</sup> The Lin and Xu's group reported that ruthenium catalysts with an unsymmetric diamine ligand such as **C15** induce excellent enantioselectivities (Scheme 14).<sup>57</sup>

*Org. Lett.* **2012**, *14*, 4522.

<sup>51</sup> (a) Baratta, W.; Chelucci, G.; Herdtweck, E.; Magnolia, S.; Siega, K.; Rigo, P. *Angew. Chem. Int. Ed.* **2007**, *46*, 7651.

<sup>52</sup> Guo, R.; Elpelt, C.; Chen, X.; Song, D.; Morris, R. H. *Chem. Commun.* **2005**, 3050.

<sup>53</sup> Mikami, K.; Wakabayashi, K.; Yusa, Y.; Aikawa, K. *Chem. Commun.* **2006**, 2365.

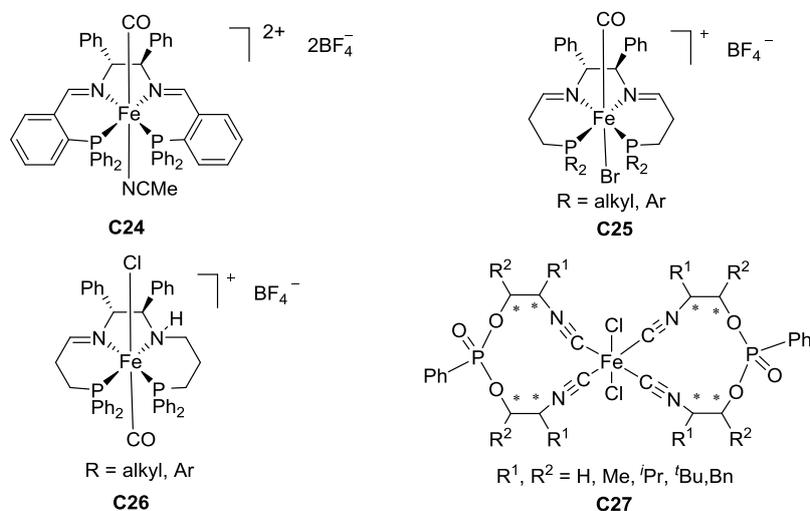
<sup>54</sup> Sortais, J.; Ritleng, V.; Voelklin, A.; Holuigue, A.; Smail, H.; Barloy, L.; Sirlin, C.; Verzijl, G. K. M.; Boogers, J. A. F.; de Vries, A. H. M.; de Vries, J. G.; Pfeffer, M. *Org. Lett.* **2005**, *7*, 1247.

<sup>55</sup> Arita, S.; Koike, T.; Kayaki, Y.; Ikariya, T. *Organometallics* **2008**, *27*, 2795.

<sup>56</sup> (a) Mashima, K.; Abe, T.; Tani, K. *Chem. Lett.* **1998**, 1199. (b) Mashima, K.; Abe, T.; Tani, K. *Chem. Lett.* **1998**, 1201.

<sup>57</sup> Zhang, B.; Wang, H.; Lin, G.; Xu, M. *Eur. J. Org. Chem.* **2011**, 4205.

Iron catalysts such as **C24**,<sup>58</sup> **C25**,<sup>59</sup> **C26**<sup>60</sup> and **C27**<sup>61</sup> have also been successfully used for the ATH of ketones (Scheme 16).



Scheme 16

## 1.1.7 The various hydrogen sources

### 1.1.7.1 Short description

By definition,<sup>4</sup> hydrogen transfer is a reaction in which two hydrogens of a hydrogen donor (other than molecular hydrogen) are transferred to an acceptor substrate. Theoretically, the hydrogen donor could be any compound that can transfer its hydrogens in the presence of a catalyst and under appropriate conditions. Another requirement is that the hydrogen donor must have an affinity with the catalytic center, but this affinity should not be too strong once the hydrogen transfer has been effected. The choice of the hydrogen donor therefore depends on a number of parameters such as the type of reaction (Meerwein-Ponndorf-Verley or Oppenauer reaction catalyzed by a transition metal), its solubility in the reaction medium or its ability to dissolve all the reagents, its influence on the equilibrium of the reaction, the nature of the

<sup>58</sup> (a) Meyer, N.; Lough, A. J.; Morris, R. H. *Chem. Eur. J.* **2009**, *15*, 5605. (b) Morris, R. H. *Chem. Soc. Rev.* **2009**, *38*, 2282. (c) Mikhailine, A. a; Maishan, M. I.; Lough, A. J.; Morris, R. H. *J. Am. Chem. Soc.* **2012**, *134*, 12266. (d) Gopalaiah, K. *Chem. Rev.* **2013**, *113*, 3248. (e) Riener, K.; Haslinger, S.; Raba, A.; Högerl, M. P.; Cokoja, M.; Herrmann, W. a; Kühn, F. E. *Chem. Rev.* **2014**, *114*, 5215.

<sup>59</sup> (a) Lagaditis, P. O.; Lough, A. J.; Morris, R. H. *J. Am. Chem. Soc.* **2011**, *133*, 9662. (b) Sues, P. E.; Lough, A. J.; Morris, R. H. *Organometallics* **2011**, *30*, 4418. (c) Sues, P. E.; Demmans, K. Z.; Morris, R. H. *Dalton Trans.* **2014**, 43,7650.

<sup>60</sup> (a) Mikhailine, A.; Lough, A. J.; Morris, R. H. *J. Am. Chem. Soc.* **2009**, *13*, 1394. (b) Zuo, W.; Tauer, S.; Prokopchuk, D. E.; Morris, R. H. *Organometallics* **2014**, *33*, 5791; (c) Zuo, W.; Lough, A. J.; Li, Y. F.; Morris, R. H. *Science* **2013**, *342*, 1080.

<sup>61</sup> Naik, A.; Maji, T.; Reiser, O. *Chem. Commun.* **2010**, 4475.

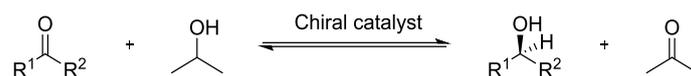
molecule obtained after dehydrogenation, the nature of the functional group to be reduced, the temperature of the reaction, *etc.*

### 1.1.7.2 Examples of hydrogen donors

*In this section, we will only focus on the sources of hydrogen used for the reduction of ketones. Isopropanol and formic acid (and its salts) are the most frequently used sources of hydrogen for hydrogen transfer because of their low cost and low toxicity.*

#### Isopropanol:

When isopropanol is used as a reducing agent, the dehydrogenation product is acetone, a non-toxic compound, making the reduction reaction reversible, which is the main disadvantage of using this donor. This is why a large excess is often necessary to shift the equilibrium of the reaction. Isopropanol is often used as a solvent because of the stability of the catalysts in this solvent, which results in excellent conversions (Scheme 17).

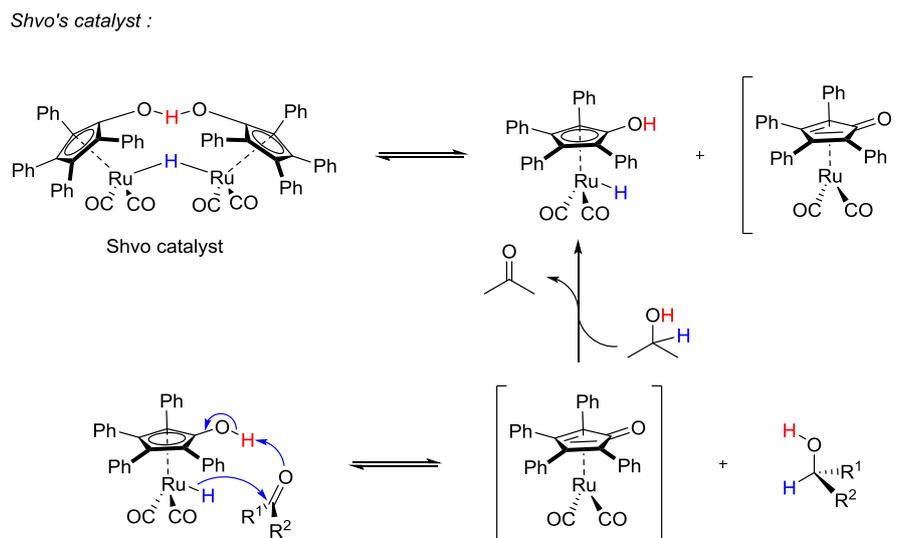
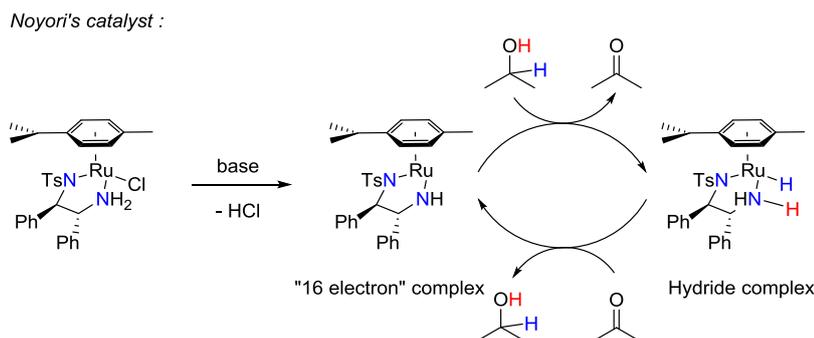


**Scheme 17**

When isopropanol is used as a hydrogen donor, it is necessary to use a base (alkoxide or hydroxide salt) to allow the formation of the 16-electron complex via a dissociative mechanism ( $S_N1CB$ ). The required quantity of base depends on the nature of the catalyst. For example, for the Shvo's catalyst,<sup>62</sup> there is no need to use a base whereas for the Noyori catalyst, two equivalents per metal atom are required (Scheme 18).

---

<sup>62</sup> (a) Shvo, Y.; Czarkie, D.; Rahamim, Y.; Chodosh, D. F. *J. Am. Chem. Soc.* **1986**, *108*, 7400. (b) Menashe, N.; Shvo, Y. *Organometallics* **1991**, *10*, 3885. (c) Menashe, N.; Salant, E.; Shvo, Y. *J. Organomet. Chem.* **1996**, *514*, 97. (d) Casey, C. P.; Singer, S. W.; Powell, D. R.; Hayashi, R. K.; Kavana, M. *J. Am. Chem. Soc.* **2001**, *123*, 1090. (e) Conley, B. L.; Pennington-Boggio, M. K.; Boz, E.; Williams, T. J. *Chem. Rev.* **2010**, *110*, 2294.



Scheme 18

The presence of this base can also create secondary reactions and promote racemization. Although reactions with chiral ruthenium catalysts give satisfactory results in isopropanol in terms of reactivity and selectivity<sup>11a</sup> the major disadvantage is its reversibility, leading to a limited conversion. Because of this reversibility, a dramatic decrease in the enantiomeric excess of the products is observed during long-term exposure of the reaction mixture to the catalyst.

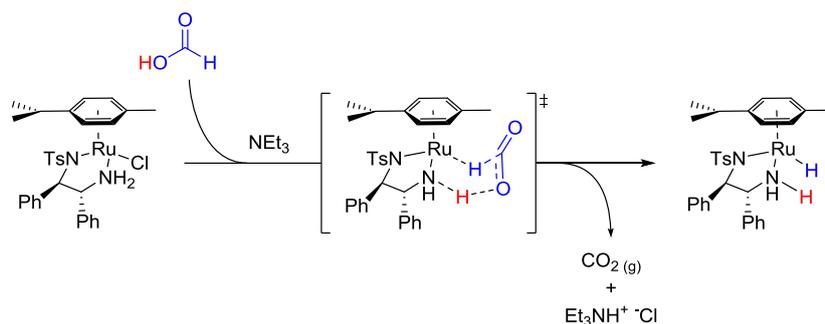
Other alcohols such as methanol or ethanol may be used but are generally less effective than secondary alcohols (in terms of the sum of  $\delta$  inductive electronic effects) and the aldehydes formed may interfere with the reaction medium although these are volatile.

#### Formic acid and its salts:

Formic acid and its salts are the hydrogen donors of choice for the reduction of carbonyl compounds. Indeed, the dehydrogenation product is CO<sub>2</sub> gas making the reaction irreversible and under kinetic control.<sup>27a,63</sup> When formic acid is used, it is necessary to use a base such as

<sup>63</sup> Koike, T.; Ikariya, T. *Adv. Synth. Catal.* **2004**, 346, 37.

triethylamine to deprotonate the formic acid and release the formate ion required for the formation of the metal hydride (Scheme 19).



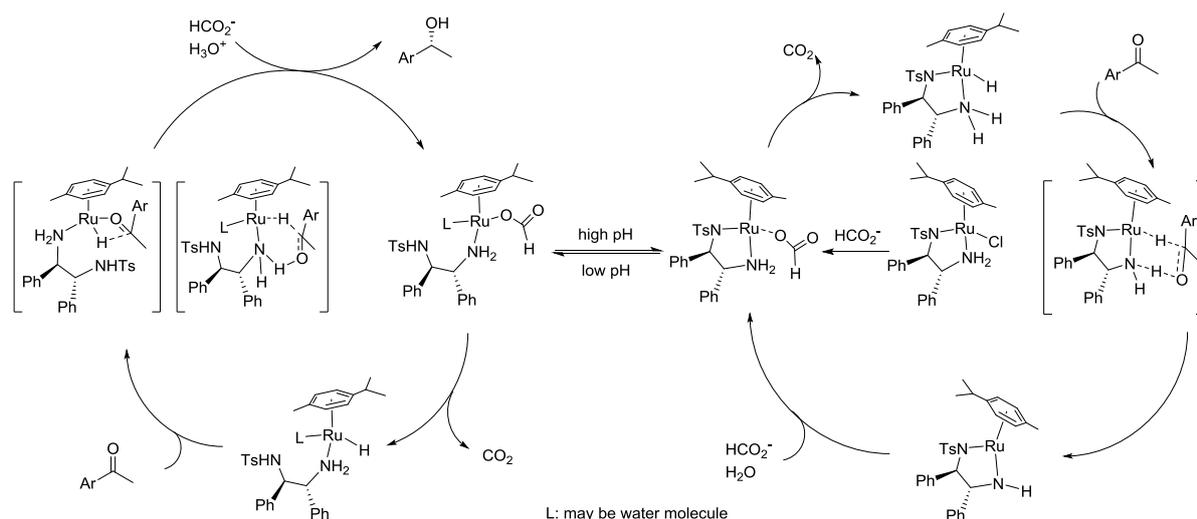
**Scheme 19**

In addition, the azeotropic mixture HCOOH/Et<sub>3</sub>N (5/2) is commercially available, soluble in various solvents and is the most frequently used. Xiao *et al.* showed that this azeotropic mixture could also be used in water. They observed that the enantioselectivity of the ATH catalyzed by the Noyori's complex [RuCl( $\eta^6$ -*p*-cymene)((*R,R*)-TsDPEN)] formed *in situ* was dependent on the pH of the medium. At pH > 7, high catalytic activities and high enantioselectivities were obtained, resulting from two competitive catalytic cycles (Scheme 20) depending on the pH value of the solution.<sup>64</sup> Other research groups studied the influence of the formic acid/triethylamine ratio and concluded that the ratios leading to the best reactivity and selectivity were 0.2/1 and 1/1.<sup>65</sup> Finally, Zhang's group reported that the formic acid/DIPEA mixture (5/2) provided the best enantioselectivity compared to other chiral and nonchiral tertiary amines for asymmetric hydrogen transfer of  $\alpha$ -ketopantolactam (Scheme 21).<sup>66</sup>

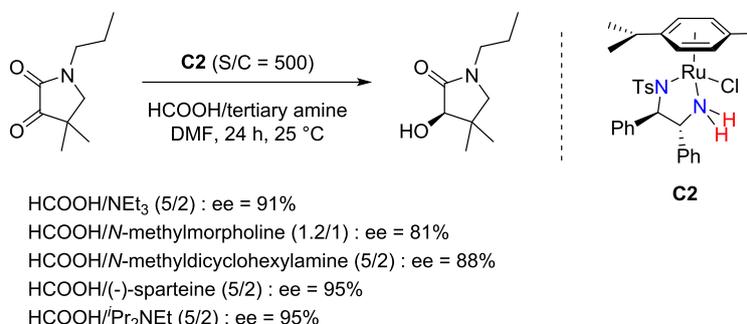
<sup>64</sup> (a) Wu, X.; Li, X.; King, F.; Xiao, J. *Angew. Chem. Int. Ed.* **2005**, *44*, 3407. (b) Zhou, X.; Wu, X.; Yang, B.; Xiao, J. *J. Mol. Catal. A Chem.* **2012**, *357*, 133.

<sup>65</sup> (a) Tanaka, K.; Katsurada, M.; Ohno, F.; Shiga, Y.; Oda, M.; Miyagi, M.; Takehara, J.; Okano, K. *J. Org. Chem.* **2000**, *65*, 432. (b) Miyagi, M.; Takehara, J.; Collet, S.; Okano, K. *Org. Process Res. Dev.* **2000**, *4*, 346. Also see the reference on ATH of imines: (c) Shende, V. S.; Deshpande, S. H.; Shingote, S. K.; Joseph, A.; Kelkar, A. A. *Org. Lett.* **2015**, *17*, 2878.

<sup>66</sup> Zhang, J.; Blazecka, P. G.; Bruendl, M. M.; Huang, Y. *J. Org. Chem.* **2009**, *74*, 1411.



Scheme 20



Scheme 21

The azeotropic mixture  $\text{HCOOH/Et}_3\text{N}$  (5/2) has an acidic pH and its value depends on the solvent used. This acidity is a major disadvantage since some complexes can decompose under acidic conditions.

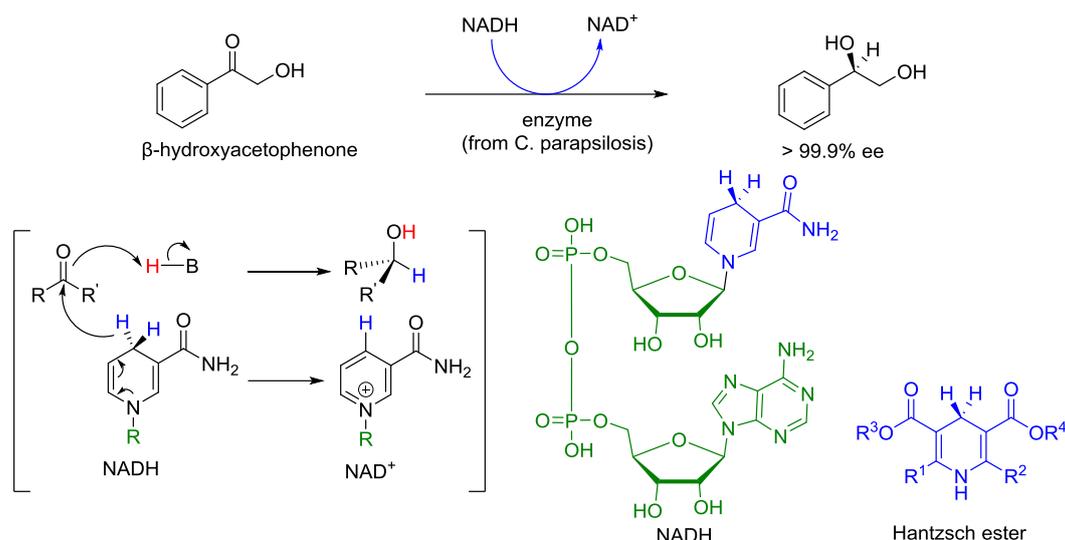
Finally, formic acid salts are also used as hydrogen donors. In particular, sodium formate ( $\text{HCOONa}$ ) is very often used for ATH in water.<sup>31,67</sup>

### Hantzsch ester:

Inspired by the way nature achieves asymmetric reductions, chemists have developed a biomimetic approach to asymmetric hydrogen transfer using Hantzsch ester<sup>68a-b</sup> as the hydrogen donor and thus mimicking the role of  $\text{NADH}^{68c-d}$  (Scheme 22).

<sup>67</sup> (a) Wu, X.; Li, X.; Hems, W.; King, F.; Xiao, J. *Org. Biomol. Chem.* **2004**, *2*, 1818. (b) Wu, X.; Xiao, J. *Chem. Commun.* **2007**, 2449. (c) Wu, X.; Li, X.; Zanotti-Gerosa, A.; Pettman, A.; Liu, J.; Mills, A. J.; Xiao, J. *Chem. Eur. J.* **2008**, *14*, 2209.

<sup>68</sup> (a) Hantzsch, A. *Ber. Dtsch. Chem. Ges.* **1881**, *14*, 1637. (b) Hantzsch, A. *Justus Liebigs Ann. Chem.* **1882**, 215, 1. (c) Nie, Y.; Xu, Y.; Mu, X. Q. *Org. Process Res. Dev.* **2004**, *8*, 246. (d) Wang, S.; Nie, Y.; Xu, Y.; Zhang, R.; Ko, T.-P.; Huang, C.-H.; Chan, H.-C.; Guo, R.-T.; Xiao, R. *Chem. Commun.* **2014**, *50*, 7770.



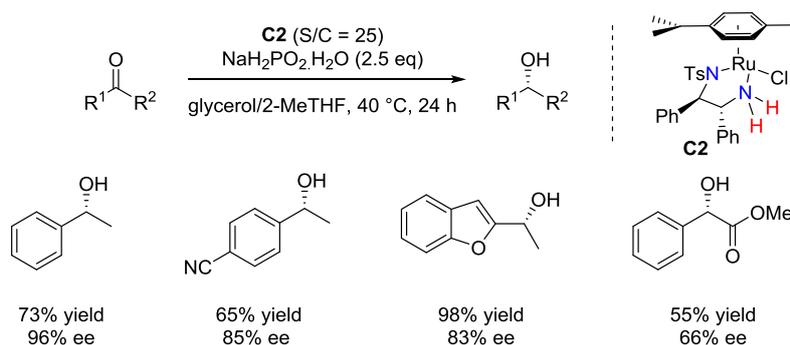
Scheme 22

The use of Hantzsch ester for organocatalyzed reduction of C=C, C=N or C=O bonds has grown particularly rapidly in recent years.<sup>69</sup>

However, its application for the metal-catalyzed ATH has few precedents in the literature because it is not atom-economical. In addition, the resulting dehydrogenated product causes purification issues.

#### Other donors:

In 2013, Lemaire *et al.* used  $\text{NaH}_2\text{PO}_2 \cdot \text{H}_2\text{O}$  as a hydrogen donor for the ATH of a wide range of ketones catalyzed by the Noyori's complex  $[\text{RuCl}(\eta^6\text{-}p\text{-cymene})((R,R)\text{-TsDPEN})]$  **C2** in a glycerol/2-MeTHF biphasic system (Scheme 23).<sup>70</sup>

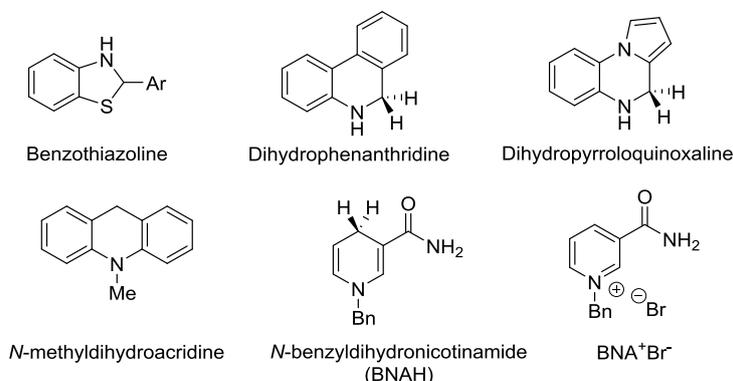


Scheme 23

<sup>69</sup> (a) Ouellet, S. G.; Walji, A. M.; MacMillan, D. W. C. *Acc. Chem. Res.* **2007**, *40*, 1327. (b) Rueping, M.; Dufour, J.; Schoepke, F. R. *Green Chem.* **2011**, *13*, 1084. (c) Zheng, C.; You, S. *Chem. Soc. Rev.* **2012**, *41*, 2498 and references therein.

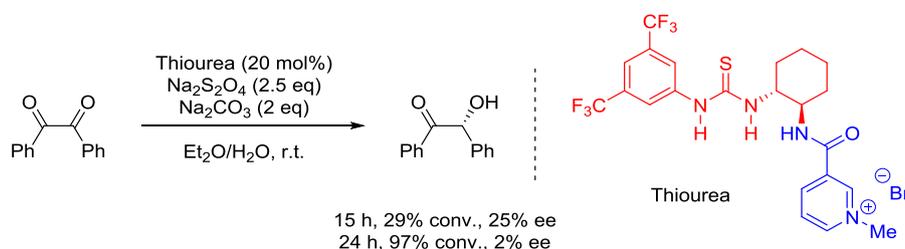
<sup>70</sup> Guyon, C.; Méta y, E.; Duguet, N.; Lemaire, M. *Eur. J. Org. Chem.* **2013**, 5439.

The hydrogen donors shown in Scheme 24 are used mostly for organocatalyzed reduction of C=N bonds. Their structures are always based on NADH biomimetic approach. Examples include benzothiazoline derivatives,<sup>71</sup> dihydrophenanthridine (DHPD),<sup>72</sup> dihydropyrroloquinoxaline<sup>73</sup> or dihydronicotinamide.<sup>74</sup>



Scheme 24

For example, Connon's group proposed an organocatalyst bearing the hydrogen donor (MNA<sup>+</sup>Br<sup>-</sup>: methylnicotinamide) part and the substrate activating fragment (thiourea) for the transfer hydrogenation of 1,2-diketones in the presence of sodium dithionate as a co-reductant for 'cofactor' generation/recycling. However, this approach suffers from a racemization problem due to a long reaction time (Scheme 25).<sup>75</sup>



Scheme 25

After describing the general principles of asymmetric transfer hydrogenation reaction (mechanisms, bifunctional metal-ligand catalysis, hydrogen donors), the next section will address the recent developments on metal-catalyzed asymmetric transfer hydrogenation of ketones from 2015 to August 2018 in terms of new metal precatalysts, and their application to

<sup>71</sup> Henseler, A.; Kato, M.; Mori, K.; Akiyama, T. *Angew. Chem. Int. Ed.* **2011**, *50*, 8180.

<sup>72</sup> Lu, L.-Q.; Li, Y.; Junge, K.; Beller, M. *Angew. Chem. Int. Ed.* **2013**, *52*, 8382.

<sup>73</sup> Chen, Z.-P.; Chen, M.-W.; Guo, R.-N.; Zhou, Y.-G. *Org. Lett.* **2014**, *16*, 1406.

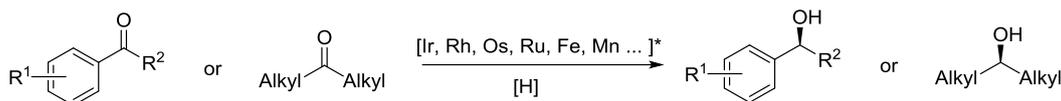
<sup>74</sup> Xu, H.-J.; Liu, Y.-C.; Fu, Y.; Wu, Y.-D. *Org. Lett.* **2006**, *8*, 3449.

<sup>75</sup> Procuranti, B.; Connon, S. *J. Chem. Commun.* **2007**, 1421.

*synthetic chemistry.*

## 2. Reaction scope: catalysts and chiral ligands

Different transition metals (Ru, Rh, Ir, Fe, Os, Mn) in combination with a number of chiral ligands bearing coordinating heteroatoms (N, O, P, S) have been developed and investigated in asymmetric transfer hydrogenation of aromatic or aliphatic ketones (Scheme 26).



**Scheme 26**

### 2.1 Ruthenium catalysts

#### 2.1.1 Aminoalcohols as ligands

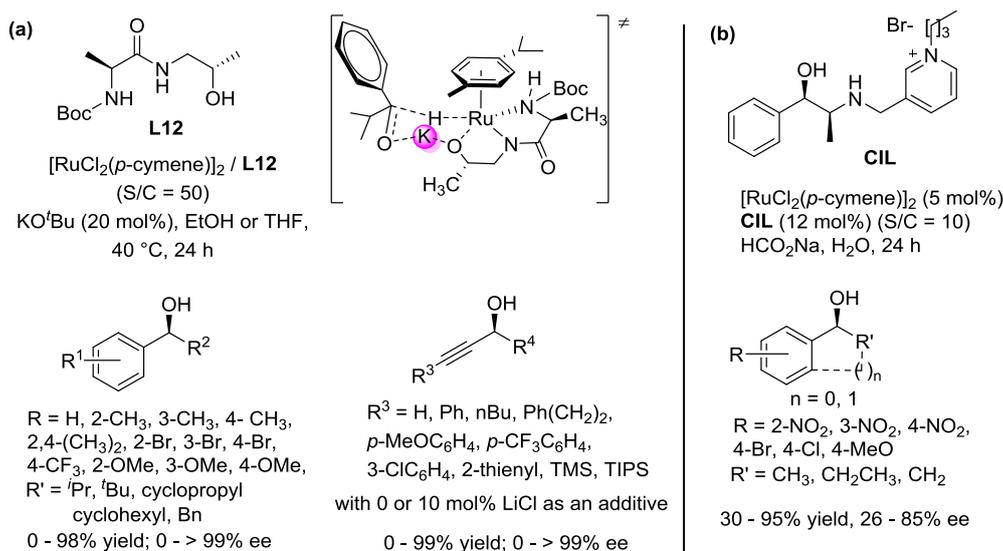
Chiral aminoalcohols are one type of the most common used ligands in asymmetric transfer hydrogenation and have been well documented in the literature. Developing novel chiral aminoalcohols as ligands is still ongoing, because they are easily available from natural or unnatural chiral amino acids.

Adolfsson *et al.* reported, in 2015, a Ru(II) complex bearing a chiral amino acid derived ligand **L12** formed *in situ* for ATH of a series of challenging sterically hindered aryl ketones using EtOH/KO<sup>t</sup>Bu system as a hydrogen donor to provide the chiral alcohols with high conversions and enantioselectivities.<sup>76</sup> The same group reported in 2015 the use of the above catalytic system with different ratios of KO<sup>t</sup>Bu/LiCl for ATH of various propargylic ketones to give the corresponding propargylic alcohols, in most cases, with yields up to 99% and with excellent enantioselectivities >90% (Scheme 27a).<sup>77</sup> A new type of hydrophilic chiral ionic liquid (CIL) bearing amino alcohol unit was developed and coordinated with [RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub> precursor for ATH of simple ketones to yield moderate to high enantioselectivities. However, recovery experiments showed the limited reactivity of these systems because of the catalyst leaching (Scheme 27b).<sup>78</sup>

<sup>76</sup> Slagbrand, T.; Kivijärvi, T.; Adolfsson, H. *ChemCatChem* **2015**, *7*, 3445.

<sup>77</sup> Shatskiy, A.; Kivijärvi, T.; Lundberg, H.; Tinnis, F.; Adolfsson, H. *ChemCatChem* **2015**, *7*, 3818.

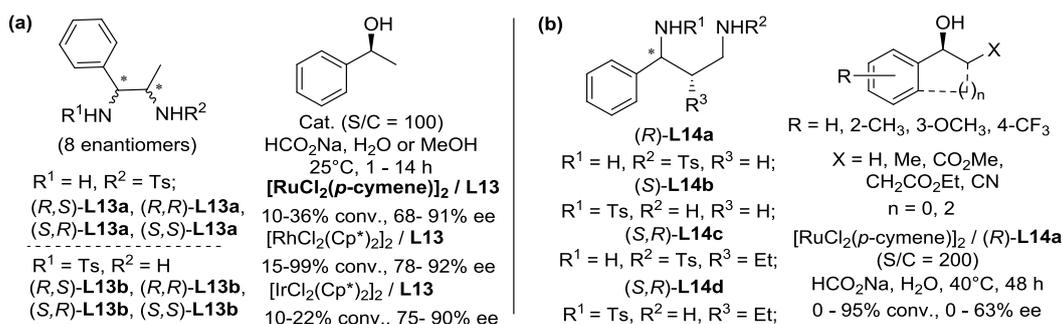
<sup>78</sup> Vasiloiu, M.; Gaertner, P.; Zirbs, R.; Bica, K. *Eur. J. Org. Chem.* **2015**, 2374.



Scheme 27

### 2.1.2 Diamines as ligands

Based on commercially available norephedrine, several unsymmetrical vicinal diamine ligands **L13** were prepared and evaluated in combination with  $[\text{RuCl}_2(p\text{-cymene})]_2$ ,  $[\text{RhCl}_2\text{Cp}^*]_2$ ,  $[\text{IrCl}_2\text{Cp}^*]_2$  for ATH of acetophenone with sodium formate as the hydrogen source in aqueous phase (Scheme 28a).<sup>79</sup> Moreover, simple unsymmetric monotosylated 1,3-diamines **L14** were developed and combined with  $[\text{RuCl}_2(p\text{-cymene})]_2$  for the ATH of phenones to give the corresponding alcohols in low to moderate ee (0–63%) (Scheme 28b).<sup>80</sup>



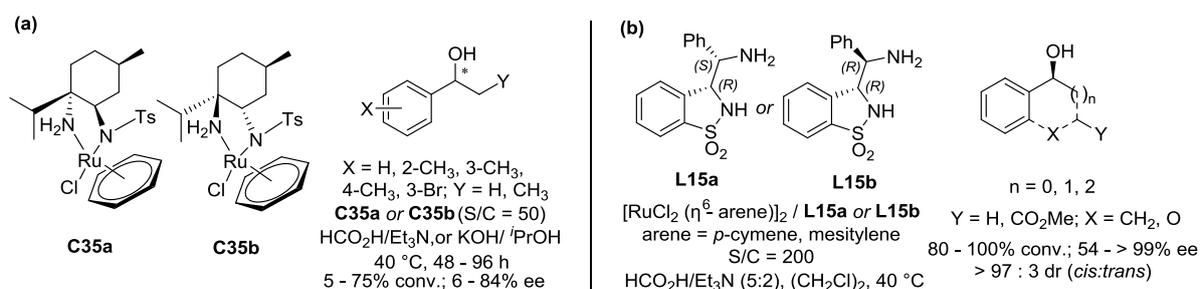
Scheme 28

Chiral monotosylated diamines based on natural (–)-menthol were synthesized and used to form Ru(II) complexes **C35**. These complexes catalyzed the ATH of simple aromatic ketones

<sup>79</sup> Deshpande, S. H.; Shende, V. S.; Shingote, S. K.; Chakravarty, D.; Puranik, V. G.; Chaudhari, R. V.; Kelkar, A. *RSC Adv.* **2015**, *5*, 51722.

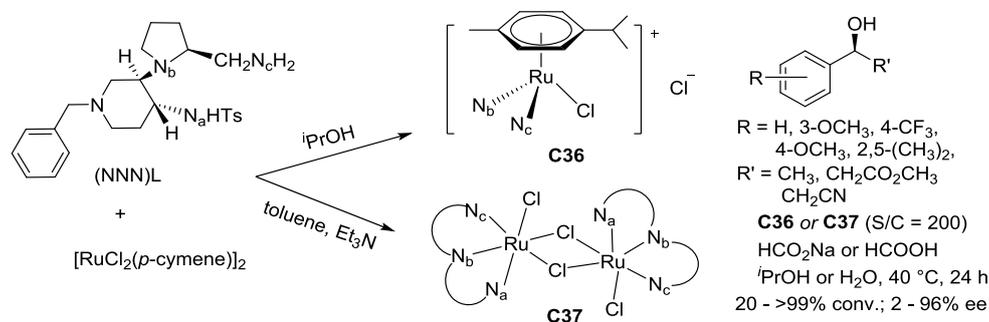
<sup>80</sup> Facchetti, G.; Gandolfi, R.; Fusè, M.; Zerla, D.; Cesarotti, E.; Pellizzoni, M.; Rimoldi, I. *New J. Chem.* **2015**, *39*, 3792.

with  $\text{HCO}_2\text{H}/\text{Et}_3\text{N}$  or  $\text{KOH}/i\text{PrOH}$  as the hydrogen source to generate chiral alcohols with moderate activities and good enantioselectivities (up to 84% ee) (Scheme 29a).<sup>81</sup> In 2016, Mohar *et al.* developed a new type of diamine ligands **L15** used in Ru(II)-catalyzed ATH of simple aryl ketones as well as cyclic aryl ketones using  $\text{HCO}_2\text{H}/\text{Et}_3\text{N}$  as hydrogen source under mild conditions to furnish the corresponding alcohols in 54–99% yields and up to 99% enantioselectivities (Scheme 29b).<sup>82</sup>



Scheme 29

A novel (*N,N,N*) chiral ligand was prepared and combined with  $[\text{RuCl}_2(p\text{-cymene})]_2$  to form bidentate complex **C36** and tridentate complex **C37**. The catalytic activity of these complexes in ATH of aromatic ketones largely depended on the reaction conditions and the substituents on the ketones (Scheme 30).<sup>83</sup>



Scheme 30

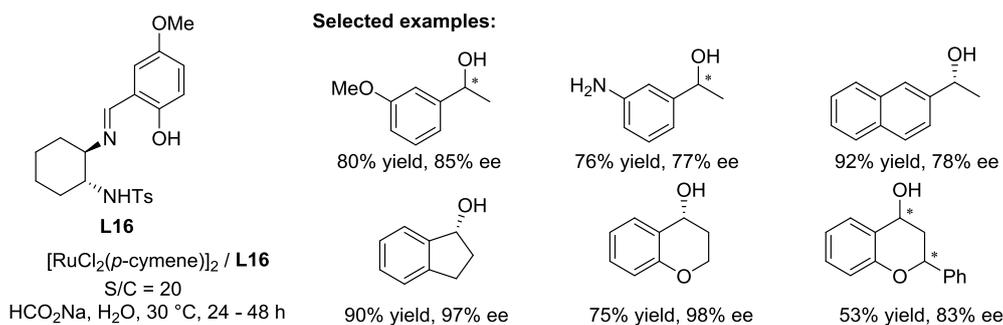
A number of hemisalen type ligands **L16** were prepared and evaluated with  $[\text{RuCl}_2(p\text{-cymene})]_2$  complex for ATH of acetophenone in water. Chiral cyclohexyl diamine based hemisalen ligand displayed high catalytic activity and was investigated for the reduction of a broad range of ketones to deliver the corresponding alcohols in yields ranging from 53 to 92% and ee values from 77 to 97% (Scheme 31).<sup>84</sup>

<sup>81</sup> Roszkowski, P.; Maurin, J. K.; Czarnocki, Z. *Tetrahedron Lett.* **2018**, *59*, 2184.

<sup>82</sup> Rast, S.; Modéc, B.; Stephan, M.; Mohar, B. *Org. Biomol. Chem.* **2016**, *14*, 2112.

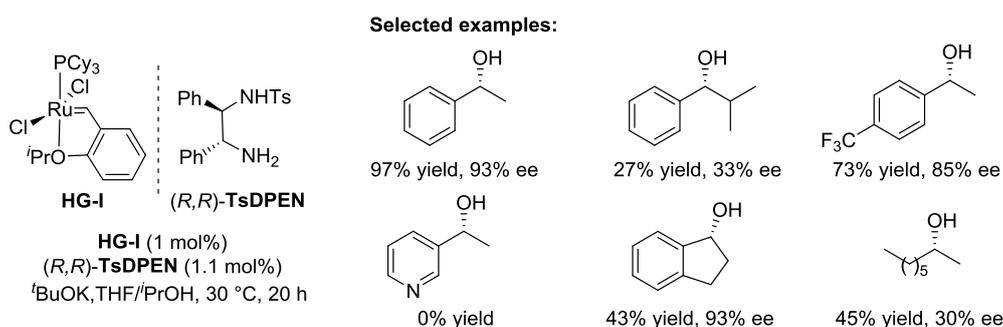
<sup>83</sup> Pellegrino, S.; Facchetti, G.; Gandolfi, R.; Fusè, M.; Erba, E.; Rimoldi, I. *Can. J. Chem.* **2018**, *96*, 40.

<sup>84</sup> Boukachabia, M.; Aribi-Zouiouèche, L.; Riant, O. *J. Organomet. Chem.* **2018**, *868*, 95.



Scheme 31

The 1<sup>st</sup> generation Hoveyda-Grubbs metathesis catalyst in association with (*R,R*)-TsDPEN ligand was successfully evaluated in the ATH of simple aromatic ketones in the presence of *i*PrOH as a hydrogen donor. High activities and enantioselectivities (up to 97% ee) were obtained in the ATH of several ketones. Moreover, a tandem reaction including metathesis reaction and ketone transfer reduction was achieved (Scheme 32).<sup>85</sup>



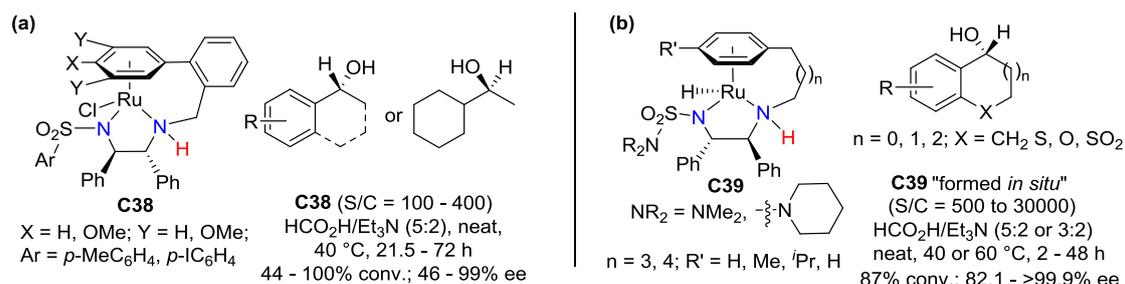
Scheme 32

A new family of benzyl-tethered Ru(II)/arene/TsDPEN complexes **C38** was developed through a direct arene-exchange process. These complexes were applied in the ATH of a broad range of ketones to generally provide the chiral alcohols in high conversions and enantioselectivities up to 99% (Scheme 33a).<sup>86</sup> In 2015, Mohar *et al.* reported a new series of 3<sup>rd</sup> generation *ansa*-Ru(II) complexes **C39** bearing a sulfamoylamino (NSO<sub>2</sub>N) moiety (Scheme 33b).<sup>87</sup>

<sup>85</sup> Renom-Carrasco, M.; Gajewski, P.; Pignataro, L.; de Vries, J. G.; Piarulli, U.; Gennari, C.; Lefort, L. *Adv. Synth. Catal.* **2016**, *358*, 515.

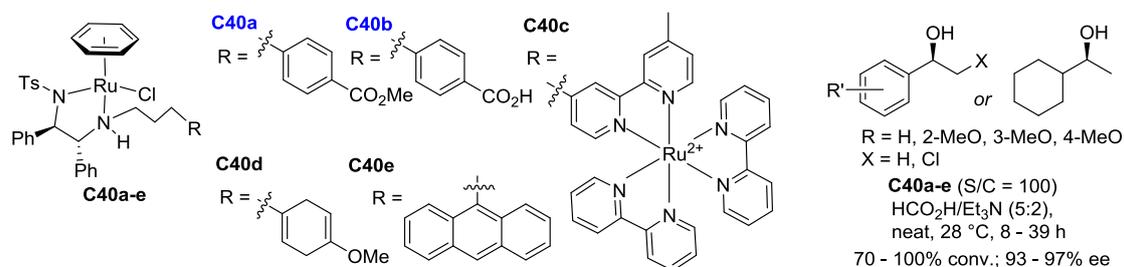
<sup>86</sup> (a) Soni, R.; Jolley, K. E.; Gosiewska, S.; Clarkson, G. J.; Fang, Z.; Hall, T. H.; Treloar, B. N.; Knighton, R. C.; Wills, M. *Organometallics* **2018**, *37*, 48. (b) Knighton, R. C.; Vyas, V. K.; Mailey, L. H.; Bhanage, B. M.; Wills, M. *J. Organomet. Chem.* **2018**, *875*, 72.

<sup>87</sup> (a) Kišić, A.; Stephan, M.; Mohar, B. *Adv. Synth. Catal.* **2015**, *357*, 2540. (b) Hodgkinson, R.; Jurčák, V.; Nedden, H.; Blackaby, A.; Wills, M. *Tetrahedron Lett.* **2018**, *59*, 930.



Scheme 33

In 2015, Wills *et al.* developed a number of Ru(II)(benzene)/*N*-alkyl-TsDPEN complexes **C40a–e** and evaluated their catalytic activities and enantioinductions for the ATH of acetophenone. They used **C40a** and **C40b** for the ATH of a broad range of ketone derivatives by using HCO<sub>2</sub>H/Et<sub>3</sub>N under mild conditions to give 1-phenyl ethanol in high conversions and ees (Scheme 34).<sup>88f</sup>

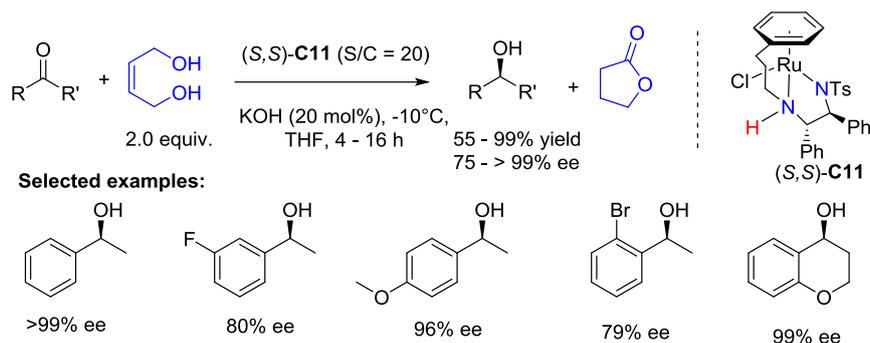


Scheme 34

In 2015, Wakeham *et al.* described a new approach by using *cis*-1,4-butanediol as a hydrogen donor with Wills' catalyst (*S,S*)-**C11** in the ATH of simple aryl ketones to yield the chiral alcohols in 75 to 99% ee values (Scheme 35).<sup>89</sup>

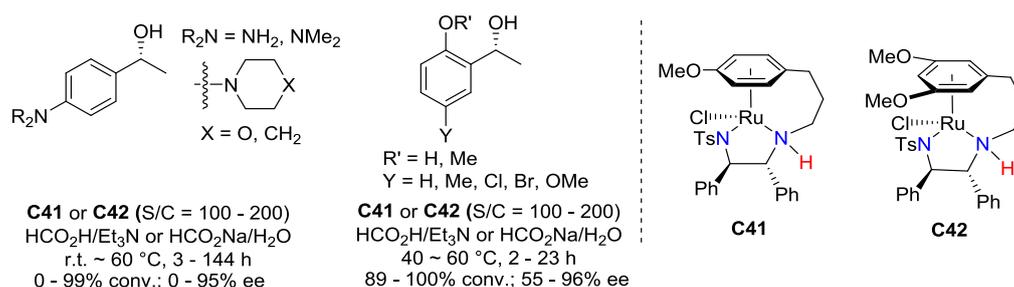
<sup>88</sup> (a) Soni, R.; Hall, T. H.; Morris, D. J.; Clarkson, G. J.; Owen, M. R.; Wills, M. *Tetrahedron Lett.* **2015**, *56*, 6397. Also see previous work : (b) Koike, T.; Ikariya, T. *Adv. Synth. Catal.* **2004**, *346*, 37; (c) Koike, T.; Ikariya, T. *J. Organomet. Chem.* **2007**, *692*, 408. (d) Martins, J. E. D.; Clarkson, G. J.; Wills, M. *Org. Lett.* **2009**, *11*, 847; (e) Martins, J. E. D.; Contreras Redondo, M. A.; Wills, M. *Tetrahedron: Asymmetry* **2010**, *21*, 2258; (f) Zammit, C. M.; Wills, M. *Tetrahedron: Asymmetry* **2013**, *24*, 844.

<sup>89</sup> Wakeham, R. J.; Morris, J. A.; Williams, J. M. J. *ChemCatChem* **2015**, *7*, 4039.



Scheme 35

Considering the ATH of challenging electron-rich aromatic ketones, the two tethered Ru(II) complexes **C41** and **C42** were investigated in the presence of  $\text{HCO}_2\text{H}/\text{Et}_3\text{N}$  or aqueous sodium formate as the hydrogen source, and exhibited efficient catalytic activities. For the aniline ketones, the reaction worked well in aqueous sodium formate; whereas for *ortho*-methoxy substituted ketones, a  $\text{HCO}_2\text{H}/\text{Et}_3\text{N}$  system exhibited high performance (Scheme 36).<sup>90</sup>

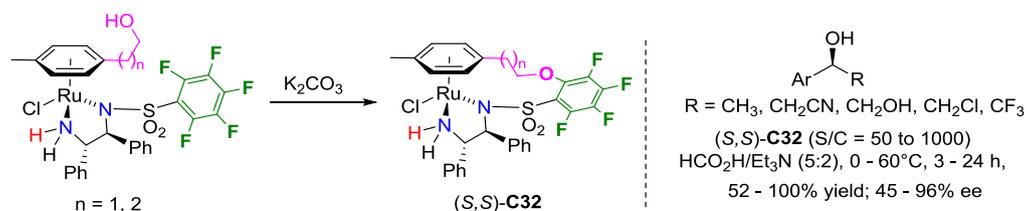


Scheme 36

In 2018, Kayaki and coworkers presented a concise approach for the synthesis of new oxy-tethered ruthenium complexes **C32**, which were effective for the ATH of aromatic ketones. The key step involves a defluorinative etherification reaction to construct an oxy-tether arising from an intramolecular nucleophilic substitution of a perfluorinated phenylsulfonyl substituent. The resulting tethered complexes exhibited high catalytic activity and selectivity for ATH of functionalized aromatic ketones. Their superior catalytic performances relative to the nontethered prototype complex owe to the robustness and rigidity of the tether (Scheme 37).<sup>91</sup>

<sup>90</sup> Soni, R.; Hall, T. H.; Mitchell, B. P.; Owen, M. R.; Wills, M. J. *Org. Chem.* **2015**, *80*, 6784.

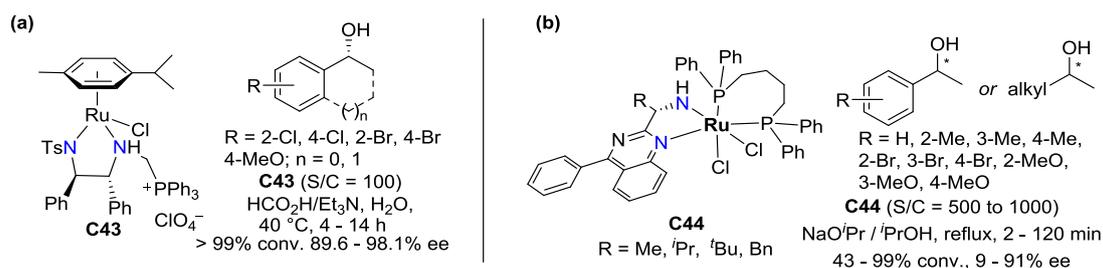
<sup>91</sup> Matsunami, A.; Ikeda, M.; Nakamura, H.; Yoshida, M.; Kuwata, S.; Kayaki, Y. *Org. Lett.* **2018**, *20*, 5213.



Scheme 37

### 2.1.3 Phosphorus containing ligands

A Noyori-Ikariya tetraarylphosphonium salt (TAP)-supported catalyst **C43** was reported for ATH of aryl ketones in water with HCO<sub>2</sub>H/Et<sub>3</sub>N as a hydrogen donor. Additionally, the supported catalyst could be recycled 5 times after simple manipulation with good results (Scheme 38a).<sup>92</sup> A series of *N,N*-containing quinazoline-based Ru(II) complexes **C44** were developed and proved to be efficient in ATH of ketones with NaO<sup>*i*</sup>Pr/<sup>*i*</sup>PrOH as the hydrogen source. For aryl ketones, up to 91 % enantioselectivities were obtained, whereas alkyl alkyl ketones were reduced with lower ee values (33–52%) (Scheme 38b).<sup>93</sup>



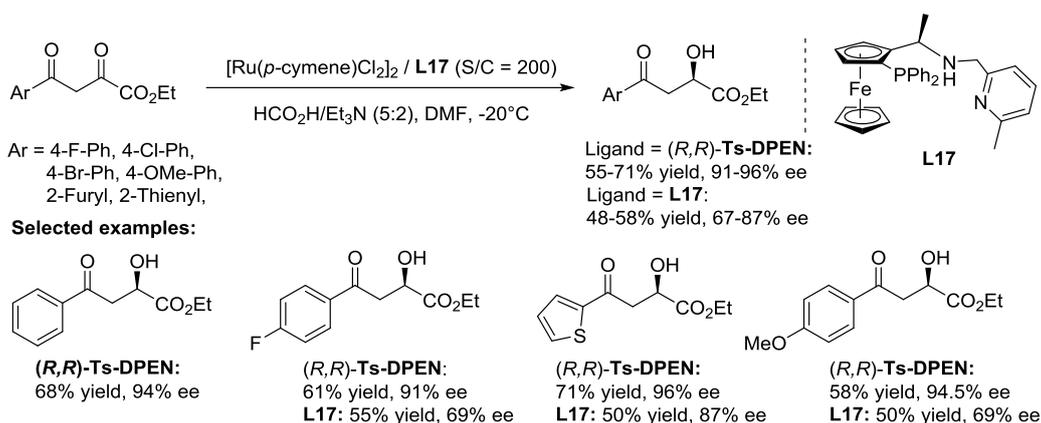
Scheme 38

A convenient approach to access chiral  $\alpha$ -hydroxy- $\gamma$ -keto-butyrac acid ethyl esters was described by using a Ru(II) catalyst with chiral ferrocene-based *P,N,N* ligand **L17** for the ATH of the corresponding ketones in the presence of HCO<sub>2</sub>H/Et<sub>3</sub>N as a hydrogen source. Meanwhile, chiral TsDPEN ligand has been evaluated to provide the products in 55–71% yields with 91–96% ee (Scheme 39).<sup>94</sup>

<sup>92</sup> Zimbron, J. M.; Dauphinais, M.; Charette, A. B. *Green Chem.* **2015**, *17*, 3255.

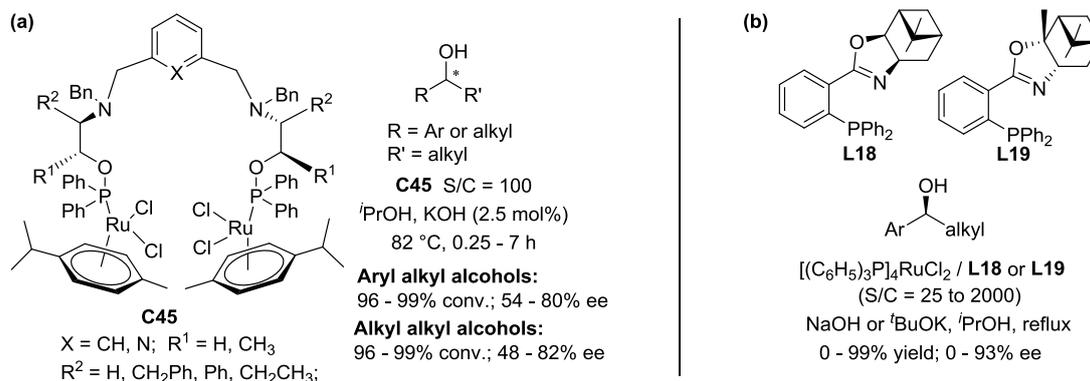
<sup>93</sup> Kucukturkmen, C.; Agac, A.; Eren, A.; Karakaya, I.; Aslantas, M.; Celik, O.; Ulukanli, S.; Karabuga, S. *Catal. Commun.* **2016**, *74*, 122.

<sup>94</sup> Mo, Y.-Z.; Nie, H.-F.; Lei, Y.; Zhang, D.-X.; Li, X.-Y.; Zhang, S.-Y.; Wang, Q.-F. *RSC Adv.* **2016**, *6*, 33126.



Scheme 39

A series of binuclear Ru(II) precatalysts was prepared and used for ATH of aryl methyl ketones and alkyl alkyl ketones to furnish the corresponding alcohols in high conversions and moderate to high enantioselectivities (Scheme 40a).<sup>95</sup> In 2017, Krzemiński *et al.* reported a new type of terpene derived PHOX ligands **L18**, **L19** and their application in the presence of  $[\text{Ru}(\text{PPh}_3)_4\text{Cl}_2]$  complex for ATH of aromatic ketones to give chiral alcohols in moderate to high yields and enantioselectivities (Scheme 40b).<sup>96</sup>



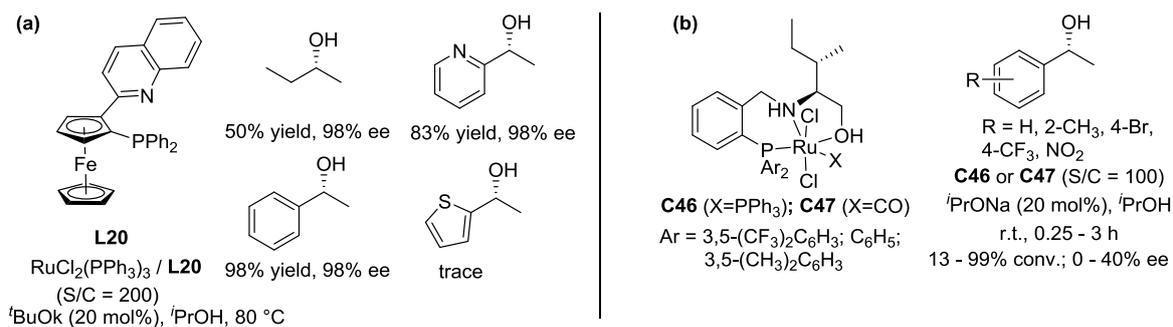
Scheme 40

New planar chiral ferrocene *P,N*-ligands **L20** were designed and evaluated with  $\text{RuCl}_2(\text{PPh}_3)_2$  complex in the ATH of acetophenone to give (*R*)-1-phenyl ethanol in high yield (98%) and excellent ee. Heteroaryl methyl ketones and alkyl alkyl ketones were also investigated using  $\text{RuCl}_2(\text{PPh}_3)_2/\text{L20}$  to provide the chiral alcohols up to 98% yields and up to 98% ees (Scheme 41a).<sup>97</sup>

<sup>95</sup> Karakaş, D. E.; Aydemir, M.; Durap, F.; Baysal, A. *Inorg. Chim. Acta* **2018**, 471, 430.

<sup>96</sup> Kmiecik, A.; Krzemiński, M. P. *Tetrahedron: Asymmetry* **2017**, 28, 467.

<sup>97</sup> Utepova, I. A.; Serebrennikova, P. O.; Streltsova, M. S.; Musikhina, A. A.; Fedorchenko, T. G.; Chupakhin, O. N.; Antonchick, A. P. *Molecules* **2018**, 23, 1311.



Scheme 41

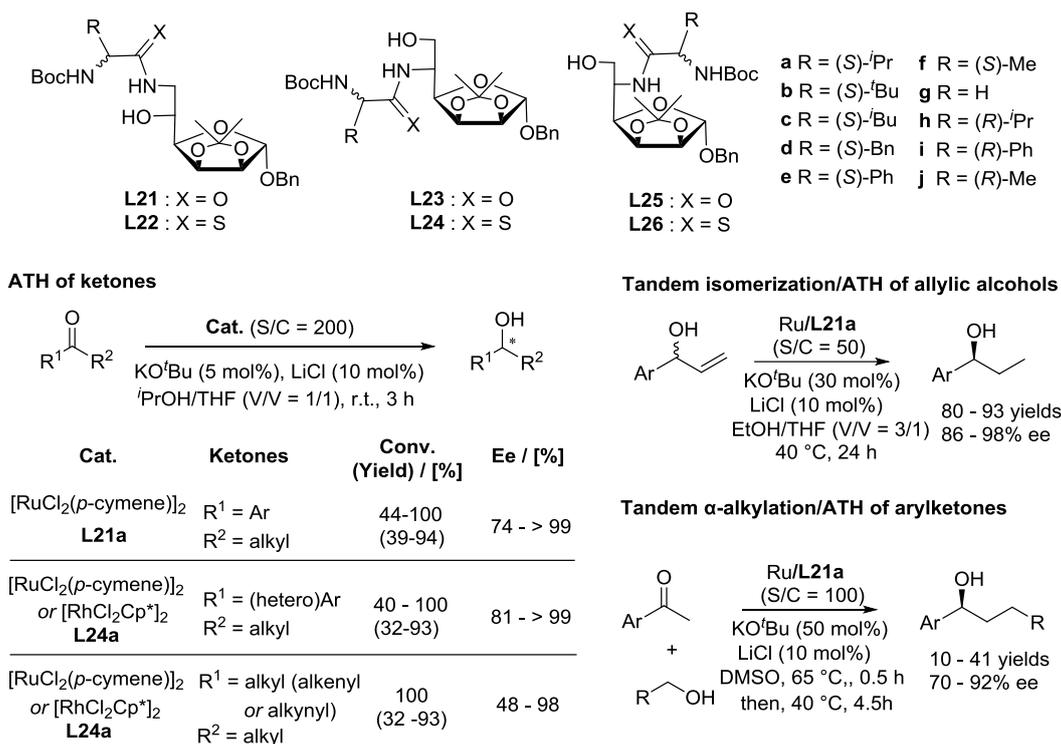
Several new chiral tridentate Ru(II)/*N,O,P* complexes **C46** and **C47** were synthesized and characterized. The precatalysts were investigated in ATH of simple aryl methyl ketones using  $\text{NaO}^i\text{Pr}/i\text{PrOH}$  system as the hydrogen source to provide the corresponding chiral secondary alcohols. Although high catalytic activities (up to 99% yields) were observed for most of the substrates, the enantioselectivities were only moderate (up to 40% ee) (Scheme 41b).<sup>98</sup>

### 2.1.4 Sugar containing ligands

A number of sugar-based hydroxyamide and thioamide ligands **L21–L26(a-j)** were prepared and evaluated with  $[\text{RuCl}_2(p\text{-cymene})]_2$  or  $[\text{RhCl}_2\text{Cp}^*]_2$  complexes for ATH of a wide variety of ketones, including more challenging trifluoromethyl ketones, propargylic and alkyl alkyl ketones. In general, when the optimized ligand was selected, excellent enantioselectivities (95 to >99% ee) were observed for a broad range of ketones. Moreover, tandem isomerization/ATH reactions of racemic allylic alcohols by using  $\text{Ru}/\text{L21a}$  yields chiral aryl alkyl alcohols in excellent ee. In addition, tandem  $\alpha$ -alkylation/ATH of arylketones with various primary alcohols was also investigated to release the corresponding chiral alcohols in good to high enantioselectivities (70–92%), albeit with low yields (10–41%) (Scheme 42).<sup>99</sup>

<sup>98</sup> Altan, O.; Yilmaz, M. K. *J. Organomet. Chem.* **2018**, *861*, 252.

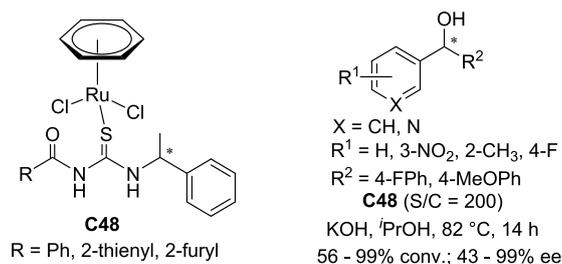
<sup>99</sup> (a) Margalef, J.; Slagbrand, T.; Tinnis, F.; Adolfsson, H.; Diéguez, M.; Pàmies, O. *Adv. Synth. Catal.* **2016**, *358*, 4006. (b) Margalef, J.; Pàmies, O.; Diéguez, M. *Tetrahedron Lett.* **2016**, *57*, 1301.



Scheme 42

### 2.1.5 Sulfur containing ligands

A new type of chiral acyl/aryloyl thioureas containing [RuCl<sub>2</sub>( $\eta^6$ -benzene)] complexes **C48** were reported in 2015 and used in the ATH of aromatic ketones to access chiral aryl alcohols in moderate to excellent enantioselectivities (43–99%) (Scheme 43).<sup>100</sup>



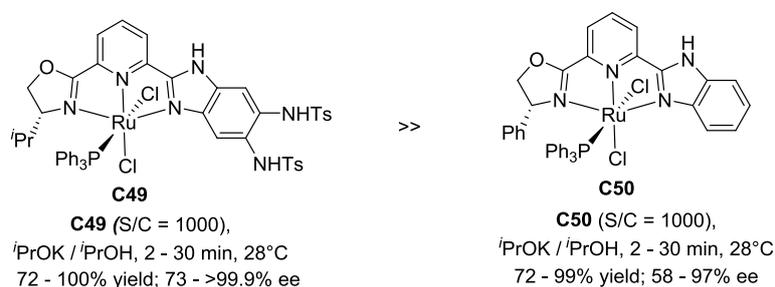
Scheme 43

### 2.1.6 Heterocyclic ligands

In 2017, Yu *et al.* described a series of new Ru(II)-*N,N,N* complexes **C49** containing a chiral pincer type ligand with a chiral (NHTs)<sub>2</sub>-substituted imidazolyl-oxazolynyl-pyridine

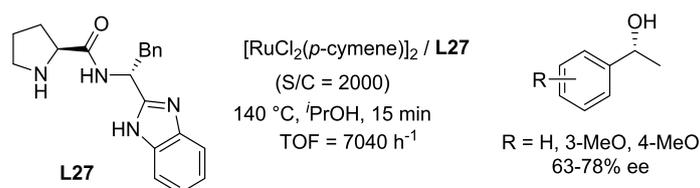
<sup>100</sup> Mary Sheeba, M.; Preethi, S.; Nijamudheen, A.; Muthu Tamizh, M.; Datta, A.; Farrugia, L. J.; Karvembu, R. *Catal. Sci. Tech.* **2015**, *5*, 4790.

moiety. By comparison with the non-substituted Ru(II)-*N,N,N* complex **C50**,<sup>101</sup> a remarkable NHTs effect was observed for the (NHTs)<sub>2</sub>-substituted Ru(II)/*N,N,N* precatalyst **C49** in the ATH of ketones since higher enantiomeric excesses were obtained (Scheme 44).<sup>102</sup>



Scheme 44

Chiral amino acid derived benzylimidazole **L27** was synthesized and evaluated in Ru(II)-catalyzed ATH of acetophenone to efficiently provide the chiral alcohols with ees ranging from 63 to 78% using a low catalyst loading (S/C = 2000) (Scheme 45).<sup>103</sup>



Scheme 45

### 2.1.7 Other type of chiral Ru complexes

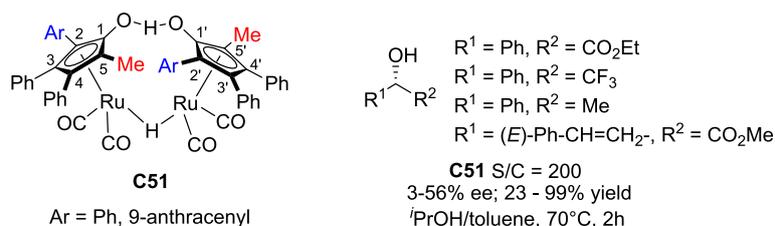
A new type of planar chiral Shvo's catalysts with various substituents next to the Cp-OH moiety was prepared. The chiral Ru(II) complex **C51** bearing 9-anthracenyl- and methyl- next to Cp-OH ring was efficient for the enantioselective transfer hydrogenation of activated ketones, such as trifluoromethyl ketone,  $\alpha$ -keto ester, and  $\beta,\gamma$ -unsaturated  $\alpha$ -keto ester, providing the highest enantioselectivity (up to 56% ee) described so far for chiral Shvo's catalysts (Scheme 46).<sup>104</sup>

<sup>101</sup> Ye, W. J.; Zhao, M.; Du, W. M.; Jiang, Q. B.; Wu, K. K.; Wu, P.; Yu, Z. K. *Chem. Eur. J.* **2011**, *17*, 4737.

<sup>102</sup> Chai, H.; Liu, T.; Yu, Z.. *Organometallics* **2017**, *36*, 4136.

<sup>103</sup> Li, X. -N.; Wang, L. -H.; Zhou, H. -Y.; Wang, J. -X. *Chin. J. Org. Chem.* **2016**, *36*, 2175.

<sup>104</sup> Dou, X.; Hayashi, T. *Adv. Synth. Catal.* **2016**, *358*, 1054.

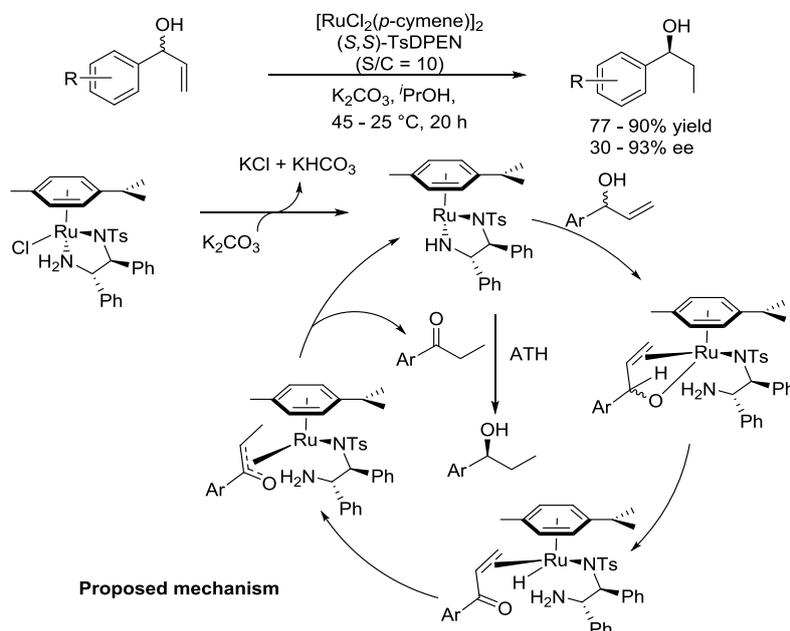


### Scheme 46

A new type of artificial metalloenzymes was developed involving combination of several organometallic complexes  $\{[\text{RuCl}_2(\text{benzene})]_2, [\text{RuCl}_2(p\text{-cymene})]_2, [\text{RuCl}_2(\text{mesitylene})]_2, [\text{RhCl}_2\text{Cp}^*]_2, [\text{IrCl}_2\text{Cp}^*]_2\}$  with proteins (bovine  $\beta$ -lactoglobulin ( $\beta$ LG) or hen egg white lysozyme) as chiral macromolecular ligands. Among the protein-based metal complexes,  $[\text{RuCl}(\text{benzene})(\beta\text{LG})]$  complex displayed good catalytic activities and enantioselectivities for ATH of various aromatic ketones.<sup>105</sup>

## 2.2 Tandem reactions using Ruthenium catalysts

Sowa *et al.* reported the preparation of optically active secondary alcohols through a combined Ru-catalyzed isomerization<sup>106</sup>/ATH reaction. The corresponding alcohols were obtained in yields up to 97% with up to 93% enantiomeric excess (Scheme 47).<sup>107</sup>



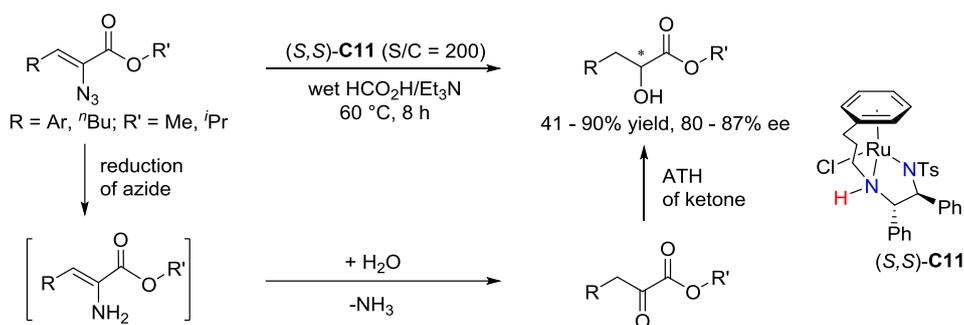
<sup>105</sup> Cazares-Marinero, J. de J.; Przybylski, C.; Salmain, M. *Eur. J. Inorg. Chem.* **2018**, 1383.

<sup>106</sup> (a) Uma, R.; Crevisy, C.; Gree, R. *Chem. Rev.* **2003**, *103*, 27; (b) van der Drift, R. C.; Bouwman, E.; Drent, E. *J. Organomet. Chem.* **2002**, *650*, 1; (c) Arai, N.; Sato, K.; Azuma, K.; Ohkuma, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 7500; (d) Mantilli, L.; Mazet, C. *Chem. Lett.* **2011**, *40*, 341; (e) Watson, A. J. A.; Atkinson, B. N.; Maxwell, A. C.; Williams, J. M. J. *Adv. Synth. Catal.* **2013**, *355*, 734.

<sup>107</sup> Shoola, C. O.; DelMastro, T.; Wu, R.; Sowa, J. R. *Eur. J. Org. Chem.* **2015**, 1670.

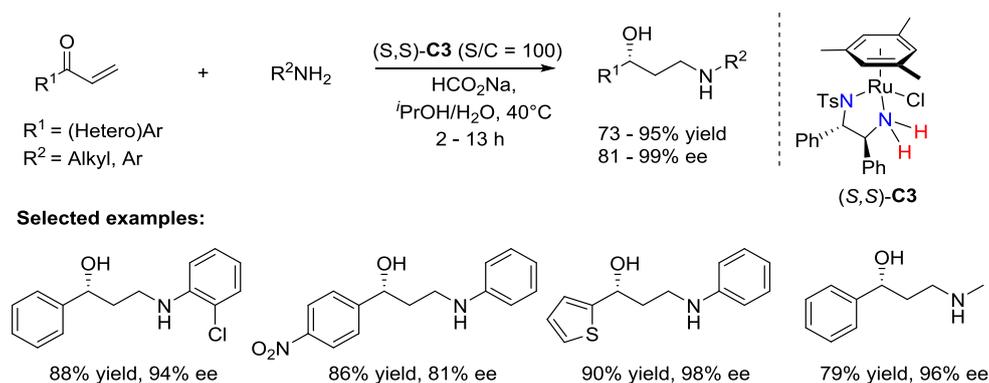
## Scheme 47

Another route was described to access chiral  $\alpha$ -hydroxy esters through reduction of  $\alpha$ -azido acrylates by using teth-Ru-TsDPEN complex (*S,S*)-**C11** as a catalyst in the presence of wet  $\text{HCO}_2\text{H}/\text{Et}_3\text{N}$  as the hydrogen source. This three-step sequence includes azide reduction, enamine hydrolysis and ATH of ketones to deliver the products in good to excellent enantioselectivities (Scheme 48).<sup>108</sup>



## Scheme 48

In 2017, Liu's group reported complex (*S,S*)-**C3**-catalyzed Michael-ATH tandem reaction for the one-pot transformation of a series of enones to efficiently access chiral (*R*)-secondary amino alcohols under mild conditions. This practical process produced the corresponding amino alcohols with 73–95% yields and up to 99% ees and provided another way for the synthesis of chiral antidepressants (Scheme 49).<sup>109</sup>



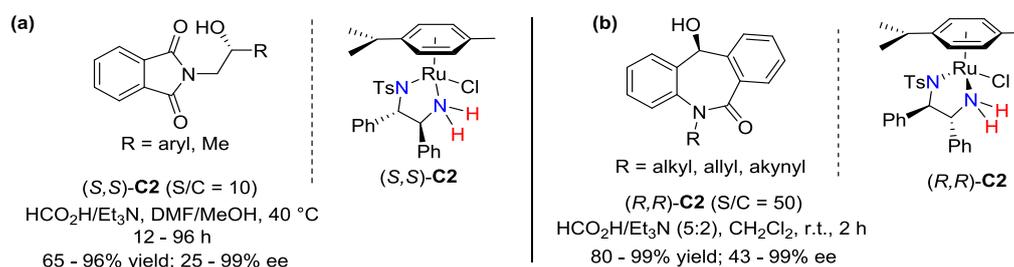
## Scheme 49

<sup>108</sup> Ji, Y.; Xue, P.; Ma, D.-D.; Li, X.-Q.; Gu, P.; Li, R. *Tetrahedron Lett.* **2015**, *56*, 192.

<sup>109</sup> Wu, L.; Jin, R.; Li, L.; Hu, X.; Cheng, T.; Liu, G. *A Org. Lett.* **2017**, *19*, 3047.

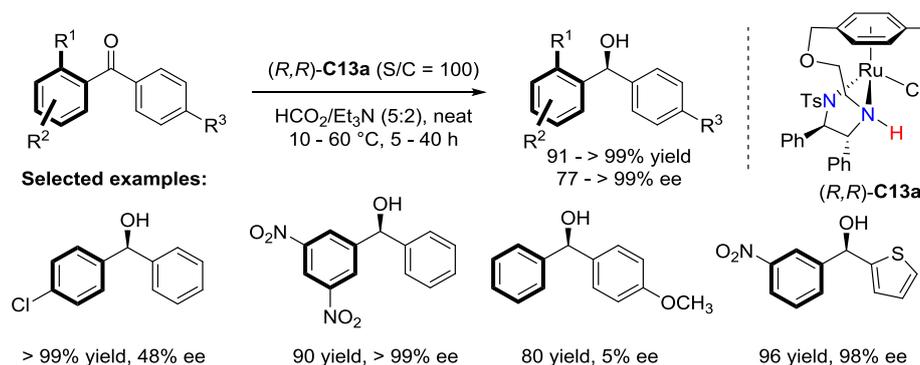
## 2.3 ATH of functionalized ketone derivatives with Ruthenium catalysts

Liu *et al* reported, in 2015, complex (*S,S*)-**C2**-catalyzed ATH of  $\alpha$ -phthalimido ketones with the mixture of HCO<sub>2</sub>H/Et<sub>3</sub>N to yield the corresponding amino alcohols in high yields and excellent enantioselectivities (Scheme 50a).<sup>110</sup> In 2016, Bhanage *et al.* reported the use of complex **C2** in ATH of *N*-alkylated dibenzo [*b,e*]-azepine-6,11-dione by using HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) to provide the corresponding alcohols with fair to excellent enantioselectivities. (43→ 99% ee) (Scheme 50b).<sup>111</sup>



Scheme 50

Touge, Kayaki *et al.* first reported in 2016, an oxo-containing tethered Ru(II) complex (*R,R*)-**C13a** used in the ATH of a wide variety of unsymmetrical benzophenones to access chiral diarylmethanols with high yields (up to >99%) and enantioselectivities (up to > 99% ee). The high enantioinductions can be explained by the discrimination for substituents at the *ortho* position on the aryl group, as well as the differentiation between electron-poor and electron-rich arene rings (Scheme 51).<sup>112</sup>



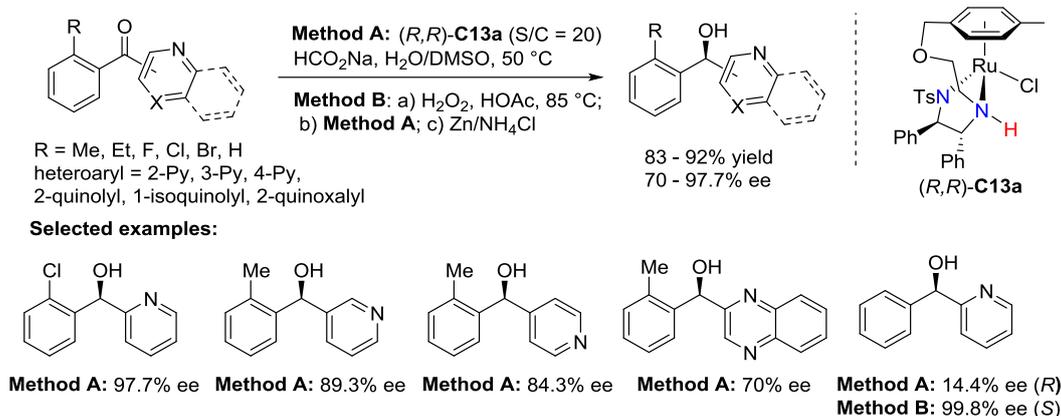
Scheme 51

<sup>110</sup> Xu, Z.; Li, Y.; Liu, J.; Wu, N.; Li, K.; Zhu, S.; Zhang, R.; Liu, Y. *Org. Biomol. Chem.* **2015**, *13*, 7513.

<sup>111</sup> Vyas, V. K.; Bhanage, B. M. *Org. Chem. Front.* **2016**, *3*, 614.

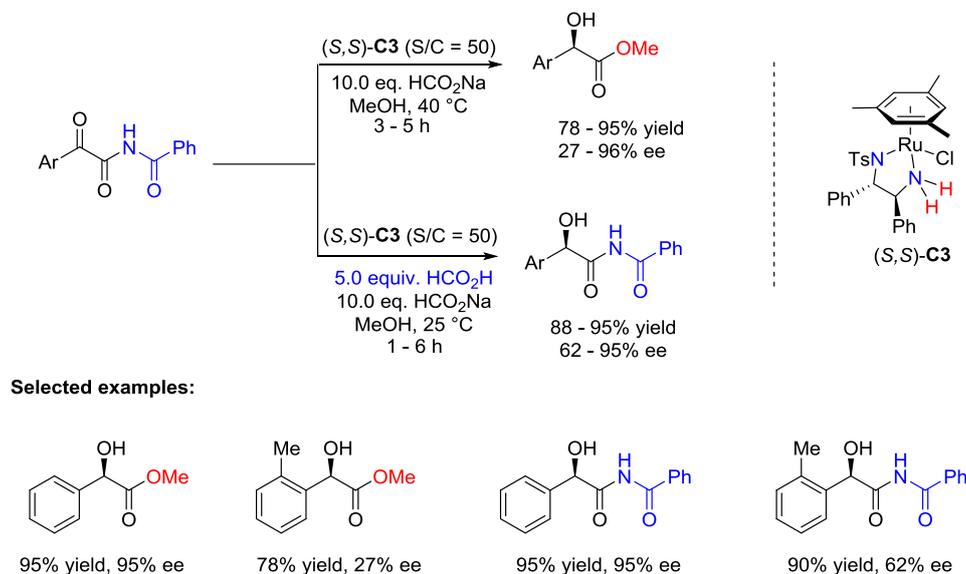
<sup>112</sup> Touge, T.; Nara, H.; Fujiwhara, M.; Kayaki, Y.; Ikariya, T. *J. Am. Chem. Soc.* **2016**, *138*, 10084.

In 2017, Zhou *et al.* described an efficient approach to access a variety of chiral aryl *N*-heteroaryl methanols through commercially available bifunctional oxo-tethered ruthenium complex (*R,R*)-**C13a**-catalyzed ATH of the corresponding *ortho*- or non-*ortho*-substituted ketones in an aqueous solution, leading to the reduced products in high yields (83–92%) and enantioinductions (70–97.7% ee) (Scheme 52).<sup>113</sup>



Scheme 52

In 2016, Liu *et al.* described ATH of  $\alpha$ -ketoimides catalyzed by Ru(II) complex (*S,S*)-**C3** to produce a wide variety of aromatic chiral  $\alpha$ -hydroxy imides (88–95% yield, 62–95% ee) or  $\alpha$ -hydroxy esters (78–95% yield, 27–96% ee) through a slight adjustment of the reaction conditions (Scheme 53).<sup>114</sup>

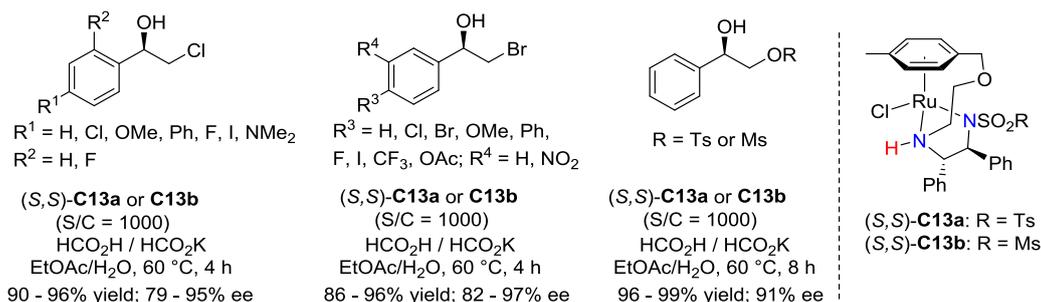


Scheme 53

<sup>113</sup> Wang, B.; Zhou, H.; Lu, G.; Liu, Q.; Jiang, X. *Org. Lett.* **2017**, *19*, 2094.

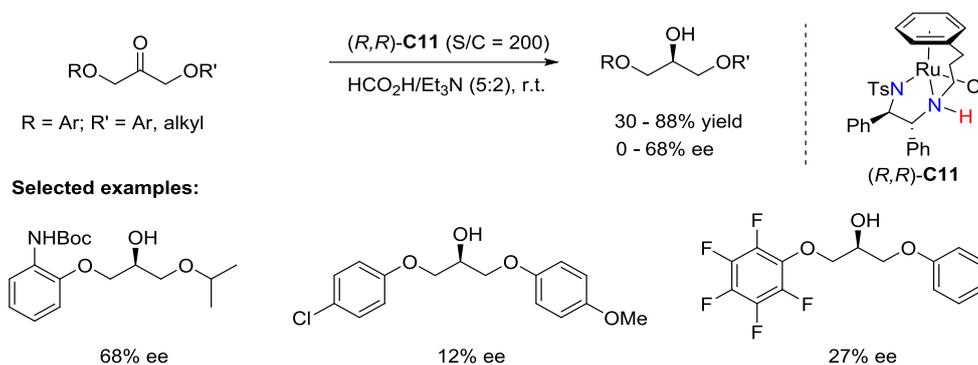
<sup>114</sup> Zhao, Q.; Zhao, Y.; Liao, H.; Cheng, T.; Liu, G. *ChemCatChem* **2016**, *8*, 412.

In 2017, Kayaki, Yuki *et al.* developed an effective system for the ATH of  $\alpha$ -substituted (Br, Cl, OMs, OTs) aromatic ketone derivatives in the presence of (*S,S*)-**C13a** and (*S,S*)-**C13b** by using HCO<sub>2</sub>H/HCO<sub>2</sub>K in aqueous EtOAc to afford a wide variety of  $\alpha$ -substituted chiral secondary alcohols in high yields (86–98%) and good to excellent enantioselectivities (79–97% ee). The useful  $\alpha$ -functionalized chiral alcohols allow further transformations. This system is more practical and selective than previously reported approaches,<sup>115</sup> which led to byproducts (Scheme 54).<sup>116</sup>



Scheme 54

In 2017, Wills *et al.* reported the ATH of a number of propanones bearing aryloxy and alkoxy substituents at the 1- and 3-positions using the Ru(II)/TsDPEN tethered complex **C11**. The enantioselectivity of the reduction was highly dependent of the combination of steric and electronic effects for this challenging type of substrates, and ees up to 68% ee could be attained (Scheme 55).<sup>117</sup>



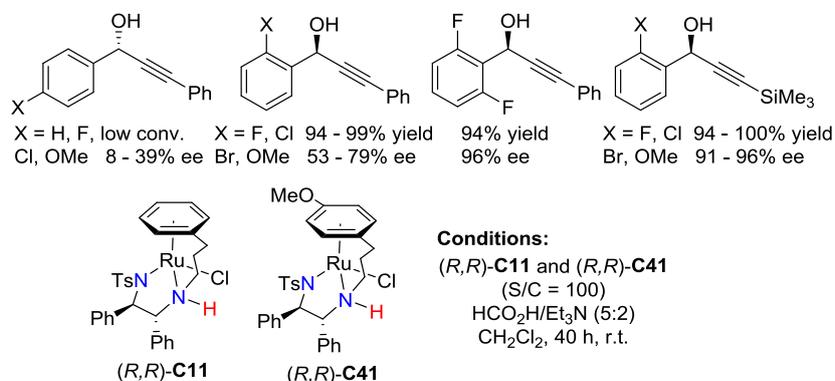
Scheme 55

<sup>115</sup> (a) Ma, Y.; Liu, H.; Chen, L.; Cui, X.; Zhu, J.; Deng, J. *Org. Lett.* **2003**, *5*, 2103. (b) Komiyama, M.; Itoh, T.; Takeyasu, T. *Org. Process Res. Dev.* **2015**, *19*, 315.

<sup>116</sup> Yuki, Y.; Touge, T.; Nara, H.; Matsumura, K.; Fujiwhara, M.; Kayaki, Y.; Ikariya, T. *Adv. Synth. Catal.* **2017**, *360*, 568.

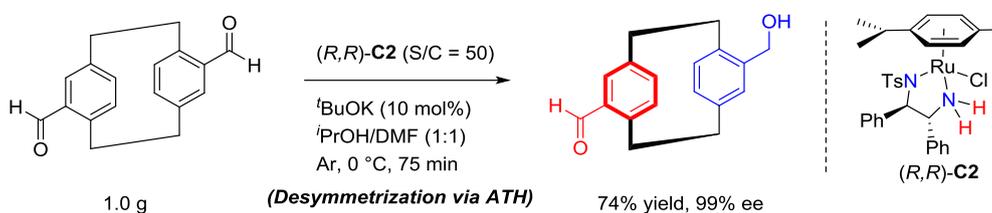
<sup>117</sup> Forshaw, S.; Matthews, A. J.; Brown, T. J.; Diorazio, L. J.; Williams, L.; Wills, M. *Org. Lett.* **2017**, *19*, 2789.

A number of hindered aryl propargylic ketones were transformed into the corresponding chiral aryl propargylic alcohols in high yields and moderate to excellent enantioselectivities through an ATH process with tethered Ru(II) complexes **C11** and **C41** as catalysts in the presence of HCO<sub>2</sub>H/Et<sub>3</sub>N as the hydrogen source (Scheme 56).<sup>118</sup>



Scheme 56

In 2018, Benedetti and Micouin *et al.* reported the use of Noyori's catalyst (R,R)-**C2** in the desymmetrization of a centrosymmetric pseudo-para-diformyl[2.2]paracyclophane via ATH. A monohydroxymethylated product was obtained in good yields and excellent enantioselectivities (up to 74% isolated yield and 99% ee) during the gram scale experiment without any significant loss in the reaction efficiency (Scheme 57).<sup>119</sup>



Scheme 57

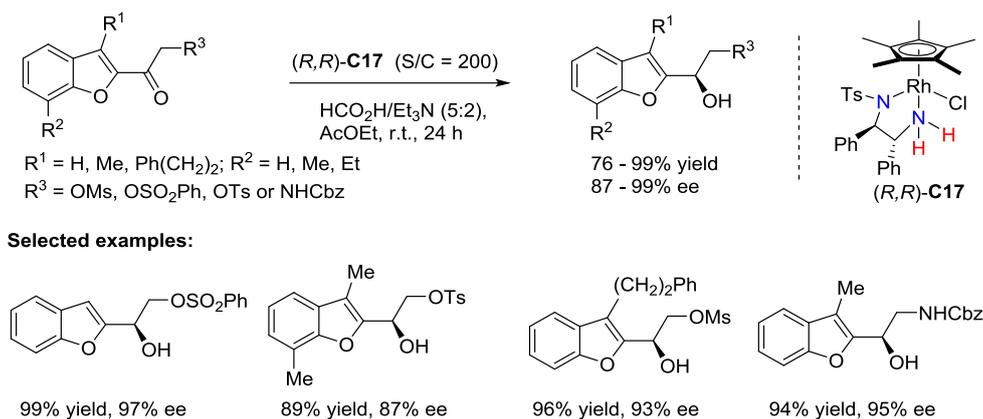
## 2.4 Rhodium catalysts

In 2017, Tafelska-Kaczmarek *et al.* reported the use of [RhClCp\*(R,R)-TsDPEN] complex (R,R)-**C17** in the ATH of benzofuryl  $\alpha$ -sulfonyloxy ketones and *N*-protected  $\alpha$ -amino ketones by using HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) to give the corresponding alcohols in high yields and high enantioselectivities (Scheme 58).<sup>120</sup>

<sup>118</sup> Vyas, V. K.; Knighton, R. C.; Bhanage, B. M.; Wills, M. *Org. Lett.* **2018**, *20*, 975.

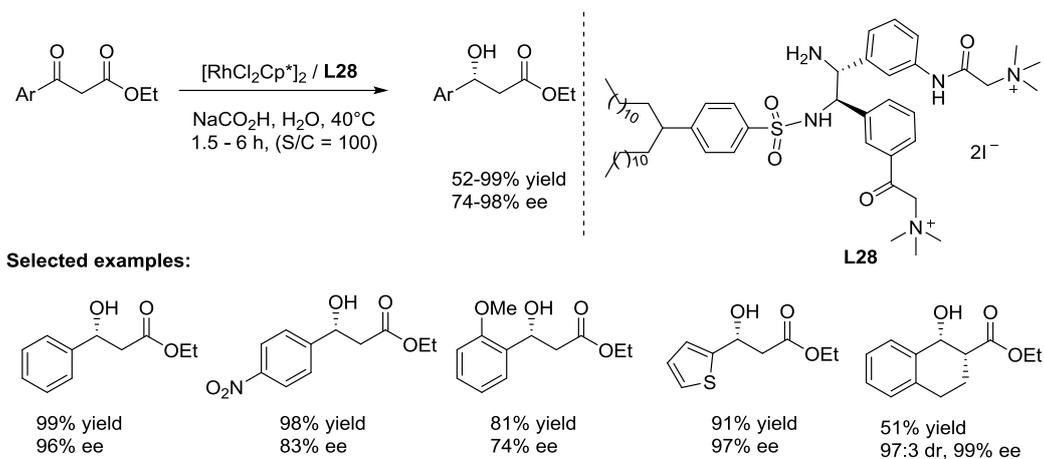
<sup>119</sup> Delcourt, M.-L.; Felder, S.; Benedetti, E.; Micouin, L. *ACS Catal.* **2018**, *8*, 6612.

<sup>120</sup> Tafelska-Kaczmarek, A.; Krzemiński, M. P.; Ćwiklińska, M. *Tetrahedron* **2017**, *73*, 3883.



Scheme 58

In 2017, Deng *et al.* used  $[\text{RhCl}_2\text{Cp}^*]_2$  complex combined with a new chiral double-chain surfactant-type ligand **L28** to form the catalyst *in situ*, which can self-assemble into chiral vesicular aggregates in water. The catalyst was highly efficient for the ATH of various aromatic  $\beta$ -ketoesters, with yields from 52 to 99% and good to excellent enantioselectivities (74–99% ee). In addition, this double-chain surfactant-type catalyst could also be applied to the dynamic kinetic resolution of bicyclic  $\beta$ -ketoesters in water (Scheme 59).<sup>121</sup>



Scheme 59

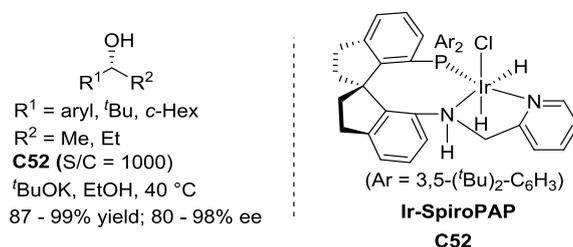
## 2.5 Iridium catalysts

A chiral spiro iridium complex (**Ir-SpiroPAP**) **C52** was developed, by Zhou's group, for the ATH of various alkyl aryl ketones to provide chiral alcohols in high yields and excellent enantioselectivities (Scheme 60).<sup>122</sup> The same group synthesized an efficient iridium complex **C53** used in the ATH of alkynyl ketones to deliver optically active propargylic alcohols. By

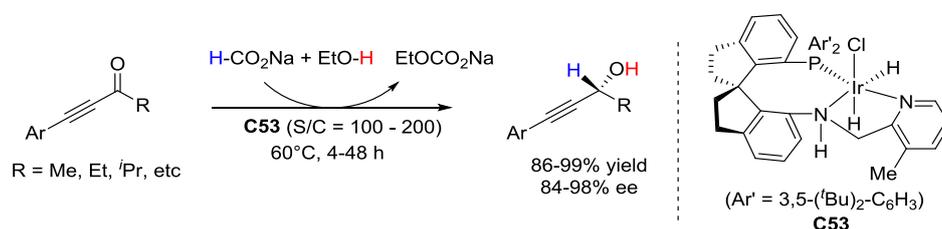
<sup>121</sup> Li, J.; Lin, Z.; Huang, Q.; Wang, Q.; Tang, L.; Zhu, J.; Deng, J. *Green Chem.* **2017**, *19*, 5367.

<sup>122</sup> Liu, W.-P.; Yuan, M.-L.; Yang, X.-H.; Li, K.; Xie, J.-H.; Zhou, Q.-L. *Chem. Commun.* **2015**, *51*, 6123.

using sodium formate and ethanol, a broad range of alkynyl ketones were hydrogenated to provide a practical and sustainable approach to access enantioenriched propargylic alcohols with up to 98% ee under base-free conditions (Scheme 61).<sup>123</sup>

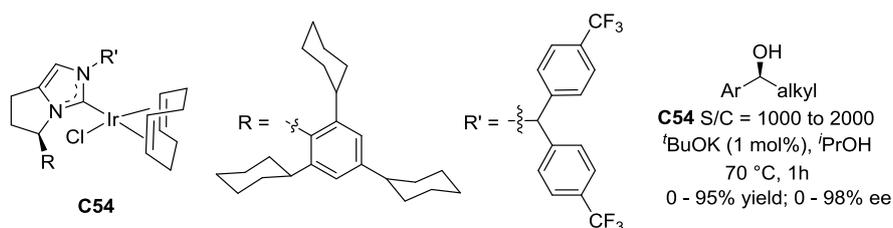


Scheme 60



Scheme 61

An air-stable and efficient NHC/Ir complex **C54** was developed for the asymmetric transfer hydrogenation of aryl alkyl ketones by using isopropanol as a hydrogen donor in the presence of  $^t\text{BuOK}$ . The enantioenriched alcohols were obtained in up to 95% yields and up to 98% ee (Scheme 62).<sup>124</sup>



Scheme 62

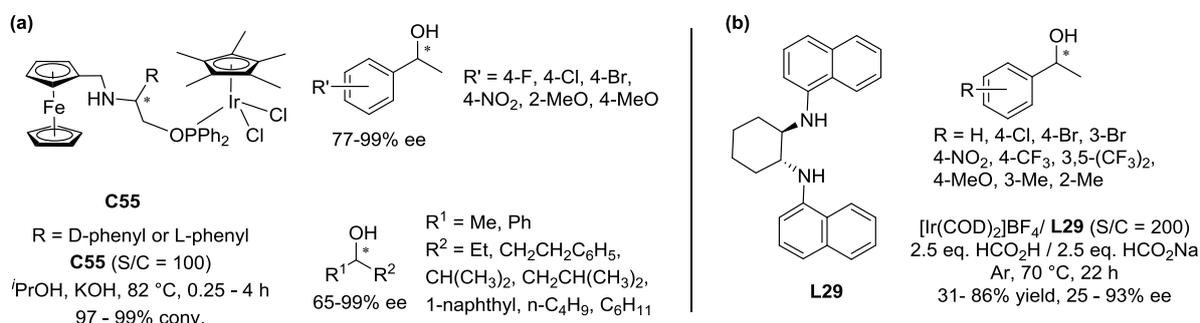
A series of ferrocenyl-phosphinite ligands was developed and used to prepare Ir(III) complexes **C55**. The latter were evaluated in the ATH of a wide range of ketones to provide the corresponding alcohols with high conversions (97–99%) and enantioselectivities ranging from 65 to 99% ee (Scheme 63a).<sup>125</sup> Chiral *N,N'*-diaryl-*trans*-1,2-diamino-cyclohexane ligand **L29** was prepared through Pd(II)-catalyzed dehydrogenative alkylation of chiral diamine with

<sup>123</sup> Zhang, Y.-M.; Yuan, M.-L.; Liu, W.-P.; Xie, J.-H.; Zhou, Q.-L. *Org. Lett.* **2018**, *20*, 4486.

<sup>124</sup> Yoshida, K.; Kamimura, T.; Kuwabara, H.; Yanagisawa, A. *Chem. Commun.* **2015**, *51*, 15442.

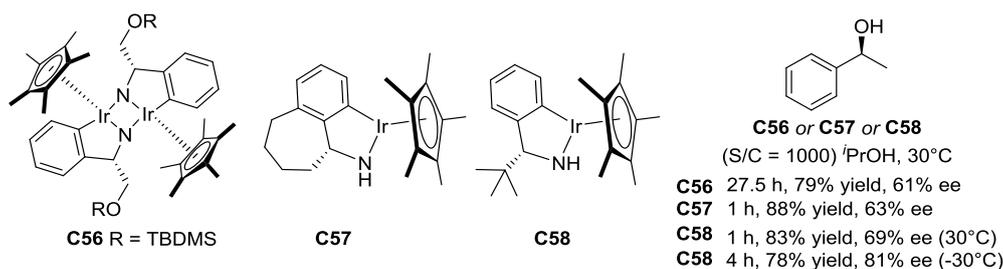
<sup>125</sup> Meriç, N.; Aydemir, M. *J. Organomet. Chem.* **2016**, *819*, 120.

cyclohexanone derivative. Moreover, the chiral aryl diamine ligand **L29** was applied for the Ir(III)-catalyzed ATH of a range of aromatic ketones with yields ranging from 96 to 100% and 52–86% ees (Scheme 63b).<sup>126</sup>



Scheme 63

In 2016, Ikariya *et al.* developed a series of new amido-bridged dinuclear Ir complex **C56** and mononuclear amido Ir complexes **C57** and **C58**, which were evaluated in the ATH of acetophenone to provide the corresponding alcohol with 61–69% ee values (Scheme 64).<sup>127</sup>



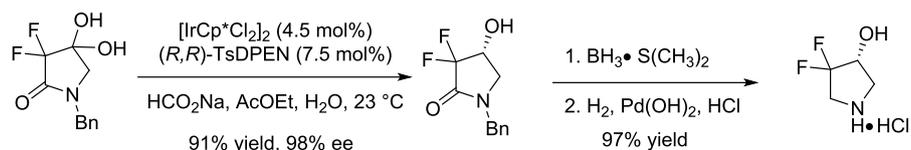
Scheme 64

A new route to (*R*)-4,4-difluoropyrrolidin-3-ol, an important building block in medicinal chemistry, was developed through ATH of *gem*-difluoro substituted benzylpyrroline-2,4-dione. The corresponding alcohol was obtained in 91% yield and 98% ee, and subsequent reduction/deprotection steps afforded the key product in good overall yield. This method avoids the use of potentially hazardous deoxofluorinating reagents and may be scalable (Scheme 65).<sup>128</sup>

<sup>126</sup> El-Asaad, B.; Guicheret, B.; Méta, E.; Karamé, I.; Lemaire, M. *J. Mol. Catal. A. Chem.* **2016**, *411*, 196.

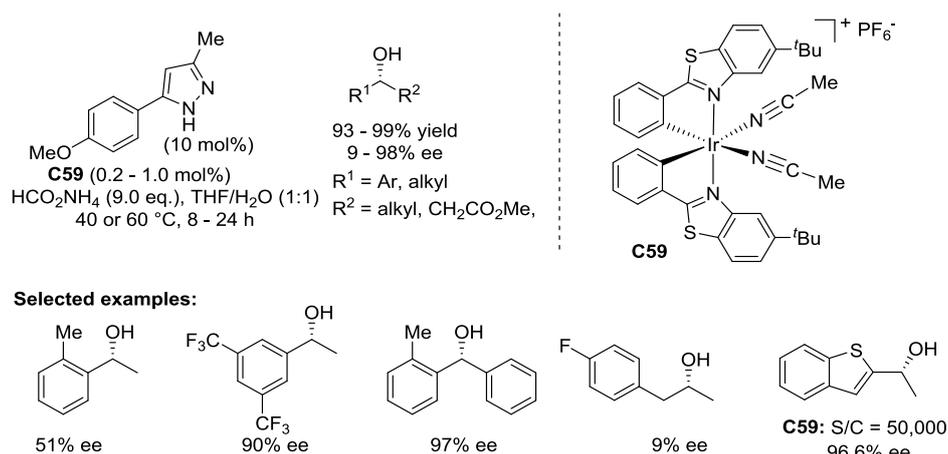
<sup>127</sup> Sato, Y.; Kayaki, Y.; Ikariya, T. *Chem. Asian J.* **2016**, *11*, 2924.

<sup>128</sup> Si, C.; Fales, K. R.; Torrado, A.; Frimpong, K.; Kaoudi, T.; Vandevveer, H. G.; Njoroge, F. G. *J. Org. Chem.* **2016**, *81*, 4359.



Scheme 65

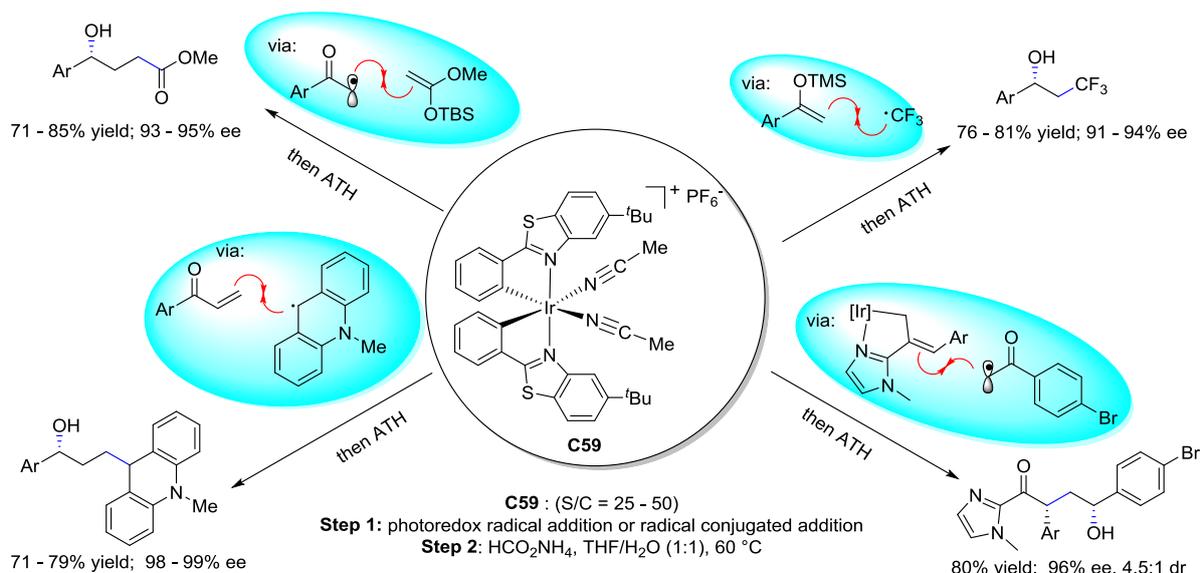
In 2016, Meggers, Gong *et al.* reported the ATH of a variety of (het)aryl and alkyl ketones using a bis-cyclometalated Ir(III) complex **C59** with metal-centered chirality in the presence of  $\alpha$ -substituted pyrazole as a co-ligand. 93–99% yields and 9–98% ees were obtained for the corresponding alcohols. A catalyst loading as low as S/C = 50,000 could be used (Scheme 66).<sup>129</sup> The same group reported, in 2018, several tandem processes by using different photoredox reactions, such as radical addition or radical conjugated addition, to generate ketone intermediates in sequence with the ATH to produce the corresponding enantioenriched alcohols (Scheme 67).<sup>130</sup>



Scheme 66

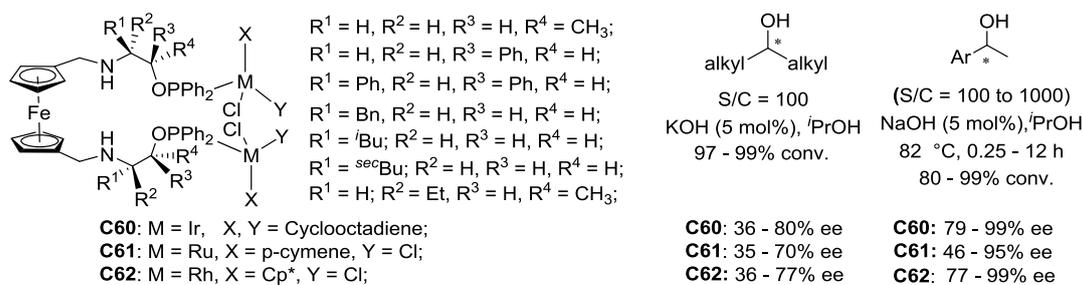
<sup>129</sup> Tian, C.; Gong, L.; Meggers, E. *Chem. Commun.* **2016**, 52, 4207.

<sup>130</sup> Zhang, X.; Qin, J.; Huang, X.; Meggers, E. *Eur. J. Org. Chem.* **2018**, 571.



Scheme 67

A library of Ir(III) (**C60**), but also Ru(II) (**C61**) and Rh(III) (**C62**) precatalysts were generated from C<sub>2</sub>-symmetric ferrocenyl phosphinite ligands and these catalysts were evaluated in the ATH of a broad range of aromatic ketones in the presence of isopropanol as the hydrogen source. High conversions (97–>99%) and enantioselectivities ranging from 46 to 99% were obtained. Furthermore, more challenging alkyl alkyl ketones were also investigated and a broad range of chiral alkyl alcohols were obtained in moderate to high enantioselectivities (35–80% ees) (Scheme 68).<sup>131</sup>

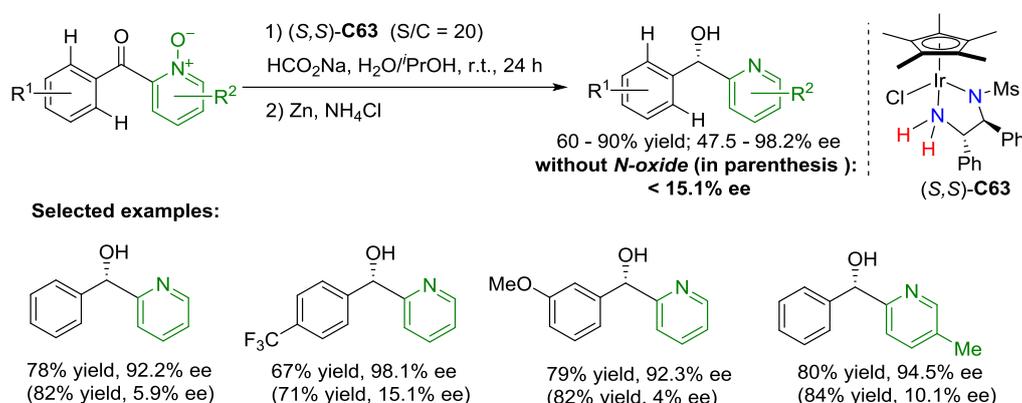


Scheme 68

Ir(III)-MsDPEN complex **C63** was used in the ATH of a range of non-*ortho*-substituted aryl *N*-heteroaryl ketones bearing *N*-oxide as a removable *ortho*-substituent. The reaction was conducted in the presence of sodium formate in aqueous isopropanol to provide the

<sup>131</sup> (a) Ak, B.; Aydemir, M.; Durap, F.; Meriç, N.; Baysal, A. *Inorganica Chimica Acta* **2015**, *438*, 42. (b) Ak, B.; Durap, F.; Aydemir, M.; Baysal, A. *Applied Organomet. Chem.* **2015**, *29*, 764. (c) Ak, B.; Aydemir, M.; Durap, F.; Meriç, N.; Elma, D.; Baysal, A. *Tetrahedron: Asymmetry* **2015**, *26*, 1307. (d) Durap, F.; Karakaş, D. E.; Ak, B.; Baysal, A.; Aydemir, M. *J. Organomet. Chem.* **2016**, *818*, 92. (e) Baysal, A.; Karakaş, D. E.; Meriç, N.; Ak, B.; Aydemir, M.; Durap, F. *Transit. Met. Chem.* **2017**, *42*, 365.

corresponding chiral aryl *N*-heteroaryl methanols in high yields and excellent enantioselectivities. This study showed that substrates not carrying an *N*-oxide functional group led to lower enantioselectivity (Scheme 69).<sup>132</sup>



Scheme 69

In 2018, Deng and Xiao *et al.* reported a selective approach to prepare *N,C*- or *N,O*-chelated Cp\*Ir(III) complex by reacting [Cp\*IrCl<sub>2</sub>]<sub>2</sub> with methyl (*S*)-2-phenyl-4,5-dihydrooxazole-4-carboxylate in the presence of NaOAc, depending on whether or not water was present in the reaction. Further investigation displayed that the enantioselectivity and the effective HCOOH/amine ratios were considerably influenced by the base additive. The above observations show the importance of ligand coordination mode and using the right base for the ATH reactions.<sup>133</sup>

## 2.6 Iron catalysts

Iron as an inexpensive, non-toxic and environment friendly metal has already been studied with different types of C<sub>2</sub>-symmetric macrocyclic N<sub>2</sub>P<sub>2</sub> and open-chain NPPN chiral ligands for ATH of aryl alkyl ketones, and challenging dialkyl ketones in highly catalytic activities with poor to high enantioselectivities,<sup>134</sup> and the design of novel efficient iron complexes is still ongoing. A well-defined bis(isonitrile) iron(II) complex **C64** containing a C<sub>2</sub>-symmetric diamino (NH)<sub>2</sub>P<sub>2</sub> macrocyclic ligand was described. This Fe(II) complex exhibited effective catalytic activities (catalyst loading S/C = 1000) and excellent enantioselectivities for the ATH of a broad range of aromatic ketones (Scheme 70a).<sup>135</sup> Another type of Fe(II)/*P-NH*-

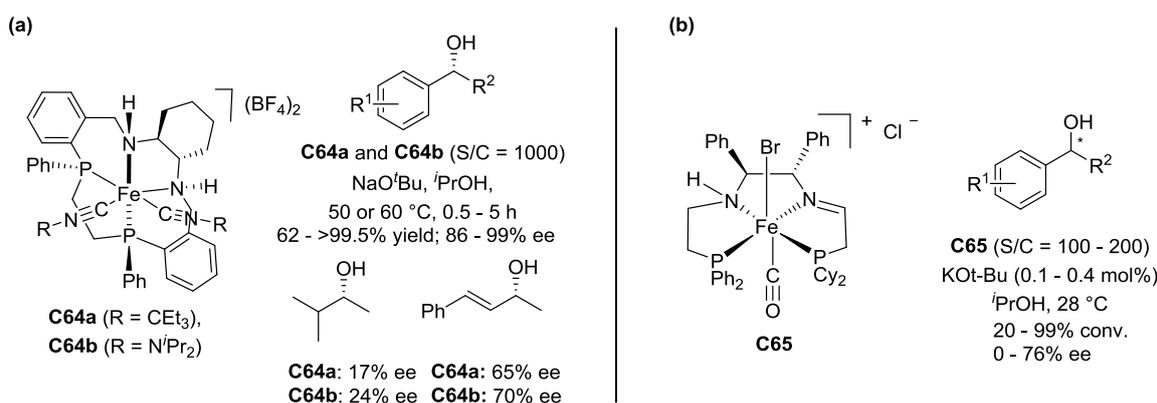
<sup>132</sup> Liu, Q.; Wang, C.; Zhou, H.; Wang, B.; Lv, J.; Cao, L.; Fu, Y. *Org. Lett.* **2018**, *20*, 971.

<sup>133</sup> Zhou, G.; Aboo, A. H.; Robertson, C. M.; Liu, R.; Li, Z.; Luzyanin, K.; Berry, N. G.; Chen, W.; Xiao, J. *ACS Catalysis* **2018**, *8*, 8020.

<sup>134</sup> Bigler, R.; Huber, R.; Mezzetti, A. *Synlett* **2016**, *27*, 831.

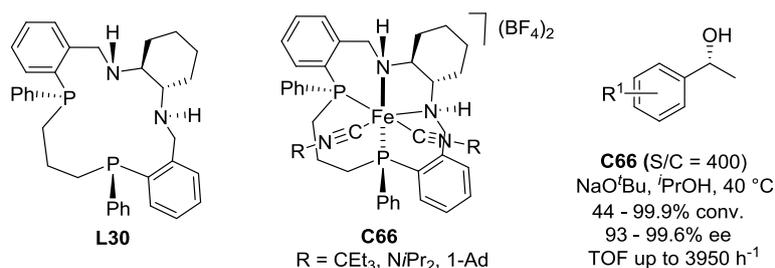
<sup>135</sup> Bigler, R.; Huber, R.; Mezzetti, A. *Angew. Chem. Int. Ed.* **2015**, *54*, 5171.

*N-P'* complex **C65** was designed and examined in the ATH of various simple ketones in the presence of KO<sup>t</sup>Bu/<sup>i</sup>PrOH. The precatalyst displayed high catalytic activity (TON up to 4300) and excellent enantioselectivities (up to 99% ee) (Scheme 70b).<sup>136</sup> Complex **C65** was also investigated for the ATH of simple ketones in biphasic catalytic system employing water as the proton donor and potassium formate as the hydride source to provide enantioenriched alcohols with conversions up to 99% and good enantioselectivities up to 76% ee.<sup>137</sup>



Scheme 70

In 2016, Mezzetti *et al.* described iron complexes [Fe(CNR)<sub>2</sub>((*S<sub>P</sub>,S<sub>P</sub>,S<sub>C</sub>,S<sub>C</sub>)-L30)](BF<sub>4</sub>)<sub>2</sub> **C66** wherein **L30** is a 15-membered (*S<sub>P</sub>,S<sub>P</sub>,S<sub>C</sub>,S<sub>C</sub>)-(NH)<sub>2</sub>P<sub>2</sub> macrocycle ligand bearing a propane-1,3-diyl bridge. The catalyst was evaluated for the ATH of a range of aromatic ketones in the presence of a base under mild conditions to provide enantioenriched alcohols (Scheme 71).<sup>138</sup>**



Scheme 71

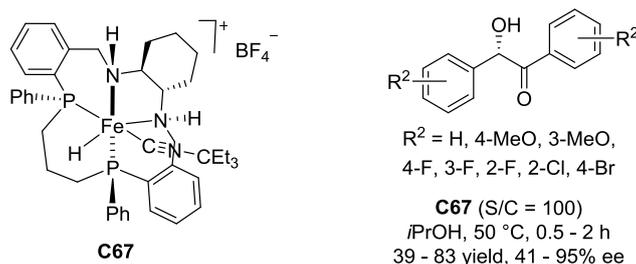
In 2017, they reported a hydride iron(II) complex **C67** which exhibited high selectivity in ATH of a number of benzils to access benzoin with acceptable yields (39–83%) and

<sup>136</sup> Smith, S. A. M.; Morris, R. H. *Synthesis* **2015**, 47, 1775.

<sup>137</sup> Demmans, K. Z.; Ko, O. W. K.; Morris, R. H. *RSC Adv.* **2016**, 6, 88580.

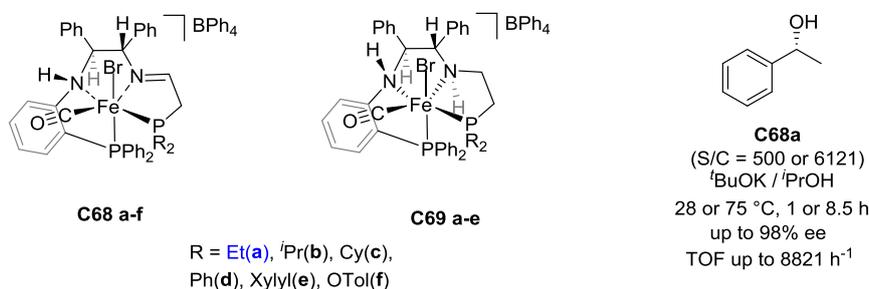
<sup>138</sup> Bigler, R.; Huber, R.; Stöckli, M.; Mezzetti, A. *ACS Catal.* **2016**, 6, 6455.

enantioinductions ranging from 41 to 95% (Scheme 72).<sup>139</sup>



**Scheme 72**

In 2017, Morris *et al.* reported a series of novel *cis*- $\beta$  iron(II) precatalysts **C68a-f**, **C69a-e** bearing a *P,N,N,P'* pincer ligand with a bulky *ortho*-phenylene group and an imine or amine unit. In the ATH of acetophenone, *Cis*- $\beta$  iron(II)/*P,N,N,P* complexes **C69a-e** with an amine ligand displayed higher performances than the imine complexes **C68a-f**, leading to (*S*)-1-phenylethanol with excellent enantioselectivities (up to 98% ee). Furthermore, amine precatalyst **C68a** containing a  $\text{PEt}_2$  part shows a more stable hydride species when activated compared to the other complexes, with powerful catalytic activity (TON = 8821) and high enantioselectivity in the reduction of acetophenone to (*S*)-1-phenylethanol (95% ee) (Scheme 73).<sup>140</sup>



**Scheme 73**

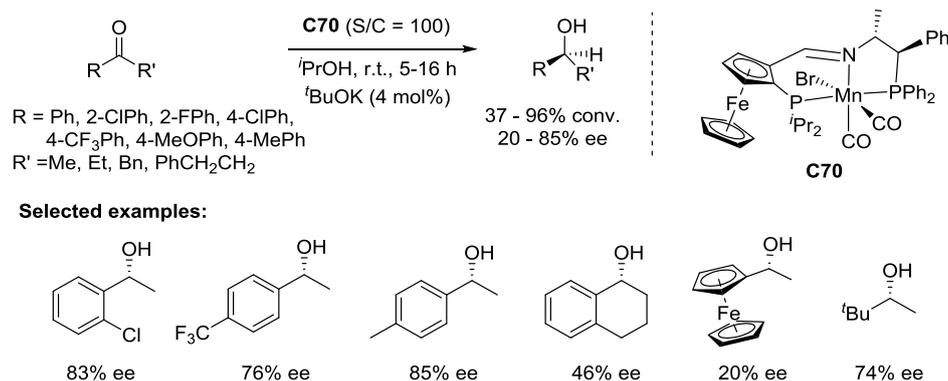
## 2.7 Manganese catalysts

In 2017, Kirchner, Zirakzadeh *et al.* developed a new type of manganese complex  $[\text{Mn}(\text{PNP}')(\text{Br})(\text{CO})_2]$  **C70**. Complex **C70** displayed a good activity and low to high selectivity ranging from 20 to 85% ee for the ATH of aromatic ketones, albeit with low selectivities for 1-tetralone (46% ee) and acetylferrocene (20% ee) (Scheme 74).<sup>141</sup>

<sup>139</sup> De Luca, L.; Mezzetti, A. *Angew. Chem. Int. Ed.* **2017**, *56*, 11949.

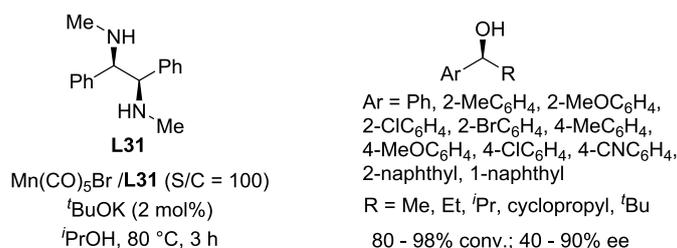
<sup>140</sup> Demmans, K. Z.; Seo, C. S. G.; Lough, A. J.; Morris, R. H. *Chem. Sci.* **2017**, *8*, 6531.

<sup>141</sup> Zirakzadeh, A.; de Aguiar, S. R. M. M.; Stöger, B.; Widhalm, M.; Kirchner, K. *ChemCatChem* **2017**, *9*, 1744.



Scheme 74

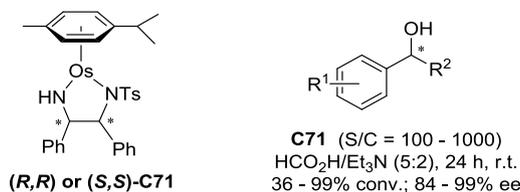
Chiral diamine **L31** was used in combination with  $[\text{Mn}(\text{CO})_5\text{Br}]$  to form *in situ* the corresponding complex which was used in the ATH of ketones in the presence of  $t\text{BuOK}/t\text{PrOH}$  as the hydrogen source. The corresponding chiral alcohols were obtained in conversions up to 98% and enantioselectivities up to 90% (Scheme 75).<sup>142</sup>



Scheme 75

## 2.8 Osmium catalyst

Based on Noyori-Ikariya's catalyst  $[\text{Ru}(\eta^6\text{-arene})(\text{TsDPEN})]$ , a novel type of [osmium(II)/arene/TsDPEN] complex **C71** was developed and evaluated in the ATH of simple aryl ketones in the presence of  $\text{HCO}_2\text{H}/\text{Et}_3\text{N}$ . Chiral alcohols were obtained with conversions up to 99% and enantioselectivities up to 99% (Scheme 76).<sup>143</sup>

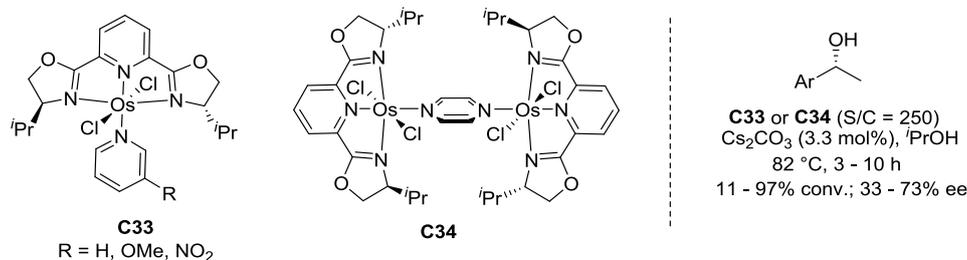


Scheme 76

<sup>142</sup> Wang, D.; Bruneau-Voisine, A.; Sortais, J.-B. *Catal. Commun.* **2018**, *105*, 31 and references cited.

<sup>143</sup> Coverdale, J. P. C.; Sanchez-Cano, C.; Clarkson, G. J.; Soni, R.; Wills, M.; Sadler, P. J. *Chem. Eur. J.* **2015**, *21*, 8043.

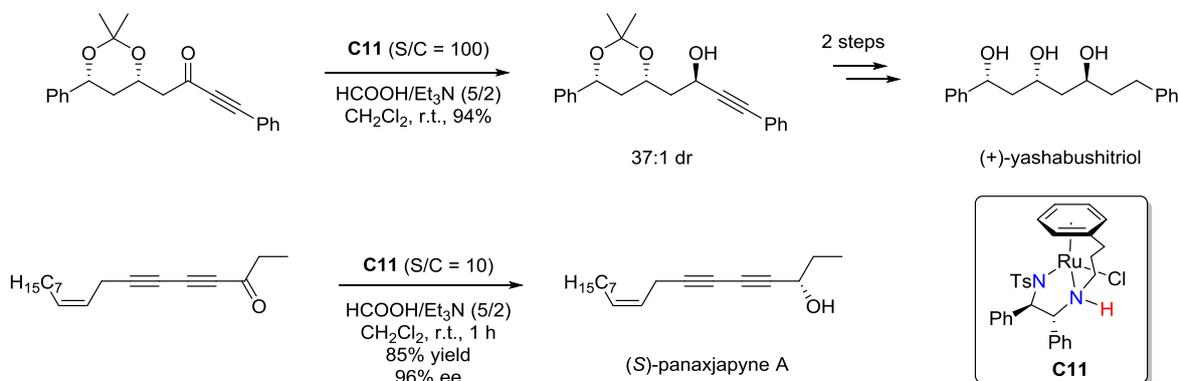
In 2018, Gamasa *et al.* reported various *trans*-[OsCl<sub>2</sub>(L){(*S,S*)-*i*Pr-pybox}] complexes, as well as the dinuclear complexes. The catalytic properties of osmium complexes **C33** and dinuclear complex [(OsCl<sub>2</sub>{(*S,S*)-*i*Pr-pybox})<sub>2</sub>(μ-N,N-C<sub>4</sub>H<sub>4</sub>N<sub>2</sub>)] **C34** have been evaluated in the ATH of a variety of aromatic ketones providing the corresponding (*R*)-benzylalcohols in conversions up to 97% and enantioselectivities up to 73% (Scheme 77).<sup>144</sup>



Scheme 77

### 3. Applications in total synthesis

The tethered complex **C11** described by Will *et al.* was used in the ATH of ketones for several total syntheses. Examples include the synthesis of (+)-yashabushitriol<sup>145</sup> and (*S*)-panaxjapyne A (Scheme 78).<sup>146</sup>



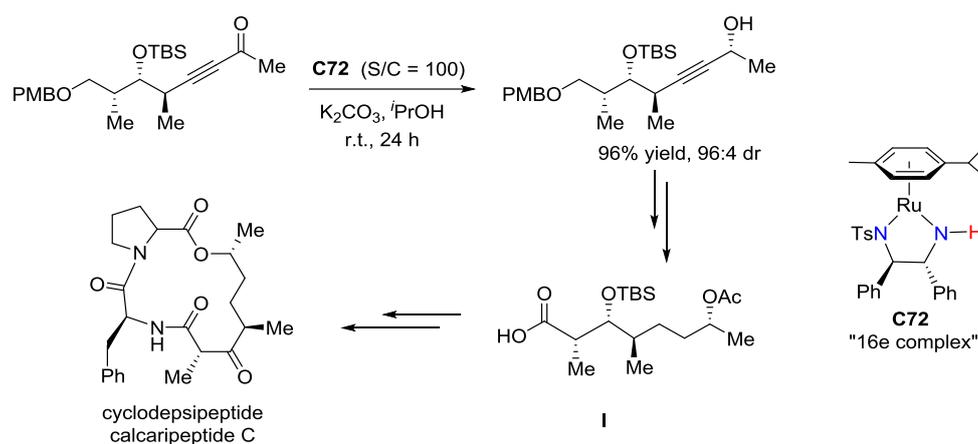
Scheme 78

Ru(II) complex **C72** was used in the ATH of a propargylic ketone bearing multiple stereocenters using *i*PrOH as the hydrogen source under mild conditions to produce the corresponding propargylic alcohol in 96% yield and 94:6 dr. The latter compound was transformed into the key carboxylic acid intermediate **I** for total synthesis of cyclodepsipeptide

<sup>144</sup> de Julián, E.; Fernández, N.; Díez, J.; Lastra, E.; Gamasa, M. P. *Molecular Catalysis* **2018**, 456, 75.

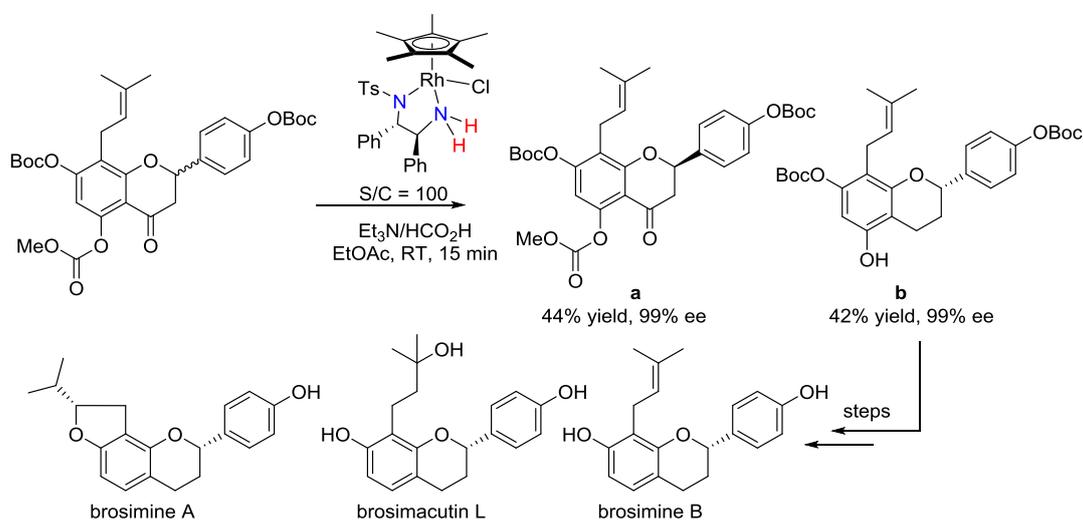
<sup>145</sup> (a) Fang, Z. A.; Clarkson, G. J.; Wills, M. *Tetrahedron Lett.* **2013**, 54, 6834. (b) Fang, Z.; Wills, M. *J. Org. Chem.* **2013**, 78, 8594.

<sup>146</sup> Fang, Z.; Wills, M. *Org. Lett.* **2014**, 16, 374.

calcaripeptide C (Scheme 79).<sup>147</sup>

Scheme 79

In 2016, Metz' group reported a concise and efficient method to access flavonoids brosimine A, brosimine B, and brosimacutin L, starting from commercially available racemic naringenin. The key step was a rhodium-catalyzed ATH/deoxygenation cascade reaction containing a kinetic resolution process to transform flavanone into flavans in high enantioselectivity. After several functional group interconversion reactions, the natural compounds were obtained with >99% ee (Scheme 80).<sup>148</sup>



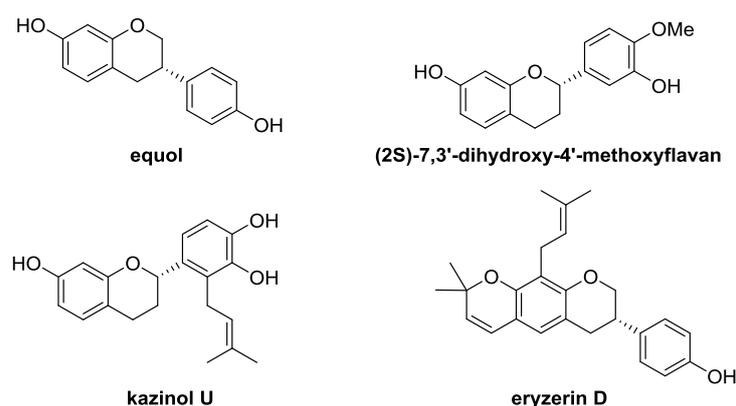
Scheme 80

The same group utilized this strategy of domino rhodium-catalyzed ATH/deoxygenation reaction to synthesize the key intermediates of kazinol U, (2*S*)-7,3'-

<sup>147</sup> Kumaraswamy, G.; Narayanarao, V.; Raju, R. *Org. Biomol. Chem.* **2015**, *13*, 8487.

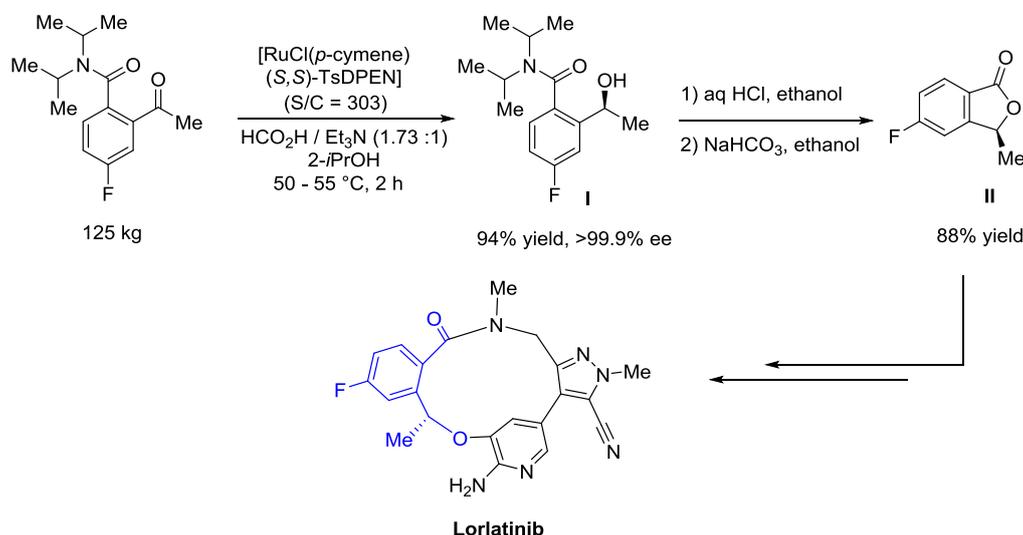
<sup>148</sup> Keßberg, A.; Metz, P. *Angew. Chem. Int. Ed.* **2016**, *55*, 1160.

dihydroxy-4'-methoxyflavan, equol and eryzerin D (Scheme 81).<sup>149,150</sup>



**Scheme 81**

In 2017, Pfizer researchers reported an approach to (*S*)-5-fluoro-3-methylisobenzofuran-1(*3H*)-one, which is the key intermediate of Lorlatinib, an investigational medicine for inhibiting the anaplastic lymphoma kinase (ALK) and ROS1 proto-oncogene. The synthesis relied on the ATH of an *ortho*-diisopropylamide aromatic ketone using [RuCl(*p*-cymene)(*S,S*)-TsDPEN]. The reaction was performed on large scale (125 kg) and gave the corresponding (*S*)-alcohol (**I**) with 94% yield and >99.9% ee. Hydrolysis of the latter allowed the formation of (*S*)-5-fluoro-3-methylisobenzofuran-1(*3H*)-one (**II**) in 88% yield (Scheme 82).<sup>151</sup>



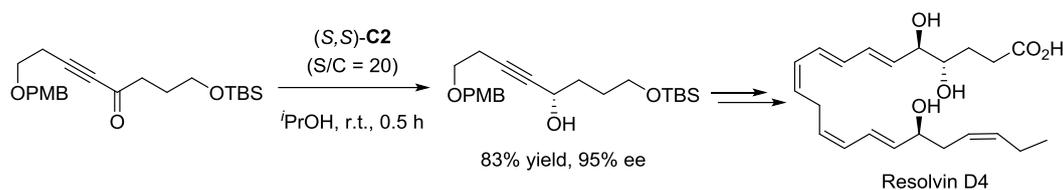
**Scheme 82**

<sup>149</sup> Keßberg, A.; Metz, P. *Org. Lett.* **2016**, *18*, 6500.

<sup>150</sup> Keßberg, A.; Lübken, T.; Metz, P. *Org. Lett.* **2018**, *20*, 3006.

<sup>151</sup> Duan, S.; Li, B.; Dugger, R. W.; Conway, B.; Kumar, R.; Martinez, C.; Makowski, T.; Pearson, R.; Olivier, M.; Colon-Cruz, R. *Org. Process Res. Dev.* **2017**, *21*, 1340.

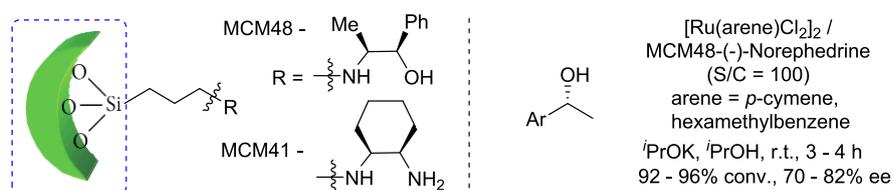
A key intermediate for the total synthesis of Resolvin D4 was prepared through the ruthenium-catalyzed ATH of a propargylic ketone, with 83% yield and 95% ee (Scheme 83).<sup>152</sup>



Scheme 83

## 4. Immobilized catalysts

Cubic mesoporous silica MCM41-supported chiral diamine and MCM-48 silica-supported optically active (-)-norephedrine chiral amino alcohol were prepared and incorporated in Ru(II) complexes for the ATH of aromatic ketones in the presence of *i*PrOK/*i*PrOH as hydrogen source to provide the corresponding alcohols with good enantioselectivities. The supported catalysts could be reused for four times with the same high performance (Scheme 84).<sup>153</sup>



Scheme 84

In 2015, Abu-Reziq described the preparation of magnetically recoverable catalytic silica microcapsules. The catalytic activity of these microreactors was tested in the asymmetric transfer hydrogenation of ketones in an aqueous medium to provide chiral alcohols in high catalytic activities (90–99% conv.) and enantioselectivities (82–99% ee).<sup>154</sup>

In 2016, Reiser *et al.* reported magnetic ATH catalysts based on Noyori's catalyst [RuCl(*R,R*)-TsDPEN], which were assembled on organic/inorganic hybrids containing carbon-coated cobalt nanoparticles (Co/C) and different organic polymers.<sup>155</sup> Hou *et al.* developed a new type of reusable homogeneous catalyst P(DMAPM<sub>1,2</sub>-TsDPEN)-Ru<sub>0.74</sub> catalyst which

<sup>152</sup> Morita, M.; Kobayashi, Y. *J. Org. Chem.* **2018**, *83*, 3906.

<sup>153</sup> (a) Sarkar, S. M.; Yusoff, M. M.; Rahman, M. L. *J. Chin. Chem. Soc.* **2015**, *62*, 177. (b) Sarkar, S. M.; Ali, M. E.; Rahman, M. L.; Mohd Yusoff, M. *J. Nanomater.* **2015**, ID381836

<sup>154</sup> Zoabi, A.; Omar, S.; Abu-Reziq, R. *Eur. J. Inorg. Chem.* **2015**, 2101.

<sup>155</sup> Eichenseer, C. M.; Kastl, B.; Pericàs, M. A.; Hanson, P. R.; Reiser, O. *ACS Sustain. Chem. Eng.* **2016**, *4*, 2698.

showed high levels of activity and enantioinduction in the ATH of the aromatic ketones and recycled for at least eight times without much loss of the catalytic activity.<sup>156</sup>

In 2016, Cheng, Liu *et al.* described a heterogeneous catalyst named Imidazolium@Cp\*RhArDPEN@PMO. The catalyst displayed high catalytic activity and excellent enantioselectivity in the ATH of  $\alpha$ -halo aromatic ketones and benzils in water, and can be recovered and recycled seven times without loss of its catalytic activity.<sup>157</sup> In 2017, the same group reported a mesoporous silica-based ruthenium/diamine-functionalized heterogeneous catalyst. The supported catalyst could be recovered and reused seven times.<sup>158</sup>

In 2016, Cheng *et al.* reported a fluorescence-marked core-shell structured heterogeneous ruthenium catalyst. The catalyst can be recycled by following the tracks of fluorescent emission and reused at least six times without loss of the catalytic activity.<sup>159</sup> Liu *et al.* reported a new type of heterogeneous chiral catalyst synthesized by anchoring a chiral cinchona alkaloid ligand. The supported catalyst was stable and could be easily recovered and reused at least 4 times with no loss of enantioselectivity.<sup>160</sup> Badyrova *et al.* reported a series of Rh(I) nanoparticles. The colloidal Rh/(8*S*,9*R*)-(-)-cinchonidine nanoparticle was employed in the ATH of acetophenone.<sup>161</sup>

In 2017, Itsuno *et al.* developed a chiral main-chain polyamide containing an (*R,R*)-TsDPEN unit,<sup>162,163</sup> which was combined with [RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub> for the ATH of aromatic ketones.

A heterogeneous Rh catalyst was generated *in situ* through coordination between the metal precursor [RhCl<sub>2</sub>Cp\*]<sub>2</sub> and MMP@HMSN supported ligand. In addition, the supported catalyst could be easily recycled at least 4 times.<sup>164</sup>

In 2017, Liu developed a bifunctional heterogeneous catalyst **C80** through the immobilization of palladium nanoparticles with ethylene-bridged chiral ruthenium/diamine-functionalized periodic mesoporous organosilica. It could be used for the ATH–Sonogashira

---

<sup>156</sup> Xie, Y.; Wang, M.; Wu, X.; Chen, C.; Ma, W.; Dong, Q.; Yuan, M.; Hou, Z. *ChemPlusChem* **2016**, *81*, 541.

<sup>157</sup> Zhou, F.; Hu, X.; Gao, M.; Cheng, T.; Liu, G. *Green Chem.* **2016**, *18*, 5651.

<sup>158</sup> Wang, J.; Wu, L.; Hu, X.; Liu, R.; Jin, R.; Liu, G. *Catal. Sci. Technol.* **2017**, *7*, 4444.

<sup>159</sup> An, J.; Zhao, J.; Liu, G.; Cheng, T. *Sens. Actuators B Chem.* **2016**, *224*, 333.

<sup>160</sup> Lou, L.-L.; Li, S.; Du, H.; Zhang, J.; Yu, W.; Yu, K.; Liu, S. *ChemCatChem* **2016**, *8*, 1199.

<sup>161</sup> (a) Nindakova, L. O.; Badyrova, N. M.; Smirnov, V. V.; Kolesnikov, S. S. *J. Mol. Catal. A: Chem.* **2016**, *420*, 149.

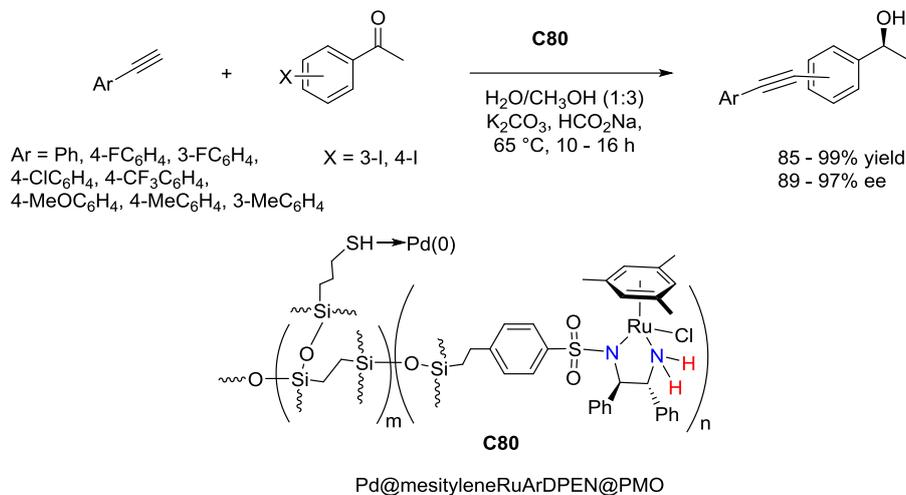
(b) Nindakova, L. O.; Badyrova, N. M.; Smirnov, V. V.; Strakhov, V. O.; Kolesnikov, S. S. *Russ. J. Gen. Chem.* **2016**, *86*, 1240.

<sup>162</sup> Itsuno, S.; Takahashi, S. *ChemCatChem* **2017**, *9*, 385.

<sup>163</sup> Liu, P. N.; Deng, J. G.; Tu, Y. Q.; Wang, S. H. *Chem. Commun.* **2004**, 2070

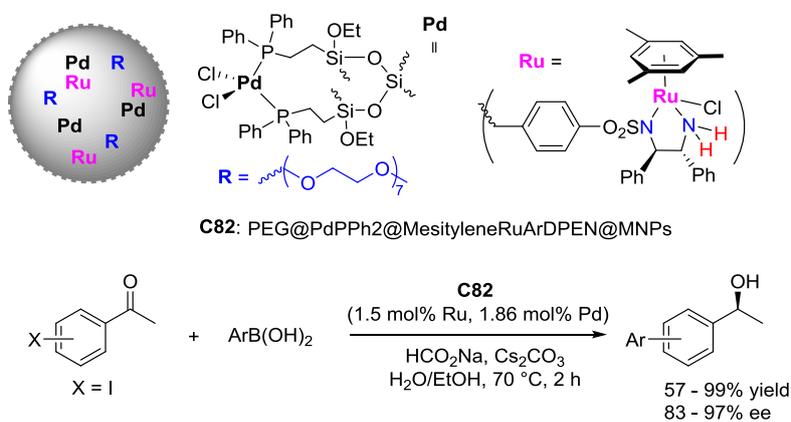
<sup>164</sup> Jing, L.; Zhang, X.; Guan, R.; Yang, H. *Catal. Sci. Technol.* **2018**, *8*, 2304.

coupling one-pot enantioselective tandem reaction of 4-iodoacetophenone and ethynylbenzene at least seven times without loss of its catalytic activity (Scheme 85).<sup>165</sup>



**Scheme 85**

Another type of bimetallic (Ru/Pd) supported catalyst **C82** bearing functionalized mesoporous silica, phosphine ligand and PEG was described. This catalyst allowed a one-pot tandem Suzuki cross-coupling and ATH reaction of iodoacetophenones and arylboronic acids in aqueous ethanol in high yields and excellent enantioinductions (up to 97% ee) (Scheme 86).<sup>166</sup>



**Scheme 86**

## 5. Conclusions

For asymmetric transfer hydrogenation in general, ruthenium complexes bearing tosyl diamine ligands (TsDPEN as the most commonly used diamine ligand) were widely evaluated

<sup>165</sup> Zhao, Y.; Jin, R.; Chou, Y.; Li, Y.; Lin, J.; Liu, G. *RSC Adv.* **2017**, *7*, 22592.

<sup>166</sup> Zhang, G.; Liu, R.; Chou, Y.; Wang, Y.; Cheng, T.; Liu, G. *Chemcatchem* **2018**, *10*, 1882.

and applied in organic synthesis chemistry. In the past few years, special attention has been paid to develop new transition metal complexes or new ligands. Usually (het)aryl ketones give high yields and excellent enantioselectivities in the ATH reactions, whereas aliphatic ketones generally yield lower conversions and enantioselectivities. In the context of sustainable chemistry, the design of efficient non-noble metal complexes has recently emerged as an attractive alternative. In addition, supported catalysts by modification of known Ru, Rh or Ir complexes are also welcomed in academic research and will be possible for industrial process.

**PART B:**

**ATH of (hetero)aryl ketones and  $\alpha,\alpha$ -  
dihalogeno  $\beta$ -Ketoesters**



## Part B: ATH of (hetero)aryl ketones and $\alpha,\alpha$ -dihalogeno $\beta$ -Ketoesters

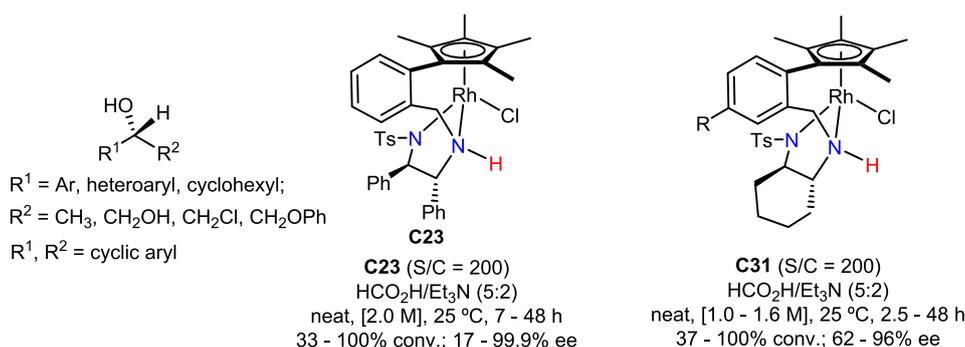
### 1. ATH of (hetero)aryl ketones catalyzed with tethered rhodium complexes

#### 1.1 Introduction

The importance of enantiomerically pure alcohols as synthetic building blocks in the manufacturing of pharmaceuticals, flavors, and fragrances, has led to significant efforts to develop efficient and atom-economical stereoselective processes for the synthesis of these compounds.<sup>167</sup> In this area, transition metal-catalyzed ATH reaction is one of the most powerful and useful methods for the generation of enantiomerically enriched secondary alcohols from the corresponding prochiral ketones, owing not only to its high performance in terms of activity and selectivity, but also to its operational simplicity and wide substrate scope.<sup>11</sup> Moreover, a variety of convenient, safe, and inexpensive non-H<sub>2</sub> hydrogen sources can be used for this reaction, typically 2-propanol, formic acid/triethylamine mixtures, or formate salts. Promising results were obtained with the tethered Ru(II)/TsDPEN complex **C11**, which showed higher catalytic activity than the untethered complex **C3** in the ATH of ketones.<sup>44</sup> Based on the successes in introducing a tether in the Ru(II) complex, Wills *et al.* developed in 2005, a tethered Rh(III) complex **C23** (Scheme 87). The catalytic properties of complex **C23** were evaluated in the ATH of functionalized ketones, leading to enantioselectivities ranging from 90 to 98%. The tethered Rh(III) complexes **C31** (R = H, OMe) were also introduced by switching the ligand from chiral TsDPEN to TsDACH (monotosylated-1,2-diaminocyclohexane), and were evaluated in the ATH of the same set of ketones, delivering 62–99% ees (Scheme 87).<sup>43</sup>

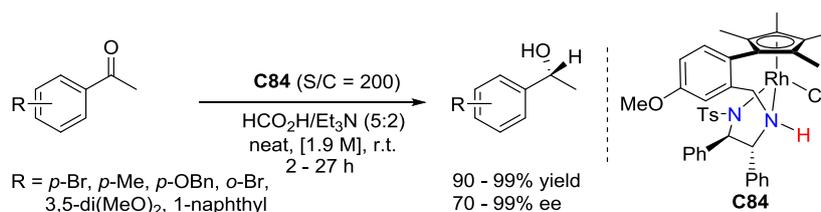
---

<sup>167</sup> (a) Bartoszewicz, A.; Ahlsten, N.; Martín-Matute, B. *Chem. Eur. J.* **2013**, *19*, 7274. (b) Ahn, Y.; Ko, S.-B.; Kim, M.-J.; Park, J. *Coord. Chem. Rev.* **2008**, *252*, 647.



Scheme 87

To develop more efficient catalysts for the reduction of unsaturated compounds, our group reported in 2015 the synthesis and evaluation of complex **C84** bearing a methoxy group on the phenyl tether ring as an analogue of Wills complex **C23**. Complex **C84** exhibited excellent catalytic performances in terms of reactivity (90–99% yields) and enantioselectivity (up to 99% ee) for the ATH of various functionalized ketones (Scheme 88).<sup>168</sup>

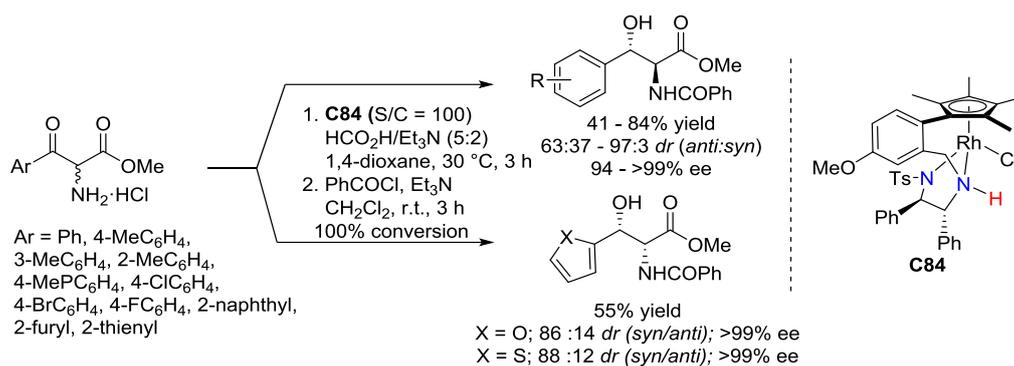


Scheme 88

The ATH of  $\alpha$ -amino  $\beta$ -keto ester hydrochlorides catalyzed by complex **C84** through a DKR process afforded the corresponding *anti*  $\alpha$ -amino  $\beta$ -hydroxy ester derivatives with good yields, fair diastereoselection and excellent enantioselectivities. Interestingly, the asymmetric reduction of heteroaromatic ketones proceeded with a reversal of diastereoselection delivering the corresponding *syn* products with good diastereoselectivities and a high level of enantioselectivities (Scheme 89).<sup>169</sup>

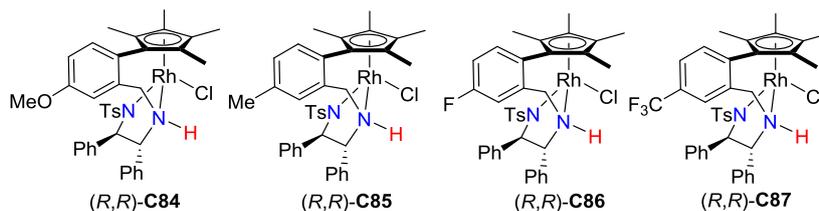
<sup>168</sup> Echeverria, P.-G.; Féraud, C.; Phansavath, P.; Ratovelomanana-Vidal, V. *Catal. Commun.* **2015**, *62*, 95.

<sup>169</sup> Llopis, Q.; Féraud, C.; Guillamot, G.; Phansavath, P.; Ratovelomanana-Vidal, V. *Synthesis* **2016**, *48*, 3357.



Scheme 89

Following these initial studies, we synthesized a series of novel Rh(III)–TsDPEN-based tethered complexes **C85–C87** having electron-donating methyl substituent and electron-withdrawing fluorine and trifluoromethyl substituents, respectively, on the 2-benzyl tether to evaluate the electronic effect of the 2-benzyl tether substituent on the catalytic performance of the resulting complexes (Scheme 90).



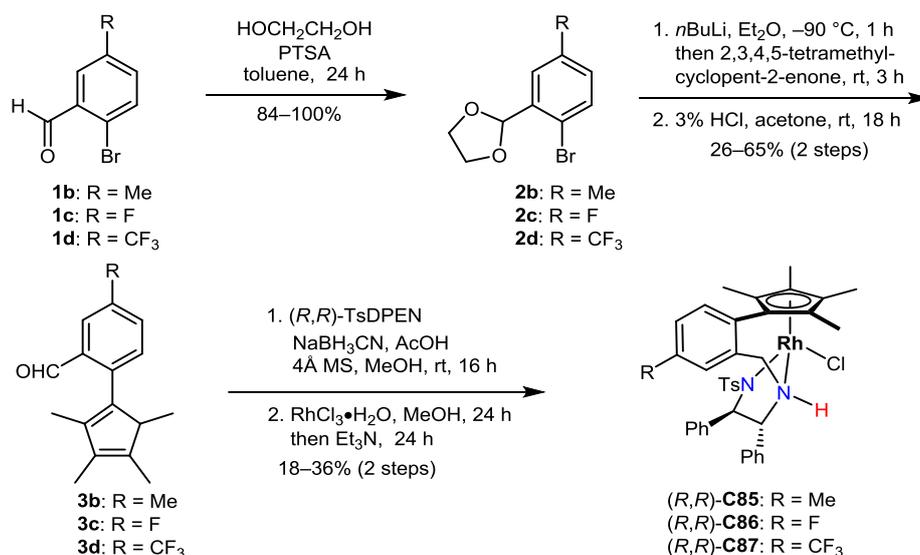
Scheme 90

## 1.2 Results and discussion

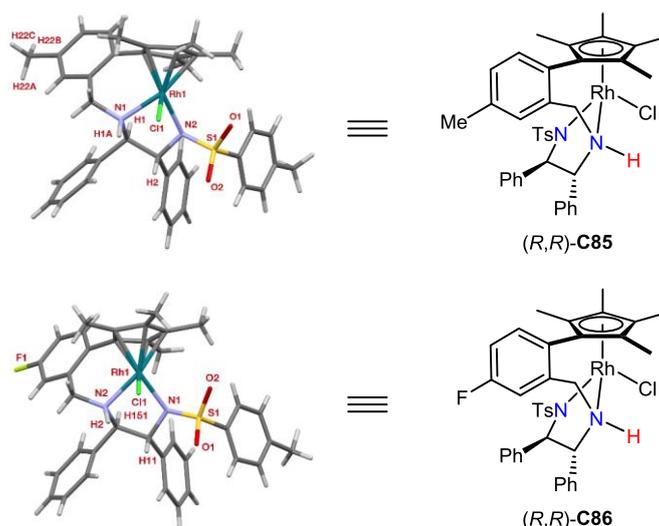
### 1.2.1 Synthesis of novel complexes (*R,R*)-**C85–C87**

Novel complexes **C85–C87** were first prepared from commercially available 2-bromo-5-methylbenzaldehyde (**1b**), 2-bromo-5-fluorobenzaldehyde (**1c**), and 2-bromo-5-(trifluoromethyl)benzaldehyde (**1d**), which were protected as their 1,3-dioxolane derivatives **2b–d** (Scheme 91). Treatment of these compounds with <sup>n</sup>BuLi followed by addition of 2,3,4,5-tetramethylcyclopent-2-enone furnished the corresponding alcohols, which were then subjected to 3% hydrochloric acid in acetone. The latter conditions led to both deprotection of the aldehyde function and dehydration of the tertiary alcohol, providing compounds **3b–d**.

Subsequent reductive amination using (*R,R*)-TsDPEN in the presence of sodium cyanoborohydride then delivered the corresponding diamines, and the targeted complexes (*R,R*)-**C85**-**C87** were obtained through heating the latter in refluxing methanol in the presence of rhodium(III) chloride followed by treatment with triethylamine. The three complexes were isolated after flash chromatography as orange solids and as single diastereomers, whereas their structures were confirmed by X-ray crystallographic analysis in the case of (*R,R*)-**C85**, and (*R,R*)-**C86** (Figure 1).

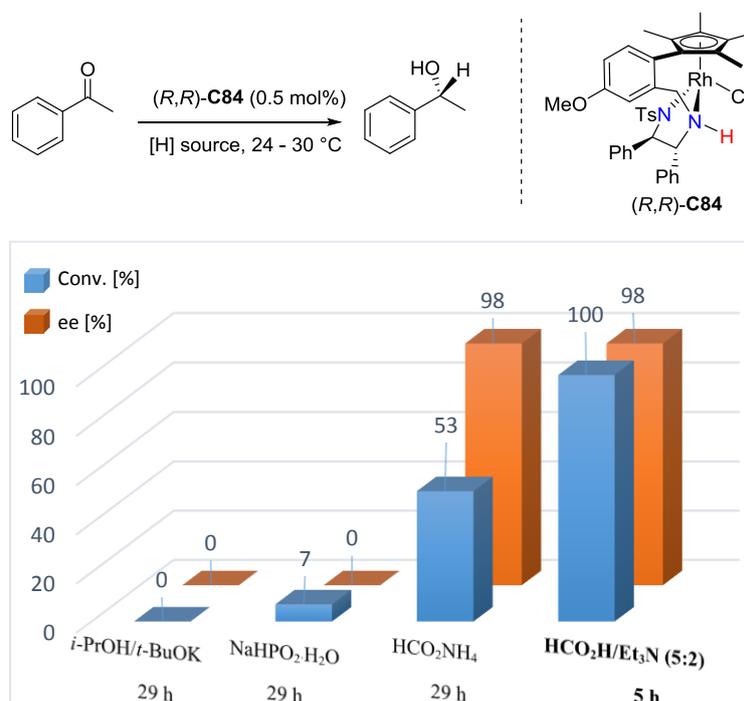


Scheme 91

Figure 1 X-ray structure of complexes (*R,R*)-**C85** and **C86**

### 1.2.2 Optimisation of the reaction conditions for the ATH of acetophenone with complex $(R,R)$ -C84

Evaluation of these complexes started with the ATH of acetophenone as the standard substrate using  $(R,R)$ -C84 in combination with various hydrogen donor systems (**Figure 2**). The reaction was carried out at 24–30 °C with 0.5 mol % of  $(R,R)$ -C84. A comparison of various hydrogen donor sources highlighted the choice of a formic acid/triethylamine (5:2) system in preference to sodium hypophosphite, ammonium formate, or an  $i$ PrOH/ $t$ BuOK system. Indeed, in the presence of a formic acid/triethylamine (5:2) system, a full conversion was attained within 5 h, and the reduced compound,  $(R)$ -1-phenylethanol, was obtained with a very high enantiomeric excess of 98%. On the other hand, in the presence of sodium hypophosphite, the conversion dramatically decreased to 7%. In the same manner, an unsatisfactory conversion of 53% was observed with ammonium formate. Upon using the  $i$ PrOH/ $t$ BuOK system as the reducing agent, only degradation products were formed. Finally, the optimized reaction conditions for the ATH of acetophenone with  $(R,R)$ -C84 were set as follows: 0.5 mol % concentration of tethered Rh(III) complex  $(R,R)$ -C84 in neat HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) at 24–30 °C.



**Figure 2**



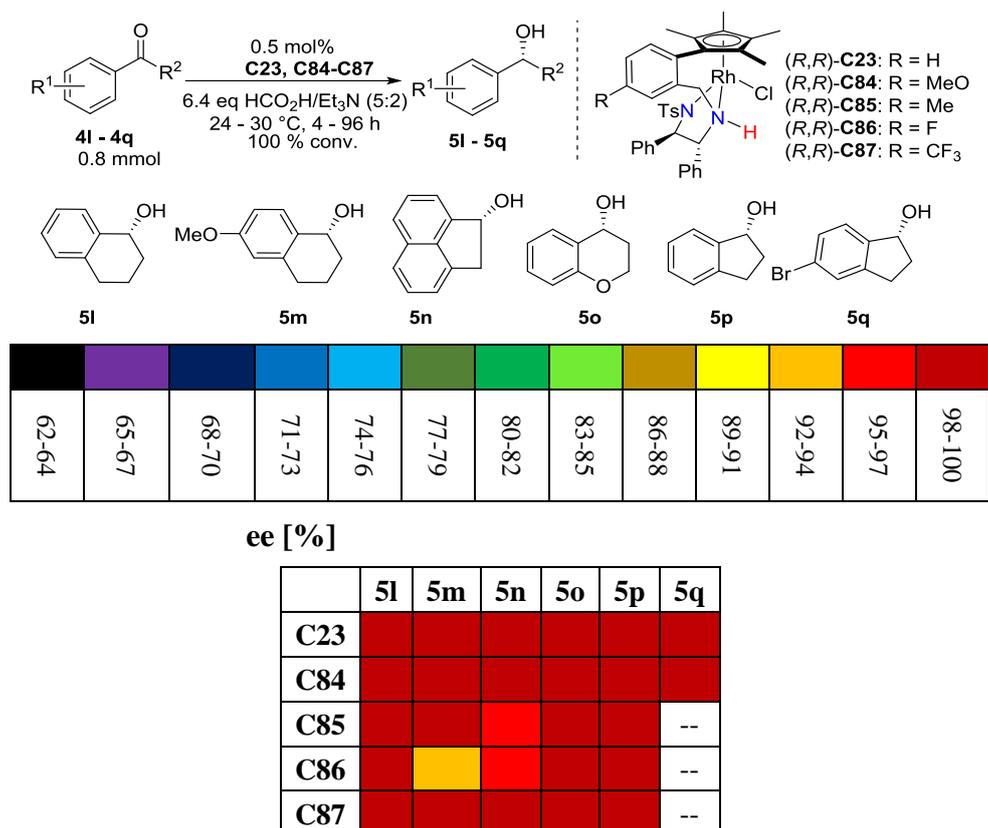
similarly except for (*R,R*)-**C87** which failed to afford complete conversion even after a prolonged reaction time of 96 h, and with a significantly higher catalytic activity observed for complexes (*R,R*)-**C85** and (*R,R*)-**C86** which gave full conversions in only 6 h as compared to 22h with (*R,R*)-**C23**. On the other hand, 2-chloroacetophenone (**4c**) was readily reduced with all five complexes with ee values ranging from 95% to >99%. (Scheme 92)

The catalytic reduction of acetophenones bearing substituents in the *para* or *meta* positions of the phenyl ring (**4d-4g**) led to high levels of stereoselectivity as well with a higher catalytic activity observed with (*R,R*)-**C84** and (*R,R*)-**C85**, whereas complex (*R,R*)-**C87** led only to 62–64% conversions after 100–110 h of reaction for 4'-benzyloxy-acetophenone (**4f**) and 3',5'-dimethoxyacetophenone (**4g**). In contrast, lower enantiofacial discriminations were observed for aryl ketones possessing an *ortho* substituent as for 2'-bromoacetophenone (**4h**) (64–71% ee) and 1-acetonaphthone (**4j**) (78–85% ee). In both instances, compared to complex (*R,R*)-**C23**, slightly higher ee values could be attained with complexes (*R,R*)-**C84**, (*R,R*)-**C85** and (*R,R*)-**C86**. (Scheme 92)

In addition, fair enantioselectivities (88% ee) were reached within a short reaction time for 4'-nitroacetophenone (**4i**) containing a highly electron-poor  $-\text{NO}_2$  group. Furthermore, we studied the ATH of a highly electron-rich aryl ketone (**4k**) bearing a morpholine substituent in the *para* position. Although this challenging family of substrates was recently efficiently reduced through ATH with tethered ruthenium-TsDPEN catalysts,<sup>90</sup> no example of catalytic reduction with a rhodium catalyst has been reported to our knowledge. The use of complexes (*R,R*)-**C23** and (*R,R*)-**C84** under the defined standard conditions smoothly afforded the desired reduced compound in quantitative yield and with an excellent enantiopurity (99% ee). (Scheme 92)

However, polycyclic aryl ketones **4l-4q**, such as six-membered and five-membered cycles, afforded uniformly high enantioinductions with ee values ranging from 92% to >99%. A gram-scale ATH of 4-chromanone (**4o**) was also carried out with complex (*R,R*)-**C84** under the standard conditions and furnished quantitatively the desired (*R*)-chroman-4-ol (**5o**) with the same enantiomeric purity (>99% ee). (Scheme 93)

It appears from the above surveys that complexes  $(R,R)$ -**C23**, **C84-C87** exhibited comparable stereoselectivities, providing the corresponding alcohols with mainly high enantioselectivities for *para*- and *meta*-substituted ketones (up to >99% ee) whereas lower enantioinductions were observed for the *ortho*-substituted compounds. (Scheme 92 and Scheme 93)



Scheme 93

From the above results, although ATH of ketones catalyzed by these new Rh(III) complexes **C84-C87** resulted in the same high enantioselectivities as compared to Wills' complex **C23**, we found the reaction rates to be highly dependent of the nature of the 2-benzyl tether substituent. Complex **C87** possessing an electron-withdrawing trifluoromethyl substituent displayed a lower catalytic activity, and generally required longer reaction times. On the other hand, complex **C84** having an electron-donating substituent showed a higher catalytic activity, and required shorter reaction times (Figure 3).

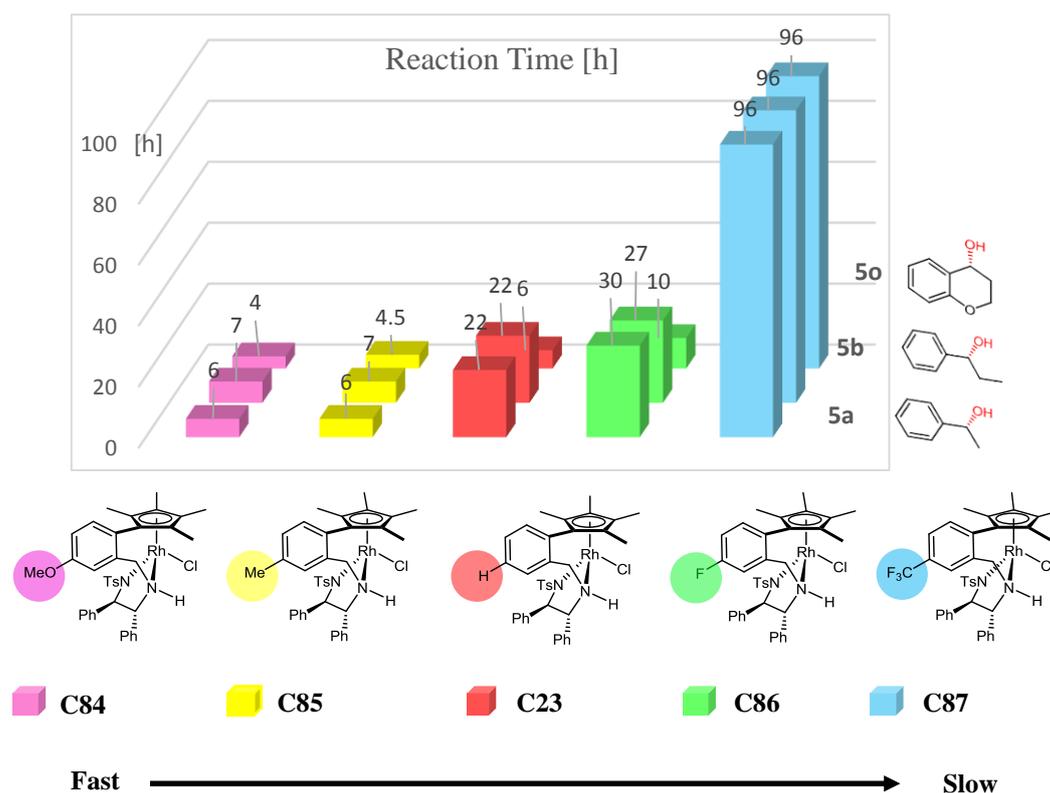


Figure 3

### 1.2.4 ATH of heteroaryl and alkyl ketones mediated by complexes (*R,R*)-C23, C84–C87

To test the substrate scope further, we next explored the (*R,R*)-C23, C84–C87-mediated ATH of heteroaryl and alkyl ketones (6a–6f). The former compounds underwent the catalytic reduction in good yields with systematically high asymmetric inductions observed with all the examined tethered Rh(III)/Cp\* complexes, for (*R*)-1-(2-furyl)ethanol (7a), (*R*)-1-(2-thienyl)ethanol (7b), (1*R*)-1-(benzofuran-2-yl)ethanol (7c) and (*R*)-1-(2-pyridyl)ethanol (7d). With regard to non-aromatic ketones (6e, 6f),  $\beta$ -tetralone (6e) yielded moderate ee values (80–83%), whereas pleasingly high stereoselectivities were obtained for the ATH of acetylcyclohexane 6f (93–95% ee). Indeed, Wills and co-workers previously reported the asymmetric reduction of acetylcyclohexane with two parent tethered rhodium complexes<sup>43</sup> for which lower ee values of 84% and 87%, respectively, were observed. (Figure 4)

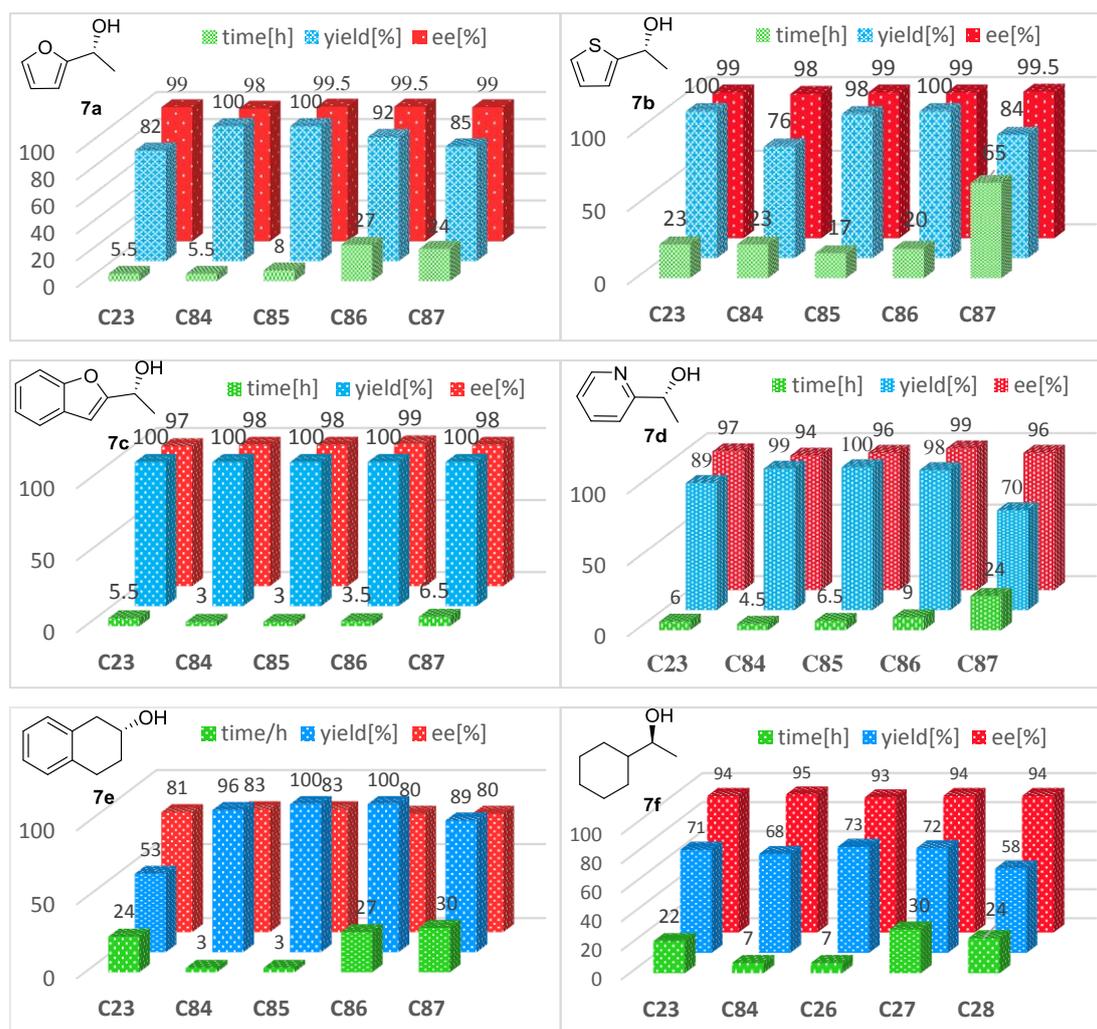
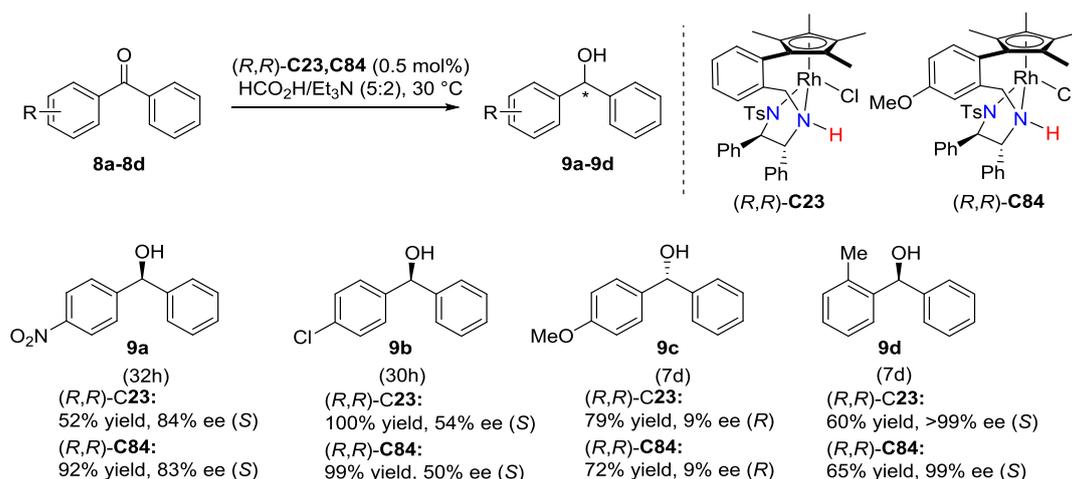


Figure 4

### 1.2.5 ATH of unsymmetrical benzophenones mediated by complexes (*R,R*)-C23, C84

In addition, because the catalytic asymmetric reduction of unsymmetrical benzophenones has been less investigated,<sup>112</sup> we were keen to evaluate the catalytic performance of our new complexes in the ATH of these more challenging substrates wherein a catalyst has to discriminate structural differences in the two aromatic moieties (Scheme 94). Interestingly, upon using the tethered Rh-TsDPEN complex (*R,R*)-C84 under the standard reaction conditions, 4'-nitrobenzophenone underwent the ATH with a satisfactory enantiomeric

excess of 83% (Scheme 94). On the other hand, the asymmetric transfer hydrogenation proceeded with low enantioinductions for 4'-chlorobenzophenone and 4'-methoxybenzophenone. Unsurprisingly, the highest stereoselectivity was observed with the *ortho*-substituted substrate, 2'-methylbenzophenone, which was converted into the corresponding alcohol in 99% ee.

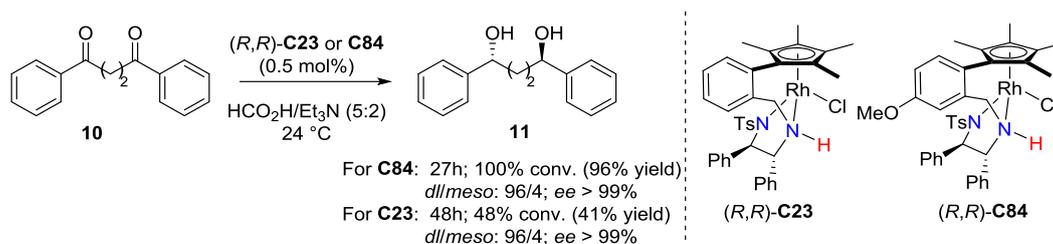


Scheme 94

### 1.2.6 ATH of 1,4-diaryl diketone mediated by complexes (R,R)-C23, C84

The ATH reaction was also carried out with a 1,4-diaryl diketone **10** (Scheme 95). Thus, 1,4-diphenyl-1,4-butanedione was successfully reduced with (R,R)-C84 under the standard conditions, giving the corresponding (*1R,4R*)-1,4-diphenyl-1,4-butanediol **11** with a very high dl/meso ratio (96:4) and an excellent enantioselectivity (>99% ee). When the reaction was performed with (R,R)-C23, an incomplete conversion was observed even after a prolonged reaction time of 48 h (48% conversion, 41% isolated yield), whereas the stereochemical outcome remained unchanged. This compound is a precursor of (*2R,5R*)-diphenylpyrrolidine, which is commonly used in asymmetric organocatalytic reactions.<sup>170</sup>

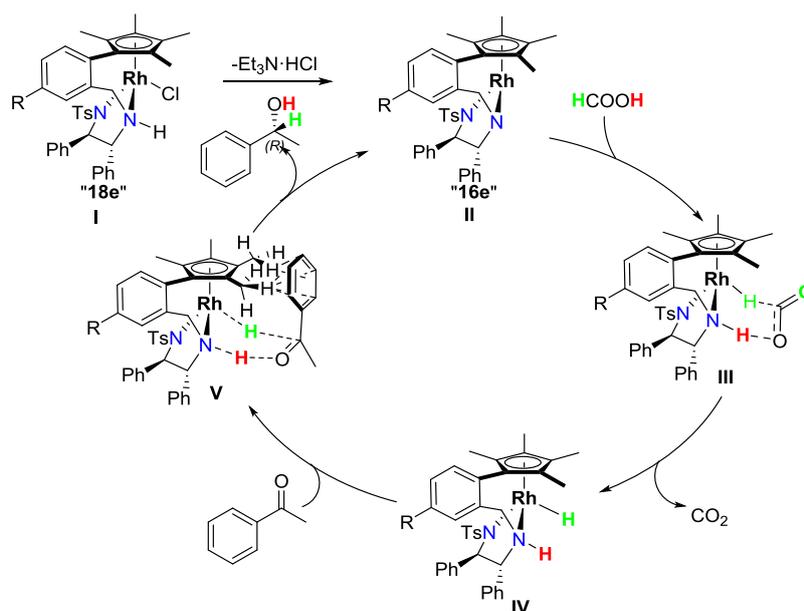
<sup>170</sup> Halland, N.; Braunton, A.; Bachmann, S.; Marigo, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 4790.



Scheme 95

### 1.2.7 Proposed mechanism of ATH of ketones with tethered Rh(III) complex

Based on the mechanism proposed for the ATH of ketones using Noyori's ruthenium complex,<sup>63</sup> we assumed the mechanism of these tethered rhodium complexes in the asymmetric transfer hydrogenation of ketones was as follows: first, a chiral unsaturated 16-electron amido rhodium complex **II** is formed by elimination of HCl from complex **I**. Then, the rhodium complex **II** readily reacts with HCOOH to give the corresponding formate complex **III**, which subsequently undergoes decarboxylation leading to the chiral hydrido-amine complex **IV** and CO<sub>2</sub>. This chiral hydrido rhodium complex **IV** readily reacts with ketonic substrates to provide optically active alcohols with regeneration of the amide complex **II** through transition state **V** showing N–H···O hydrogen-bonding interaction, Rh–H···C interaction, and C–H··· $\pi$  interaction between Cp\* ring and ketone aryl substituent (Scheme 96).



Scheme 96

### 1.3 Conclusion

The synthesis, characterization, and evaluation of complex (*R,R*)-**C84** as well as novel tethered Rh(III) complexes (*R,R*)-**C85-C87** having electron-donating groups as well as electron-withdrawing substituents on the tethering phenyl ring were successfully accomplished. These new complexes showed high stability and were easy to handle. As far as the synthesis, characterization, and applications of novel tethered Rh(III) complexes is concerned, a complete comparative study of the catalytic performances of complexes (*R,R*)-**C84-C87** was conducted. This study demonstrated that these complexes exhibited excellent activities for the asymmetric transfer hydrogenation of a wide range of functionalized ketones. In this survey, the catalytic performance of the Wills complex (*R,R*)-**C23** was also evaluated on a broad scope of new substrates. Selectivities obtained with complexes (*R,R*)-**C84-C87** were comparable to those obtained with (*R,R*)-**C23** or slightly higher in a few instances, and with a better catalytic activity observed in several cases. A wide range of (hetero)aryl ketones underwent the (*R,R*)-**C84-C87**-promoted ATH using formic acid/triethylamine with high levels of enantioselectivities under mild reaction conditions at a low catalyst loading. The scope of the prochiral ketones for the ATH promoted by tethered Rh-TsDPEN/Cp\* complexes has been consistently expanded,

including notably unsymmetrical benzophenones, a highly electron-rich acetophenone bearing a morpholine substituent, and a highly electronpoor aryl ketone possessing a nitro substituent. Moreover, 1,4-diphenyl-1,4-butanedione **10** was efficiently reduced upon using the Rh-TsDPEN complex (*R,R*)-**C84** into the enantiomerically pure 1,4-diphenyl-1,4-butanediol **11**, a valuable intermediate in the preparation of the (*2R,5R*)-diphenylpyrrolidine organocatalyst. In addition, the ATH of 4-chromanone was performed with (*R,R*)-**C84** on the gram scale without a detrimental impact on the yield and the stereochemical outcome of the reaction, demonstrating the potential usefulness of these new complexes.

## 2. Synthesis of enantioenriched $\alpha,\alpha$ -dichloro and $\alpha,\alpha$ -difluoro $\beta$ -hydroxy esters and amides *via* ruthenium-catalyzed asymmetric transfer hydrogenation

### 2.1 Introduction

Because of the ability of halogen atoms to improve oral absorption, blood-brain barrier permeability, or metabolic and chemical stability, halogenated compounds play a significant role in medicinal chemistry. The majority of the halogenated drugs approved by the FDA are fluorine and chlorine compounds<sup>171,172</sup> and the introduction of a dichloro- or difluoromethylene fragment into bioactive molecules has created a new trend in drug discovery. Enantiomerically pure  $\alpha,\alpha$ -dichloro- or  $\alpha,\alpha$ -difluorosubstituted secondary alcohols are found in a number of biologically relevant molecules such as statine analogues,<sup>173a</sup> a potent inhibitor of hepatitis C virus replication,  $\beta$ -D-2'-deoxy-2'-dichlorouridine prodrug,<sup>173b</sup> and the fluorinated Enigmol analog CF<sub>2</sub>-Enigmol, having enhanced anti-tumor activity.<sup>173c</sup> Alternatively,  $\alpha,\alpha$ -dichloro- or  $\alpha,\alpha$ -difluorosubstituted secondary alcohols can serve as valuable building blocks in medicinal chemistry as with 3,3-difluoropyrrolidin-4-ol<sup>128</sup> (Figure 5).

<sup>171</sup> Hernandez, M. Z.; Cavalcanti, S. M. T.; Moreira, D. R. M.; de Azevedo Jr, W. F.; Leite, A. C. L. *Current Drug Targets* **2010**, *11*, 303.

<sup>172</sup> Wilcken, R.; Zimmermann, M. O.; Lange, A.; Joerger, A. C.; Boeckler, F. M. *J. Med. Chem.* **2013**, *56*, 1363

<sup>173</sup> (a) Yamamoto, T.; Ishibuchi, S.; Ishizuka, T.; Haratake, M.; Kunieda, T. *J. Org. Chem.* **1993**, *58*, 1997. (b) Pinho, P.; Kalayanov, G.; Westerlind, H.; Rosenquist, Å.; Wähling, H.; Sund, C.; Almeida, M.; Ayesa, S.; Tejbrant, J.; Targett-Adams, P.; Eneroth, A.; Lindqvist, A. *Bioorg. Med. Chem. Lett.* **2017**, *27*, 3468. (c) Miller, E. J.; Mays, S. G.; Baillie, M. T.; Howard, R. B.; Culver, D. G.; Saindane, M.; Pruett, S. T.; Holt, J. J.; Menaldino, D. S.; Evers, T. J.; Reddy, G. P.; Arrendale, R. F.; Natchus, M. G.; Petros, J. A.; Liotta, D. C. *ACS Med. Chem. Lett.* **2016**, *7*, 537. (d) Si, C.; Fales, K. R.; Torrado, A.; Frimpong, K.; Kaoudi, T.; Vandevveer, H. G.; Njoroge, F. G. *J. Org. Chem.* **2016**, *81*, 4359.

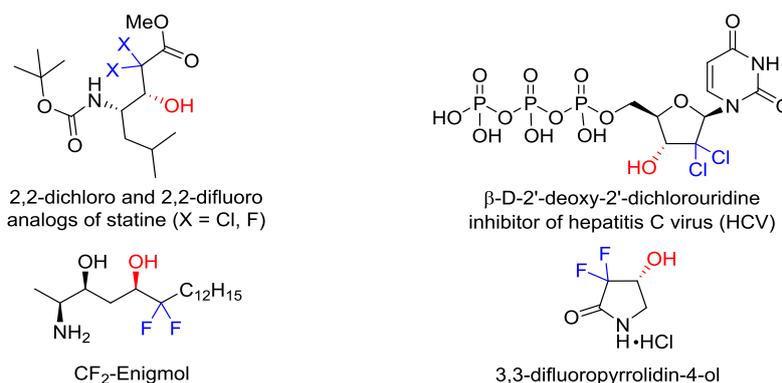


Figure 5

## 2.2 Different routes to access $\alpha,\alpha$ -dihalogeno $\beta$ -hydroxyester derivatives

Access to  $\alpha,\alpha$ -dichloro and  $\alpha,\alpha$ -difluoro  $\beta$ -hydroxyester derivatives has been reported with different methods. Kitazume *et al.*, in 2005, reported lipase-catalyzed asymmetric hydrolysis of 2,2-difluoro-3-hydroxyamides through kinetic resolution to prepare  $\alpha,\alpha$ -difluoro alcohol derivatives (Scheme 97).<sup>174a</sup> In 2008, Chen *et al.* described the same strategy to access 2,2-difluoro-3-hydroxy-3-aryl-propionates by switching from enzymes to organocatalysts (Scheme 97).<sup>174b</sup> The main disadvantage of kinetic resolution is the theoretically limited to 50% yield for the desired enantiomer. Enantioselective Mukaiyama aldol reactions catalyzed with different Lewis acids have also been investigated for preparing  $\alpha,\alpha$ -dihalogeno  $\beta$ -hydroxyester derivatives, albeit with low catalytic activities, harsh reaction conditions and limited substrate scope (Scheme 98).<sup>174c-e</sup> As far as reduction of  $\alpha,\alpha$ -dihalogeno  $\beta$ -keto esters is concerned, rhodium- or ruthenium-catalyzed asymmetric hydrogenation have been described with high performances (Scheme 99).<sup>174f-g</sup> Furthermore, bioreduction or stoichiometric enantio-reduction have also been reported for  $\alpha,\alpha$ -difluoro  $\beta$ -keto esters with varying efficiency (Scheme 100).

<sup>174h-i</sup>

<sup>174</sup> (a) Kaneda, T.; Komura, S.; Kitazume, T. *J. Fluorine Chem.* **2005**, *126*, 17. (b) Zhou, H.; Xu, Q.; Chen, P. *Tetrahedron* **2008**, *64*, 6494. (c) Iseki, K.; Kuroki, Y.; Asada, D.; Takahashi, M.; Kishimoto, S.; Kobayashi, Y. *Tetrahedron* **1997**, *53*, 10271. (d) Iseki, K.; Kuroki, Y.; Asada, D.; Kobayashi, Y. *Tetrahedron Lett.* **1997**, *38*, 1447. (e) Imashiro, R.; Kuroda, T. *J. Org. Chem.* **2003**, *68*, 974. (f) Kuroki, Y.; Asada, D.; Iseki, K. *Tetrahedron Lett.* **2000**, *41*, 9853 (g) Blanc, D.; Ratovelomanana-Vidal, V.; Gillet, J.-P.; Genêt, J.-P. *J. Organomet. Chem.* **2000**, *603*, 128. (h) Mochizuki, N.; Sugai, T.; Ohta, H. *Biosci. Biotech. Biochem.* **1994**, *58*, 1666. (i) Ema, T.; Kadoya, T.; Akihara, K.; Sakai, T. *J. Mol. Catal. B: Enzymatic* **2010**, *66*, 198.



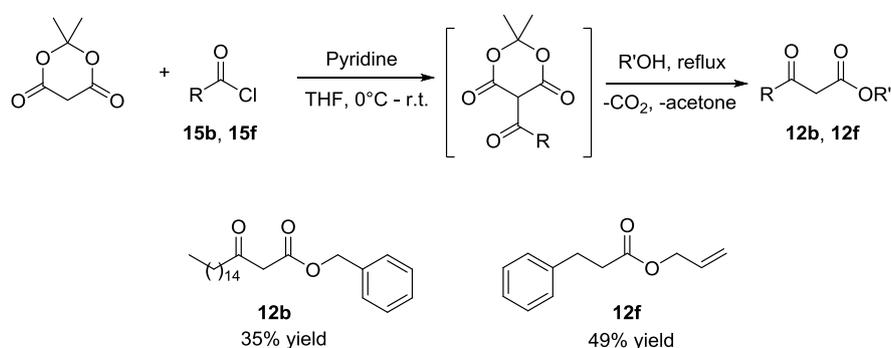
of functionalized ketones,<sup>176,272</sup> we studied the ruthenium- and rhodium-catalyzed ATH of  $\alpha,\alpha$ -dichloro and  $\alpha,\alpha$ -difluoro  $\beta$ -ketoester derivatives to access the corresponding enantiomerically enriched dihalogenated alcohols.

## 2.3 Results and discussion

### 2.3.1 Synthesis of $\alpha,\alpha$ -dihalogeno $\beta$ -ketoesters

#### 2.3.1.1 Preparation of $\beta$ -ketoesters

$\beta$ -Ketoesters **12b**, **12f** were prepared by reacting Meldrum's acid with acyl chlorides **15b** and **15f** in the presence of pyridine as the base, followed by treatment with various alcohols to release CO<sub>2</sub> and acetone (Scheme 101).<sup>177</sup>



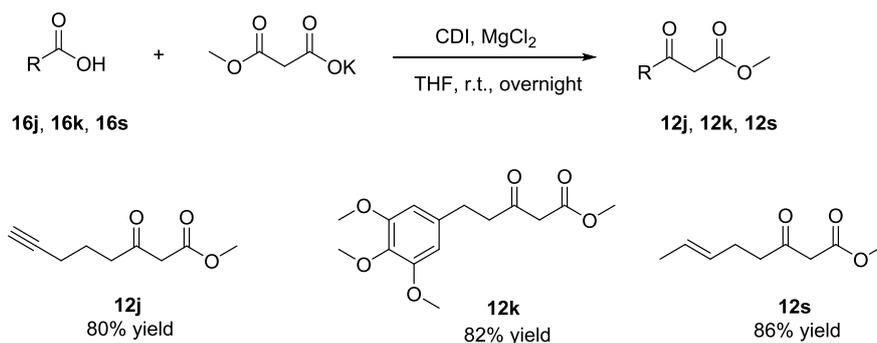
Scheme 101

On the other hand,  $\beta$ -ketoesters **12j**, **12k** and **12s** were prepared from the fatty acids **16j**, **16k** and **16s** in the presence of potassium mono-methyl malonate, CDI and magnesium chloride (Scheme 102).<sup>178</sup>

<sup>176</sup> (a) Echeverria, P.-G.; Cornil, J.; Féraud, C.; Guérinot, A.; Cossy, J.; Phansavath, P.; Ratovelomanana-Vidal, V. *RSC Adv.* **2015**, *5*, 56815. (b) Monnereau, L.; Cartigny, D.; Scalone, M.; Ayad, T.; Ratovelomanana-Vidal, V.; *Chem. Eur. J.*, **2015**, *21*, 11799. (c) Perez, M.; Echeverria, P.-G.; Martinez-Arripe, E.; Ez Zoubir, M.; Touati, R.; Zhang, Z.; Genet, J.-P.; Phansavath, P.; Ayad, T.; Ratovelomanana-Vidal, V. *Eur. J. Org. Chem.* **2015**, 5949.

<sup>177</sup> Palos Pacheco, R.; Eismin, R. J.; Coss, C. S.; Wang, H.; Maier, R. M.; Polt, R.; Pemberton, J. E. *J. Am. Chem. Soc.* **2017**, *139*, 5125.

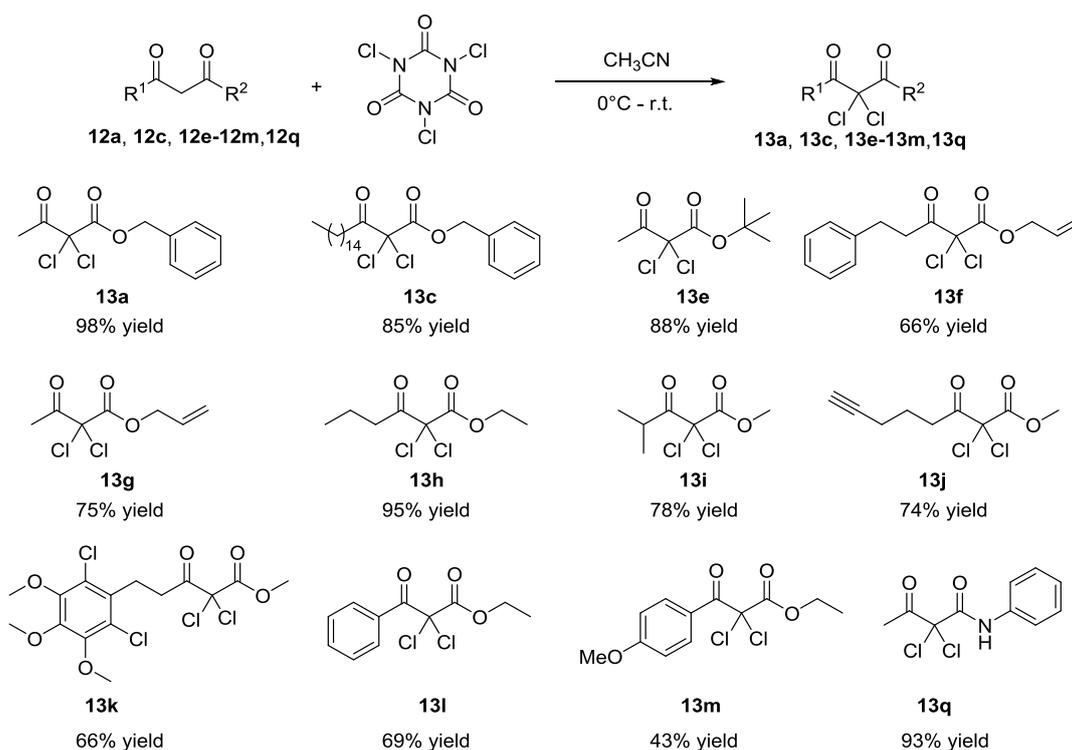
<sup>178</sup> Qin, J.; Rao, A.; Chen, X.; Zhu, X.; Liu, Z.; Huang, X.; Degrado, S.; Huang, Y.; Xiao, D.; Aslanian, R.; Cheewatrakoolpong, B.; Zhang, H.; Greenfeder, S.; Farley, C.; Cook, J.; Kurowski, S.; Li, Q.; van Heek, M.; Chintala, M.; Wang, G.; Hsieh, Y.; Li, F.; Palani, A. *ACS Med. Chem. Lett.* **2011**, *2*, 171.



Scheme 102

### 2.3.1.2 General procedure for preparation of $\alpha,\alpha$ -dichloro $\beta$ -ketoesters

$\alpha,\alpha$ -Dichloro  $\beta$ -ketoesters **13a**, **13c**, **13e-13m** and **13q** were prepared from the corresponding  $\beta$ -ketoesters by using trichloroisocyanuric acids (TCCA) as the electrophilic chlorinating reagent under mild conditions in yields ranging from 43% to 98% (Scheme 103).<sup>179</sup>

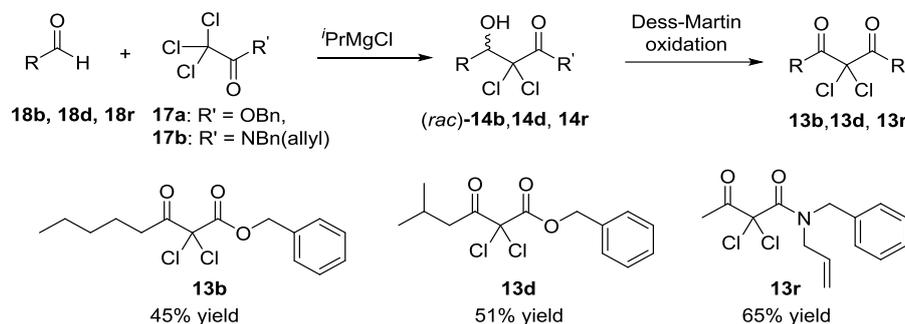


Scheme 103

$\alpha,\alpha$ -Dichloro  $\beta$ -ketoesters **13b**, **13d** and **13r** were synthesized through Dess-Martin oxidation of the corresponding  $\alpha,\alpha$ -dichloro  $\beta$ -hydroxy esters **14b**, **14d** and **14r**. The latter were obtained by reaction of benzyltrichloroacetate **17a** or *N*-allyl-*N*-benzyl-2,2,2-

<sup>179</sup> Mendonça, G. F.; Sindra, H. C.; de Almeida, L. S.; Esteves, P. M.; de Mattos, M. C. S. *Tetrahedron Lett.* **2009**, *50*, 473.

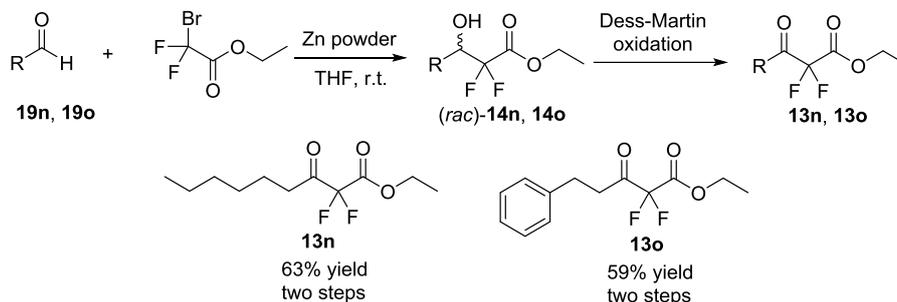
trichloroacetamide **17b** with aldehyde **18b**, **18d** and **18r** in the presence of isopropylmagnesium chloride (Scheme 104).<sup>180</sup>



Scheme 104

### 2.3.1.3 General procedure for preparation of $\alpha,\alpha$ -difluoro $\beta$ -ketoesters

$\alpha,\alpha$ -Difluoro  $\beta$ -ketoesters **13n** and **13o** were prepared by Dess-Martin oxidation of  $\alpha,\alpha$ -difluoro  $\beta$ -hydroxy esters (rac)-**14n** and **14o**, which were synthesized through a Reformatsky reaction using aldehydes **19n** and **19o** and ethyl bromodifluoroacetate as the starting materials (Scheme 105).<sup>181</sup>



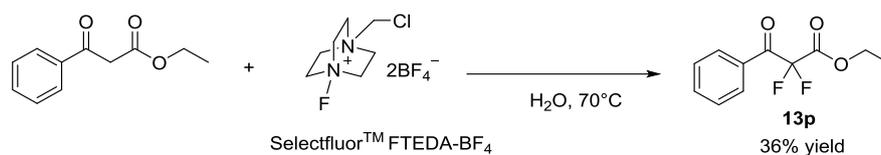
Scheme 105

Following a reported procedure, ethyl 2,2-difluoro-3-oxo-3-phenylpropanoate **13p** was prepared by fluorination of the commercially available ethyl benzoylacetate with selectfluor<sup>TM</sup> FTEDA-BF<sub>4</sub> in the presence of water under mild conditions (Scheme 106).<sup>182</sup>

<sup>180</sup> Bellesia, F.; Forti, L.; Ghelfi, F.; Ghirardki, G.; Libertini, E.; Pagnoni, U. M.; Pinetti, A.; Prochilo, N. *Synth. Commun.* **1999**, *29*, 3739.

<sup>181</sup> (a) Linderman, R. J.; Graves, D. M. *J. Org. Chem.* **1989**, *54*, 661. (b) Yang, M.-H.; Hunt, J. R.; Sharifi, N.; Altman, R. A. *Angew. Chem. Int. Ed.* **2016**, *55*, 9080.

<sup>182</sup> Stavber, G.; Stavber, S. *Adv. Synth. Catal.* **2010**, *352*, 2838.

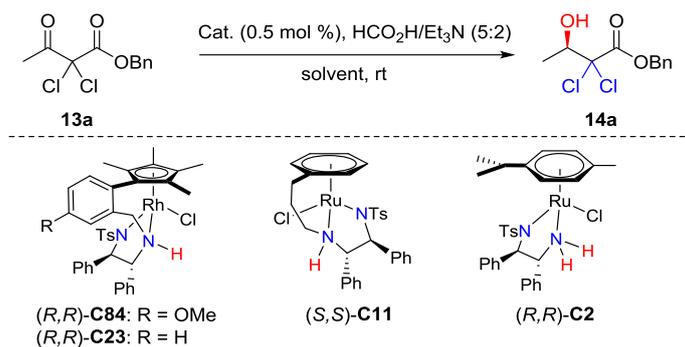


Scheme 106

## 2.3.2 ATH of $\alpha,\alpha$ -dichloro $\beta$ -ketoesters - optimisation of the reaction conditions

### 2.3.2.1 Catalysts screening

We first investigated the enantioselective reduction of benzyl 2,2-dichloro-3-oxobutanoate **13a** as a model reaction by using the tethered rhodium complex (*R,R*)-**C84** (0.5 mol %),<sup>168,178,272</sup> HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) azeotropic mixture as the hydrogen source, and CH<sub>2</sub>Cl<sub>2</sub> as a solvent at room temperature. Under these conditions, full conversion was achieved within 4 h and the corresponding alcohol (*R*)-**14a** was obtained in 77% yield with a high enantioselectivity (98% ee, Table 2, entry 1). Wills' tethered rhodium complex (*R,R*)-**C23**<sup>42b</sup> afforded the same enantioinduction (98% ee) and a better yield (84% yield, Table 2, entry 2). The catalyst screening included tethered ruthenium complexes as well. Thus, (*S,S*)-**C11**<sup>38</sup> was used in the ATH of **13a** to give (*S*)-**14a** in 91% yield and 99% ee, albeit with a longer reaction time of 20 h (Table 2, entry 3). We also examined Noyori's catalyst (*R,R*)-**C2**,<sup>11a,27</sup> [RuCl(*p*-cymene)(*R,R*)-TsDPEN], which gave a slightly higher yield (92%) and excellent enantioselectivity (> 99%) after 20 h (Table 2, entry 4). Therefore, we selected Noyori's catalyst (*R,R*)-**C2** as the best catalyst for further optimization.

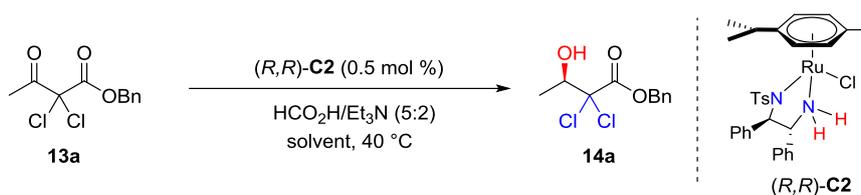
Table 2. Catalysts screening for the ATH of benzyl 2,2-dichloro-3-oxobutanoate (**13a**)<sup>a</sup>

| Entry | cat.              | solvent                         | Time (h) | yield <sup>b</sup> (%) | ee <sup>c</sup> (%) |
|-------|-------------------|---------------------------------|----------|------------------------|---------------------|
| 1     | (R,R)- <b>C84</b> | CH <sub>2</sub> Cl <sub>2</sub> | 4        | 77                     | 98                  |
| 2     | (R,R)- <b>C23</b> | CH <sub>2</sub> Cl <sub>2</sub> | 5        | 84                     | 98                  |
| 3     | (S,S)- <b>C11</b> | CH <sub>2</sub> Cl <sub>2</sub> | 20       | 91                     | -99                 |
| 4     | (R,R)- <b>C2</b>  | CH <sub>2</sub> Cl <sub>2</sub> | 20       | 92                     | >99                 |

<sup>a</sup> General conditions: **13a** (0.6 mmol), catalyst (0.006 mmol), HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) (101  $\mu$ L), CH<sub>2</sub>Cl<sub>2</sub> (3.0 mL) <sup>b</sup> Isolated yield, full conversion except where indicated. <sup>c</sup> Determined by SFC.

### 2.3.2.2 Solvents screening

Interestingly, the reaction time was shortened to 5 h when the ATH was conducted at 40  $^{\circ}$ C, affording (*R*)-**14a** in 91% yield and >99% ee (Table 3, entry 1). We pursued the optimization of the reaction parameters by a solvent screening at 40  $^{\circ}$ C. Excellent ee values were obtained in EtOAc and THF after 17 h albeit in lower yields, with only 92% conversion observed in the latter case (Table 3, entries 2 and 3). *i*Pr<sub>2</sub>O and *i*PrOH were then investigated, giving full conversions in either 3 h or 5 h, with 86% and 81% yields, respectively, and >99% ee (Table 3, entries 4 and 5). From the above results, dichloromethane appeared as the best solvent for further studies.

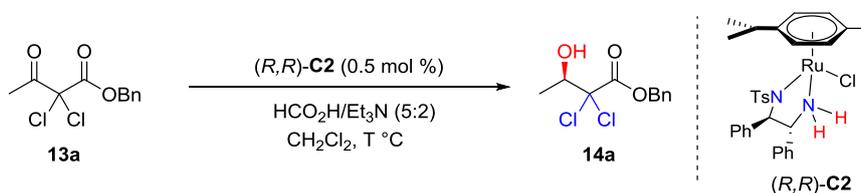
**Table 3. Solvent optimization for the ATH of benzyl 2,2-dichloro-3-oxobutanoate (13a)<sup>a</sup>**

| Entry | solvent                         | Time (h) | yield <sup>b</sup> (%) | ee <sup>c</sup> (%) |
|-------|---------------------------------|----------|------------------------|---------------------|
| 1     | CH <sub>2</sub> Cl <sub>2</sub> | 5        | 91                     | >99                 |
| 2     | EtOAc                           | 17       | 64                     | >99                 |
| 3     | THF                             | 17       | 67 <sup>d</sup>        | >99                 |
| 4     | <sup>i</sup> Pr <sub>2</sub> O  | 3        | 86                     | >99                 |
| 5     | <sup>i</sup> PrOH               | 5        | 81                     | >99                 |

<sup>a</sup> General conditions: **13a** (0.6 mmol), catalyst (*R,R*)-**C2** (0.006 mmol), HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) (101  $\mu$ L), Solvent (3.0 mL) <sup>b</sup> Isolated yield, full conversion except where indicated. <sup>c</sup> Determined by SFC. <sup>d</sup> 92% conversion.

### 2.3.2.3 Concentration and temperature screening

An increase of the reaction concentration from 0.2 to 0.4 and 0.6 mol·L<sup>-1</sup> led to a faster reaction at 40 °C, but with a lower yield (87% or 83%, respectively, Table 4, entries 2 and 3). A slightly higher 96% yield could even be attained by running the reduction at 30 °C for 7 h instead of 40 °C (Table 4, entries 1 and 4). Based on the above screenings, the optimized conditions were set as follows: (*R,R*)-**C2** (0.5 mol %) as the precatalyst, HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) (2.0 equiv), CH<sub>2</sub>Cl<sub>2</sub> (0.2 M) at 30 °C.

**Table 4. Optimization of Reaction Concentration and Temperature for ATH of Benzyl 2,2-dichloro-3-oxobutanoate (13a)<sup>a</sup>**

| Entry          | Temperature (°C) | Concentration (mol·L <sup>-1</sup> ) | Time (h) | yield <sup>b</sup> (%) | ee <sup>c</sup> (%) |
|----------------|------------------|--------------------------------------|----------|------------------------|---------------------|
| 1 <sup>d</sup> | 40               | 0.2                                  | 5        | 91                     | >99                 |
| 2              | 40               | 0.4 <sup>e</sup>                     | 3        | 87                     | >99                 |
| 3              | 40               | 0.6 <sup>f</sup>                     | 3        | 83                     | >99                 |
| 4              | 30               | 0.2                                  | 7        | 96                     | >99                 |

<sup>a</sup> General conditions: **13a** (0.6 mmol), catalyst (*R,R*)-**C2** (0.006 mmol), HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) (101  $\mu$ L), CH<sub>2</sub>Cl<sub>2</sub> (3.0 mL). <sup>b</sup> Isolated yield, full conversion except where indicated. <sup>c</sup> Determined by SFC. <sup>d</sup> The results were taken from Table 2, entry 1. <sup>e</sup> [0.4 M]: CH<sub>2</sub>Cl<sub>2</sub> (1.5 mL). <sup>f</sup> [0.6 M]: CH<sub>2</sub>Cl<sub>2</sub> (1.0 mL).

## 2.3.3 Substrate scope

### 2.3.3.1 ATH of benzyl 2,2-dichloro-3-oxo-alkanoates

With these optimized conditions in hand, we then investigated the scope of the Ru-catalyzed ATH of  $\alpha,\alpha$ -dihalogeno  $\beta$ -ketoester derivatives with a series of variously substituted dichloro and difluoro compounds **13b–13d** (Table 5). The asymmetric reduction of these compounds bearing a benzyl ester and an alkyl ketone proceeded with longer reaction times (21–24 h) compared to the reaction with **13a**, and afforded alcohols **14b–14d** with excellent enantioselectivities, although a lower yield was obtained in the latter case probably because of the more sterically demanding isobutyl substituent (Table 5, entries 2–4 vs entry 1).

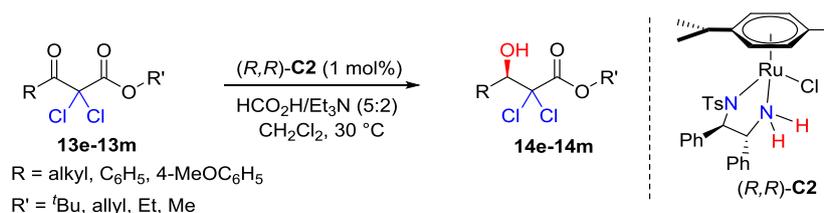
**Table 5.** ATH of benzyl 2,2-dichloro-3-oxo-alkanoates<sup>a</sup>

| entry | product    | time (h) | yield (%) <sup>b</sup> | ee (%) <sup>c</sup> |
|-------|------------|----------|------------------------|---------------------|
| 1     | <b>14a</b> | 7        | 96                     | >99                 |
| 2     | <b>14b</b> | 22       | 70                     | >99                 |
| 3     | <b>14c</b> | 21       | 90                     | 98                  |
| 4     | <b>14d</b> | 24       | 26 <sup>d</sup>        | >99                 |

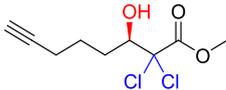
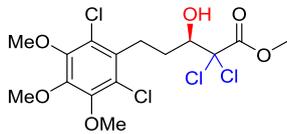
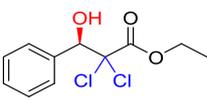
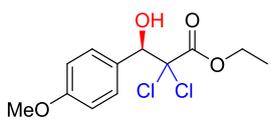
<sup>a</sup> Conditions: **13a–13d** (0.6 mmol), (*R,R*)-**C2** (0.006 mmol), CH<sub>2</sub>Cl<sub>2</sub> (3.0 mL), HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) azeotropic mixture (101  $\mu$ L), 30 °C. The reaction was monitored by TLC and/or <sup>1</sup>H NMR. <sup>b</sup> Isolated yield. <sup>c</sup> Determined by SFC or HPLC analysis. <sup>d</sup> 51% conversion.

## 2.3.3.1 ATH of 2,2-dichloro alkyl or aryl ketones bearing various alkyl esters

The *tert*-butyl and allylester analogues **13e** and **13f** of the standard substrate **13a**, were readily reduced to **14e** and **14f** with high levels of enantioselectivity (Table 6, entries 1 and 2). The ruthenium-mediated reduction of allyl, ethyl or methylester derivatives **13g**, **13h** and **13i** afforded the corresponding alcohols **14g** and **14h** in 98% and 72% yields, and 99% ee, whereas only traces of **14i** having a more hindered isopropyl substituent, were detected (Table 6, entries 3–5). On the other hand,  $\alpha,\alpha$ -dichloro  $\beta$ -ketoester **13j** having a pentynyl substituent on the ketone was converted into **14j** in 76% yield and 98.5% ee (Table 6, entry 6). Although a high enantioselectivity was observed for the ATH of compound **13k** bearing a hexasubstituted benzene ring on the alkyl residue, the reaction proceeded with only 48% yield (Table 6, entry 7). Furthermore, the reduction of aromatic  $\beta$ -ketoesters **13l** and **13m** was also investigated. Both the yields and ee values were moderate for these substrates (Table 6, entries 8 and 9).

Table 6. ATH of 2,2-dichloro alkyl or aryl ketone bearing various alkyl esters<sup>a</sup>

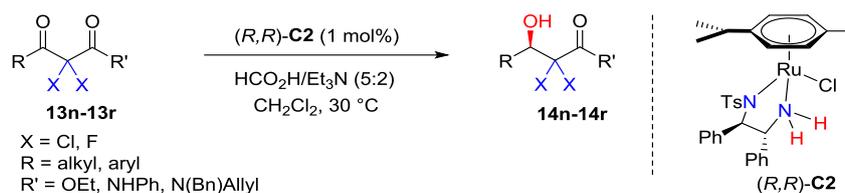
| entry          | product        | time (h) | yield (%) <sup>b</sup> | ee (%) <sup>c</sup> |
|----------------|----------------|----------|------------------------|---------------------|
| 1 <sup>d</sup> | <b>14e</b><br> | 2.5      | 95                     | 99                  |
| 2 <sup>d</sup> | <b>14f</b><br> | 2.5      | 88                     | >99                 |
| 3              | <b>14g</b><br> | 8        | 98                     | 99                  |
| 4              | <b>14h</b><br> | 22       | 72                     | >99                 |
| 5              | <b>14i</b><br> | 22       | -- <sup>e</sup>        | -- <sup>e</sup>     |

|   |            |   |    |    |      |
|---|------------|---|----|----|------|
| 6 | <b>14j</b> |  | 9  | 76 | 98.5 |
| 7 | <b>14k</b> |  | 24 | 48 | 98   |
| 8 | <b>14l</b> |  | 24 | 50 | 70   |
| 9 | <b>14m</b> |  | 24 | 34 | 71   |

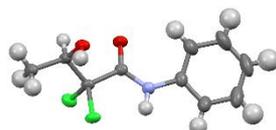
<sup>a</sup> Conditions: **13a-13r** (0.6 mmol), (*R,R*)-**C2** (0.006 mmol), CH<sub>2</sub>Cl<sub>2</sub> (3.0 mL), HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) azeotropic mixture (101  $\mu$ L), 30 °C. The reaction was monitored by TLC and/or <sup>1</sup>H NMR. <sup>b</sup> Isolated yield. <sup>c</sup> Determined by SFC or HPLC analysis. <sup>d</sup> Reaction conducted on 1.0 mmol of **13e-13f** with 0.005 mmol of (*R,R*)-**C2**. <sup>e</sup> Traces of product **14i**, ee not measured.

Additionally, fluorinated alkyl compounds were also evaluated and  $\alpha,\alpha$ -difluoro  $\beta$ -ketoesters **13n** and **13o** were efficiently reduced, even at room temperature, in excellent 99% yields and 98% ee (Table 7, entries 1 and 2). A quantitative yield was also obtained in the preparation of the benzylalcohol derivative **14p**, although the ee was only moderate as previously observed for the parent dichlorinated compound **14l** (Table 7, entries 3 and Table 6, entry 8). Furthermore, the substrate scope was extended to  $\alpha,\alpha$ -dichloro  $\beta$ -keto amides with the ATH of compounds **13q** and **13r**. Thus, enantiomerically enriched *N*-phenyl 2,2-dichloro-3-hydroxybutanamide **14q** and *N*-allyl-*N*-benzyl 2,2-dichloro-3-hydroxybutanamide **14r** were readily prepared with high yields and ee values (Table 7, entries 4 and 5). The absolute configuration of alcohol **14q** was unambiguously assigned as (*R*) by X-ray crystallographic analysis. In addition, comparison of the optical rotation value of compound **14p** with the reported literature data confirmed its (*R*) absolute configuration ( $[\alpha]_{\text{D}}^{25} = -6.8$  (c 1.0, CHCl<sub>3</sub>), lit.<sup>183</sup>  $[\alpha]_{\text{D}}^{24} = -13.4$  (c 1.29, CHCl<sub>3</sub>, 97% ee). By analogy, we conjecture that the remainder of the ATH products **14** followed the same trend.

<sup>183</sup> Iseki, K.; Kuroki, Y.; Asada, D.; Takahashi, M.; Kishimoto, S.; Kobayashi, Y. *Tetrahedron* **1997**, *53*, 10271.

Table 7. ATH of  $\alpha,\alpha$ -Dichloro- and  $\alpha,\alpha$ -Difluoro-Alkyl Ketone Derivatives <sup>a</sup>

| entry          | product    | time (h) | yield (%) <sup>b</sup> | ee (%) <sup>c</sup> |      |
|----------------|------------|----------|------------------------|---------------------|------|
| 1 <sup>d</sup> | <b>14n</b> |          | 5                      | 99                  | 98   |
| 2 <sup>d</sup> | <b>14o</b> |          | 13                     | 99                  | 98   |
| 3              | <b>14p</b> |          | 5                      | 99                  | 56   |
| 4 <sup>e</sup> | <b>14q</b> |          | 14                     | 93                  | 98.5 |
| 5              | <b>14r</b> |          | 3                      | 99                  | 98   |

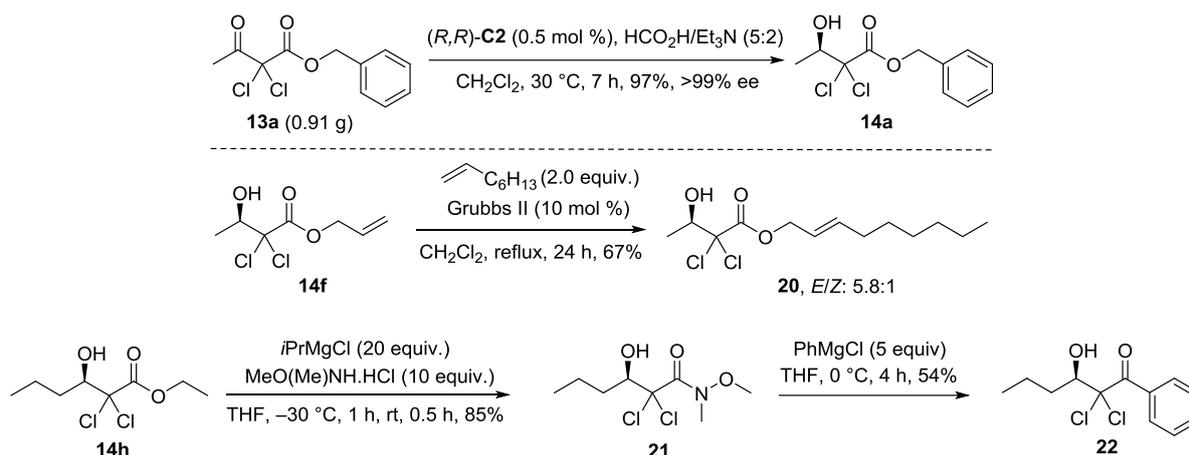
X-ray crystallographic structure of **14q**

<sup>a</sup> Conditions: **13n-13r** (0.6 mmol),  $(R,R)\text{-C2}$  (0.006 mmol),  $\text{CH}_2\text{Cl}_2$  (3.0 mL),  $\text{HCO}_2\text{H}/\text{Et}_3\text{N}$  (5:2) azeotropic mixture (101  $\mu\text{L}$ ), 30  $^\circ\text{C}$ . The reaction was monitored by TLC and/or  $^1\text{H}$  NMR. <sup>b</sup> Isolated yield. <sup>c</sup> Determined by SFC or HPLC analysis. <sup>d</sup> Reaction carried out at rt. <sup>e</sup> Reaction conducted on 1.0 mmol of **13** with 0.005 mmol of  $(R,R)\text{-C2}$ .

## 2.4 Scale up experiment and post-functionalization reaction

Additionally, a scale-up experiment was carried out on compound **13a** (0.91 g, 3.48 mmol) using a lower catalyst loading of 0.5 mol% and furnished the same yield and ee value as observed on a 0.6 mmol scale (Scheme 108). Furthermore, post-functionalization of **14f** and **14h** was studied. Thus, a cross metathesis between allyl (*R*)-2,2-dichloro-3-hydroxy-5-butanolate **14f** and 1-octene using Grubbs II catalyst allowed formation of alkene **20** in 67%

yield as a 5.8:1 mixture of *E* and *Z* isomers. On the other hand, ethyl (*R*)-2,2-dichloro-3-hydroxyhexanoate **14h** was readily converted into the corresponding  $\beta$ -hydroxy Weinreb amide **21** in the presence of *N,O*-dimethylhydroxylamine hydrochloride and isopropylmagnesium chloride in 85% yield. The amide could then serve as a ketone precursor and was for instance transformed into the phenyl ketone **22** by treatment with phenylmagnesium chloride (Scheme 107).



Scheme 107

## 2.5 Proposed rationale for the stereochemical outcome of the ATH

For alkyl substrates, a stabilizing  $C(sp^3)$ -H/X interaction favors the transition state shown below, leading to high enantioselectivities in favor of the (*R*)-alcohol (Figure 6).

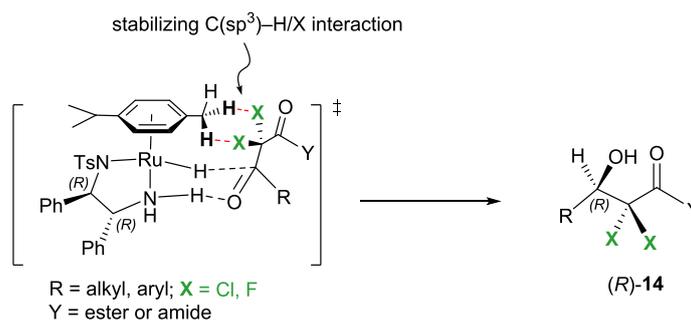


Figure 6

For aryl substrates, a competitive  $C(sp^3)$ -H/ $\pi$  interaction (shown below), which would favor formation of the (*S*)-alcohol, would explain the lower enantioselectivity observed for the (*R*)-alcohol (Figure 7).

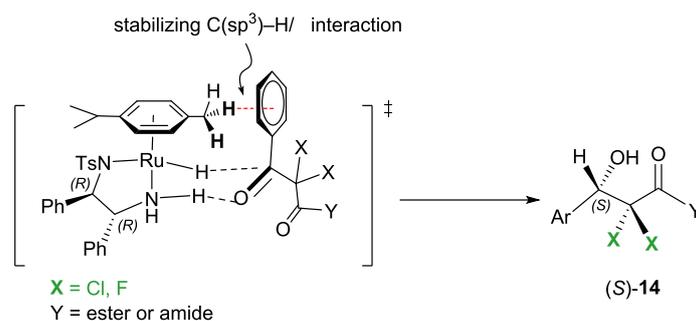


Figure 7

## 2.6 Conclusion

In conclusion, highly enantiomerically enriched  $\alpha,\alpha$ -dichloro or  $\alpha,\alpha$ -difluoro  $\beta$ -hydroxy esters and  $\beta$ -hydroxy amides can be prepared through ruthenium-catalyzed asymmetric transfer hydrogenation of the corresponding ketones under mild conditions. The use of commercially available precatalyst [RuCl(*p*-cymene)(*R,R*)-TsDPEN] (*S/C* = 100–200) in the presence of formic acid/triethylamine (5:2) as the hydrogen source allowed the efficient reduction of a wide range of non-aromatic  $\alpha,\alpha$ -dihalogeno  $\beta$ -keto esters bearing alkyl ketones in good to high yields (up to 99% yield) and with excellent enantioselectivities (up to > 99% ee) whereas aromatic derivatives led to moderate ee values. The reaction was tolerant of various esters as well as being applicable to amides. Moreover, the ATH was efficiently performed on gram-scale with compound **13a** demonstrating the usefulness of this method.



**PART C:**

**ATH of ketone derivatives *via*  
dynamic kinetic resolution**



## Part C: ATH of ketone derivatives via dynamic kinetic resolution

### 1. Short overview on ATH-DKR of ketones

#### 1.1 Resolution methods

Considering chirality is widely present in many natural products, the importance of asymmetric synthesis is now indubitable. Moreover, this concept of chirality is also directly related to the biological activity of drugs. Thus, discovering and developing new asymmetric reactions is crucial in organic synthesis.<sup>184</sup>

There are three major methods to access enantioenriched compounds:

\* Use of the chiral pool: natural amino acids, sugar, ...

\* Asymmetric synthesis: the formation of a new stereogenic center through an enantiofacial discrimination in the transition state, is controlled by either an existing stereocenter on the substrate (chiral substrate or chiral auxiliary) or a chiral reagent and/or a chiral catalyst (chiral ligands/metal complex, chiral organocatalysts, enzyme, ...).

\* Resolution allows the partial or total separation into its components of a racemic mixture through kinetic resolution (KR) or dynamic kinetic resolution (DKR).<sup>185</sup>

*In this bibliographical part, we will discuss about the resolution process and detail kinetic resolution and dynamic kinetic resolution.*

##### 1.1.1 Kinetic resolution (KR)

Kinetic resolution<sup>186</sup> is the most ancient process which allows an access to enantioenriched compounds. Louis Pasteur observed, in 1858, that fermentation of an aqueous solution of racemic ammonium tartrate by a *penicillium glaucum* mold destroyed only the dextrorotatory enantiomer.<sup>187</sup> In 1889, Marckwald and McKenzie discovered the first example of a non-enzymatic kinetic resolution while working on the esterification of mandelic acid with

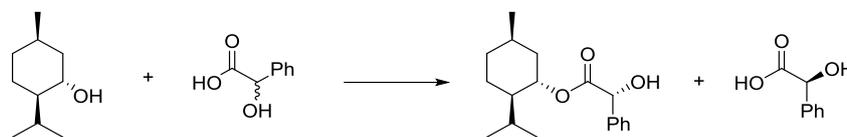
<sup>184</sup> (a) Noyori, R. *Angew. Chem. Int. Ed.* **2013**, *52*, 79. (b) Fürstner, A. *Angew. Chem. Int. Ed.* **2014**, *53*, 8587.

<sup>185</sup> Fogassy, E.; Nógrádi, M.; Kozma, D.; Egri, G.; Pálóvics, E.; Kiss, V. *Org. Biomol. Chem.* **2006**, *4*, 3011.

<sup>186</sup> (a) Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249. (b) Vedejs, E.; Jure, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 3974.

<sup>187</sup> Pasteur, L. *C. R. Hebd. Séances Acad. Sci.* **1858**, *46*, 615.

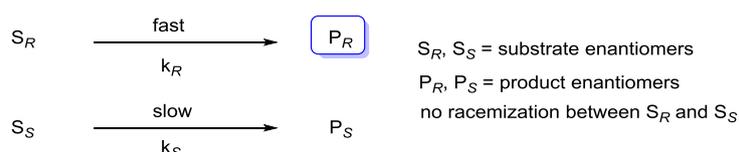
(-)-menthol. When they stopped the reaction before full conversion was reached, the authors found the reaction mixture was enriched with the less reactive enantiomer, *i.e.* (-)-mandelic acid (Scheme 108).<sup>188</sup>



Scheme 108

Principle of kinetic resolution:

To carry out a kinetic resolution process, the two enantiomers  $S_R$  and  $S_S$  of a racemate must react at different rates with a chiral reagent (reagent control) or an achiral reagent when the reaction is catalyzed by a chiral catalyst (chiral catalyst control), to generate two enantiomeric products ( $P_R$  and  $P_S$ ). To achieve an efficient kinetic resolution process, the reaction rates of the two enantiomers should be sufficiently different:  $k_R \gg k_S$  ( $k_R/k_S$  ratio should be at least 20). If the kinetic resolution is efficient enough, and in an ideal case, the  $S_R$  enantiomer is transformed into the desired product  $P_R$  while the  $S_S$  enantiomer is recovered unchanged. However, the major limitation of this process is a maximum theoretical yield of 50%. Moreover, the case where the  $S_S$  enantiomer does not react corresponds to an ideal state. In fact, for kinetic reasons, the enantiomeric excess of  $P_R$  decreases when approaching 50% conversion because the reactivity of the  $S_S$  is increased. (Scheme 109)<sup>189</sup>



Scheme 109

Therefore, 50% of the undesired enantiomer must be separated and eliminated (or recycled). To overcome this drawback, addition of a racemizing agent would allow rapid interconversion of the unreacted  $S_S$  enantiomer into the  $S_R$  enantiomer, and the latter could then react and be converted into the desired product  $P_R$ . This is called dynamic kinetic resolution (DKR).

<sup>188</sup> Marckwald, W.; McKenzie, A. *Ber. Dtsch. Chem. Ges.* **1899**, 32, 2130.

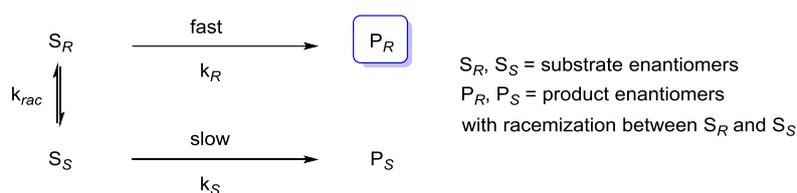
<sup>189</sup> (a) Ward, R. S. *Tetrahedron: Asymmetry* **1995**, 6, 1475. (b) Pellissier, H. *Tetrahedron* **2003**, 59, 8291.

### 1.1.2 Dynamic kinetic resolution (DKR)

Dynamic kinetic resolution<sup>190</sup> is a combination between a kinetic resolution and a dynamic racemization process. The kinetic resolution step ensures the efficient transformation into one enantiomer of the product (enantioinduction). Meanwhile, the rapid epimerization between the two enantiomers of the racemic mixture makes it possible to have a theoretical 100% yield.

#### Conditions for an efficient DKR process

To achieve an efficient DKR process, the racemic starting material has to racemize rapidly under the reaction conditions. This racemization can be bio-catalyzed, chemically induced or can occur spontaneously *in situ*. The DKR process applies to substrates bearing a labile stereocenter. However, if the latter point is a necessary condition, it is not sufficient. Indeed, the following conditions have to be fulfilled to obtain an efficient DKR (Scheme 110):



**Scheme 110**

- \*  $k_{\text{rac}} \gg k_R, k_S$ : the racemization rate ( $k_{\text{rac}}$ ) has to be faster than the rate of the asymmetric transformation ( $k_R$  and  $k_S$ ).
- \*  $k_R > k_S$ : one of the enantiomers has to react faster than the other one with the chiral reagent
- \* The reaction with the chiral reagent has to be irreversible.
- \* The products formed during the reaction have to be stable enough to avoid any racemization.

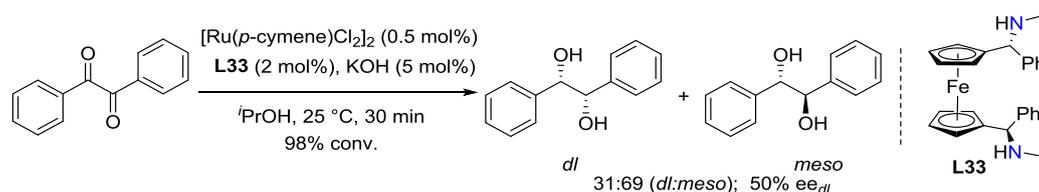
Provided all the above conditions are respected, the DKR process would be likely to provide the product with a 100% theoretical yield and 100% enantiomeric excess.

<sup>190</sup> Reviews on DKR: (a) Noyori, R.; Tokunaga, M.; Kitamura, M. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36. (b) Caddick, S.; Jenkins, K. *Chem. Soc. Rev.* **1996**, *25*, 447. (c) Faber, K. *Chem. Eur. J.* **2001**, 5004. (d) Huerta, F.; Minidis, A.; Bäckvall, J. *Chem. Soc. Rev.* **2001**, *30*, 321. (e) Pàmies, O.; Bäckvall, J.-E. *Chem. Rev.* **2003**, *103*, 3247. (f) Turner, N. J. *Curr. Opin. Chem. Biol.* **2004**, *8*, 114. (g) Martín-Matute, B.; Bäckvall, J.-E. *Curr. Opin. Chem. Biol.* **2007**, *11*, 226. (h) Pellissier, H. *Tetrahedron* **2008**, *64*, 1563. (i) Pellissier, H. *Adv. Synth. Catal.* **2011**, *353*, 659. (j) Pellissier, H. *Tetrahedron* **2011**, *67*, 3769. (k) Echeverria, P.-G.; Ayad, T.; Phansavath, P.; Ratovelomanana-Vidal, V. *Synthesis* **2016**, *48*, 2523 (l) Bhat, V.; Welin, E. R.; Guo, X.; Stoltz, B. M. *Chem. Rev.* **2017**, *117*, 4528 and references therein.

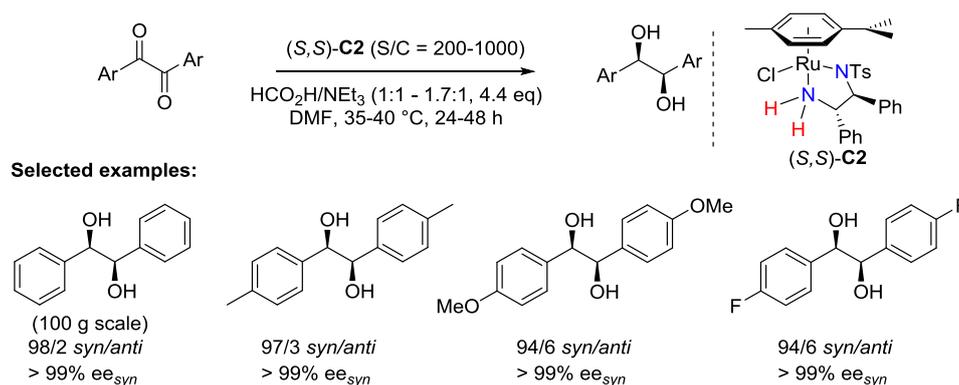
## 1.2 Examples of DKR/ATH of ketone derivatives

## 1.2.1 DKR/ATH of 1,2-diketones

In 1998, Knochel *et al.* described the first example of an asymmetric reaction based on the combination of ATH and DKR by using a ruthenium complex bearing a  $C_2$ -symmetrical ferrocenyl diamine ligand formed *in situ* and 2-propanol as hydrogen source, for the asymmetric reduction of benzyl (Scheme 111).<sup>191</sup> A moderate diastereoselectivity was observed with an enantioselectivity of 50% for the *dl* isomer.



In 1999, Noyori, Ikariya *et al.* reported the first practical asymmetric transfer reduction of 1,2-diketones via dynamic kinetic resolution to access chiral 1,2-diols catalyzed by well-defined chiral  $Ru^{II}$  catalyst with the  $HCO_2H/Et_3N(5:2)$  azeotropic mixture as a hydrogen source. This method provides (*R,R*)-hydrobenzoin quantitatively with high diastereomeric and enantiomeric purities. Furthermore, the process could be applicable to a 100 gram scale without loss of selectivity (Scheme 112).<sup>192</sup>

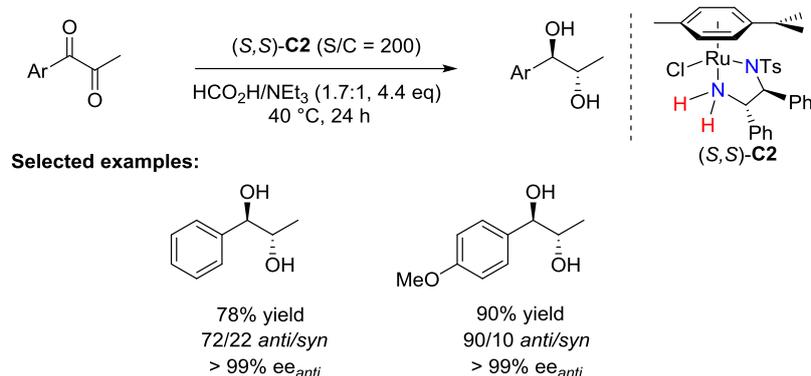


In 2000, the same group described the ATH of unsymmetrical 1,2-diketones *via* DKR using the previous conditions to prepare the corresponding *anti* diols with good

<sup>191</sup> Schwink, L.; Ireland, T.; Püntener, K.; Knochel, P. *Tetrahedron: Asymmetry* **1998**, *9*, 1143.

<sup>192</sup> Murata, K.; Okano, K.; Miyagi, M.; Iwane, H.; Noyori, R.; Ikariya, T. *Org. Lett.* **1999**, *1*, 1119.

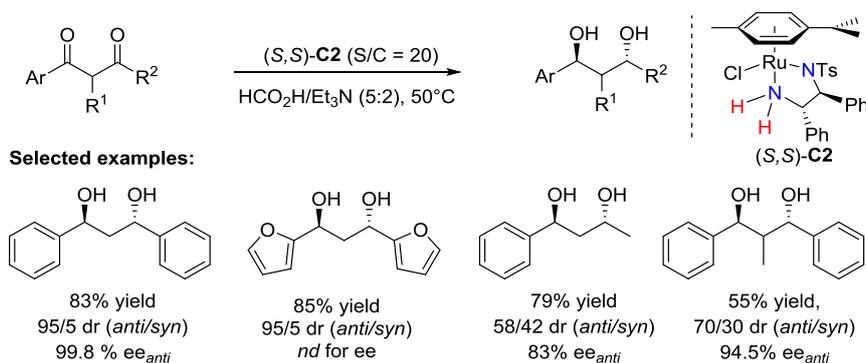
diastereoselectivities and high enantioinductions (Scheme 113).<sup>193</sup>



Scheme 113

### 1.2.2 DKR/ATH of 1,3-diketones

In 2001, Cossy *et al.* described the synthesis of *anti* 1,3-diols through transfer hydrogenation of 2-methyl-1,3-diketone by using [RuCl(*p*-cymene)((*S,S*)-Ts-DPEN)] (*S,S*)-C2 in the presence of HCO<sub>2</sub>H/Et<sub>3</sub>N (Scheme 114).<sup>194</sup>



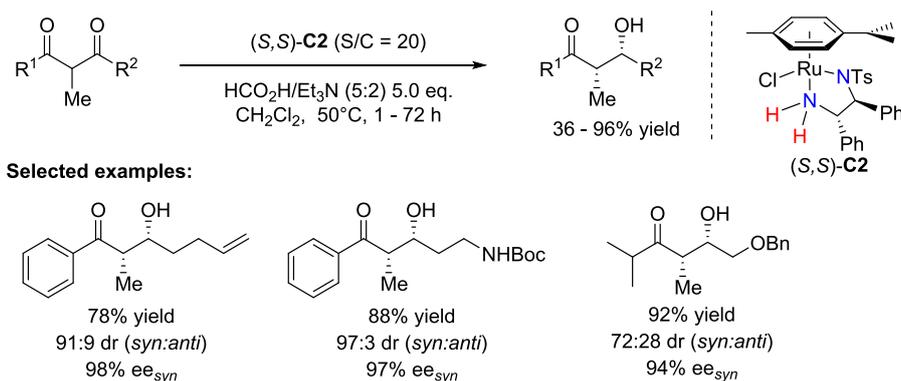
Scheme 114

In 2002, the same group reported Ru-catalyzed DKR/ATH of unsymmetrical 2-alkyl 1,3-diketones in the presence of HCO<sub>2</sub>H/Et<sub>3</sub>N, providing *syn* 2-alkyl 3-hydroxy ketones for a variety of linear substrates with acceptable to high dr (66:34 to 97:3) and high enantioselectivity (88–98% ee) (Scheme 115).<sup>195</sup>

<sup>193</sup> Koike, T.; Murata, K.; Ikariya, T. *Org. Lett.* **2000**, *2*, 3833.

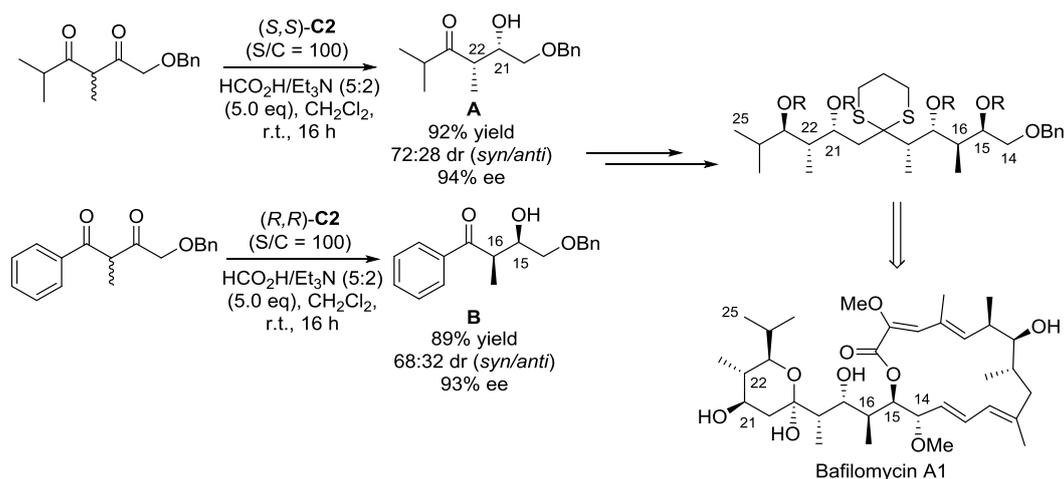
<sup>194</sup> Cossy, J.; Eustache, F.; Dalko, P. I. *Tetrahedron Lett.* **2001**, *42*, 5005.

<sup>195</sup> Eustache, F.; Dalko, P. I.; Cossy, J. *Org. Lett.* **2002**, *4*, 1263.



Scheme 115

In 2003, the same group reported an application of this method for the total synthesis of the C<sup>14</sup>-C<sup>25</sup> fragment of Bafilomycin A1. The two key intermediates *syn*-2-methyl-3-hydroxy ketones **A** and **B** were prepared via DKR/ATH of *rac* 2-methyl 1,3-diketones by using ruthenium complexes (*S,S*)-**C2** or (*R,R*)-**C2** (Scheme 116).<sup>196</sup>



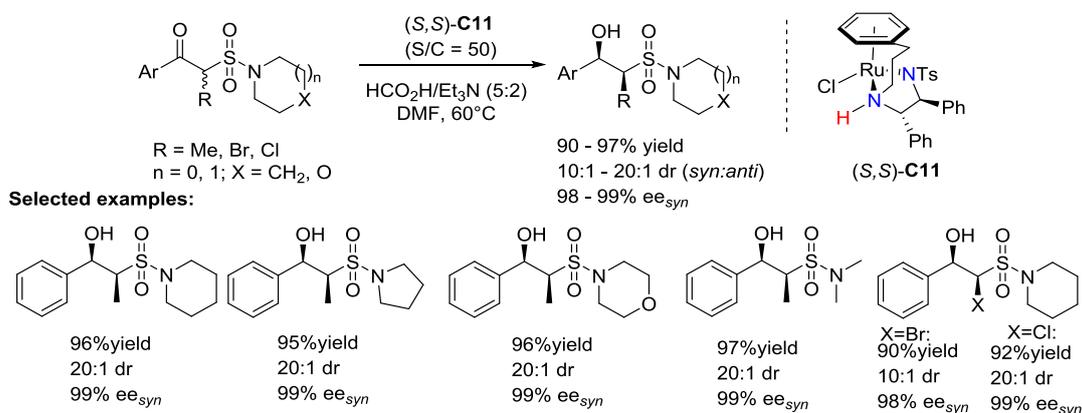
Scheme 116

In 2016, Mohar *et al.* described a diastereo- and enantio-selective synthesis of CF<sub>3</sub>-substituted 1,3-diols by Ru-catalyzed DKR/ATH of the corresponding 1,3-diketones. Highly diastereo- and enantioenriched *anti* 1,3-diols were obtained under mild conditions. In particular, CF<sub>3</sub>C(O)-substituted benzo-fused cyclic ketones underwent either a single or a double dynamic kinetic resolution during their reduction (Scheme 117).<sup>175e</sup>

<sup>196</sup> a) Eustache, F.; Dalko, P. I.; Cossy, J. *J. Org. Chem.* **2003**, *68*, 9994. b) Eustache, F.; Dalko, P. I.; Cossy, J. *Tetrahedron Lett.* **2003**, *44*, 8823.



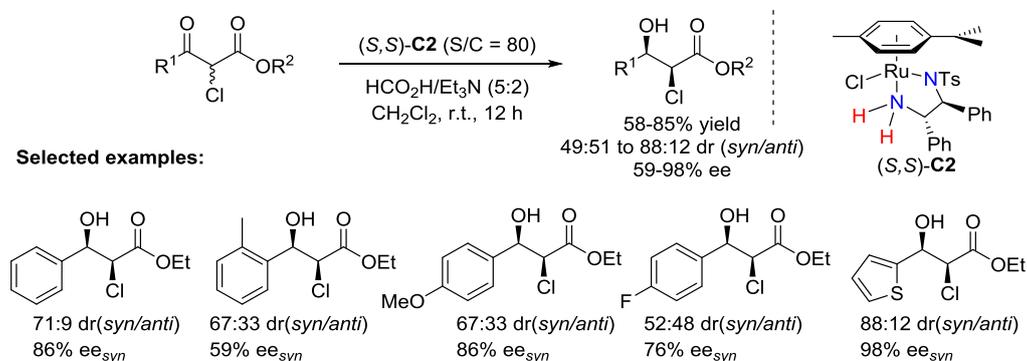
$\alpha$ -substituted  $\beta$ -hydroxy sulfonamides in good yields with excellent diastereo- and enantioselectivities (Scheme 119).<sup>198</sup>



Scheme 119

### 1.2.3.2 DKR/ATH of $\alpha$ -chloro- $\beta$ -keto esters

In 2011, Zhang and coworkers reported the synthesis of 2-chloro-3-hydroxy esters via the Ru-catalyzed DKR/ATH of 2-chloro-3-ketoesters using HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) as a hydrogen source under mild conditions. The reaction proceeded with moderate to good yields (up to 85%), and diastereo- and enantio-selectivities (up to 98% *ee*, 88:12 *dr*) (Scheme 120).<sup>199</sup>



Scheme 120

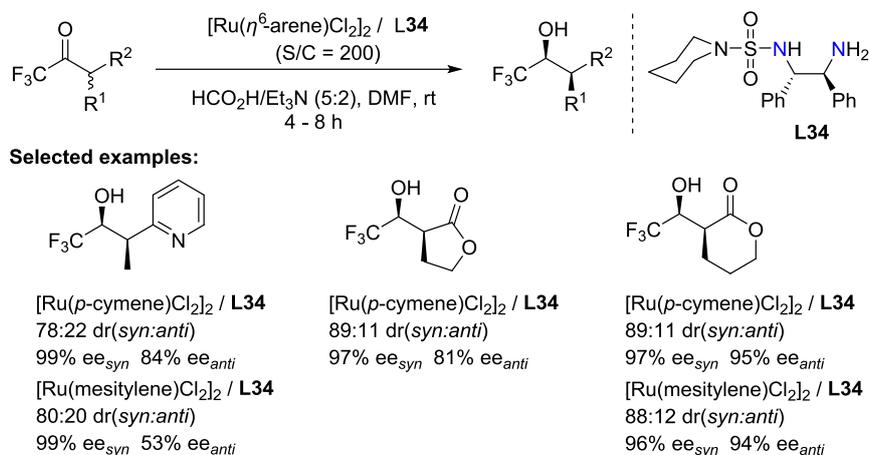
### 1.2.3.3 DKR/ATH of $\alpha$ -alkyl $\beta$ -ketoesters and $\beta$ -ketoamides

In 2006, Mohar, Stephan *et al.* reported a [RuCl( $\eta^6$ -arene)((*S,S*)-R<sub>2</sub>NSO<sub>2</sub>DPEN)] complex formed *in situ* for the ATH of fluoroalkyl ketones by using HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) to give the corresponding alcohols with high *ee* and in excellent yields. The catalysts were also investigated in the DKR/ATH of 1-(pyridin-2-yl)ethyl trifluoromethyl ketone and  $\alpha$ -

<sup>198</sup> Xiong, Z.; Pei, C.; Xue, P.; Lv, H.; Zhang, X. *Chem. Commun.* **2018**, 54, 3883.

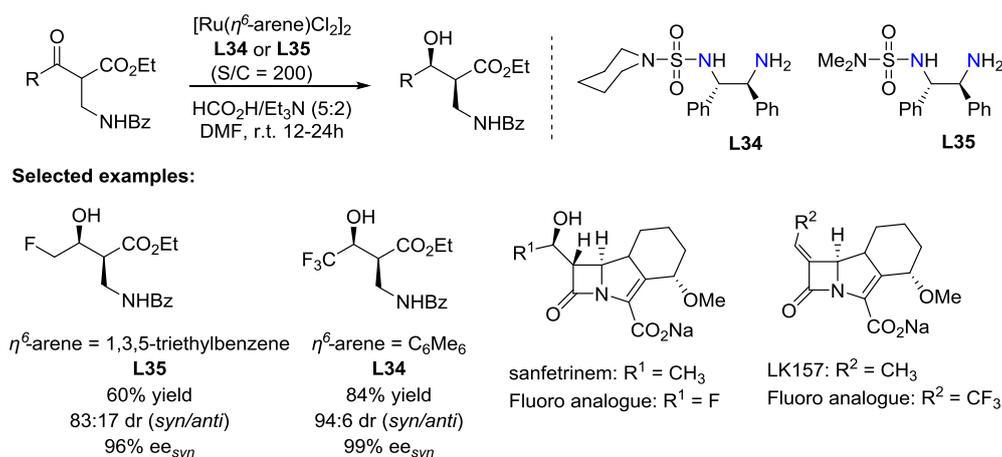
<sup>199</sup> Bai, J.; Miao, S.; Wu, Y.; Zhang, Y. *Chin. J. Chem.* **2011**, 29, 2476.

trifluoroacetyl-lactones, giving excellent enantioselectivities and good diastereoselectivities (Scheme 121).<sup>175c</sup>



Scheme 121

In 2009-2010, the same group reported the application of this method to the synthesis of fluorine substituted β-lactam antibiotic analogues (Scheme 122).<sup>200</sup>

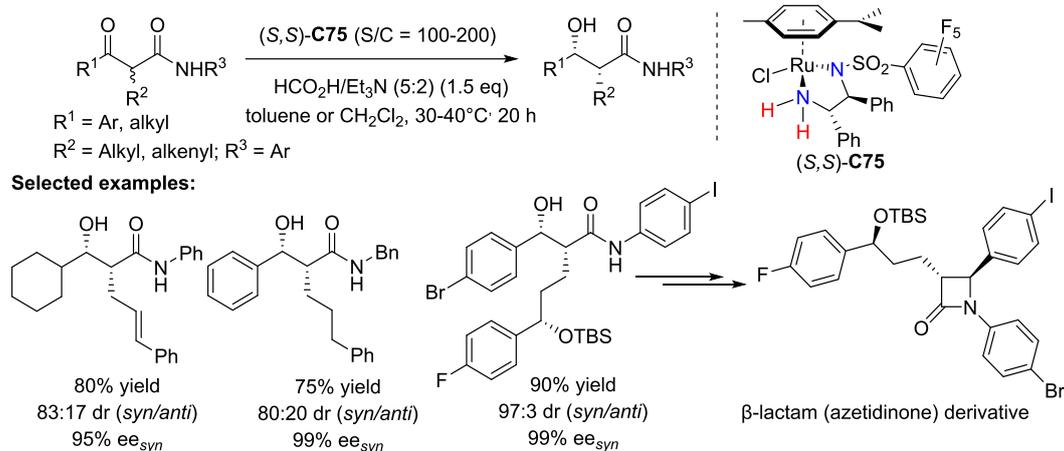


Scheme 122

In 2010, Limanto, Krska *et al.* described the DKR/ATH of various  $\alpha$ -alkyl-substituted  $\beta$ -ketoamides using 0.5–1 mol % of *p*-fluorobenzenesulfonyl-DPEN-Ru catalyst and HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) as the hydrogen source at 30–40 °C in either PhCH<sub>3</sub> or CH<sub>2</sub>Cl<sub>2</sub>. The corresponding *syn*- $\beta$ -hydroxy amides were obtained in good yields (75–88%), high diastereo- (15–33:1 dr) and enantioselectivities (93–97% ee). This method was applied to the synthesis of

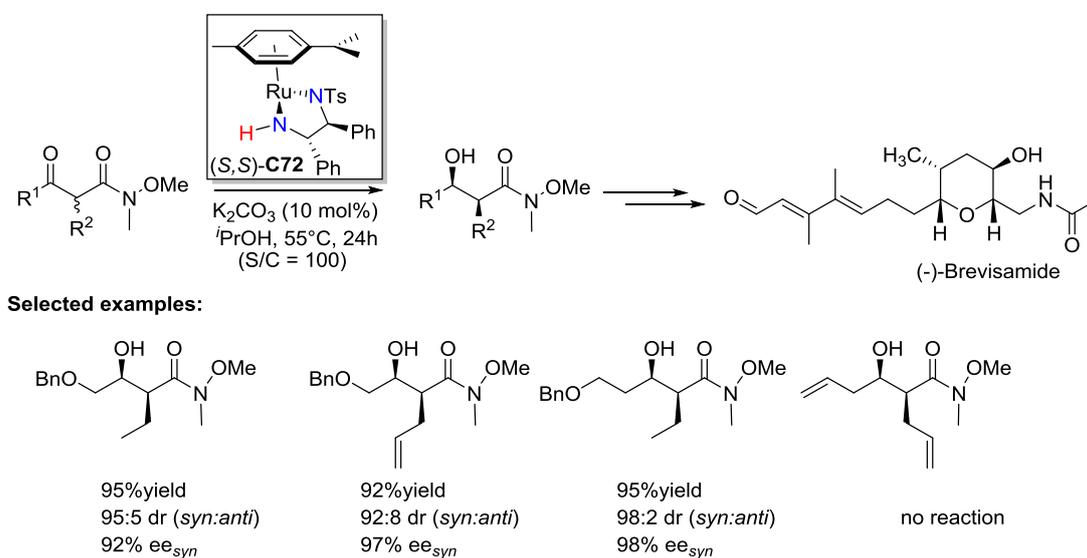
<sup>200</sup> (a) Plantan, I.; Stephan, M.; Urleb, U.; Mohar, B. *Tetrahedron Lett.* **2009**, *50*, 2676. (b) Mohar, B.; Stephan, M.; Urleb, U. *Tetrahedron* **2010**, *66*, 4144.

an azetidinone derivative (Scheme 123).<sup>201</sup>



Scheme 123

In 2013, Kumaraswamy *et al.* reported an access to stereodefined  $\delta$ - and  $\gamma$ -alkoxy- $\beta$ -hydroxy- $\alpha$ -alkyl-substituted Weinreb amides encompassing two contiguous hydroxyl-bearing and alkyl-bearing stereocenters *via* Ru-catalyzed the DKR/ATH of the corresponding ketoamides by using *i*PrOH as the hydrogen source and  $K_2CO_3$  as a base. Further, this strategy coupled with organo-catalyzed asymmetric epoxidation culminates in the synthesis of a critical intermediate of (–)-brevisamide and its diastereomers (Scheme 124).<sup>202</sup>



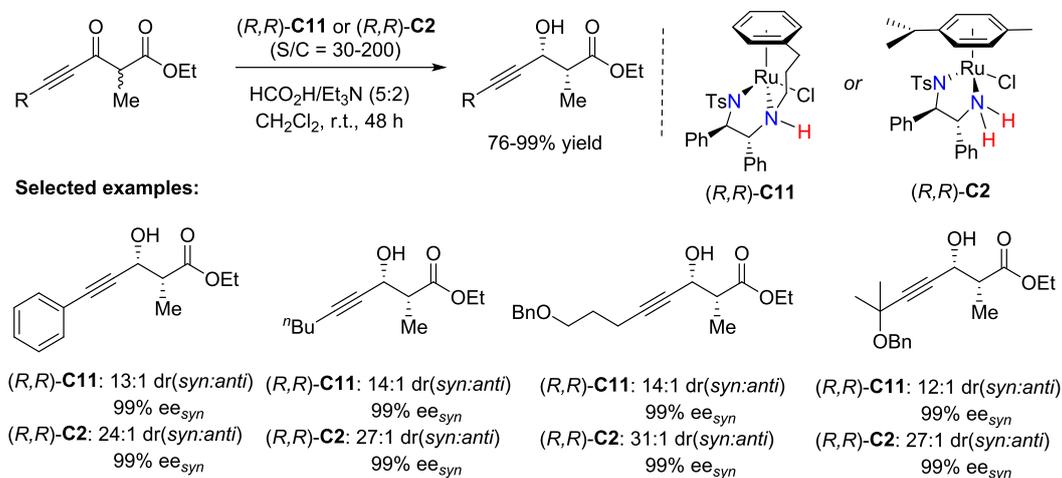
Scheme 124

In 2013, Wills *et al.* reported the DKR/ATH of a range of  $\alpha$ -methyl alkynyl substituted

<sup>201</sup> Limanto, J.; Krska, S. W.; Dorner, B. T.; Vazquez, E.; Yoshikawa, N.; Tan, L. *Org. Lett.* **2010**, *12*, 512.

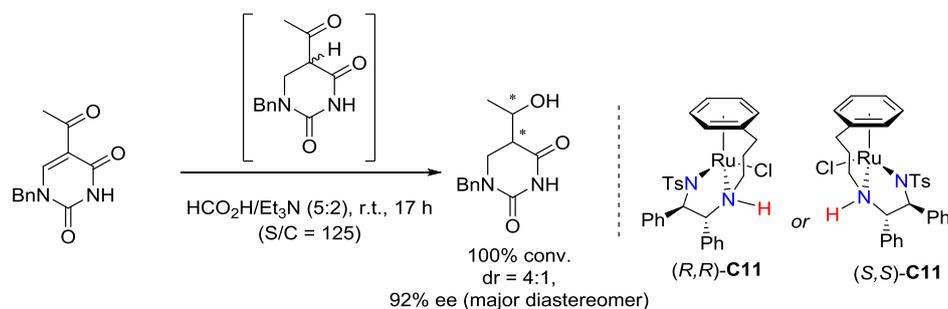
<sup>202</sup> Kumaraswamy, G.; Narayana Murthy, A.; Narayanarao, V.; Vemulapalli, S. P. B.; Bharatam, J. *Org. Biomol. Chem.* **2013**, *11*, 6751.

$\beta$ -ketoamides catalyzed by [RuCl(*p*-cymene)((*R,R*)-TsDPEN)] (*R,R*)-**C2** or [RuCl((*R,R*)-teth-TsDPEN)] (*R,R*)-**C11** in the presence of HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) as the hydrogen source under mild conditions, to generate the corresponding *syn*-products with a higher diastereomeric ratio for the former catalyst (Scheme 125).<sup>145b</sup>



Scheme 125

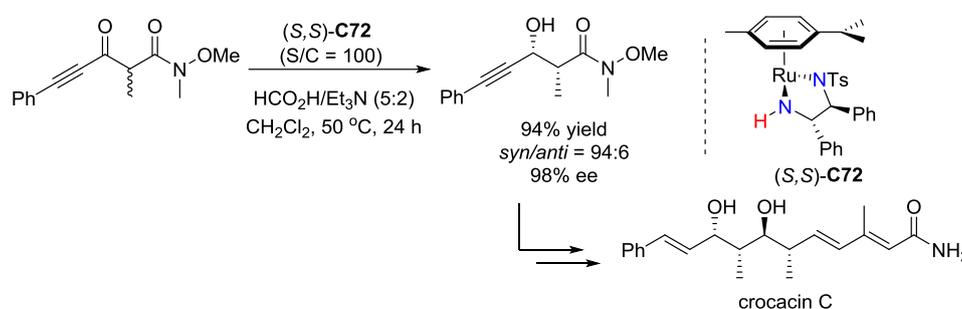
In 2014, Wills and coworkers described the ATH of *N*-benzyl-5-acetyluracil catalyzed by ruthenium catalysts (*R,R*)-**C11** or (*S,S*)-**C11** by using HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) as the hydrogen source (Scheme 126).<sup>203</sup> Interestingly, the use of catalyst (*R,R*)-**C11** resulted in the formation of the reduced compound in a 4:1 diastereomeric ratio (the relative configurations of the diastereomers were not determined) in 92% and 33% ee, respectively, whilst catalyst (*S,S*)-**C11** gave similar results in terms of stereoselectivity delivering the same major diastereomer. These results suggest that conjugate addition occurred first, resulting in the formation of an enol intermediate, which would tautomerize to give a racemic ketone whose reduction may then proceed *via* a (dynamic) kinetic resolution.



Scheme 126

<sup>203</sup> Bisset, A. A.; Dishington, A.; Jones, T.; Clarkson, G. J.; Wills, M. *Tetrahedron* **2014**, *70*, 7207.

In 2015, Kumaraswamy and coworkers reported a concise diastereoselective formal synthesis of the potent antifungal and cytotoxic agent (+)-crocacin C. The key step involves the Ru(II)-catalyzed ATH of an  $\alpha$ -methylated  $\beta$ -keto Weinreb amide combined with a dynamic kinetic resolution process to provide the corresponding alcohol with *syn*-configuration as the key intermediate of crocacin C. The initial experiment was carried out in dichloromethane at 50 °C by using 18-electron complex [RuCl(*p*-cymene)((*R,R*)-TsDPEN)] **C2** with a substrate to catalyst ratio (S/C = 33) in the presence of HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) azeotropic mixture as the hydrogen source. A good yield (60%), diastereoselectivity (*syn/anti* = 92:8), and high enantioselectivity (92% ee) were obtained for the acetylenic  $\alpha$ -methylated  $\beta$ -hydroxy Weinreb amide. Interestingly, better results (94% yield, 98% ee and *syn/anti* = 94:6) could be obtained by switching to isolated 16-electron Ru-TsDPEN amido complex (*S,S*)-**C72** at a lower catalyst loading (S/C = 100) (Scheme 127).<sup>204</sup>



Scheme 127

### 1.2.3.4 DKR/ATH of $\alpha$ -alkoxy (or silyloxy) $\beta$ -keto esters (or phosphonates)

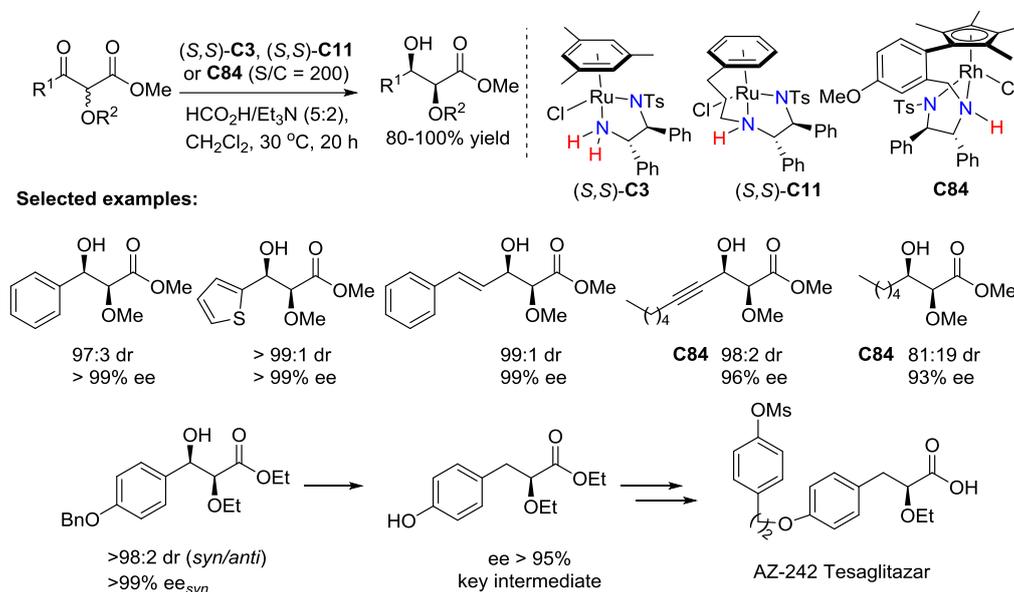
In 2010, our group reported the enantio- and diastereoselective approach to access  $\alpha$ -alkoxy-substituted *syn*  $\beta$ -hydroxy esters through highly efficient Ru-catalyzed ATH *via* DKR. In this atom-economical process, excellent diastereoselectivities (up to 99/1 dr) and almost perfect enantioselectivities (up to 99% ee) were obtained for a wide variety of aromatic and heteroaromatic monodifferentiated *syn*-1,2-diols that are otherwise difficult to prepare by asymmetric catalysis. However, the drawback of a narrow substrate scope for aryl and heteroaryl substituents limits its application (Scheme 128).<sup>205</sup>

Following this study, our group described in 2015, Ru(II) complexes (*S,S*)-**C3**, (*S,S*)-**C11** and Rh(III) tethered precatalyst **C84** in this reaction for more challenging substrates bearing alkenyl-, alkynyl-, and alkyl substituents to provide the corresponding *syn*  $\alpha$ -alkoxy- $\beta$ -

<sup>204</sup> Kumaraswamy, G.; Narayanarao, V.; Shanigaram, P.; Balakishan, G. *Tetrahedron* **2015**, *71*, 8960.

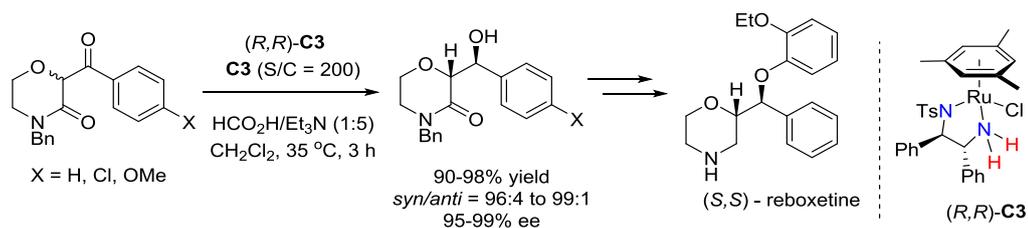
<sup>205</sup> Cartigny, D.; Püntener, K.; Ayad, T.; Scalone, M.; Ratovelomanana-Vidal, V. *Org. Lett.* **2010**, *12*, 3788.

hydroxy esters with excellent enantiocontrol (up to 99% ee) and good to perfect diastereocontrol (70:30 to >99:1 dr). Moreover, to demonstrate the usefulness of this ATH/DKR protocol, a short synthetic pathway was developed to access a key intermediate to AZ-242 Tesaglitazar possessing type II antidiabetic properties (Scheme 128).<sup>206</sup>



Scheme 128

In 2013, Lee *et al.* reported Ru-catalyzed DKR/ATH of 2-benzoylmorpholin-3-ones to efficiently produce the corresponding (2*R*,3*S*)- or (2*S*,3*R*)-2-(hydroxyphenylmethyl) morpholin-3-ones with an excellent level of diastereo- and enantioselectivity for controlling two contiguous stereogenic centers in a single step (Scheme 129).<sup>207</sup> Additionally, this process was employed to prepare all four stereoisomers of the antidepressant reboxetine.



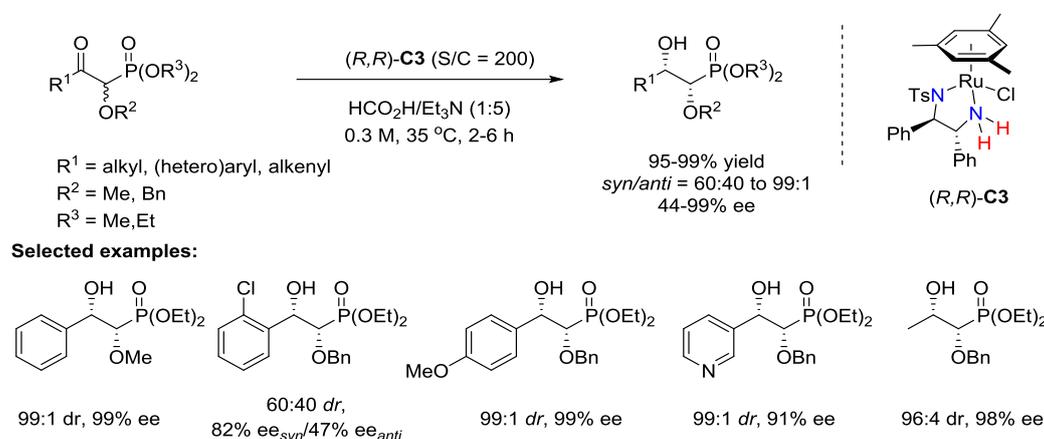
Scheme 129

In 2014, Lee and co-worker described a general protocol for the ATH of a wide range of *racemic* 2-substituted  $\alpha$ -alkoxy  $\beta$ -keto phosphonates employing a HCO<sub>2</sub>H/Et<sub>3</sub>N (1:5) azeotropic mixture as the hydrogen source and solvent, along with the well-defined chiral

<sup>206</sup> Monnereau, L.; Cartigny, D.; Scalone, M.; Ayad, T.; Ratovelomanana-Vidal, V. *Chem. Eur. J.* **2015**, *21*, 11799.

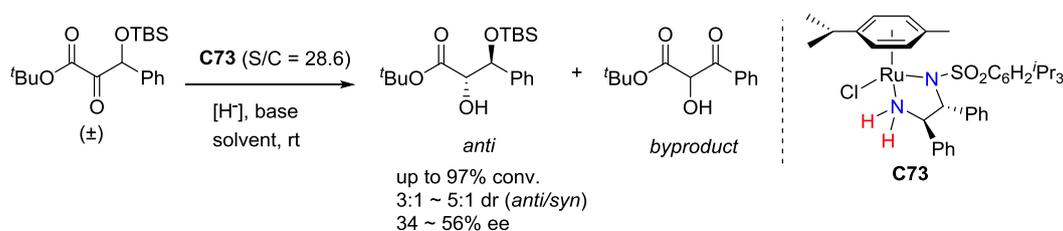
<sup>207</sup> Son, S.-M.; Lee, H.-K. *J. Org. Chem.* **2013**, *78*, 8396.

catalyst [Ru(mesitylene)Cl(*R,R*)-TsDPEN] **C3** (Scheme 130).<sup>208</sup> The corresponding *syn* monohydroxy-protected 2-aryl-, 2-heteroaryl-, 2-alkyl-, and 2-alkenyl-substituted 1,2-dihydroxy phosphonates were produced in high yields (95–99%) and mainly excellent diastereo- and enantioselectivities (*syn/anti* up to 99:1, up to 99% ee).



Scheme 130

In 2010, Johnson *et al.* reported the complex **C73** catalyzed the ATH/DKR of a  $\beta$ -siloxy  $\alpha$ -keto ester in the presence of HCO<sub>2</sub>H or HCO<sub>2</sub>Na as the hydrogen source combined with a broad range of bases to access the corresponding enantioenriched monoprotected diol with moderate enantioselectivities (up to 56% ee) and good diastereoselectivities (up to 5:1 dr) (Scheme 131).<sup>209</sup>



Scheme 131

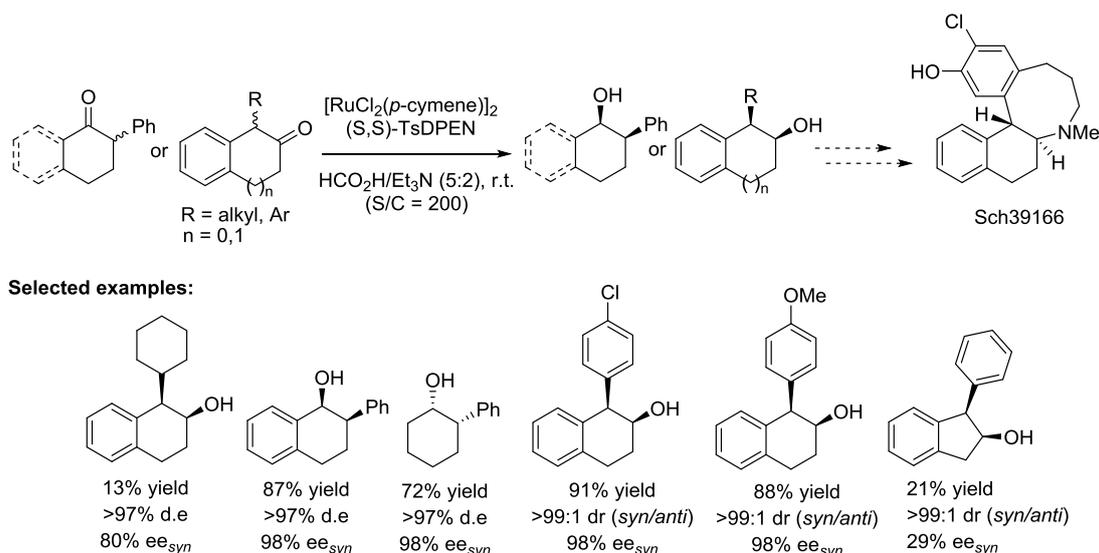
### 1.2.4 DKR/ATH of $\alpha$ -substituted cyclic ketone derivatives

In 2002, Wills *et al.* developed the Ru-catalyzed DKR/ATH of 1-aryl-substituted cyclic ketones to synthesize the corresponding 1-aryl-2-tetranols, or 1-phenyl-2-indan-2-ols in the presence of HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2), providing excellent dr (>99:1 *syn/anti*) and ee (up to 98%) for 6-membered cyclic substrates. However, for 5-membered cyclic substrates, only low yields and

<sup>208</sup> Son, S.-M.; Lee, H.-K. *J. Org. Chem.* **2014**, *79*, 2666.

<sup>209</sup> Steward, K. M.; Johnson, J. S. *Org. Lett.* **2010**, *12*, 2864.

enantioselectivities were obtained. This approach was applied to prepare benzazepine dopamine D<sub>1</sub> antagonist Sch39166.<sup>210</sup> In 2006, they investigated the DKR/ATH of 1-*n*-cyclohexyl-substituted 6-membered cyclic ketones which afforded 1-alkyl-2-tetranols with high diastereo- and enantioselectivities, but with low yields. 2-Phenyl substituted 1-tetralones and cyclohexanones were reduced with good yields and high levels of diastereo- and enantio- control for the corresponding alcohols (Scheme 132).<sup>211</sup>



Scheme 132

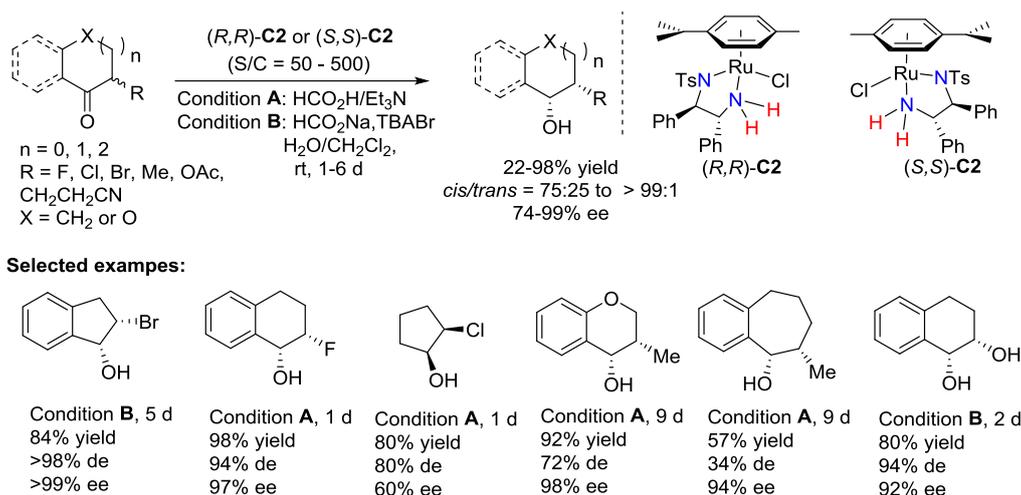
In 2006, Lassaletta *et al.* presented DKR/ATH of a variety of cyclic  $\alpha$ -halo ketones using the Noyori/Ikariya catalysts and either HCO<sub>2</sub>H/Et<sub>3</sub>N or HCO<sub>2</sub>Na/<sup>n</sup>Bu<sub>4</sub>NBr in H<sub>2</sub>O/CH<sub>2</sub>Cl<sub>2</sub> as the hydrogen sources. Good yields of vicinal bromo-, chloro-, and fluoro alcohols with excellent de and ee levels were achieved in most cases after a simple tuning of the reaction conditions.<sup>212</sup> In 2007, the same group reported DKR/ATH of 2-methyl substituted chroman-4-one. A good dr and an excellent ee were obtained for the corresponding alcohol. However, a low yield and dr was reached for transfer hydrogenation of seven-membered 2-methyl benzosuberone. Furthermore, 2-acetoxyindan-1-one and 2-acetytetral-1-one were investigated, affording the corresponding diols in good yields, high de and ee (Scheme 133).<sup>213</sup>

<sup>210</sup> Alcock, N. J.; Mann, I.; Peach, P.; Wills, M. *Tetrahedron: Asymmetry* **2002**, *13*, 2485.

<sup>211</sup> Peach, P.; Cross, D. J.; Kenny, J. A.; Mann, I.; Houson, I.; Campbell, L.; Walsgrove, T.; Wills, M. *Tetrahedron* **2006**, *62*, 1864.

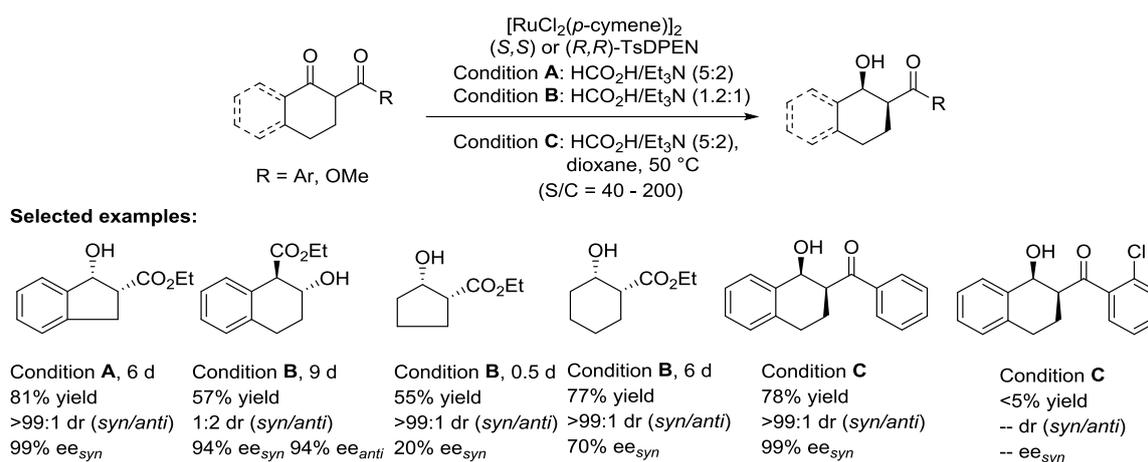
<sup>212</sup> Ros, A.; Magriz, A.; Dietrich, H.; Fernández, R.; Alvarez, E.; Lassaletta, J. M. *Org. Lett.* **2006**, *8*, 127.

<sup>213</sup> Fernández, R.; Ros, A.; Magriz, A.; Dietrich, H.; Lassaletta, J. M. *Tetrahedron* **2007**, *63*, 6755.



Scheme 133

In 2007, Lassaletta *et al.* described a stereoselective synthesis of *syn*  $\beta$ -hydroxy cycloalkane carboxylates by utilizing Ru-catalyzed DKR/ATH of cyclic  $\beta$ -keto esters in the presence of HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) as hydrogen source. Remarkable results in terms of diastereo- and enantioselectivities (>99:1 dr, 99% ee) were achieved for bicyclic  $\alpha$ -tetralone and  $\alpha$ -indanone derivatives but not for bicyclic  $\beta$ -tetralone or  $\beta$ -indanone derivatives and monocyclic  $\beta$ -keto esters (Scheme 134).<sup>214</sup> In 2011, Zhang's group reported the Ru-catalyzed DKR/ATH of 2-aryl-1-tetralones to access *syn*-2-aryl-1-tetralols, resulting in good yields, high dr and excellent ee with the exception of the substrates having a substituent at the *ortho*-position on the aryl group (Scheme 134).<sup>215</sup>



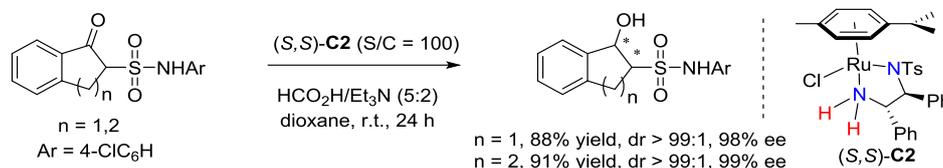
Scheme 134

In 2011, Zhang and co-workers described the DKR of cyclic  $\alpha$ -tetralone and  $\alpha$ -indanone

<sup>214</sup> Ros, A.; Magriz, A.; Dietrich, H.; Lassaletta, J. M.; Fernández, R. *Tetrahedron* **2007**, *63*, 7532.

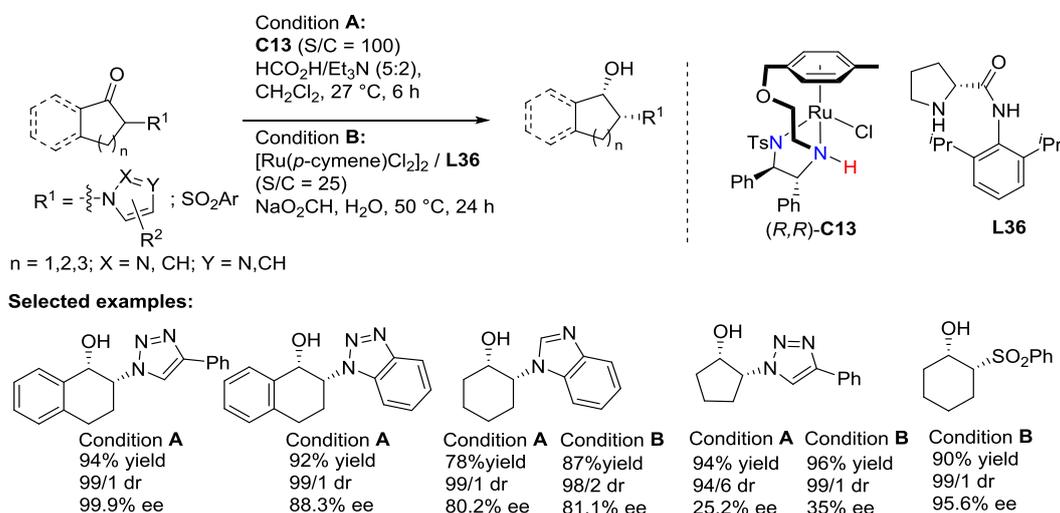
<sup>215</sup> Wu, Y.; Geng, Z.; Bai, J.; Zhang, Y. *Chin. J. Org. Chem.* **2011**, *29*, 1467.

derivatives (Scheme 135). The ATH of the corresponding  $\beta$ -ketosulfonamides proceeded under mild reaction conditions in dioxane at room temperature with high ee (98%) and dr values (>99:1 dr) using [RuCl(*p*-cymene)(*S,S*)-TsDPEN] complex (*S,S*)-**C2**.<sup>216</sup>



Scheme 135

In 2016, Bhanage *et al.* presented the Ru-catalyzed DKR/ATH of *rac*- $\alpha$ -heteroaryl amino bicyclic alkanones in the presence of HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) as the hydrogen source in a highly enantio- and diastereoselective manner to access biologically important *cis*- $\beta$ -heteroaryl amino cycloalkanols. However, monocyclic substrates were obtained with low to good enantiocontrol (Scheme 136).<sup>217</sup> In 2018, the same group further reported Ru/prolinamide-catalyzed DKR/ATH of *rac*- $\alpha$ -heteroaryl- and sulfonyl-substituted monocyclic alkanones by using sodium formate as the hydrogen source and water as a solvent. The method showed high stereoselectivities for six- or seven-membered substrates, but five-membered substrates gave low enantioselectivities (Scheme 136).<sup>218</sup>



Scheme 136

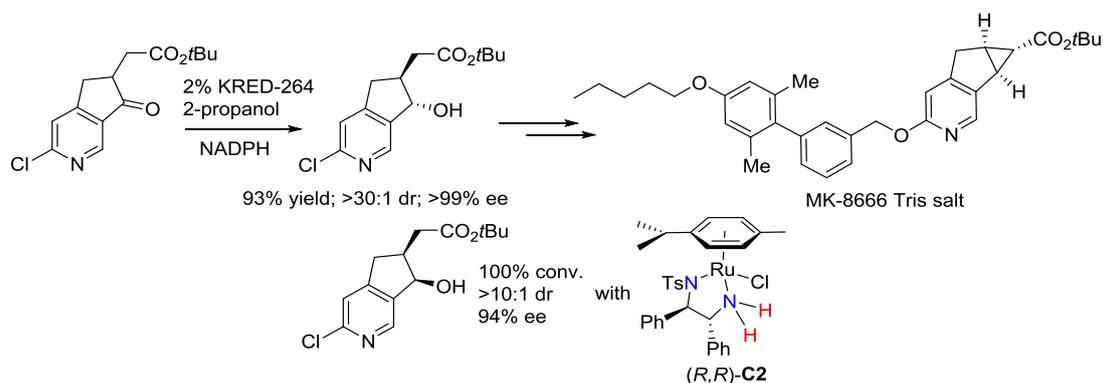
In 2016, Merck's researchers developed a scalable and efficient process to access the GPR40 agonist MK-8666 from a simple pyridine building block. The key step to set the

<sup>216</sup> Geng, Z.; Wu, Y.; Miao, S.; Shen, Z.; Zhang, Y. *Tetrahedron Lett.* **2011**, *52*, 907.

<sup>217</sup> Vyas, V. K.; Bhanage, B. M. *Org. Lett.* **2016**, *18*, 6436.

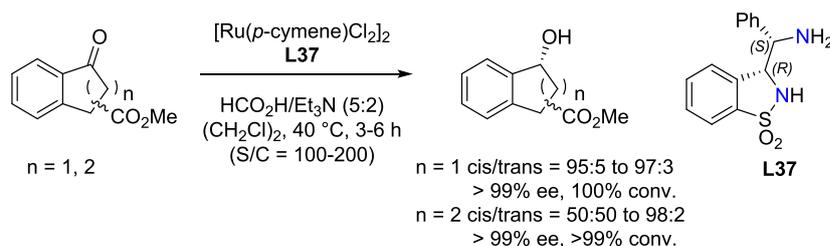
<sup>218</sup> Vyas Vijayesh K.; Bhanage Bhalchandra M. *Asian J. Org. Chem.* **2018**, *7*, 346.

stereochemistry at two centers relied on an enzymatic ATH/DKR of an unactivated ketone. An optimized ketoreductase KRED-264, provided in the presence of isopropanol and NADPH, the desired *trans* alcohol in >30:1 dr and >99% ee. Further, it was demonstrated that all four diastereomers of this hydroxy-ester could be prepared in high yield and selectivity. The *cis* product can also be prepared by Ru-catalyzed DKR/ATH of the corresponding ketone with high dr and ee (Scheme 137).<sup>219</sup>



Scheme 137

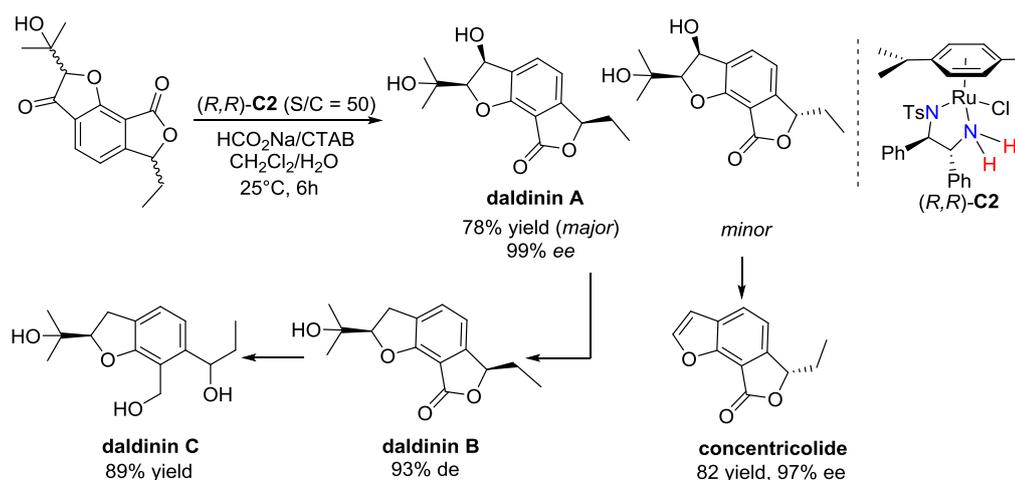
In 2016, Mohar *et al.* described the use of  $\gamma$ -sultam-cored *N,N*-ligands in Ru(II)-catalyzed ATH/DKR of aryl ketones. 2-Substituted benzo-fused five- or six-membered cyclic ketones were reduced to give high levels of diastereo- and enantio-selectivities (95:5 to 97:3 dr; >99% ee) by using [Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub> with a *syn*- $\gamma$ -sultam-cored *N,N*-ligand **L37** (Scheme 138).<sup>82</sup>



Scheme 138

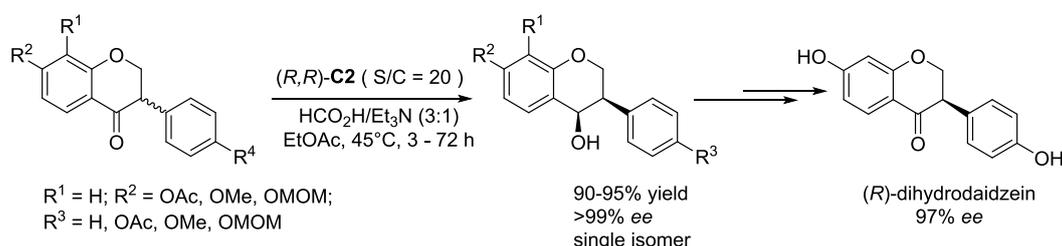
In 2016, Fang *et al.* reported a new strategy for the total synthesis of daldinin **A** and concentricolide by using Ru-catalyzed DKR/ATH of the corresponding ketones in the presence of sodium formate as the hydrogen source under mild conditions. Daldinin **A** could be transformed into daldinin **B** and **C**. The protocol shows a mild, facile, and practical access to a variety of *syn* dihydrobenzofuran and phthalide motifs in enantiomerically pure form (Scheme

<sup>219</sup> Hyde, A. M.; Liu, Z.; Kosjek, B.; Tan, L.; Klapars, A.; Ashley, E. R.; Zhong, Y.-L.; Alvizo, O.; Agard, N. J.; Liu, G.; Gu, X.-Y.; Yasuda, N.; Limanto, J.; Huffman, M. A.; Tschaen, D. M. *Org. Lett.* **2016**, *18*, 5888.

139).<sup>220</sup>

Scheme 139

In 2017, Metz *et al.* reported a simple method for preparing enantioenriched isoflavanones such as (*R*)-dihydrodaidzein, through ruthenium-catalyzed DKR/ATH of easily available racemic substrates followed by oxidation of the resulting isoflavanols (Scheme 140).<sup>221</sup>



Scheme 140

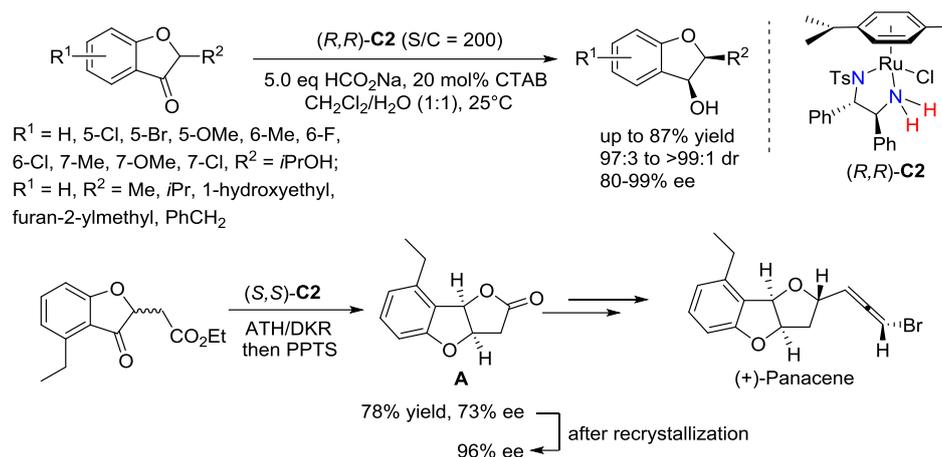
In 2017, Fang *et al.* reported Ru-catalyzed DKR/ATH of *rac*-2,3-dihydrobenzofuran  $\alpha$ -substituted ketones to obtain *cis*-2,3-dihydrobenzofuran-3-ols in CH<sub>2</sub>Cl<sub>2</sub>/water under mild conditions. This mild, efficient route proceeded with excellent stereoselectivities and offers an interesting alternative to the asymmetric hydrogenation of benzofurans.<sup>222</sup> Before Fang's work, McErlean and coworkers reported in 2016 the preparation of compound **A** (78% yield, 73% ee, after recrystallization in 93% ee) through ATH/DKR and the latter was used in total synthesis of (+)-Panacene (Scheme 141).<sup>223</sup>

<sup>220</sup> Fang, L.; Lyu, Q.; Lu, C.; Li, H.; Liu, S.; Han, L. *Adv. Synth. Catal.* **2016**, *358*, 3196.

<sup>221</sup> Qin, T.; Metz, P. *Org. Lett.* **2017**, *19*, 2981.

<sup>222</sup> Fang, L.; Liu, S.; Han, L.; Li, H.; Zhao, F. *Organometallics* **2017**, *36*, 1217.

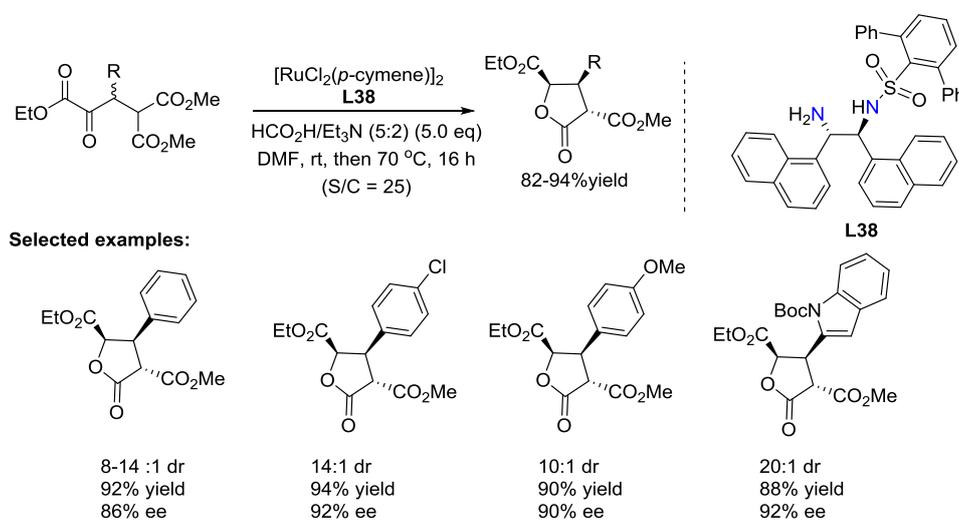
<sup>223</sup> Alnafta, N.; Schmidt, J. P.; Nesbitt, C. L.; McErlean, C. S. P. *Org. Lett.* **2016**, *18*, 6520.



Scheme 141

### 1.2.5 DKR/ATH of $\beta$ -substituted $\alpha$ -keto esters and phosphonates

In 2012, Johnson *et al.* described the first example of the DKR/ATH of  $\alpha$ -keto esters catalyzed by a Ru complex having a *m*-terphenylsulfonamide ligand. Structurally diverse  $\gamma$ -butyrolactone derivatives were readily obtained by warming the reaction mixture at 70 °C to induce lactonisation of the corresponding hydroxy esters (Scheme 142).<sup>224</sup>



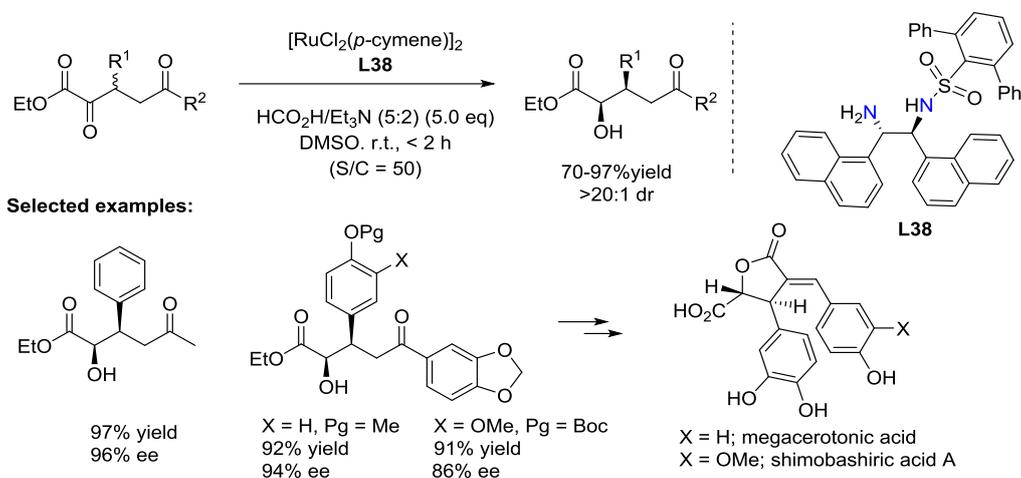
Scheme 142

The same group studied the ATH/DKR of  $\alpha,\delta$ -diketo esters to give the *syn* products with high diastereoselectivities and good enantioselectivities. Interestingly, the reaction conditions allowed the chemoselective reduction of the  $\alpha$ -keto ester in the presence of an aryl ketone.<sup>225</sup>

<sup>224</sup> (a) Steward, K. M.; Gentry, E. C.; Johnson, J. S. *J. Am. Chem. Soc.* **2012**, *134*, 7329. (b) Steward, K. M.; Gentry, E. C.; Johnson, J. S. *J. Am. Chem. Soc.* **2015**, *137*, 3715

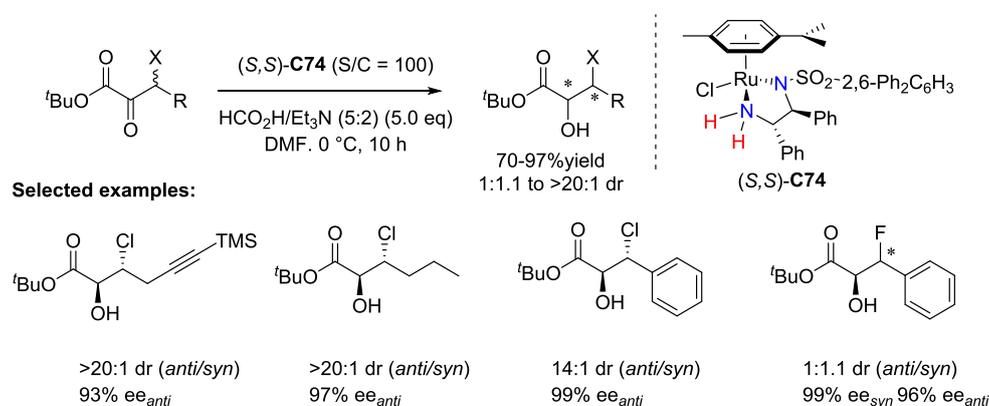
<sup>225</sup> Steward, K. M.; Corbett, M. T.; Goodman, C. G.; Johnson, J. S. *J. Am. Chem. Soc.* **2012**, *134*, 20197.

The authors used this strategy to achieve the asymmetric total syntheses of the  $\alpha$ -benzylidene- $\gamma$ -butyrolactone natural products megacerotonic acid and shimobashiric acid A (Scheme 143).<sup>226</sup>



Scheme 143

This DKR/ATH approach was also used to achieve *anti*-chlorohydrins with high diastereo- and enantio-inductions starting from a wide range of  $\beta$ -chloro- $\alpha$ -ketoesters. However, low diastereoselectivities for  $\beta$ -fluoro- $\alpha$ -ketoesters were observed (Scheme 144).

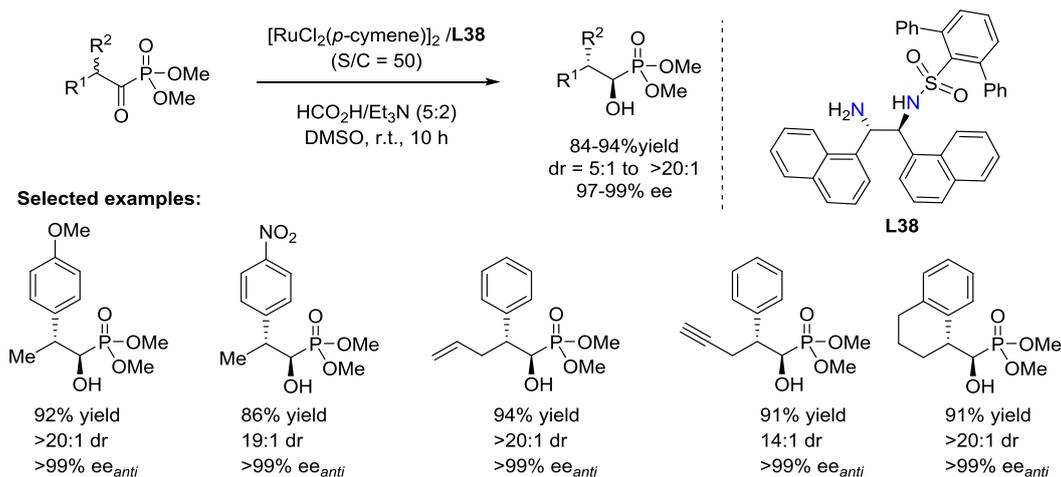


Scheme 144

In 2013, Johnson *et al.* reported an access to chiral  $\beta$ -aryl- $\alpha$ -hydroxy phosphonates with *anti* configuration by Ru-catalyzed DKR/ATH of the corresponding  $\alpha$ -aryl acyl phosphonates. It is worth noting that the DKR/ATH of  $\alpha$ -keto esters gave the *syn* products (Scheme 142) as opposed to the *anti* products observed for the DKR/ATH of  $\beta$ -aryl acyl phosphonates (Scheme 145).<sup>227</sup>

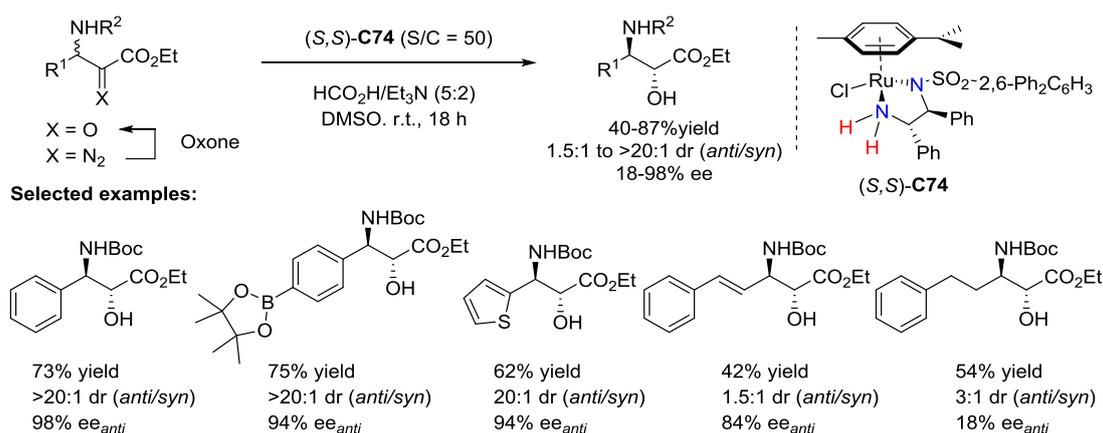
<sup>226</sup> Krabbe, S. W.; Johnson, J. S. *Org. Lett.* **2015**, *17*, 1188.

<sup>227</sup> Corbett, M. T.; Johnson, J. S. *J. Am. Chem. Soc.* **2013**, *135*, 594.



Scheme 145

The same group<sup>228</sup> described the asymmetric synthesis of enantioenriched *anti*- $\alpha$ -hydroxy- $\beta$ -amino acid derivatives with high diastereo- and enantioselectivities catalyzed by [RuCl(*p*-cymene)(*S,S*)-(2,6-Ph<sub>2</sub>C<sub>6</sub>H<sub>3</sub>)SO<sub>2</sub>DPEN] (*S,S*)-**C74** via DKR/ATH of  $\beta$ -amino- $\alpha$ -keto esters in the presence of HCO<sub>2</sub>H/Et<sub>3</sub>N(5:2) as a hydrogen source under mild conditions. The substrates were prepared through Mannich addition of ethyl diazoacetate to imines followed by oxidation of the diazo group with Oxone (Scheme 146). The same year, Somfai *et al.* reported an access to *anti*- $\beta$ -amido- $\alpha$ -hydroxy esters by using [RuCl(*p*-cymene)(*S,S*)-(C<sub>6</sub>F<sub>5</sub>)SO<sub>2</sub>DPEN] (*S,S*)-**C75** (see Scheme 148 for structure) as a catalyst with shorter reaction times and comparable diastereoselectivities.<sup>229</sup>



Scheme 146

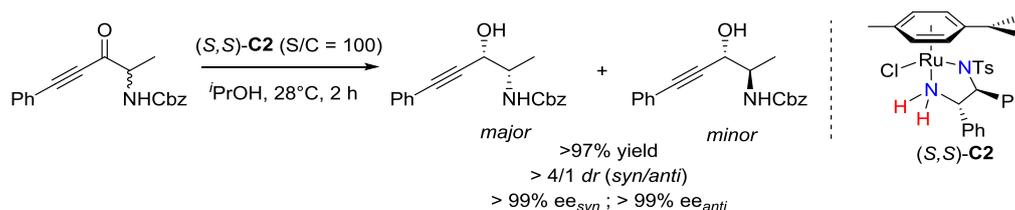
<sup>228</sup> Goodman, C. G.; Do, D. T.; Johnson, J. S. *Org. Lett.* **2013**, *15*, 2446.

<sup>229</sup> Villacrez, M.; Somfai, P. *Tetrahedron Lett.* **2013**, *54*, 5266.

## 1.3 DKR/ATH of $\alpha$ -amino $\beta$ -keto derivatives

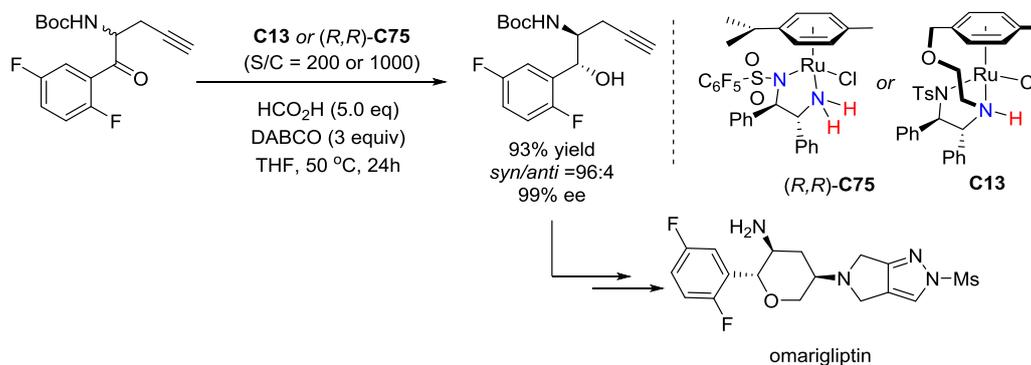
### 1.3.1 DKR/ATH of $\alpha$ -amino $\beta$ -ketones to access chiral 1,2-amino alcohols

In 1997, Noyori *et al.* reported  $[\text{RuCl}(p\text{-cymene})[(S,S)\text{-Ts-DPEN}]]$  (*S,S*)-**C2** catalyzed DKR/ATH of *racemic*  $\alpha$ -amido phenylethynyl ketone in 2-propanol to provide the corresponding amino alcohol derivative with high yield, good diastereoselectivity and excellent ee (Scheme 147).<sup>27c</sup>



**Scheme 147**

Omarigliptin is a long-acting DPP-4 inhibitor for the treatment of type 2 diabetes. In 2014, scientists from Merck Research Laboratories first presented a DKR/ATH process catalyzed by  $[\text{RuCl}(p\text{-cymene})((R,R)\text{-C}_6\text{F}_5\text{SO}_2\text{DPEN})]$  complex (*R,R*)-**C75** (0.5 mol%) to access the key intermediate *anti*-1,2-amino alcohol in the presence of  $\text{HCO}_2\text{H}/\text{DABCO}$  (5.0 eq / 3.0 eq) with high yield, good diastereoselectivity (89:11 dr) and excellent enantioselectivity (>99% ee<sub>syn</sub>) (Scheme 149).<sup>230</sup> In 2015, the same research group reported an improved process by replacing the catalyst with the oxo-tethered  $[\text{RuCl}((R,R)\text{-Ts-DENEB})]$  complex **C13a** (0.1 mol%) to obtain higher diastereoselection (24:1 dr) for the desired intermediate (Scheme 148).<sup>231</sup>



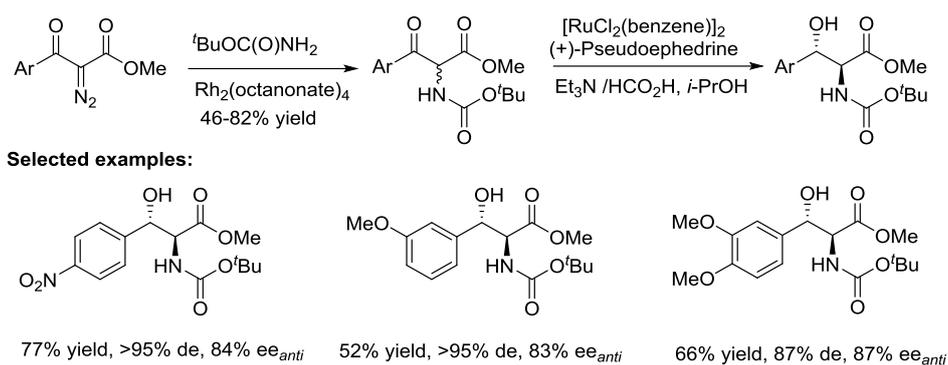
**Scheme 148**

<sup>230</sup> Xu, F.; Zacuto, M. J.; Kohmura, Y.; Rosen, J.; Gibb, A.; Alam, M.; Scott, J.; Tschaen, D. *Org. Lett.* **2014**, *16*, 5422.

<sup>231</sup> Chung, J. Y. L.; Scott, J. P.; Anderson, C.; Bishop, B.; Bremeyer, N.; Cao, Y.; Chen, Q.; Dunn, R.; Kassim, A.; Lieberman, D.; Moment, A. J.; Sheen, F.; Zacuto, M. *Org. Process Res. Dev.* **2015**, *19*, 1760.

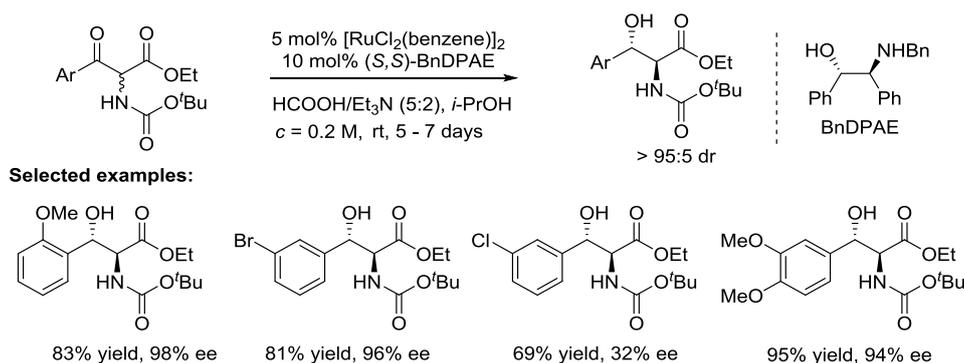
### 1.3.2 DKR/ATH of $\alpha$ -amino $\beta$ -keto esters to access *anti* $\beta$ -hydroxy $\alpha$ -amino esters

In 2004, Fairfax *et al.* reported rhodium-mediated insertion of *tert*-butylcarbamate into the corresponding 3-keto-2-diazoester, affording the *N*-protected  $\alpha$ -amino  $\beta$ -keto esters, followed by an ATH-DKR process to afford the corresponding *N*-protected 3-arylserine esters in fair to good yields (47–78%), high diastereoselectivities (87 to >95% de) and in most cases high enantiomeric excess (up to 87%) (Scheme 149).<sup>232</sup>



Scheme 149

In 2010, Somfai *et al.* developed an operationally straightforward synthesis of  $\beta$ -hydroxy- $\alpha$ -amido esters by ruthenium-catalyzed transfer hydrogenation of the corresponding  $\alpha$ -amido  $\beta$ -keto esters via a DKR process, providing *anti*-amino alcohols with high diastereoselectivities and up to 98% ee (Scheme 150).<sup>233</sup>



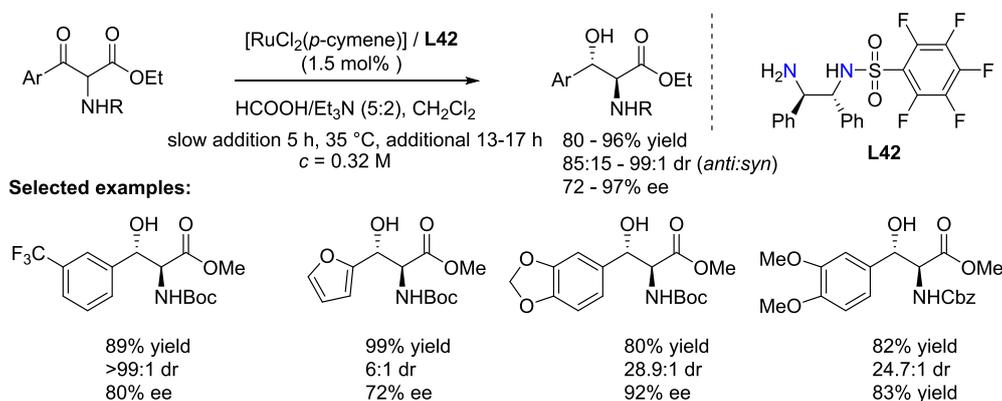
Scheme 150

In 2011, Liu, Schultz *et al.* from Merck company described an efficient preparation of enantioenriched (72–97% ee) aryl  $\beta$ -hydroxy  $\alpha$ -amino esters *via* Ru/(*R,R*)-C<sub>6</sub>F<sub>5</sub>SO<sub>2</sub>DPEN **L42**

<sup>232</sup> Bourdon, L. H.; Fairfax, D. J.; Martin, G. S.; Mathison, C. J.; Zhichkin, P. *Tetrahedron: Asymmetry* **2004**, *15*, 3485.

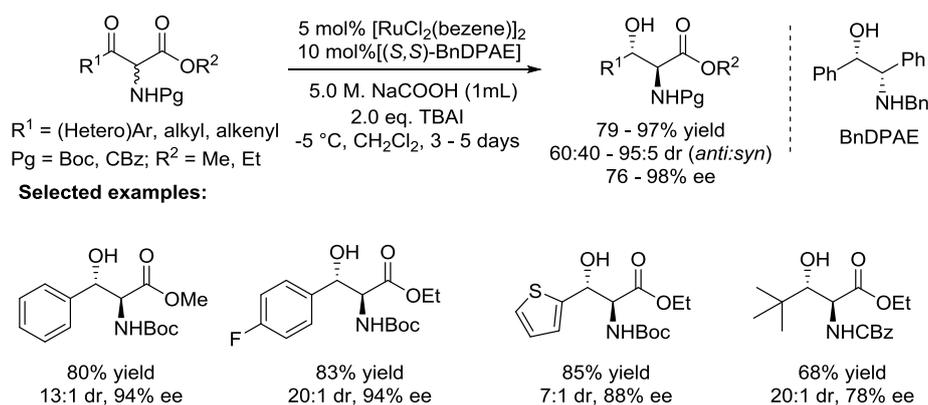
<sup>233</sup> Seashore-Ludlow, B.; Villo, P.; Häcker, C.; Somfai, P. *Org. Lett.* **2010**, *12*, 5274.

catalyzed ATH-DKR of  $\alpha$ -amino  $\beta$ -keto esters bearing Boc or Cbz protecting groups on the nitrogen atom. The *anti*  $\beta$ -hydroxy  $\alpha$ -amino esters were obtained both in high yields (80–96%) and high diastereoselectivity (85:15 to 99:1 dr). The absolute stereochemistry of the aryl  $\beta$ -hydroxy  $\alpha$ -amino esters was determined by chemical derivatization as well as Vibrational Circular Dichroism (VCD) techniques (Scheme 151).<sup>234</sup>



Scheme 151

In 2012, Somfai *et al.* described an emulsion-based operationally simple method for the ATH-DKR of  $\alpha$ -amido- $\beta$ -ketoesters with water/ $\text{CH}_2\text{Cl}_2$  as a cosolvent to yield *anti*- $\beta$ -hydroxy- $\alpha$ -amino esters in good yields (79–97%) and with good diastereo- (60:40 to 95:5 dr) and enantioselectivities (76–98% ee). This method showed a wide substrate scope, including aryl, heteroaryl, alkenyl, and alkyl substrates (Scheme 152).<sup>235</sup>



Scheme 152

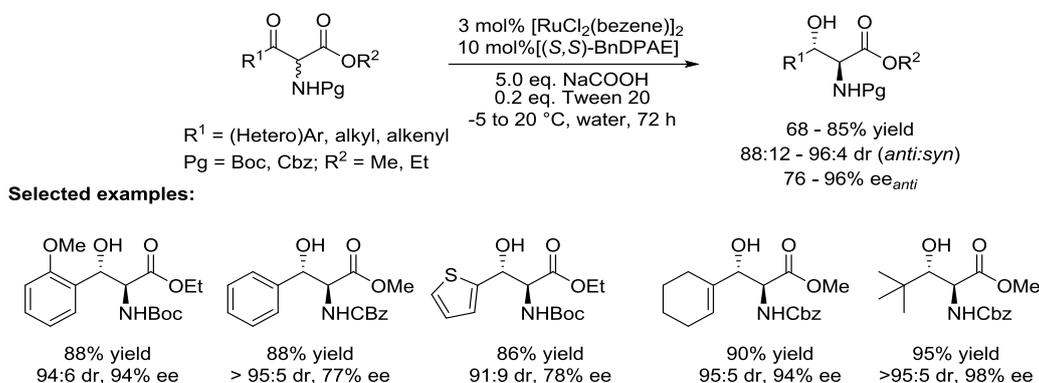
In 2012, Somfai *et al.* reported an efficient and more environmentally friendly method for the construction of *anti*- $\beta$ -hydroxy- $\alpha$ -amino acid derivatives by omitting the organic solvent

<sup>234</sup> Liu, Z.; Shultz, C. S.; Sherwood, C. A.; Krska, S.; Dormer, P. G.; Desmond, R.; Lee, C.; Sherer, E. C.; Shpungin, J.; Cuff, J.; Xu, F. *Tetrahedron Lett.* **2011**, *52*, 1685.

<sup>235</sup> Seashore-Ludlow, B.; Saint-Dizier, F.; Somfai, P. *Org. Lett.* **2012**, *14*, 6334.

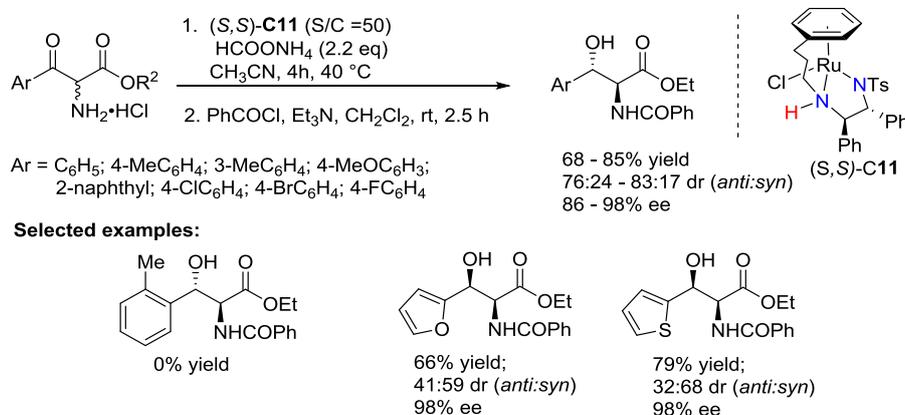
## Part C: ATH of ketone derivatives via dynamic kinetic resolution

and utilizing only water with a surfactant. The method proceeds in high yields (68–85%), diastereoselectivities (88:12 to 96:4 dr), and enantioselectivities (76–96% ee) for a broad range of substrates, including aryl-, alkenyl-, and alkyl-substituted  $\alpha$ -amino  $\beta$ -ketoesters with *N*-Boc and *N*-Cbz protected amines (Scheme 153).<sup>236</sup>



**Scheme 153**

In 2015, our group reported the first example of tethered Ru-catalyzed ATH of  $\alpha$ -amino  $\beta$ -keto ester hydrochlorides via DKR to access *anti*  $\beta$ -hydroxy  $\alpha$ -amino esters in good yields (68–85%), good diastereomeric ratios (76:24 to 83:17 dr) and high enantioselectivities (86–98% ee) (Scheme 154).<sup>176a</sup>

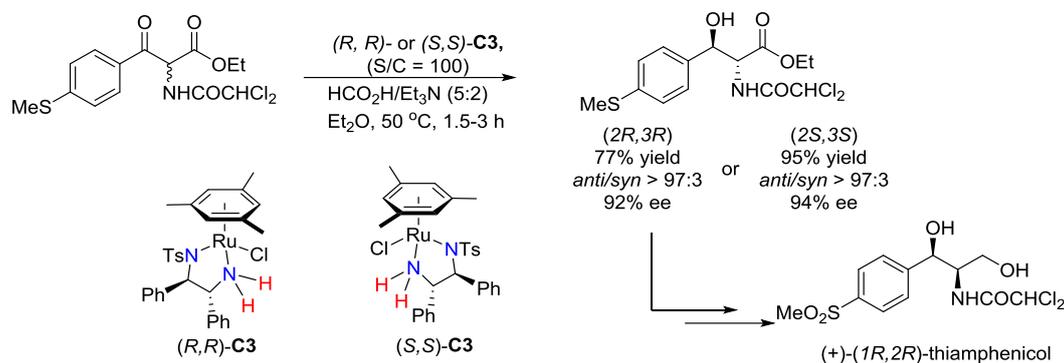


**Scheme 154**

In addition, an efficient, flexible and atom-economical synthesis of the four stereoisomers of (+)-(1*R*,2*R*)-thiamphenicol, used for its antibacterial activities against several Gram-positive and Gram-negative microorganisms was disclosed, through the ATH/DKR process starting from a racemic  $\alpha$ -amido  $\beta$ -keto ester. The ATH was performed with (*S,S*)- or (*R,R*)-C3 and HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) as the hydrogen source, and provided, at 50 °C, the *anti*-

<sup>236</sup> Seashore-Ludlow, B.; Villo, P.; Somfai, P. *Chem. Eur. J.* **2012**, *18*, 7219.

(2*R*,3*R*)- and (2*S*,3*S*)-isomers, respectively, in 77% and 95% isolated yields and in high diastereo- and enantioselectivities (*anti/syn* = 97:3, up to 94% ee) (Scheme 155).<sup>176c</sup>



Scheme 155

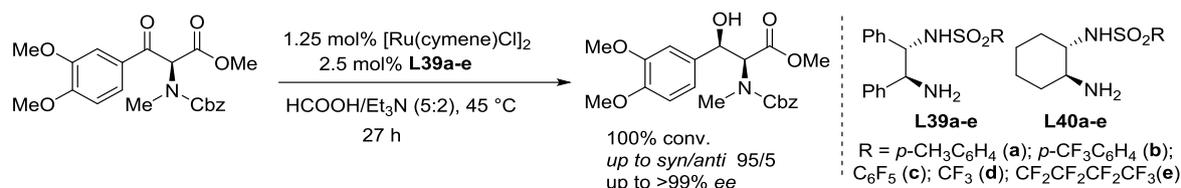
In 2016, our group reported a tethered Rh(III)-catalyzed ATH of a series of  $\alpha$ -amino  $\beta$ -keto ester hydrochlorides *via* a DKR process under mild conditions to provide the corresponding *anti* or *syn* amino alcohols (Ar substituents: 2-furyl, 2-thienyl; *syn* as the major products) with complete conversions, fair diastereoselectivities (up to 97:3 dr), and high enantioselectivities (up to >99% ee).<sup>169</sup>

### 1.3.3 DKR/ATH of $\alpha$ -amino $\beta$ -keto esters to access *syn* $\beta$ -hydroxy- $\alpha$ -amino esters

Previous work in this field only focused on  $\beta$ -keto esters that were substituted with carbamate, 2,2-dichloro *N*-acetamido or amino hydrochloride functional groups in the  $\alpha$ -position to access the *anti* amino alcohol derivatives using either ruthenium or rhodium complexes. On the other hand, scarce examples of the production of the *syn* compounds through Ru-catalyzed ATH have been described so far for *N*-diprotected compounds.

In 2001, C. Mioskowski *et al.* showed that the introduction of a better withdrawing group ( $\text{C}_6\text{F}_5\text{SO}_2$ -,  $\text{CF}_3\text{SO}_2$ - or  $\text{CF}_3(\text{CF}_2)_3\text{SO}_2$ -) on chiral DPEN or DACH ligand (**L39**, **L40**) strongly improved the catalyst activity and stereoselectivity in the transfer hydrogenation of a *N*-diprotected  $\alpha$ -amino  $\beta$ -ketoester *via* DKR to give the corresponding *syn*  $\beta$ -hydroxy  $\alpha$ -amino ester (*syn/anti* = 95:5, 97–>99% ee). In particular, the catalyst obtained from the nonaflate-DPEN ligand demonstrated to be much more active than the TsDPEN ligand and provided >99% ee. Additionally, the activity and enantioselectivity were found to be influenced by the ligand's pKa values (Scheme 156).<sup>237</sup>

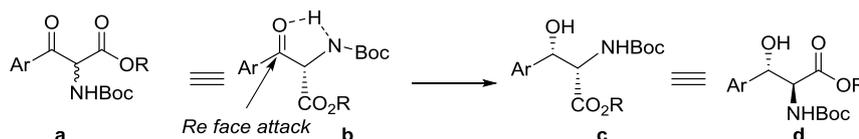
<sup>237</sup> Mohar, B.; Valleix, A.; Desmurs, J. R.; Felemez, M.; Wagner, A.; Mioskowski, C. *Chem. Commun.* **2001**, 24,



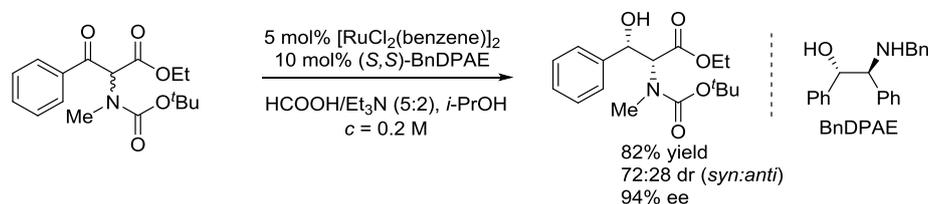
Scheme 156

Somfai *et al.* have demonstrated that the ATH-DKR of mono-protected  $\alpha$ -amido  $\beta$ -keto esters gave the *anti* products, and the authors proposed a cyclic intermediate with a hydrogen bond between the N-H and the carbonyl moiety (Scheme 157, structure **b**) with subsequent hydride addition occurring from the least hindered face of the carbonyl. When the same conditions were employed for an *N*-Boc, *N*-alkyl di-protected  $\alpha$ -amido  $\beta$ -keto ester analogue, for which no hydrogen bond can be invoked the *syn* amino alcohol was obtained as the major product (Scheme 157).<sup>235</sup>

I) stereochemical model with mono-protected  $\alpha$ -amido  $\beta$ -ketoester



II) ATH-DKR for diprotected  $\alpha$ -amido  $\beta$ -ketoester

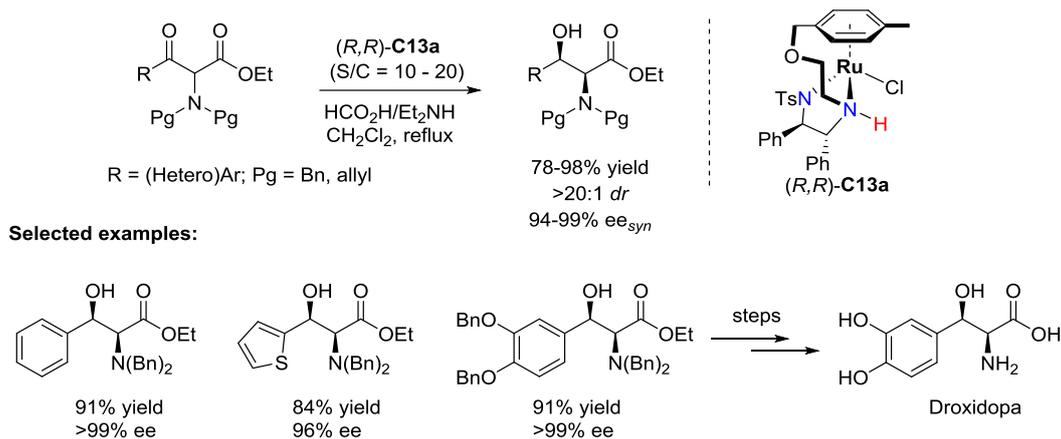


Scheme 157

In 2017, Wang *et al.* developed a highly efficient method to access enantiomerically pure *syn* aryl  $\beta$ -hydroxy  $\alpha$ -dibenzylamino esters through the ATH/DKR of aryl  $\alpha$ -dibenzylamino  $\beta$ -keto esters, in high yields (78–98%) with excellent diastereoselectivities (>20:1 dr) and enantioselectivities (94 to >99% ee). Furthermore, this method was applied for the gram-scale preparation of droxidopa (Scheme 158).<sup>238</sup>

2572.

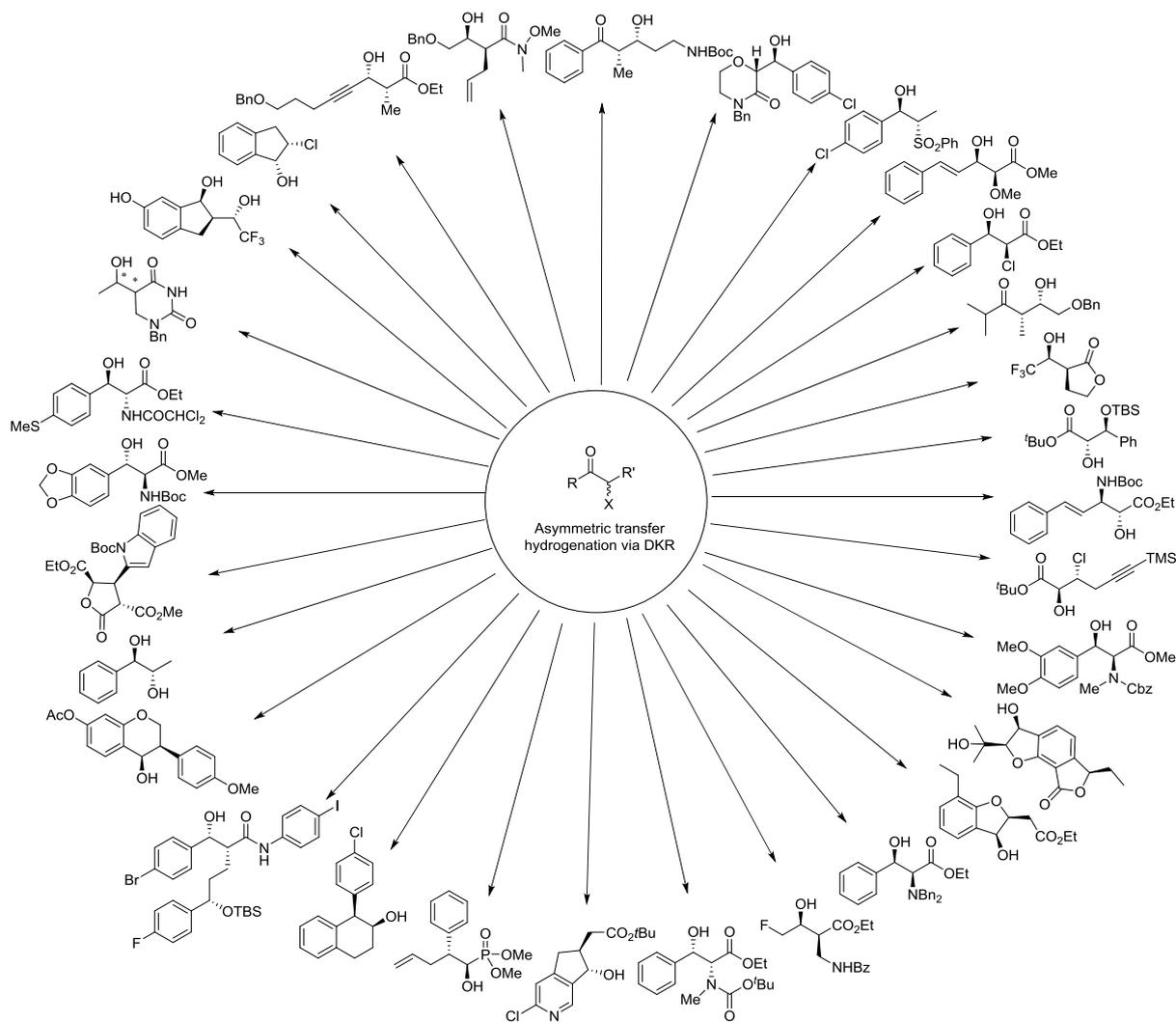
<sup>238</sup> Sun, G.; Zhou, Z.; Luo, Z.; Wang, H.; Chen, L.; Xu, Y.; Li, S.; Jian, W.; Zeng, J.; Hu, B.; Han, X.; Lin, Y.; Wang, Z. *Org. Lett.* **2017**, *19*, 4339.



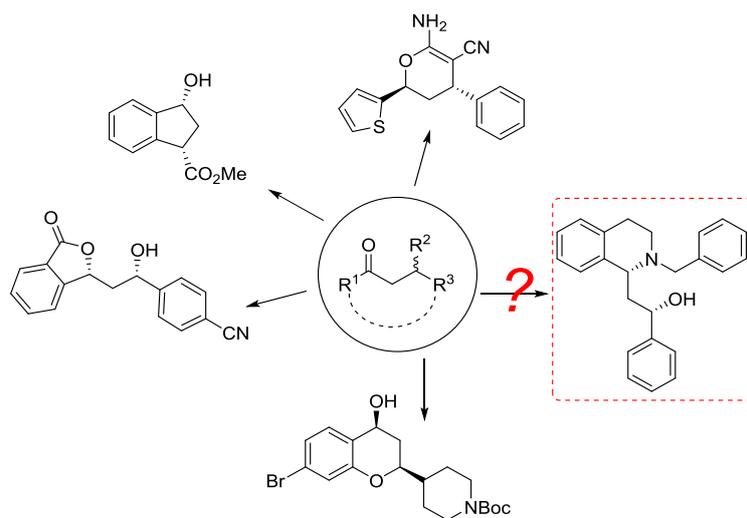
Scheme 158

From the above short overview, a broad range of chiral alcohol derivatives bearing two contiguous stereocenters, which play a significant role for key intermediates in natural or pharmaceutical products, has been synthesized through asymmetric transfer hydrogen involving an efficient DKR process (Scheme 159). However, in some cases, they were suffering from low diastereoselectivity, high catalyst loading, as well as limited substrate scope. In addition, to the best of our knowledge, there are scarce reports on highly efficient asymmetric transfer reduction of  $\alpha$ -amino  $\beta$ -ketoesters to access *syn*- $\alpha$ -amino  $\beta$ -hydroxy esters, as well as *syn*- $\alpha$ -alkoxy  $\beta$ -hydroxy esters.

Furthermore, examples involving  $\beta$ -substituted ketones are scarce and usually require racemization of the  $\beta$ -stereocenter through elimination-induced epimerization by either an intra- or intermolecular conjugate elimination/conjugate addition pathway. To the best of our knowledge, there is no report on transition metal-catalyzed ATH-DKR of  $\beta$ -amino ketones to access chiral 1,3-aminoalcohols (Scheme 160).



Scheme 159



Scheme 160

## 2. Rhodium-mediated ATH: a diastereo- and enantioselective synthesis of *syn*- $\alpha$ -amido $\beta$ -hydroxy esters

### 2.1 Interest of *syn*- $\alpha$ -amino $\beta$ -hydroxy derivatives

Enantiomerically pure  $\beta$ -amino alcohol derivatives bearing two contiguous stereocenters are valuable building blocks in natural products and pharmaceuticals, as for example, droxidopa,<sup>239</sup> chloramphenicol,<sup>240</sup> thiamphenicol,<sup>177c</sup> florfenicol,<sup>241</sup> BMS drug candidate,<sup>242</sup> Eliglustat,<sup>243</sup> cyclomarin A<sup>244</sup> and gymnangiamide<sup>245</sup> (Figure 8). Besides, they can also be used as ligands in asymmetric catalysis,<sup>246</sup> thus an efficient synthesis of these scaffolds is highly desirable. A straightforward and atom-economical access to such compounds involves the DKR of racemic  $\alpha$ -amino  $\beta$ -keto ester derivatives that can be performed through either asymmetric hydrogenation AH or ATH, to obtain the *syn* or *anti* reduced products. However, although the DKR of  $\alpha$ -amido  $\beta$ -keto esters through asymmetric hydrogenation is now well established, the asymmetric transfer hydrogenation of these compounds to access *syn*  $\alpha$ -amino  $\beta$ -hydroxy derivatives is much less documented.

<sup>239</sup> George, S.; Narina, S. V.; Sudalai, A. *Tetrahedron Lett.* **2007**, *48*, 1375.

<sup>240</sup> (a) Bhaskar, G.; Satish Kumar, V.; Venkateswara Rao, B. *Tetrahedron: Asymmetry* **2004**, *15*, 1279. (b) Hajra, S.; Karmakar, A.; Maji, T.; Medda, A. K. *Tetrahedron* **2006**, *62*, 8959.

<sup>241</sup> Zhang, B.; Shi, L.; Chen, D. Method for preparing florfenicol sodium succinate microcrystal, CN104003917 A, **2014**.

<sup>242</sup> (a) Goldberg, S. L.; Goswami, A.; Guo, Z.; Chan, Y.; Lo, E. T.; Lee, A.; Truc, V. C.; Natalie, K. J.; Hang, C.; Rossano, L. T.; Schmidt, M. A. *Org. Process Res. Dev.* **2015**, *19*, 1308. (b) Schmidt, M. A.; Reiff, E. A.; Qian, X.; Hang, C.; Truc, V. C.; Natalie, K. J.; Wang, C.; Albrecht, J.; Lee, A. G.; Lo, E. T.; Guo, Z.; Goswami, A.; Goldberg, S.; Pesti, J.; Rossano, L. T. *Org. Process Res. Dev.* **2015**, *19*, 1317.

<sup>243</sup> Feng, P.; Liu, S.; Xu, J.; Zhou, J. Method for preparing eliglustat, CN105646442 A, **2016**.

<sup>244</sup> Renner, M. K.; Shen, Y. C.; Cheng, X. C.; Jensen, P. R.; Frankmoelle, W.; Kauffman, C. A.; Fenical, W.; Lobkovsky, E.; Clardy, J. *J. Am. Chem. Soc.* **1999**, *121*, 11273.

<sup>245</sup> Milanowski, D. J.; Gustafson, K. R.; Rashid, M. A.; Pannell, L. K.; McMahon, J. B.; Boyd, M. R. *J. Org. Chem.* **2004**, *69*, 3036. (b) Tone, H.; Buchotte, M.; Mordant, C.; Guittet, E.; Ayad, T.; Ratovelomanana-Vidal, V. *Org. Lett.* **2009**, *11*, 1995.

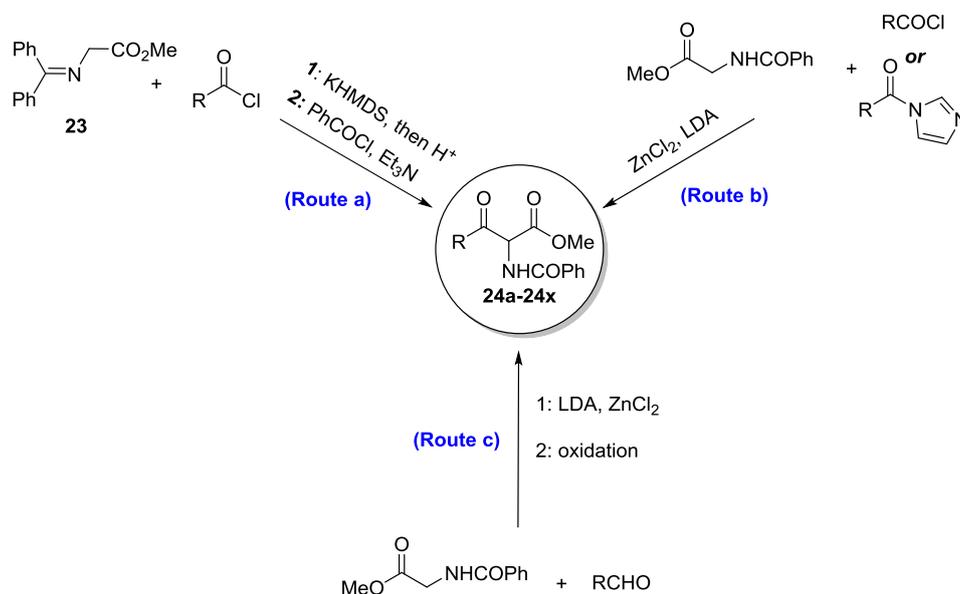
<sup>246</sup> (a) Wang, X.-L.; Xu, L.; Xiong, F.-J.; Wu, Y.; Chen, F. -E. *RSC Adv.* **2016**, *6*, 37701. (b) Wang, X.; Xu, L.; Yan, L.; Wang, H.; Han, S.; Wu, Y.; Chen, F. *Tetrahedron* **2016**, *72*, 1787.



## 2.2 Results and discussion

### 2.2.1 Preparation of $\alpha$ -amido $\beta$ -ketoesters **24a-z**

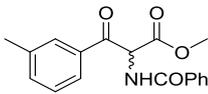
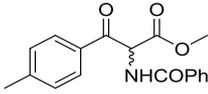
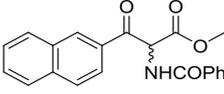
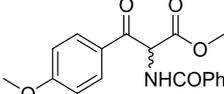
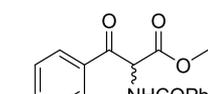
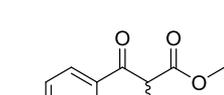
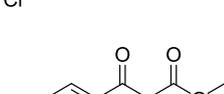
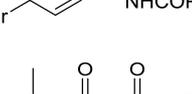
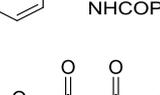
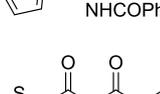
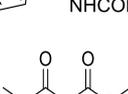
For this study, we first had to prepare a wide range of  $\alpha$ -amido  $\beta$ -ketoesters, bearing either aryl or alkyl ketones. To this end, several synthetic routes were studied (Scheme 161).



**Scheme 161**

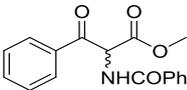
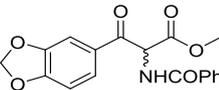
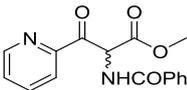
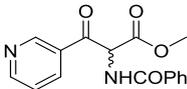
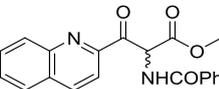
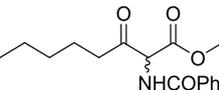
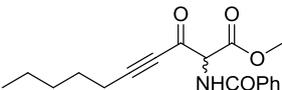
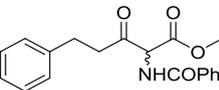
A first possible pathway is the condensation of the Schiff base **23** on an acid chloride, followed by an acidic hydrolysis to lead to the corresponding  $\alpha$ -ammonium  $\beta$ -ketoester hydrochloride which is subsequently protected with benzoyl chloride to give the desired benzoylamino  $\beta$ -ketoester (Scheme 161, route a). Using this approach, compounds **24b-e**, **24g-j**, **24n-o**, **24t** were prepared in 8–97% yields (Table 8).

Table 8. preparation of benzoylamino  $\beta$ -ketoesters using route a

| Entry |            | Substrates  | Yield / % |
|-------|------------|---|-----------|
| 1     | <b>24b</b> |    | 24        |
| 2     | <b>24c</b> |    | 32        |
| 3     | <b>24d</b> |    | 60        |
| 4     | <b>24e</b> |    | 43        |
| 5     | <b>24g</b> |    | 9         |
| 6     | <b>24h</b> |   | 25        |
| 7     | <b>24i</b> |  | 57        |
| 8     | <b>24j</b> |  | 8         |
| 9     | <b>24n</b> |  | 43        |
| 10    | <b>24o</b> |  | 76        |
| 11    | <b>24t</b> |  | 97        |

Another approach involves the reaction of *N*-benzoyl protected glycine ester with an acid chloride or an amide, in the presence of LDA as a base, and zinc chloride (Scheme 161, route b). This one-step route allowed the preparation of compounds **24a**, **24f**, **24k-m**, **24q-s** in 20–93% yields (Table 9).

Table 9. preparation of benzoylamino  $\beta$ -ketoesters using route b

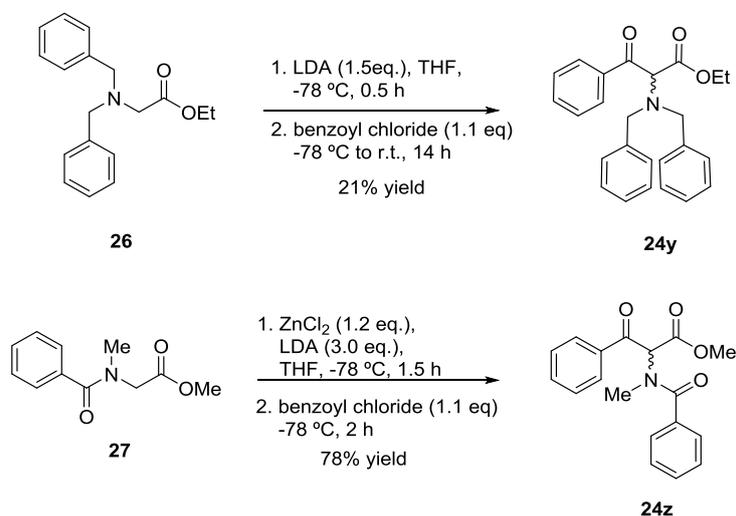
| Entry |            | Substrates  | Yield / % |
|-------|------------|---|-----------|
| 1     | <b>24a</b> |    | 72        |
| 2     | <b>24f</b> |    | 70        |
| 3     | <b>24k</b> |    | 35        |
| 4     | <b>24l</b> |    | 20        |
| 5     | <b>24m</b> |    | 28        |
| 6     | <b>24q</b> |   | 93        |
| 7     | <b>24r</b> |  | 58        |
| 8     | <b>24s</b> |  | 44        |

Finally, a third pathway has been used, which relied on addition of *N*-benzoyl protected glycine ester onto an aldehyde to provide the corresponding  $\beta$ -hydroxy ester followed by Dess-Martin oxidation to yield the expected  $\alpha$ -amido  $\beta$ -ketoesters **24p**, **24u-x** in 51–81% yields (Scheme 161, route c and Table 10).

Table 10. preparation of benzoylamino  $\beta$ -ketoesters using route c

| Entry |            | Substrates | Yield / % |
|-------|------------|------------|-----------|
| 1     | <b>24p</b> |            | 51        |
| 2     | <b>24u</b> |            | 81        |
| 3     | <b>24v</b> |            | 66        |
| 4     | <b>24w</b> |            | 72        |
| 5     | <b>24x</b> |            | 55        |

Furthermore, diprotected  $\alpha$ -amino  $\beta$ -ketoesters **24y** and **24z** were also synthesized from the corresponding *N*-diprotected glycins **26** and **27** by using a reported approach<sup>239</sup> and route b (Scheme 162), respectively.



Scheme 162

## 2.2.2 Optimization of the reaction conditions

### 2.2.2.1 Precatalysts screening

We started our study with the racemic methyl 2-benzoylamino-3-oxo-3-

phenylpropanoate *rac*-**24a** as the standard substrate (Table 11). The initial asymmetric transfer hydrogenation experiments were carried out in CH<sub>2</sub>Cl<sub>2</sub> at 30 °C using ruthenium complexes (*R,R*)-**C1**, (*S,S*)-**C11** and (*R,R*)-**C13a** in the presence of a 5:2 HCO<sub>2</sub>H/Et<sub>3</sub>N azeotropic mixture as the hydrogen source, and afforded the corresponding *anti* amino alcohol derivatives as the major isomers albeit with low enantiomeric excesses (Table 11, entries 1-3). The sense of diastereoselectivity observed here was in agreement with the results reported previously for the ruthenium-catalyzed ATH of the parent  $\alpha$ -*N*-Boc or  $\alpha$ -*N*-Cbz  $\beta$ -keto ester compounds. To our surprise, however, we found that with the tethered rhodium complex (*R,R*)-**C84**,<sup>168,169,272</sup> the reaction proceeded smoothly within 5 h to deliver the reduced *syn* product (*R,S*)-**25a** in 90% yield with a good 86:14 dr and an excellent enantiomeric excess of >99% for the *syn* isomer (Table 11, entry 4). The absolute configuration of the reduced product **25a** was assigned as (*2R,3S*) by converting the diastereomerically pure *syn* **25a** into the known (*1S,2S*)-2-benzoylamino-1-phenyl-propane-1,3-diol and comparing the optical rotation value with the reported data ( $[\alpha]_{\text{D}}^{20} = +80.1$  (c 1.0, EtOH), lit.:<sup>247</sup>  $[\alpha]_{\text{D}}^{20} +94.6$  (c 1.0, EtOH)). To our knowledge, this reversal of diastereoselectivity from *anti* to *syn* provided by the use of a Rh complex has never been reported to date for the ATH of *N*-monoprotected  $\alpha$ -amino  $\beta$ -keto esters. The stereochemical outcome of the transfer hydrogenation reaction was not altered by switching from (*R,R*)-**C84** to (*R,R*)-**C85**, (*R,R*)-**C86** or (*R,R*)-**C87**<sup>272</sup> bearing respectively, methyl, trifluoromethyl or fluoro groups on the aryl ring, even though the reactions required more time (Table 11, entries 5–7).

<sup>247</sup> Zhang, X.-M.; Zhang, H.-L.; Lin, W.-Q.; Gong, L.-Z.; Mi, A.-Q.; Cui, X.; Jiang, Y.-Z.; Yu, K.-B. *J. Org. Chem.* **2003**, *68*, 4322.

Table 11. Precatalysts screening <sup>a</sup>

*rac*-**24a** conditions → **25a**

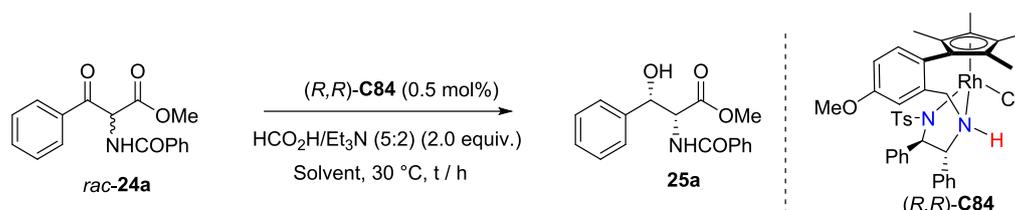
| Entry          | Catalyst                        | Time (h) | Yield (%) | dr ( <i>syn/anti</i> ) <sup>b</sup> | ee <sub>syn</sub> <sup>c</sup> (%) |
|----------------|---------------------------------|----------|-----------|-------------------------------------|------------------------------------|
| 1              | <br>( <i>R,R</i> )- <b>C1</b>   | 96       | 96        | 15 : 85                             | 28 <sup>d</sup>                    |
| 2              | <br>( <i>S,S</i> )- <b>C11</b>  | 7        | 95        | 10 : 90                             | 36 <sup>d</sup>                    |
| 3              | <br>( <i>R,R</i> )- <b>C13a</b> | 9        | 94        | 8 : 92                              | 25 <sup>d</sup>                    |
| 4              | <br>( <i>R,R</i> )- <b>C84</b>  | 5        | 90        | 86 : 14                             | > 99                               |
| 5 <sup>f</sup> | <br>( <i>R,R</i> )- <b>C85</b>  | 7        | 89        | 86 : 14                             | > 99                               |
| 6              | <br>( <i>R,R</i> )- <b>C87</b>  | 7        | 88        | 86 : 14                             | > 99                               |
| 7 <sup>f</sup> | <br>( <i>R,R</i> )- <b>C86</b>  | 20       | 89        | 84 : 16                             | > 99                               |

<sup>a</sup> Conditions: 0.8 mmol of **24a**, 0.5 mol% of precatalyst, 134  $\mu$ L of HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) in 4 mL of solvent [0.2 M] at 30 °C. Complete conversions in all cases. <sup>b</sup> Determined by <sup>1</sup>H NMR of the crude product. <sup>c</sup> Determined by SFC analysis. <sup>d</sup> ee of the *anti* compound. <sup>e</sup> 1.6 mL of solvent was used. <sup>f</sup> Neat reaction.

### 2.2.2.2 Solvents screening

The use of other solvents under otherwise identical conditions (Table 12, entry 1) afforded similar results in terms of yields and stereoselectivities although the reaction time was longer in THF and *i*PrOH (Table 12, entries 2–4). The neat reaction also led to an 86:14 dr and >99% ee (Table 12, entry 5).

**Table 12. Solvents screening<sup>a</sup>**

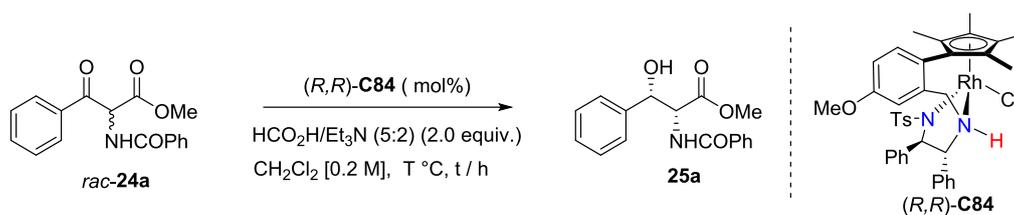


| Entry          | Solvent                         | Time (h) | Yield (%) | dr ( <i>syn/anti</i> ) <sup>b</sup> | ee <sub>syn</sub> <sup>c</sup> (%) |
|----------------|---------------------------------|----------|-----------|-------------------------------------|------------------------------------|
| 1              | CH <sub>2</sub> Cl <sub>2</sub> | 5        | 90        | 86 : 14                             | > 99                               |
| 2              | CH <sub>3</sub> CN              | 4.5      | 86        | 87 : 13                             | > 99                               |
| 3              | THF                             | 23       | 89        | 87 : 13                             | > 99                               |
| 4              | <i>i</i> PrOH                   | 28       | 88        | 83 : 17                             | > 99                               |
| 5 <sup>d</sup> | —                               | 4        | 87        | 86 : 14                             | > 99                               |

<sup>a</sup> Conditions: 0.8 mmol of **25a**, 0.5 mol% of *(R,R)*-**C84**, 134  $\mu\text{L}$  of HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) in 4 mL of solvent [0.2 M] at 30  $^\circ\text{C}$ . Complete conversions in all cases. <sup>b</sup> Determined by <sup>1</sup>H NMR of the crude product. <sup>c</sup> Determined by SFC analysis. <sup>d</sup> Neat reaction.

### 2.2.2.3 Catalyst loading and temperature screening

In view of the above results, we selected complex *(R,R)*-**C84** as the precatalyst and CH<sub>2</sub>Cl<sub>2</sub> as the solvent for further studies (Table 13). Performing the reaction at 30  $^\circ\text{C}$  with a catalyst loading of 0.1 mol% instead of 0.5 mol% resulted only in an extended reaction time without any noticeable effect on either the yield or stereoselectivity (Table 13, entries 1 and 2), whereas using a 1:1 HCO<sub>2</sub>H/Et<sub>3</sub>N azeotropic mixture rather than the 5:2 system led to incomplete conversion after 24 h of reaction (Table 13, entry 3). The temperature effect was then investigated, and the reaction was run at 18  $^\circ\text{C}$ , affording a slightly higher diastereomeric ratio of 89:11 (Table 13, entry 4). A satisfying 92:8 dr was attained at a temperature of 0  $^\circ\text{C}$  after either 47 h (Table 13, entry 5) or 94 h with a catalyst loading of 0.2 mol% (Table 13, entry 6).

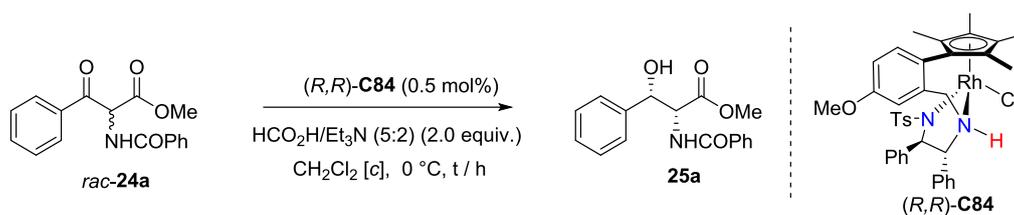
Table 13. catalyst loading and temperature screening <sup>a</sup>

| Entry          | <i>(R,R)</i> - <b>C84</b> (mol%) | Temp (°C) | Time (h) | Yield (%)       | dr ( <i>syn/anti</i> ) <sup>b</sup> | ee <sub>syn</sub> <sup>c</sup> (%) |
|----------------|----------------------------------|-----------|----------|-----------------|-------------------------------------|------------------------------------|
| 1              | 0.5                              | 30        | 5        | 90              | 86 : 14                             | > 99                               |
| 2              | 0.1                              | 30        | 23       | 91              | 86 : 14                             | > 99                               |
| 3 <sup>d</sup> | 0.5                              | 30        | 24       | 61 <sup>e</sup> | 86 : 14                             | > 99                               |
| 4              | 0.5                              | 18        | 22       | 87              | 89 : 11                             | > 99                               |
| 5              | 0.5                              | 0         | 47       | 93              | 92 : 8                              | > 99                               |
| 6              | 0.2                              | 0         | 94       | 73              | 92 : 8                              | > 99                               |

<sup>a</sup> Conditions: 0.8 mmol of **24a**, respective mol% of *(R,R)*-**C84**, 134  $\mu\text{L}$  of  $\text{HCO}_2\text{H}/\text{Et}_3\text{N}$  (5:2) in 4.0 mL of  $\text{CH}_2\text{Cl}_2$  [0.2 M] (Initial concentration of  $\alpha$ -amido  $\beta$ -keto ester). Complete conversions except where indicated. <sup>b</sup> Determined by <sup>1</sup>H NMR of the crude product. <sup>c</sup> Determined by SFC analysis. <sup>d</sup> 1:1 mixture of  $\text{HCO}_2\text{H}/\text{Et}_3\text{N}$  used. <sup>e</sup> 64% conversion obtained under these conditions.

### 2.2.2.4 Concentration screening

Finally, maintaining a 0.5 mol% catalyst loading, a variation of the initial concentration of  $\alpha$ -amido  $\beta$ -keto ester from 0.2 to 0.4 and 0.5 M showed a decrease of the reaction time from 47 h to 34 h and 28 h, respectively (Table 14, entries 1-3). Accordingly, the optimized reaction conditions were set as follows: 0.5 mol% of *(R,R)*-**C84**, a 5:2  $\text{HCO}_2\text{H}/\text{Et}_3\text{N}$  azeotropic mixture as the hydrogen source,  $\text{CH}_2\text{Cl}_2$  as the solvent (0.5 M), and a reaction temperature of 0 °C.

Table 14. Concentration screening <sup>a</sup>

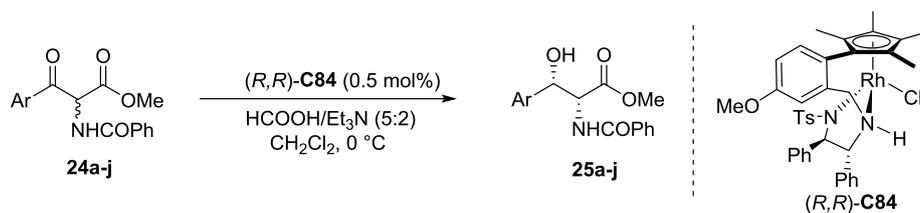
| Entry | [c M] | Time (h) | Yield (%) | dr ( <i>syn/anti</i> ) <sup>c</sup> | ee <sub>syn</sub> <sup>d</sup> (%) |
|-------|-------|----------|-----------|-------------------------------------|------------------------------------|
| 1     | 0.2   | 47       | 93        | 92 : 8                              | > 99                               |
| 2     | 0.4   | 34       | 94        | 92 : 8                              | > 99                               |
| 3     | 0.5   | 28       | 93        | 92 : 8                              | > 99                               |

<sup>a</sup> Conditions: 0.8 mmol of **24a**, 0.5 mol% of (*R,R*)-**C84**, 134  $\mu$ L of HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) in 1.6 – 4.0 mL of CH<sub>2</sub>Cl<sub>2</sub> [0.2 – 0.5 M] (Initial concentration of  $\alpha$ -amido  $\beta$ -keto ester). Complete conversions except where indicated. <sup>b</sup> Determined by <sup>1</sup>H NMR of the crude product. <sup>c</sup> Determined by SFC analysis. <sup>d</sup> 1:1 mixture of HCO<sub>2</sub>H/Et<sub>3</sub>N used. <sup>e</sup> 64% conversion obtained under these conditions.

### 2.3.3 Substrate scope

#### 2.3.3.1 ATH of aryl substituted $\alpha$ -benzoylamino $\beta$ -keto esters

With these conditions in hand, we next investigated the scope of the reaction and a series of variously substituted  $\alpha$ -benzoylamino  $\beta$ -keto esters were subjected to the ATH. Compounds bearing substituted phenyl groups on the ketone functional group generally gave the corresponding reduced *syn* products **25a–i** in high yields with high diastereoselections and excellent enantioselectivities irrespective of the electron-donating or electron-withdrawing character of the substituents (Table 15, entries 1–9). An exception to this trend was observed for **24j** having a sterically hindered *ortho*-tolyl substituent on the ketone, which delivered in moderate yield the *anti* compound as the major isomer (*syn/anti* 13:87) albeit with a low enantiomeric excess (52% ee), whereas the *syn* isomer was produced in >99% ee (Table 15, entry 10).

Table 15. ATH of aryl substituted  $\alpha$ -benzoylamino  $\beta$ -keto esters <sup>a</sup>

| Entry | Substrates | Product <b>25</b> | Time (h) | Yield (%) | dr ( <i>syn/anti</i> ) <sup>b</sup> | ee <sub>syn</sub> <sup>c</sup> (%) |
|-------|------------|-------------------|----------|-----------|-------------------------------------|------------------------------------|
| 1     | <b>24a</b> | <b>25a</b>        | 28       | 93        | 92 : 8                              | > 99                               |
| 2     | <b>24b</b> | <b>25b</b>        | 48       | 98        | 93 : 7                              | > 99                               |
| 3     | <b>24c</b> | <b>25c</b>        | 70       | 96        | 93 : 7                              | > 99                               |
| 4     | <b>24d</b> | <b>25d</b>        | 48       | 96        | 94 : 6                              | > 99                               |
| 5     | <b>24e</b> | <b>25e</b>        | 64       | 96        | 92 : 8                              | > 99                               |
| 6     | <b>24f</b> | <b>25f</b>        | 45       | 86        | 91 : 9                              | > 99                               |
| 7     | <b>24g</b> | <b>25g</b>        | 23       | 98        | 92 : 8                              | > 99                               |
| 8     | <b>24h</b> | <b>25h</b>        | 23       | 95        | 93 : 7                              | > 99                               |
| 9     | <b>24i</b> | <b>25i</b>        | 25       | 98        | 94 : 6                              | > 99                               |
| 10    | <b>24j</b> | <b>25j</b>        | 72       | 70        | 13 : 87                             | > 99<br>52 <sub>anti</sub>         |

<sup>a</sup> Conditions: 0.8 mmol of **24a-j**, 0.5 mol% of  $(R,R)$ -**C84**, 134  $\mu$ L of HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) in 1.6 mL of CH<sub>2</sub>Cl<sub>2</sub> at 0 °C. Complete conversions except for compounds **24j** for which 73% conv. were obtained. <sup>b</sup> Determined by <sup>1</sup>H NMR of the crude product. <sup>c</sup> Determined by SFC or HPLC analysis. <sup>d</sup> Reaction carried out at 30 °C.

2.3.3.2 ATH of heteroaryl substituted  $\alpha$ -benzoylamino  $\beta$ -keto esters

On the other hand, heteroaryl ketones afforded excellent levels of diastereo- and enantioinductions and the reduced compounds were obtained in very good yields with the exception of compound **24l**, which produced **25l** in 87:13 dr and 96% ee (Table 16, entries 1–5). Compound **24p** containing a *N*-methyl pyrrolidinyl substituent on the ketone part, failed to afford any conversion under the standard conditions (Table 16, entry 7). Furthermore, for the amido ester **24o** bearing a thienyl substituent on the ketone, no temperature effect was observed because the reaction could be carried out at 30 °C within only 1 h without any alteration of the dr or ee (Table 16, entries 5–6). In addition, the reduction of **24o** was efficiently performed on gram scale demonstrating the usefulness of this method. The substrate scope was then expanded to  $\alpha$ -amido  $\beta$ -keto esters containing an alkyl ketone.

Table 16. ATH of heteroaryl substituted  $\alpha$ -benzoylamino  $\beta$ -keto esters <sup>a</sup>

| Entry          | Substrate  | Product <b>25</b> | Time (h) | Yield (%) | dr ( <i>syn/anti</i> ) <sup>b</sup> | ee <sub>syn</sub> <sup>c</sup> (%) |
|----------------|------------|-------------------|----------|-----------|-------------------------------------|------------------------------------|
| 1              | <b>24k</b> | <b>25k</b>        | 22       | 96        | 97 : 3                              | > 99                               |
| 2              | <b>24l</b> | <b>25l</b>        | 42       | 63        | 87 : 13                             | 96                                 |
| 3              | <b>24m</b> | <b>25m</b>        | 15       | 93        | 98 : 2                              | > 99                               |
| 4              | <b>24n</b> | <b>25n</b>        | 24       | 96        | > 99:1                              | 99                                 |
| 5              | <b>24o</b> | <b>25o</b>        | 34       | 98        | > 99:1                              | > 99                               |
| 6              |            |                   | 1        | 96        | > 99:1                              | > 99                               |
| 7 <sup>e</sup> | <b>24p</b> | <b>25p</b>        | 48       | --        | --                                  | --                                 |

<sup>a</sup> Conditions: 0.8 mmol of **24k-p**, 0.5 mol% of (*R,R*)-**C84**, 134  $\mu$ L of HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) in 1.6 mL of CH<sub>2</sub>Cl<sub>2</sub> at 0 °C. Complete conversions except for compounds **24s** for which 82% conv. were obtained. <sup>b</sup> Determined by <sup>1</sup>H NMR of the crude product. <sup>c</sup> Determined by SFC or HPLC analysis. <sup>d</sup> Reaction carried out at 30 °C. <sup>e</sup>No reaction.

### 2.3.3.3 ATH of alkyl and alkynyl substituted $\alpha$ -benzoylamino $\beta$ -keto esters

For these compounds, the reduced *syn* products were obtained with lower diastereomeric ratios while the ee remained >99% (Table 17, entries 1–2). As for the sterically demanding substrate **24j** (Table 17, entry 3), a reversal of diastereoselectivity was observed as well, with the amido ester **24s** (Table 17, entry 3 and 4) having an isopropyl substituent on the ketone. This time the *anti* isomer was formed with a very high level of diastereo- and enantioinductions albeit after a prolonged reaction time of 10 days (Table 17, entry 3), which could be reduced to 92 h by working at 30 °C with no loss of stereoselectivity (Table 17, entry 4). Finally, the Rh-catalyzed ATH of substrate **24t** having an alkyne residue proceeded with near-perfect diastereo- and enantioselectivities in either 10 days at 0 °C (Table 17, entry 5) or in only 24 h at 30 °C (Table 17, entry 6).

**Table 17.** ATH of alkyl and alkynyl substituted  $\alpha$ -benzoylamino  $\beta$ -keto esters <sup>a</sup>

**24q-t**  
R = alkyl, alkynyl

→

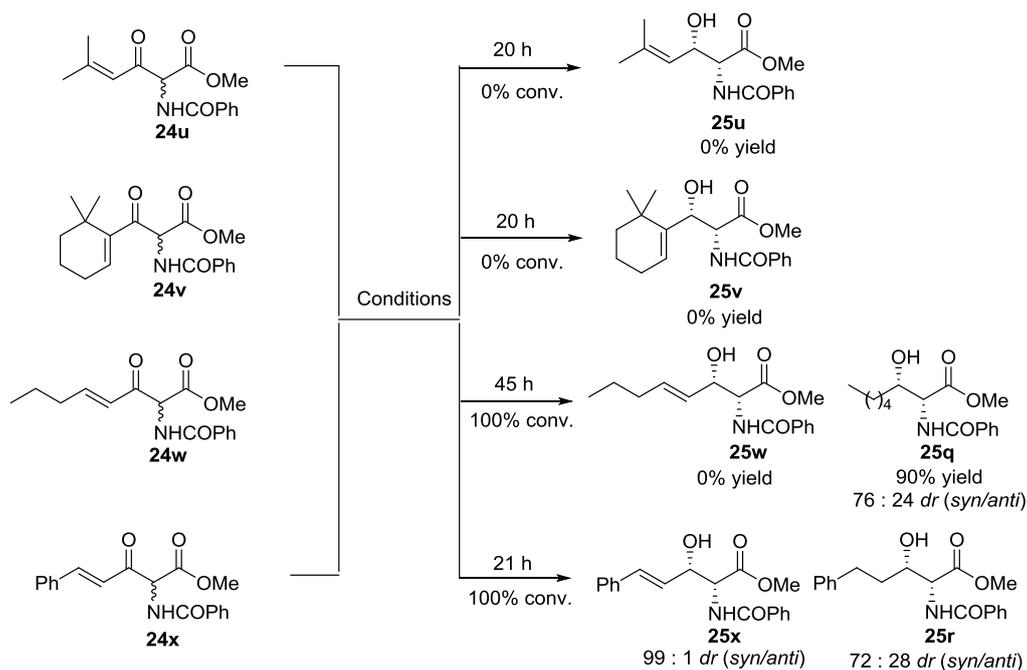
**(*R,R*)-C84**

| Entry          | Substrate  | Product <b>25</b> | Time (h) | Yield (%) | dr ( <i>syn/anti</i> ) <sup>b</sup> | ee <sub>syn</sub> <sup>c</sup> (%) |
|----------------|------------|-------------------|----------|-----------|-------------------------------------|------------------------------------|
| 1              | <b>24q</b> | <b>25q</b>        | 46       | 97        | 80 : 20                             | > 99                               |
| 2              | <b>24r</b> | <b>25r</b>        | 24       | 98        | 75 : 25                             | > 99                               |
| 3              | <b>24s</b> | <b>25s</b>        | 240      | 72        | 2 : 98                              | > 99                               |
| 4 <sup>d</sup> | <b>24s</b> | <b>25s</b>        | 92       | 74        | 3 : 97                              | 99                                 |
| 5              | <b>24t</b> | <b>25t</b>        | 240      | 86        | > 99 : 1                            | > 99                               |
| 6 <sup>d</sup> | <b>24t</b> | <b>25t</b>        | 24       | 80        | > 99 : 1                            | > 99                               |

<sup>a</sup> Conditions: 0.8 mmol of **24q-t**, 0.5 mol% of (*R,R*)-**C84**, 134  $\mu$ L of HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) in 1.6 mL of CH<sub>2</sub>Cl<sub>2</sub> at 0 °C. Complete conversions except for compounds **24s** for which 82% conv. were obtained. <sup>b</sup> Determined by <sup>1</sup>H NMR of the crude product. <sup>c</sup> Determined by SFC or HPLC analysis. <sup>d</sup> Reaction carried out at 30 °C.

2.3.3.4 ATH of alkenyl substituted  $\alpha$ -benzoylamino  $\beta$ -keto esters

Besides, conjugated alkenyl substituted  $\alpha$ -benzoylamino  $\beta$ -keto esters were examined under the above reduction conditions. However, tri-substituted enone substrates **24u** and **24v** gave no conversion whereas di-substituted enone **24w** and **24x** led to side products (Scheme 163). For  $\beta$ -keto ester **24w**, only the saturated  $\beta$ -hydroxy ester **25q** was isolated, resulting from reduction of the C=C bond in the process. For compound **24x**, a mixture of the expected product **25x** and by-product **25r** was obtained.

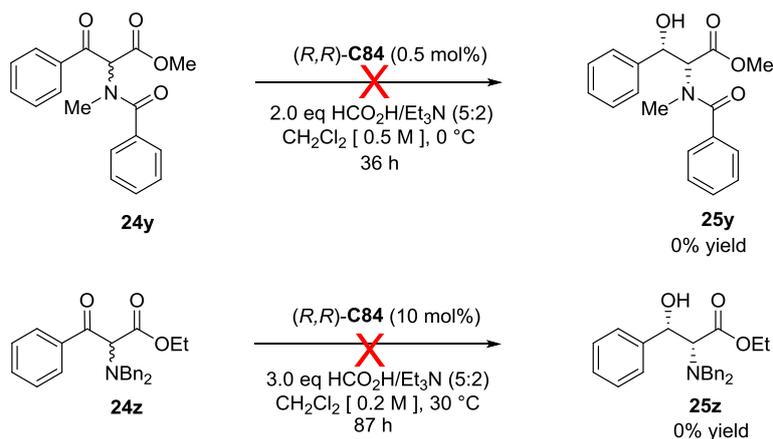


**Conditions:** 0.8 mmol of **24u-24x**, 0.5 mol% of (*R,R*)-**C84**, 134  $\mu$ L of HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) in 1.6 mL of CH<sub>2</sub>Cl<sub>2</sub> at 0 °C. Conversion and diastereoselectivity were determined by <sup>1</sup>H NMR of the crude product.

Scheme 163

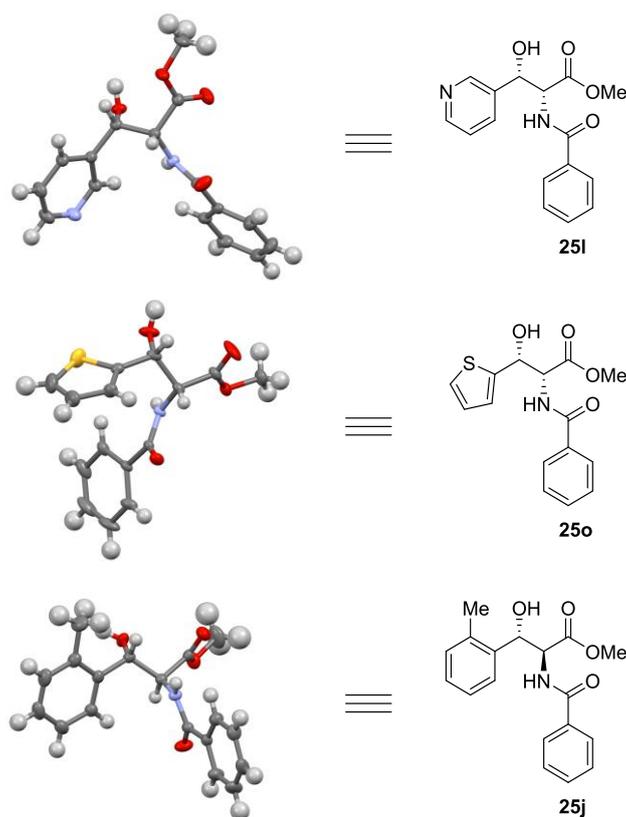
2.3.3.5 ATH of diprotected  $\alpha$ -amino  $\beta$ -keto esters

Following the above substrate scope for mono-protected  $\alpha$ -benzoylamino  $\beta$ -keto esters, we also investigated tethered rhodium complex (*R,R*)-**C84** in the ATH of *N*-di-protected  $\alpha$ -amido  $\beta$ -keto ester **24y** and  $\alpha$ -*N*-dibenzylamino  $\beta$ -keto ester **24z**. However, for these compounds, no conversion was observed under either the standard conditions for **24y**, or even by using 10 mol% of the catalyst at 30 °C for **24z** (Scheme 164).



### 2.3.4 Determination of the absolute configuration

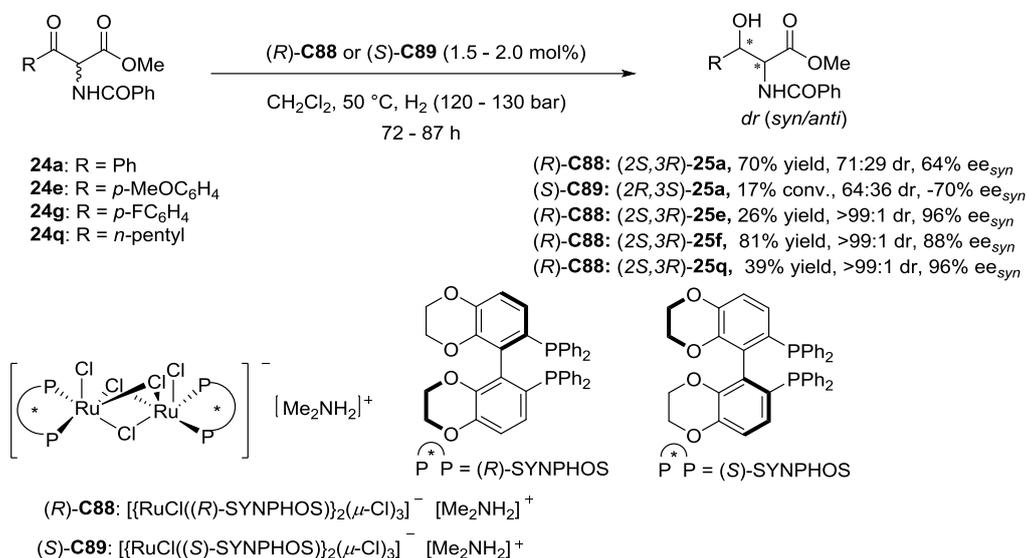
X-Ray analysis of compounds **25i** and **25o** allowed determination of their absolute configurations as (2*R*,3*S*) (Figure 9). On the other hand, the relative *anti* configuration obtained for compound **25j** was also confirmed by an X-ray crystallographic analysis (Figure 9).



**Figure 9**

Moreover, the absolute configuration of **25a** was further confirmed by comparison with authentic samples of compounds (2*R*,3*S*)-**25a** and (2*S*,3*R*)-**25a** (prepared by ruthenium-

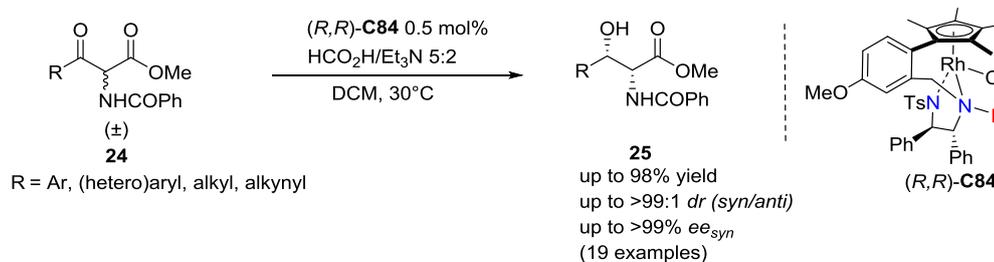
catalyzed AH of *rac*-**24a** with [ $\{\text{RuCl}((R)\text{-SYNPHOS})\}_2(\mu\text{-Cl})_3\}^- [\text{Me}_2\text{NH}_2]^+$  (*R*)-**C88** and [ $\{\text{RuCl}((S)\text{-SYNPHOS})\}_2(\mu\text{-Cl})_3\}^- [\text{Me}_2\text{NH}_2]^+$  (*S*)-**C89** respectively) using HPLC analysis. The absolute configurations of **25e**, **25f** and **25q** were assigned by using the same method (Scheme 165).



Scheme 165

## 2.3 Conclusion

In summary, the rhodium-catalyzed asymmetric transfer hydrogenation of  $\alpha$ -amido  $\beta$ -keto esters via DKR appears to be an efficient tool for the synthesis of *syn*  $\alpha$ -benzoylamido  $\beta$ -hydroxy esters, which until now were not directly attainable through ATH. The reaction proceeded under mild conditions using a low catalyst loading with tolerance for a diverse set of functional groups, delivering the reduced compounds in good yields, high diastereomeric ratios, and excellent enantioselectivities for a wide range of substrates. Furthermore, the usefulness of this method was demonstrated by the efficient gram-scale reduction of **25o** (Scheme 166).



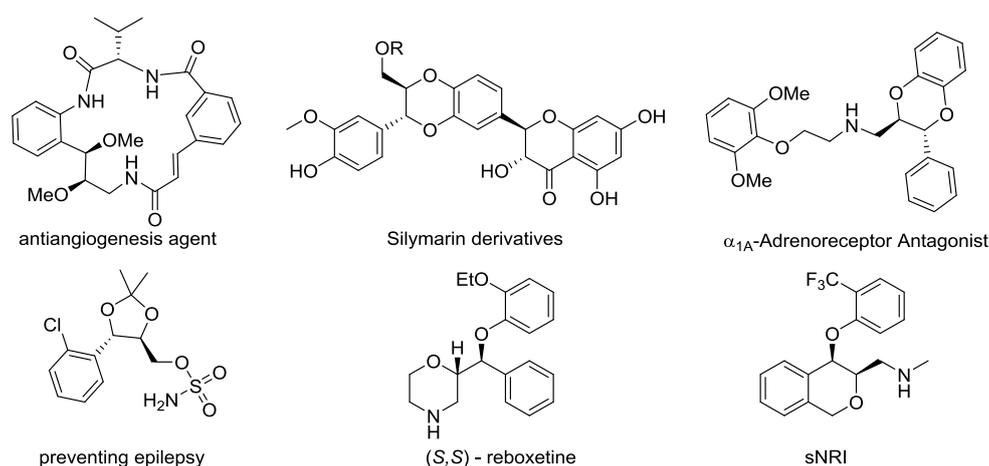
Scheme 166

### 3. Novel rhodium-mediated ATH: a diastereo- and enantioselective synthesis of *syn*- $\alpha$ -alkoxy $\beta$ -hydroxy esters

#### 3.1 Introduction

##### 3.1.1 Biological interest of *syn* diols derivatives

Chiral 1,2-diols are important structural motifs found in a number of natural and biologically active molecules, such as macrocyclic natural product,<sup>248</sup> silymarin derivatives,<sup>249</sup>  $\alpha_1$ -adrenoreceptor antagonist,<sup>250</sup> preventing epilepsy agent,<sup>251</sup> (*S,S*)-reboxetine,<sup>208</sup> selective norepinephrine reuptake inhibitors (sNRI),<sup>252</sup> carbohydrates, polyketides, or alkaloids,<sup>253</sup> and have found wide applications in organic synthesis either as chiral ligands or auxiliaries<sup>254</sup> (Figure 10).



**Figure 10**

<sup>248</sup> Aeluri, M.; Gaddam, J.; Trinath, D. V. K. S.; Chandrasekar, G.; Kitambi, S. S.; Arya, P. *Eur. J. Org. Chem.* **2013**, 3955.

<sup>249</sup> Zhuang, R.-X; Zhang, J.-K; Xi, J.-J; Zhao, Y.-M; Shao, Y.-D; Pan, X.-W; Fang, H.-Y; Cai, Z.-B; Liu S.-R; Wu, X.-M *Silybin 23-substituted derivative and preparation method and application of injection thereof*. CN106317033A, **2016**

<sup>250</sup> Romeiro, LAS; Fraga CAM; Lacerda, BEJ; Silva, CLM; Miranda, ALP; Eduardo, VT; Brito, FCF; Almeida, HCCC; NOËL, FG *Use of adrenergic n-phenylpiperazine antagonists, pharmaceutical compositions containing them, and methods of preparing them*. WO2005112538A2, **2005**

<sup>251</sup> Choi, Y.-M *Sulfamate derivative compound for use in preventing or treating epilepsy*. WO2015088271A1, **2015**

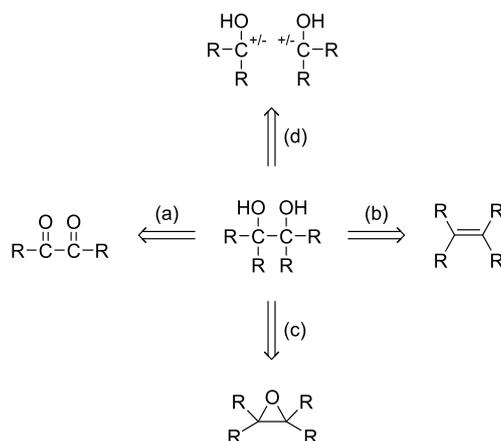
<sup>252</sup> Hudson, S.; Kiankarimi, M.; Eccles, W.; Dwight, W.; Mostofi, Y. S.; Genicot, M. J.; Fleck, B. A.; Gogas, K.; Aparicio, A.; Wang, H.; et al. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4491.

<sup>253</sup> Nicolaou, K. C.; Snyder, S. A. *Classics in Total Synthesis II*; Wiley-VCH: Weinheim, Germany, **2003**, and references therein.

<sup>254</sup> Seyden-Penn, J. In *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; Wiley-VCH: Weinheim, **1995**

### 3.1.2 Different synthetic pathways for 1,2-diols derivatives

Several efficient approaches to access enantiomerically pure 1,2-diols are described in the literature.<sup>27g,255</sup> These methods involve: (a) sequential reduction of a 1,2-diketone, (b) dihydroxylation reactions, (c) epoxide ring-opening, or (d) C-C bond formation reaction between two oxygen-bearing carbon atoms (Scheme 167).



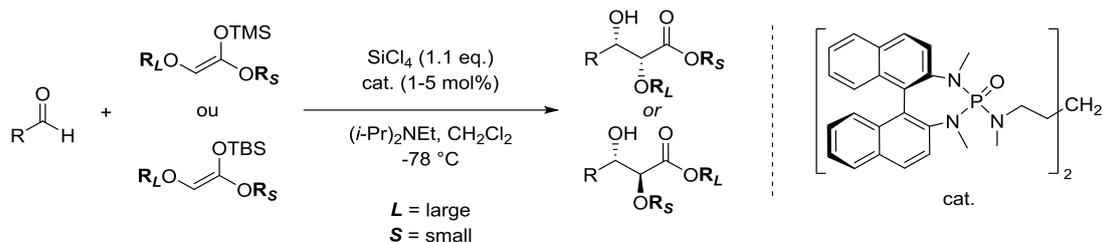
**Scheme 167**

However, in most of the methods reported in the literature, the two hydroxy groups were not differentiated. Thus, the synthesis of monodifferentiated 1,2-diols remains a challenge. To our knowledge, only few examples of the preparation of this type of compounds have been described.

In 2008, Denmark *et al.* described a catalytic pathway for the preparation of stereodefined and monodifferentiated 1,2-diols via an enantioselective aldolization reaction between a glycolate-derived silyl ketene acetal and an aldehyde, in the presence of tetrachlorosilane and a catalytic amount of a chiral bisphosphoramidate (Scheme 168).<sup>256</sup>

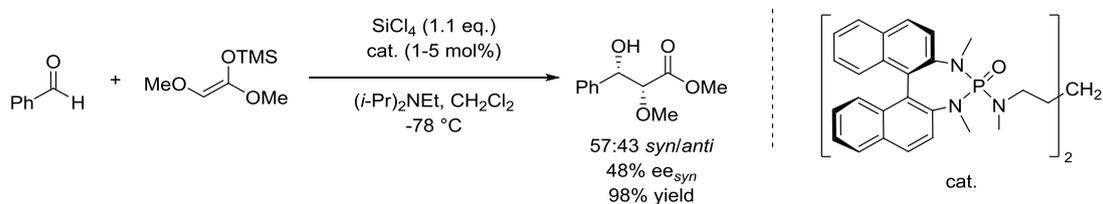
<sup>255</sup> (a) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483. (b) Shi, Y. *Acc. Chem. Res.* **2004**, *37*, 488. (c) Guillena, G.; Najera, C.; Ramon, D. *Tetrahedron: Asymmetry* **2007**, *18*, 2249. (d) Tanaka, F.; Barbas III, C. F. In *Enantioselective Organocatalysis, Reaction and Experimental Procedures*; Dalko, P. I., Ed.; Wiley-VCH: Weinheim, **2007**, pp 19-55. (e) Jiao, P.; Kawasaki, M.; Yamamoto, H. *Angew. Chem. Int. Ed.* **2009**, *48*, 1.

<sup>256</sup> Denmark, S. E.; Chung, W.-J. *Angew. Chem. Int. Ed.* **2008**, *47*, 1890.



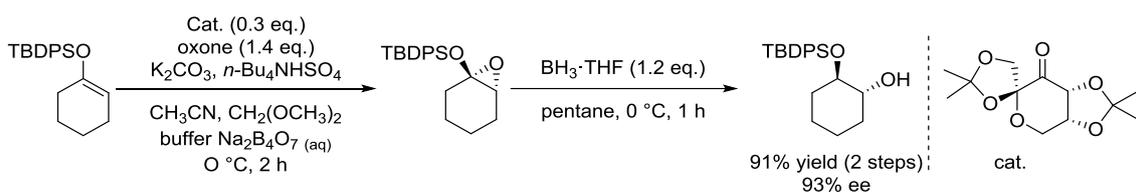
Scheme 168

Interestingly, both *syn* and *anti* 1,2-diols can be obtained with the same catalyst system. However, this reaction requires a stoichiometric amount of tetrachlorosilane, and former conversion of the ester to a more reactive silyl ketene acetal, which considerably decreases the overall reaction efficiency. In addition, when the  $\alpha$ -alkoxy group is small, such as a methoxy group, diastereoselectivity and enantioselectivity drop significantly (Scheme 169).<sup>257</sup>



Scheme 169

Myers *et al.*<sup>258</sup> reported the synthesis of enantiomerically enriched *anti* 1,2-diols monosilyl ether derivatives, with good isolated yields and good to excellent enantio- and diastereoselectivities (Scheme 4, 93% ee, 91% yield). This two-step sequence involves asymmetric Shi epoxidation and a regioselective epoxide opening (Scheme 170).



Scheme 170

Despite the good results obtained, this synthetic route has certain disadvantages that limit its practicality, such as the use of a high catalyst loading (30 mol%) and an excess of reagents. Furthermore, this method remains essentially limited to cyclic silyl enol ethers.

<sup>257</sup> Denmark, S. E.; Chung, W.-J. *J. Org. Chem.* **2008**, *73*, 4582.

<sup>258</sup> Lim, S. M.; Hill, N.; Myers, A. G. *J. Am. Chem. Soc.* **2009**, *131*, 5763.

Therefore, the development of new catalytic highly diastereo- and enantioselective methodologies to access optically active monodifferentiated 1,2-diols with a high level of selectivity and a high atom economy is still of major interest in organic synthesis. Our group and others have shown that dynamic kinetic resolution (DKR) combined with asymmetric hydrogenation catalyzed by ruthenium complexes has proven to be an effective synthetic tool for controlling two adjacent stereocentres in a single chemical operation.

*Based on our previous results on Ru-catalyzed DKR/ATH of  $\alpha$ -alkoxy  $\beta$ -keto esters, herein, we have studied this reaction by using Rh complexes and more particularly a new Rh tethered complex to evaluate their catalytic performances.*

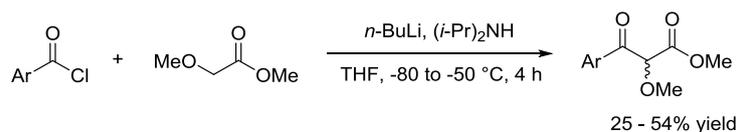
## 3.2 Results and discussion

### 3.2.1 Synthesis of aryl $\alpha$ -methoxy $\beta$ -keto esters

For this study, we first prepared a series of  $\alpha$ -alkoxy-substituted  $\beta$ -ketoesters **26**. These compounds were synthesized in either one (Method A) or two (Method B) steps as described hereafter.

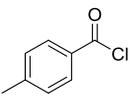
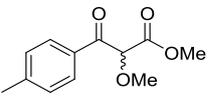
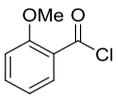
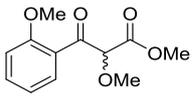
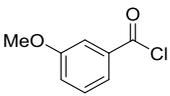
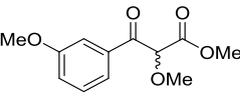
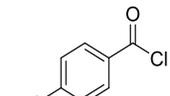
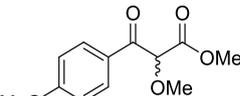
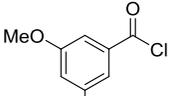
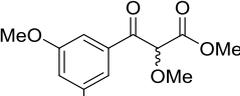
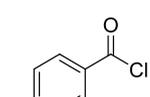
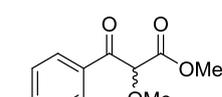
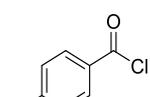
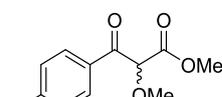
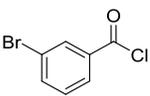
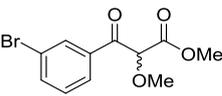
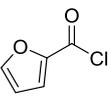
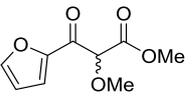
#### Method A :

This method involves addition of the lithioenolate of methyl methoxyacetate onto an aryl acyl chloride, and afforded the desired ketoesters in 25–54% yields (Scheme 171 and Table 18).



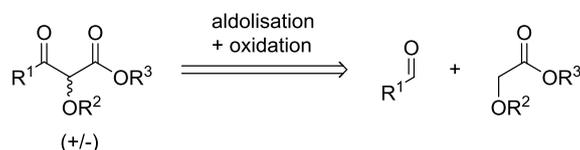
**Scheme 171**

Table 18. Preparation of aryl  $\alpha$ -methoxy  $\beta$ -keto esters using method A

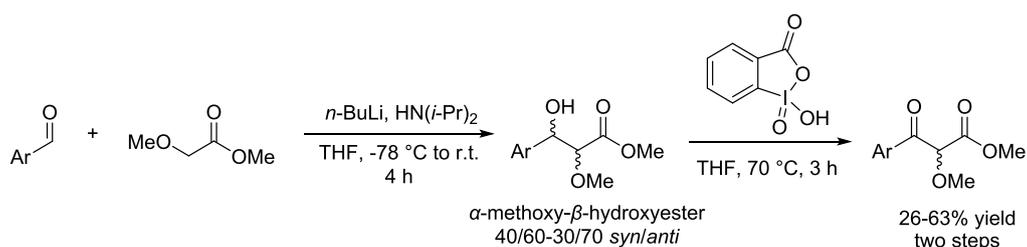
| entry | Starting material   | No.        | $\beta$ -ketoester   | Yields (%) |
|-------|---|------------|--|------------|
| 1     |    | <b>26b</b> |    | 38         |
| 2     |    | <b>26c</b> |    | 25         |
| 3     |    | <b>26d</b> |    | 54         |
| 4     |    | <b>26e</b> |    | 51         |
| 5     |  | <b>26g</b> |  | 43         |
| 6     |  | <b>26h</b> |  | 49         |
| 7     |  | <b>26j</b> |  | 26         |
| 8     |  | <b>26k</b> |  | 32         |
| 9     |  | <b>26m</b> |  | 29         |

**Mehod B :**

This two-step sequence involves an aldol reaction to give the corresponding  $\alpha$ -alkoxy- $\beta$ -ketoesters, followed by oxidation of the alcohol functional group to afford the desired  $\alpha$ -alkoxy- $\beta$ -ketoesters (Scheme 172).

**Scheme 172**

Following the above route, a series of  $\alpha$ -methoxy  $\beta$ -hydroxyesters were synthesized by aldol reaction between methyl methoxyacetate and a variety of aromatic aldehydes and subsequent oxidation of these compounds with 2-iodobenzoic acid (IBX) gave the corresponding  $\alpha$ -methoxy  $\beta$ -ketoesters in 26–63% yields over two steps (Scheme 173 and Table 19).

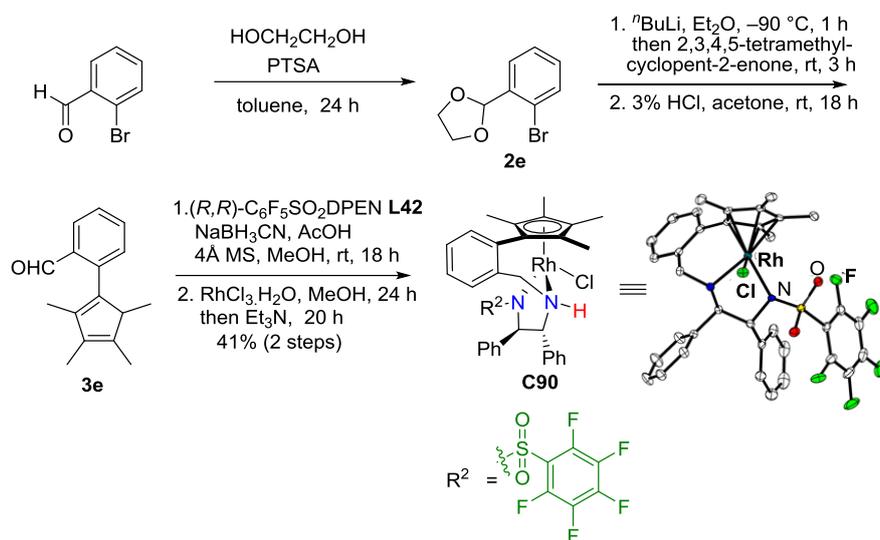
**Scheme 173****Table 19. Preparation of aryl  $\alpha$ -methoxy  $\beta$ -keto esters using method B**

| entry | Starting material | No.        | $\beta$ -ketoester | Yields (%) 2 steps |
|-------|-------------------|------------|--------------------|--------------------|
| 1     |                   | <b>26a</b> |                    | 32                 |
| 2     |                   | <b>26f</b> |                    | 36                 |
| 3     |                   | <b>26i</b> |                    | 63                 |



### 3.2.2 Synthesis of a new Rh(III)-TsDPEN-based tethered complex

For this study, we have prepared and evaluated a new Rh(III)-TsDPEN-based tethered complex wherein the tosyl group has been replaced by a pentafluorobenzenesulfonyl substituent. This complex was prepared from 2-(2,3,4,5-tetramethylcyclopenta-1,3-dien-1-yl)benzaldehyde **3e**, which was obtained by protection of 2-bromobenzaldehyde with glycol to 1,3-dioxolane derivative **2e**, followed by treatment of compound **2e** with  $n$ BuLi, and addition of 2,3,4,5-tetramethylcyclopent-2-enone to furnish the corresponding alcohol, which was then subjected to both deprotection of the aldehyde function and dehydration of the tertiary alcohol using 3% hydrochloric acid in acetone. Subsequent reductive amination using (*R,R*)-C<sub>6</sub>F<sub>5</sub>SO<sub>2</sub>DPEN **L42** in the presence of sodium cyanoborohydride then delivered the corresponding diamine. The targeted complex (*R,R*)-**C90** was then obtained through heating the latter in refluxing methanol in the presence of rhodium(III) chloride followed by treatment with triethylamine. The new complex was isolated after flash chromatography as an orange solid and as a single diastereomer, whereas its structure was confirmed by X-ray crystallographic analysis (Scheme 174).



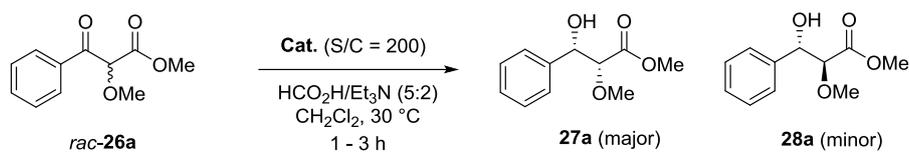
Scheme 174

### 3.2.3 Optimisation of the reaction conditions

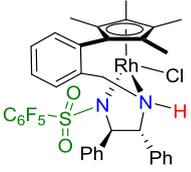
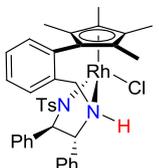
#### 3.2.3.1 Influence of the precatalyst

In a previous study, our group reported that [(*S,S*)-TsDPEN-Ru(mesitylene)Cl] (*S,S*)-**C3** allowed high diastereoselectivities and excellent enantioselectivities in ATH/DKR of  $\alpha$ -alkoxy  $\beta$ -keto esters in favour of the *syn* 1,2-diol derivatives for a variety of substrates bearing diversely functionalized (hetero)aromatic and alkenyl moieties, and moderate to good enantio- and diastereo-inductions for alkyl and alkynyl substrates.<sup>206,207</sup>

However, tethered Rh or Ru complexes were not thoroughly investigated in this work so that we decided to evaluate these catalysts for this reaction. We chose *rac*-**26a** as the standard substrate for this study and the ATH/DKR was run in dichloromethane at 30 °C with 0.5 mol% of the Rh or Ru complex and a HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) azeotropic mixture as the hydrogen source. Under these conditions, commercially available oxo-tethered Ru(II) complex (*R,R*)-TsDENE (*R,R*)-**C13a** afforded *syn* 1,2-diol **27a** with a good diastereoselectivity (85/15 dr, *syn/anti*) and an excellent enantioselectivity (99% ee) (Table 20, entry 1). Complex [(*S,S*)-teth-TsDPEN(RuCl)] (*S,S*)-**C11** also provided good yield (85%) and diastereoselectivity (70/30 dr, *syn/anti*), with a high level of enantioselectivity (97% ee) (Table 20, entry 2). Switching from tethered ruthenium to rhodium complexes allowed higher yields and diastereoselectivities whereas the enantioselectivities remained excellent and shorter reaction times were observed (Table 20, entries 3–9). When the reaction was carried out at 0 °C with complex (*R,R*)-**C84**, a longer reaction time was required with no improvement observed in terms of diastereoselectivity (88:12 dr) (Table 20, entry 4). Although all tested Rh complexes (*R,R*)-**C84-C87**, (*R,R*)-**C23** showed comparable results in terms of yields and stereoselectivity (Table 20, entries 3-7 and 9), the newly prepared complex (*R,R*)-**C90** gave the highest yield (94%) and the best level of diastereoselectivity (93:7) in favor of the *syn* 1,2-diol **27a** (Table 20, entry 8). Therefore, rhodium complex (*R,R*)-**C90** was used for further screening of the reaction parameters.

Table 20. Influence of the precatalysts<sup>d</sup>

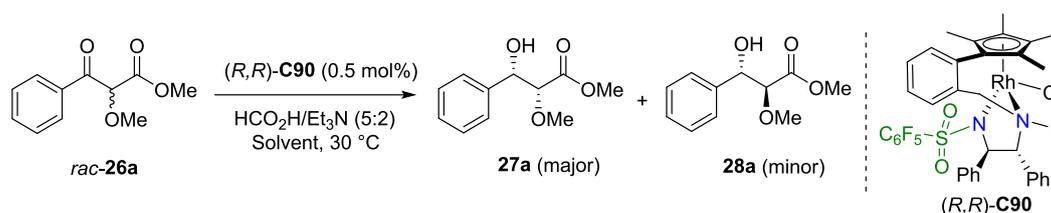
| Entry          | Cat.                     | Time (h) | Yield (%) <sup>b</sup> | dr ( <b>27a</b> : <b>28a</b> ) <sup>c</sup> | <i>ee</i> <sub>syn</sub> (%) <sup>d</sup> |
|----------------|--------------------------|----------|------------------------|---|---|
| 1              | <b>(<i>R,R</i>)-C13a</b> | 20       | 85                     | 85:15                                       | 99  |
| 2 <sup>e</sup> | <b>(<i>S,S</i>)-C11</b>  | 14       | 85                     | 70:30                                       | -97                                       |
| 3              | <b>(<i>R,R</i>)-C84</b>  | 1        | 91                     | 91:9  | 99  |
| 4 <sup>f</sup> | <b>(<i>R,R</i>)-C84</b>  | 22       | 90                     | 88:12                                       | 99  |
| 5              | <b>(<i>R,R</i>)-C85</b>  | 1        | 89                     | 91:9  | 99  |
| 6              | <b>(<i>R,R</i>)-C86</b>  | 3        | 89                     | 91:9  | 99  |
| 7              | <b>(<i>R,R</i>)-C87</b>  | 3        | 92                     | 89:11                                       | 99  |

|   |   |                            |   |    |      |    |
|---|---|----------------------------|---|----|------|----|
| 8 |  | ( <i>R,R</i> )- <b>C90</b> | 3 | 94 | 93:7 | 99 |
| 9 |  | ( <i>R,R</i> )- <b>C23</b> | 1 | 89 | 91:9 | 99 |

<sup>a</sup> Reaction conditions: **26a** (0.8 mmol), [**Rh**] or [**Ru**] (0.5 mol%), HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) (2.0 equiv.), CH<sub>2</sub>Cl<sub>2</sub> (4.0 mL, 0.2 M), 30 °C, full conversion. <sup>b</sup> Isolated yield for **27a** and **28a**. <sup>c</sup> Determined by <sup>1</sup>HNMR of the crude product after the ATH reaction. <sup>d</sup> Determined by HPLC or SFC analysis using a chiral stationary phase. <sup>e</sup> Major is **27a** enantiomer. <sup>f</sup> The reaction was carried out at 0 °C.

### 3.2.3.2 Influence of the solvent

Using (*R,R*)-**C90** as a precatalyst, we pursued our study with the investigation of the solvent influence. The reaction was carried out at 30 °C with 0.5 mol% of complex (*R,R*)-**C90** in the presence of 2 equiv. of HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) as the hydrogen source. Complete conversions were observed for all the tested solvents except for acetonitrile and diisopropylether, which led to only 46% and 75% conversions, respectively (Table 21, entries 2 and 5). Toluene, isopropanol, ethyl acetate or dimethylcarbonate (DMC) gave comparable results as those obtained with dichloromethane in terms of yields or stereoselectivities (Table 21, entries 3, 4, 6, 10 vs entry 1). The reaction was also conducted in THF as a solvent at either 30 or 50 °C using complex (*R,R*)-**C90** as the catalyst and THF as the solvent, a slight decrease for diastereoselectivity was observed at 50 °C. Therefore, the temperature was set at 30 °C for further optimization. (Table 21, entries 7 and 8) However, the best diastereoinductions were observed in THF and 2-MeTHF, and a high 97:3 diastereomeric ratio was attained in these solvents (Table 21, entries 7 and 9). Finally, under neat conditions, a lower 81:19 dr was obtained for the *syn* 1,2-diol **27a** (Table 21, entry 11). In view of these results, we privileged the use of 2-MeTHF as a green solvent for the remainder of the study and the optimized reaction conditions were set as follows: **26a** (0.8 mmol), complex (*R,R*)-**C90** (0.5 mol%), HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) (2.0 equiv.), 2-MeTHF (4.0 mL), 30 °C.

Table 21. Influence of the solvent <sup>a</sup>

| Entry | Solvent                         | Time (h) | Conv. (%) <sup>b</sup> | Yield (%) <sup>c</sup> | dr ( <b>27a</b> : <b>28a</b> ) <sup>b</sup> | ee <sub>syn</sub> (%) <sup>d</sup> |
|-------|---------------------------------|----------|------------------------|------------------------|---|------------------------------------|
| 1     | CH <sub>2</sub> Cl <sub>2</sub> | 3        | 100                    | 94                     | 93:7  | 99                                 |
| 2     | CH <sub>3</sub> CN              | 72       | 46.5                   | 42                     | 94:6  | 99                                 |
| 3     | Toluene                         | 6        | 100                    | 88                     | 95:5  | 99                                 |
| 4     | <i>i</i> PrOH                   | 6        | 100                    | 87                     | 94:6  | 99                                 |
| 5     | <i>i</i> Pr <sub>2</sub> O      | 22       | 75                     | 68                     | 86:14                                       | 99                                 |
| 6     | EtOAc                           | 3        | 100                    | 93                     | 96:4  | 99                                 |
| 7     | THF                             | 10       | 100                    | 95                     | 97:3  | 99                                 |
| 8     | THF                             | 5        | 100                    | 95                     | 95:5  | 99                                 |
| 9     | 2-MeTHF                         | 5        | 100                    | 93                     | 97:3  | 99                                 |
| 10    | DMC <sup>e</sup>                | 3        | 100                    | 92                     | 95:5  | 99                                 |
| 11    | neat                            | 6        | 100                    | 93                     | 81:19                                       | 99                                 |

<sup>a</sup> Reaction conditions: **26a** (0.8 mmol), (*R,R*)-**C90** (0.5 mol%), HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) (2.0 equiv.), solvent (4.0 mL, 0.2 M), 30 °C, the reaction was traced by TLC. <sup>b</sup> Determined by <sup>1</sup>HNMR of the crude product after the ATH reaction. <sup>c</sup> Isolated yield for **27a** and **28a**. <sup>d</sup> Determined by HPLC or SFC analysis using a chiral stationary phase. <sup>e</sup> DMC = Dimethyl carbonate

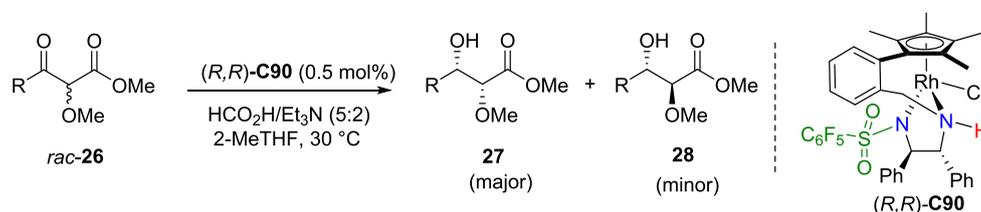
### 3.2.4 Substrate scope

#### 3.2.4.1 DKR/ATH of substrates bearing electron-rich substituents

With these optimized conditions in hand, we then investigated the scope of the Rh-catalyzed ATH/DKR of  $\alpha$ -methoxy  $\beta$ -ketoesters with a series of variously substituted aryl ketones **26**. We first studied the asymmetric reduction of substrates **26a-g** having electron-donating substituents on the aromatic ring. Compounds bearing methyl, methoxy or benzyloxy substituents on the benzene core at the *meta* or *para* positions afforded high levels of diastereoselectivities, from 95:5 to 97:3 dr, with excellent ee values observed in all cases (Table 22, entries 2, 4-7). On the other hand, ATH of the more sterically demanding ketone **26c** having

a methoxy substituent in the *ortho* position proceeded with a longer reaction time and led to a reversal of diastereoselectivity in favor of the *anti* product (*syn/anti* 4:96) although the major isomer was obtained with a lower 88% ee.

**Table 22. DKR/ATH of substrates bearing electron-rich substituents <sup>a</sup>**

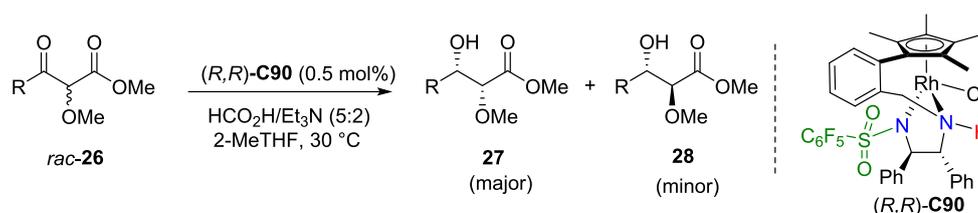


| Entry | Substrate  | Product    | Time (h) | Yield (%) <sup>b</sup> | dr ( <i>syn:anti</i> ) <sup>c</sup> | ee <sub>syn</sub> (%) <sup>d</sup> |
|-------|------------|------------|----------|------------------------|-------------------------------------|------------------------------------|
| 1     | <b>26a</b> | <b>27a</b> | 5        | 93                     | 97:3                                | 99                                 |
| 2     | <b>26b</b> | <b>27b</b> | 7        | 80                     | 97:3                                | >99                                |
| 3     | <b>26c</b> | <b>28c</b> | 111      | 67                     | 4:96                                | 88<br>ee <sub>anti</sub>           |
| 4     | <b>26d</b> | <b>27d</b> | 8        | 80                     | 96:4                                | >99                                |
| 5     | <b>26e</b> | <b>27e</b> | 45       | 82                     | 96:4                                | >99                                |
| 6     | <b>26f</b> | <b>27f</b> | 8        | 92                     | 97:3                                | >99                                |
| 7     | <b>26g</b> | <b>27g</b> | 14       | 83                     | 95:5                                | 99                                 |

<sup>a</sup> Reaction conditions: **26** (0.8 mmol), *(R,R)*-**C90** (0.5 mol%), HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) (2.0 equiv.), 2-MeTHF (4.0 mL, 0.2 M), 30 °C, the reaction was traced by TLC and <sup>1</sup>H NMR. <sup>b</sup> Isolated yield. <sup>c</sup> Determined by <sup>1</sup>H NMR of the crude product after the ATH reaction. <sup>d</sup> Determined by HPLC or SFC analysis using a chiral stationary phase.

## 3.2.4.2 DKR/ATH of substrates bearing electron-poor substituents

Furthermore, substrates **26h-k** containing electron-withdrawing groups on the benzene ring such as fluoro, trifluoromethyl or bromo substituents, were investigated as well, and displayed good to high yields (68–82%), high levels of diastereocontrol (97:3 to 99:1 dr) and excellent enantioselectivities (>99% ee) (Table 23, entries 1–4).

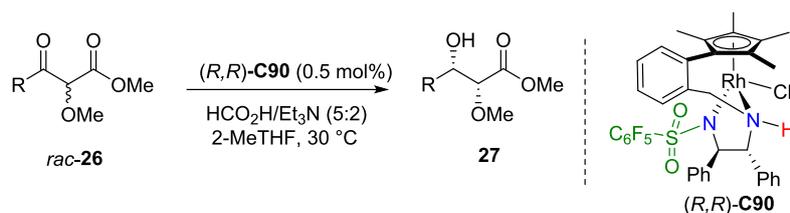
Table 23. DKR/ATH of substrates bearing electron-poor substituents <sup>a</sup>

| Entry | Substrate  | Product        | Time (h) | Yield (%) <sup>b</sup> | dr ( <i>syn:anti</i> ) <sup>c</sup> | ee <sub>syn</sub> (%) <sup>d</sup> |
|-------|------------|----------------|----------|------------------------|-------------------------------------|------------------------------------|
| 1     | <b>26h</b> | <b>27h</b><br> | 7        | 68                     | 98:2 <sup>d</sup>                   | >99                                |
| 2     | <b>26i</b> | <b>27i</b><br> | 8        | 80                     | 97:3                                | >99                                |
| 3     | <b>26j</b> | <b>27j</b><br> | 22       | 82                     | 97:3                                | >99                                |
| 4     | <b>26k</b> | <b>27k</b><br> | 8        | 68                     | 99:1 <sup>d</sup>                   | >99                                |

<sup>a</sup> Reaction conditions: **26** (0.8 mmol), *(R,R)*-**C90** (0.5 mol%), HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) (2.0 equiv.), 2-MeTHF (4.0 mL, 0.2 M), 30 °C, the reaction was traced by TLC and <sup>1</sup>H NMR. <sup>b</sup> Isolated yield. <sup>c</sup> Determined by <sup>1</sup>H NMR of the crude product after the ATH reaction. <sup>d</sup> Determined by HPLC or SFC analysis using a chiral stationary phase.

## 3.2.4.3 DKR/ATH of substrates bearing heteroaryl substituents

Interestingly, investigation of heteroaromatic substrates **26l-m** resulted in almost perfect diastereoselectivities (99:1 dr) and excellent enantioselectivities (Table 24, entries 1-2).

Table 24. DKR/ATH of substrates bearing heteroaryl substituents <sup>a</sup>

| Entry | Substrate  | Product    | Time (h) | Yield (%) <sup>b</sup> | dr ( <i>syn:anti</i> ) <sup>c</sup> | ee <sub>syn</sub> (%) <sup>d</sup> |
|-------|------------|------------|----------|------------------------|-------------------------------------|------------------------------------|
| 1     | <b>26l</b> | <b>27l</b> | 14       | 91                     | >99:1                               | >99                                |
| 2     | <b>26m</b> | <b>27m</b> | 10       | 86                     | 99:1                                | >99                                |

<sup>a</sup> Reaction conditions: **26** (0.8 mmol), **(R,R)-C90** (0.5 mol%), HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) (2.0 equiv.), 2-MeTHF (4.0 mL, 0.2 M), 30 °C, the reaction was traced by TLC and <sup>1</sup>H NMR. <sup>b</sup> Isolated yield. <sup>c</sup> Determined by <sup>1</sup>H NMR of the crude product after the ATH reaction. <sup>d</sup> Determined by HPLC or SFC analysis using a chiral stationary phase.

### 3.3 Conclusion

In summary, a new tethered Rh complex containing a penta-fluorobenzenesulfonyl diphenylethylenediamine ligand was prepared and characterized by X-ray crystallographic analysis. Evaluation of the catalytic performances of this complex was carried out through DKR/ATH of  $\alpha$ -alkoxy  $\beta$ -keto esters. A variety of enantioenriched monodifferentiated *syn* 1,2-diols were obtained with high yields (up to 93%), high levels of diastereoselectivities (up to > 99:1), and excellent ee values (up to > 99%) using this new complex with HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) at a low catalyst loading in an environmentally friendly solvent, 2-MeTHF.

## 4. Ruthenium-catalyzed dynamic kinetic asymmetric transfer hydrogenation: stereoselective access to *syn* 2-(1,2,3,4-tetrahydro-1-isoquinolyl)ethanol derivatives

### 4.1 Introduction

#### 4.1.1 Biological interest of chiral 1,3-amino alcohol derivatives

Chiral 1,3-amino alcohol is a key structural moiety found in a wide range of bioactive molecules and potent drugs, including HIV protease inhibitors ritonavir and lopinavir,<sup>259</sup> vesicular monoamine transporter type 2 (VMAT-2) inhibitor,<sup>260</sup> *N*-methyl-D-aspartate (NMDA) receptor inhibitor (2-(1,2,3,4-tetrahydro-1-isoquinolyl)ethanol derivative and isoindolyl ethanol derivative),<sup>261</sup> and *N*-methyl isoindoline moiety based 1,3-amino alcohols<sup>262</sup> (Figure 11).

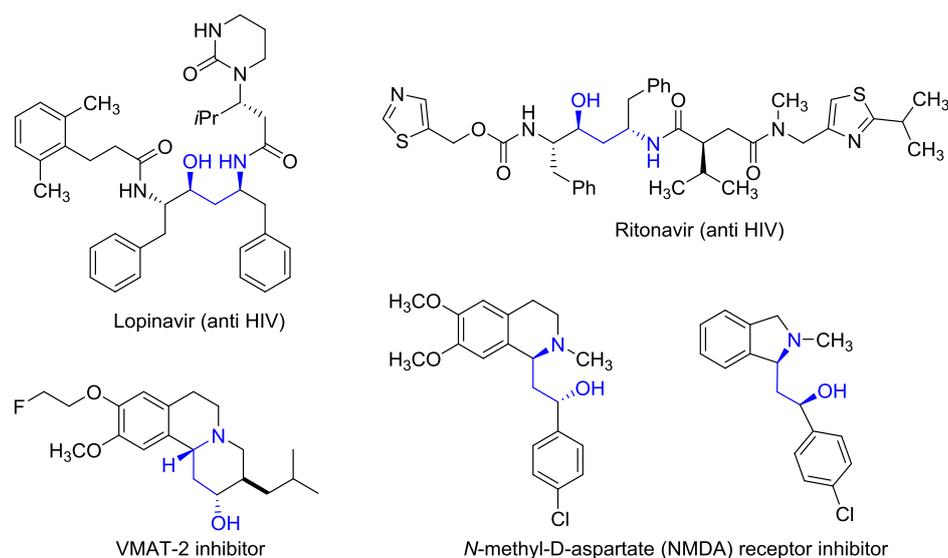


Figure 11

#### 4.1.2 Methods to access chiral 1,3-amino alcohol derivatives

Several approaches have been developed to access *syn* or *anti* 1,3-amino alcohol

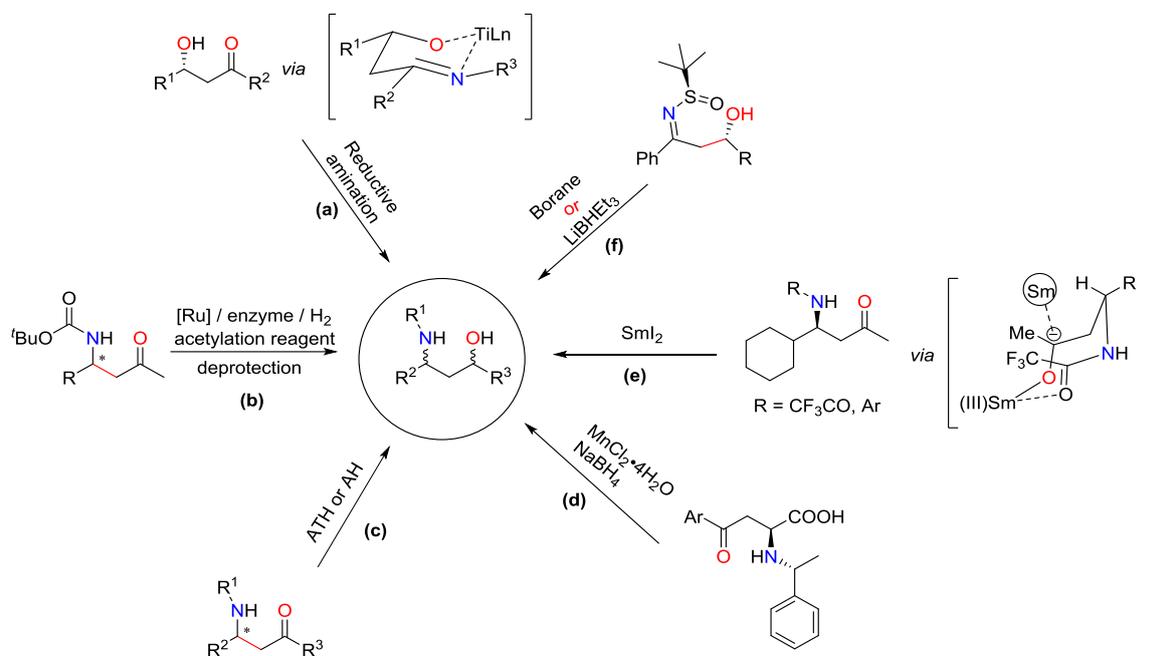
<sup>259</sup> Verkade, J. M. M.; Quaedflieg, P. J. L. M.; Verzijl, G. K. M.; Lefort, L.; van Delft, F. L.; de Vries, J. G.; Rutjes, F. P. J. T. *Chem. Commun.* **2015**, 51, 14462.

<sup>260</sup> Zheng, P.; Lieberman, B. P.; Choi, S. R.; Plöessl, K.; Kung, H. F. *Bioorg. Med. Chem. Lett.* **2011**, 21, 3435.

<sup>261</sup> Höfner, G.; Hoesl, C. E.; Parsons, C.; Quack, G.; Wanner, K. T. *Bioorg. Med. Chem. Lett.* **2005**, 15, 2231.

<sup>262</sup> Müller, A.; Höfner, G.; Renukappa-Gutke, T.; Parsons, C. G.; Wanner, K. T. *Bioorg. Med. Chem. Lett.* **2011**, 21, 5795.

moieties. All of them involve introduction of the first stereocenter through aldol or Mannich reactions, followed by reduction of the ketone or imine functional groups, respectively. To this end, reductive amination (a),<sup>263</sup> tandem hydrogenation/DKR (b),<sup>259</sup> metal-catalyzed asymmetric hydrogenation or transfer hydrogenation (c), stoichiometric reduction (d) and (f),<sup>264</sup> or radical reduction (e)<sup>265</sup> can be employed (Scheme 175).



Scheme 175

#### 4.1.3 DKR/ATH of $\beta$ -substituted ketone derivatives to access the corresponding alcohols bearing 1,3-diastereocenters

Although asymmetric transfer hydrogenation (ATH) of prochiral ketones appears as an ideal protocol to access biologically relevant enantiopure alcohols, the asymmetric reduction of racemic  $\alpha$ - or  $\beta$ -substituted ketones through a dynamic kinetic resolution (DKR) process stands as an efficient way to set multiple stereocenters in a single step. In this field, transition metal-catalyzed ATH-DKR of  $\alpha$ -substituted ketones has been extensively reported. On the other hand, examples involving  $\beta$ -substituted ketones are scarce and usually require racemization of the  $\beta$ -stereocenter through elimination-induced epimerization by either an intra- or intermolecular

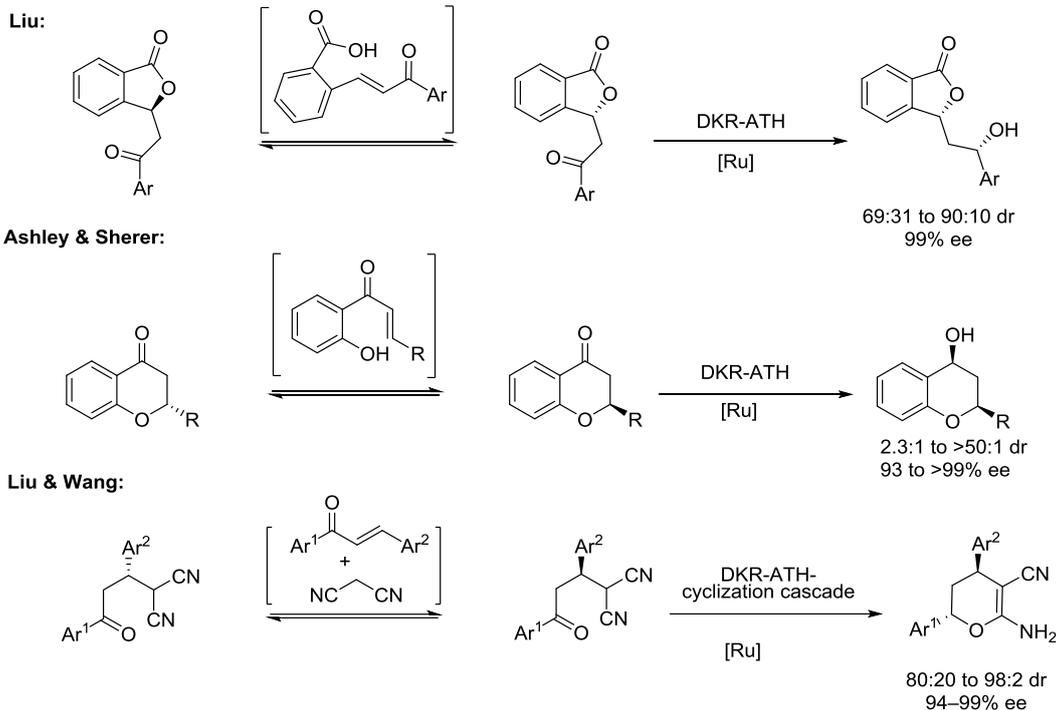
<sup>263</sup> Menche, D.; Arıkan, F.; Li, J.; Rudolph, S. *Org. Lett.* **2007**, *9*, 267.

<sup>264</sup> (a) Berkeš, D.; Kolarovič, A.; Považanec, F. *Tetrahedron Lett.* **2000**, *41*, 5257. (b) Kochi, T.; Tang, T. P.; Ellman, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 6518. (c) Kochi, T.; Tang, T. P.; Ellman, J. A. *J. Am. Chem. Soc.* **2003**, *125*, 11276.

<sup>265</sup> Keck, G. E.; Truong, A. P. *Org. Lett.* **2002**, *4*, 3131.

conjugate elimination/conjugate addition pathway (Scheme 176).

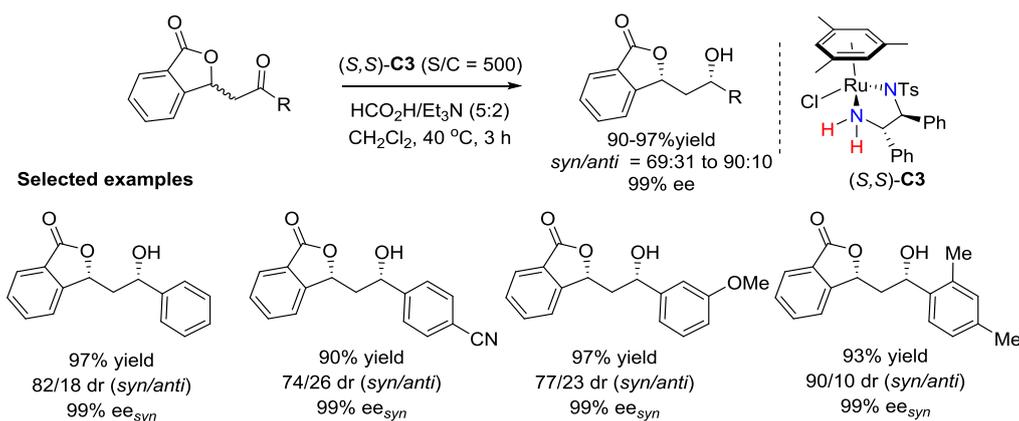
Previous work:



**Scheme 176**

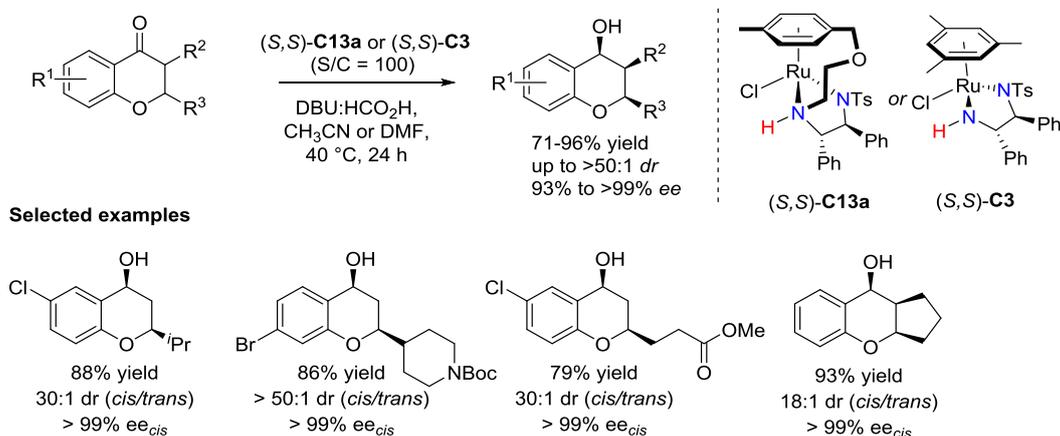
In 2015, Liu and coworkers reported that by using 0.2 mol% of Noyori's complex [RuCl(mesitylene)((*S,S*)-TsDPEN)] (*S,S*)-**C3** as the catalyst and HCO<sub>2</sub>H/Et<sub>3</sub>N as the hydrogen source in dichloromethane at 40 °C, a variety of 3-(2-oxo-arylethyl)isobenzofuran-1(3*H*)-ones could be efficiently reduced to the corresponding optically active phthalide derivatives bearing 1,3-diaxial stereocenters. High yields (90–97%) and excellent enantioselectivities (up to 99% ee) were obtained in the reduction of a broad range of substrates regardless of the position and electronic and steric properties of the substituents on the aryl ring. However, only poor to good diastereomeric ratios ranging from 69:31 to 90:10 were achieved under these conditions (Scheme 177).<sup>266</sup>

<sup>266</sup> Cheng, T.; Ye, Q.; Zhao, Q.; Liu, G. *Org. Lett.* **2015**, *17*, 4972.



Scheme 177

In 2017, Ashley and Sherer then reported the Ru-catalyzed ATH-DKR of  $\beta$ -substituted chromanones under strongly basic conditions to produce valuable chromanols in high yields (71 – 96%) and with high levels of stereocontrol (up to 50:1 dr (*cis/trans*), 93 to >99% ee). The reaction showed the racemization of the  $\beta$ -stereocenter through a conjugate elimination/conjugate addition pathway by base proceeds in concert with a highly selective ketone transfer hydrogenation step. Further experiment via computational analysis of the catalyst, substrate, and transition state structures revealed the driving interactions for diastereoselectivity as well as unexpected CH–O stabilizing interactions between the catalyst sulfonamide and the reacting substrate (Scheme 178).<sup>267</sup>

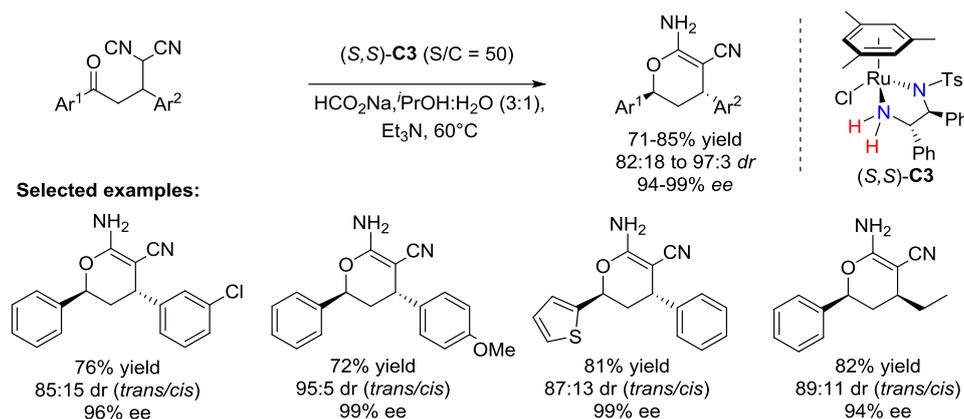


Scheme 178

In 2017, Liu and Wang *et al.* described [RuCl(*mesitylene*)]((*S,S*)-TsDPEN)] catalyzed DKR/ATH process in highly enantio- (up to 99% ee) and diastereo- (up to 98:2 dr) selective reduction of challenging racemic  $\alpha$ -aryl- $\gamma$ -keto malononitriles. The reduced product then

<sup>267</sup> Ashley, E. R.; Sherer, E. C.; Pio, B.; Orr, R. K.; Ruck, R. T. *ACS Catal.* **2017**, *7*, 1446.

undergoes a spontaneous cyclization reaction delivering a cascade process for efficient synthesis of useful enantioenriched 3,4-dihydro-2*H*-pyran- carbonitriles (Scheme 180). To further investigate the possible mechanism, they found the complete racemization of (*S*)-enantiomer starting material within 7 h in a mixture of *i*PrOH and H<sub>2</sub>O (v/v = 3:1) in the presence of an equivalent of Et<sub>3</sub>N. These findings indicated that the DKR/ATH-cyclization cascade proceeds via a *retro*-Michael addition process by Et<sub>3</sub>N (Scheme 179).<sup>268</sup>



Scheme 179

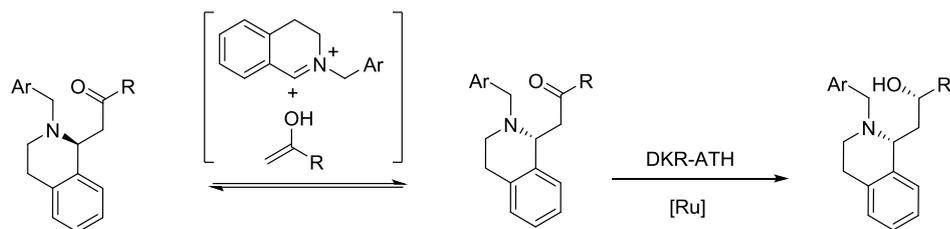
However, to the best of our knowledge, there is no report on transition metal-catalyzed ATH-DKR of  $\beta$ -amino ketones to access chiral 1,3-aminoalcohols. Because of their pivotal bioactivities in pharmaceuticals, tetrahydroisoquinoline (THIQ)-containing derivatives have attracted much attention in recent years.<sup>269, 270</sup> In the following section, a ruthenium-catalyzed ATH-DKR process will be applied to prepare enantioenriched 2-(1,2,3,4-tetrahydro-1-isoquinolyl)ethanol derivatives bearing 1,3-stereocenters through epimerization of the  $\beta$ -stereocenter by an intermolecular elimination (*retro*-Mannich)/addition pathway (Scheme 180).

<sup>268</sup> Zheng, D.; Zhao, Q.; Hu, X.; Cheng, T.; Liu, G.; Wang, W. *Chem. Commun.* **2017**, 53, 6113.

<sup>269</sup> (a) Liu, W.; Liu, S.; Jin, R.; Guo, H.; Zhao, J. *Org. Chem. Front.* **2015**, 2, 288; (b) Zhao, D.; Glorius, F. *Angew. Chem., Int. Ed.* **2013**, 52, 9616.

<sup>270</sup> (a) Anakabe, E.; Badia, D.; Carillo, L.; Vicario, J. L. *Recent Res. Dev. Org. Chem.* **2001**, 5, 63; (b) Chrzanowska, M.; Rozwadowska, M. D. *Chem. Rev.*, **2004**, 104, 3341; (c) Zein, A. L.; Valluru, G.; Georghiou, P. E. in *Studies in Natural Products Chemistry*, Elsevier B. V., Oxford, UK, **2012**, vol. 38, 53–80.

This work:

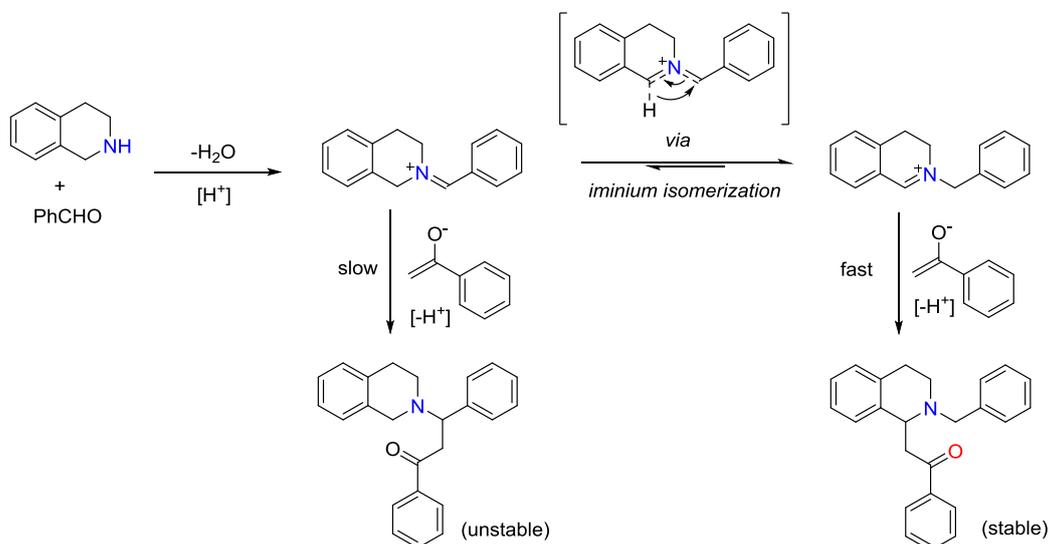


Scheme 180

## 4.2 Results and discussion

### 4.2.1 Synthesis of THIQ-based $\beta$ -amino ketones

For this study, a range of THIQ-based  $\beta$ -amino ketones **29a–j**, **29l–q** was first prepared by redox-Mannich reactions.<sup>271</sup> This reaction utilizes the same starting materials than the classic three-component Mannich reaction, but incorporates an isomerization step that enables the facile preparation of ring-substituted  $\beta$ -amino ketones. To obtain redox-Mannich products, it is crucial that the reaction is conducted under conditions at which the relative rate of iminium isomerization is sufficiently fast to effectively compete with the classic mannich pathway (Scheme 181).

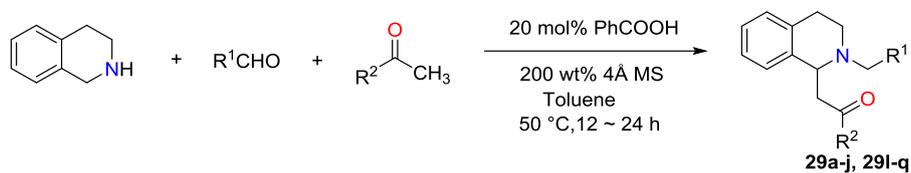


Scheme 181

<sup>271</sup> Chen, W.; Seidel, D. *Org. Lett.* **2014**, *16*, 3158.

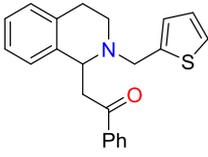
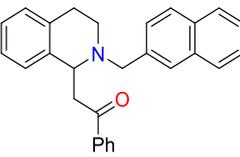
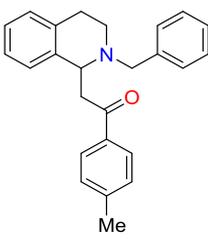
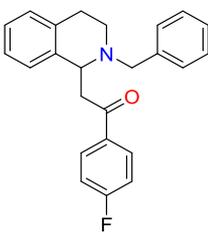
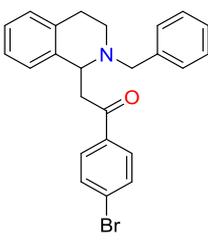
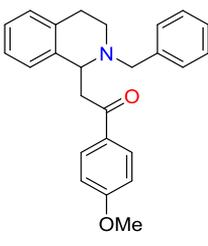
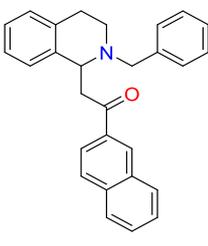
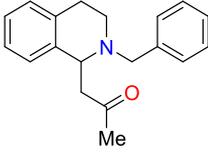
Following the conditions reported by Seidel *et al.*, we have prepared variously substituted tetrahydroisoquinoline-based  $\beta$ -amino ketones **29a-j**, **29l-q**, which were obtained in 6-43% yields (Table 25).

**Table 25.** synthesis of THIQ based  $\beta$ -amino ketones

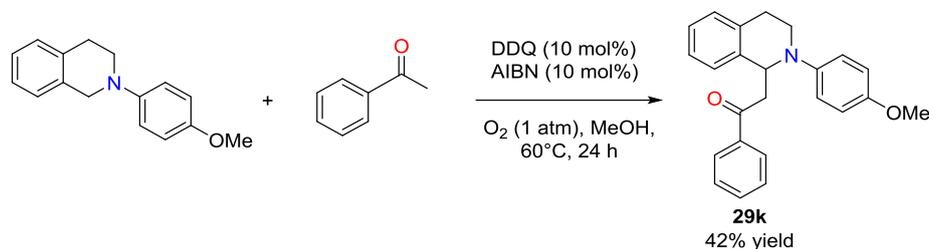


| Entry | Aldehyde ( $R^1$ )                 | Ketone ( $R^2$ ) | Product    | Yield / % |
|-------|------------------------------------|------------------|------------|-----------|
| 1     | Ph                                 | Ph               | <b>29a</b> | 31        |
| 2     | 4-ClC <sub>6</sub> H <sub>4</sub>  | Ph               | <b>29b</b> | 31        |
| 3     | 3-ClC <sub>6</sub> H <sub>4</sub>  | Ph               | <b>29c</b> | 34        |
| 4     | 2-ClC <sub>6</sub> H <sub>4</sub>  | Ph               | <b>29d</b> | 35        |
| 5     | 2-BrC <sub>6</sub> H <sub>4</sub>  | Ph               | <b>29e</b> | 27        |
| 6     | 4-MeOC <sub>6</sub> H <sub>4</sub> | Ph               | <b>29f</b> | 22        |
| 7     | 3-MeOC <sub>6</sub> H <sub>4</sub> | Ph               | <b>29g</b> | 43        |
| 8     | 4-MeC <sub>6</sub> H <sub>4</sub>  | Ph               | <b>29h</b> | 27        |

Part C: ATH of ketone derivatives via dynamic kinetic resolution

|    |            |                                    |            |  |    |
|----|------------|------------------------------------|------------|--|----|
| 9  | 2-thienyl  | Ph                                 | <b>29i</b> |    | 29 |
| 10 | 2-naphthyl | Ph                                 | <b>29j</b> |    | 40 |
| 11 | Ph         | 4-MeC <sub>6</sub> H <sub>4</sub>  | <b>29l</b> |    | 37 |
| 12 | Ph         | 4-FC <sub>6</sub> H <sub>4</sub>   | <b>29m</b> |   | 39 |
| 13 | Ph         | 4-BrC <sub>6</sub> H <sub>4</sub>  | <b>29n</b> |  | 39 |
| 14 | Ph         | 4-MeOC <sub>6</sub> H <sub>4</sub> | <b>29o</b> |  | 40 |
| 15 | Ph         | 2-naphthyl                         | <b>29p</b> |  | 30 |
| 16 | Ph         | Me                                 | <b>29q</b> |  | 6  |

In addition, THIQ-based  $\beta$ -amino ketone **29k** bearing a *p*-MeO-benzene ring on the nitrogen atom was prepared through an oxidative cross-dehydrogenative coupling (CDC) reaction using a catalytic amount of DDQ (10 mol %) under aerobic conditions with AIBN (10 mol %) and molecular oxygen as DDQ activating agent. (Scheme 182)



Scheme 182

## 4.2.2 Optimisation of the reaction parameters

### 4.2.2.1 Precatalyst screening

With these THIQ-based  $\beta$ -amino ketones in hand, the initial investigation aimed toward identifying the ideal catalyst system for the ATH of racemic  $\beta$ -amino keto derivative **29a** was carried out at 30 °C in dichloromethane, using 1.2 mol% of chiral Ru(II) complexes (*R,R*)-**C2**, (*S,S*)-**C1**, (*S,S*)-**C3**, (*R,R*)-**C13a**, (*S,S*)-**C11** or Rh(III) precatalyst (*R,R*)-**C84** in the presence of HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) as the hydrogen source (Table 26). The results showed that the ATH reactions catalyzed by the ruthenium complexes (*R,R*)-**C2**, (*S,S*)-**C1**, (*S,S*)-**C3** afforded the corresponding 1,3-aminoalcohols **30a:31a** with diastereomeric ratios from 67:33 to 76:24 in favour of the *syn* isomer **30a** and with excellent enantioselectivities (96–99% ee, Table 26, entries 1–4). Of the above-mentioned complexes (*R,R*)-**C2**, (*S,S*)-**C1**, (*S,S*)-**C3**, RuCl[(*R,R*)-TsDPEN](*p*-cymene) (*R,R*)-**C2** provided a slightly higher diastereoselectivity (76:24 dr), but with a low conversion of 47% (Table 26, entry 1) although a better 64% conversion could be achieved by increasing the amount of HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) to 11.0 equiv. (Table 26, entry 2). Interestingly, a high conversion (97%) and a good yield (76%) were obtained with RuCl[(*S,S*)-TsDPEN](benzene) (*S,S*)-**C1** (Table 26, entry 3) whereas the use of RuCl[(*S,S*)-TsDPEN](mesitylene) (*S,S*)-**C3** was less efficient in terms of conversion (Table 26, entry 4). We next examined the ruthenium- and rhodium-tethered complexes (*R,R*)-**C13a**, (*S,S*)-**C11**, and (*R,R*)-**C84**, respectively. Excellent to full conversions were attained in these cases but unfortunately with virtually no diastereoselectivity (Table 26, entries 5–7). The reaction led in all cases to varying amounts of by-products arising from a competitive reduction of the retro-Mannich adducts, which produced 1-phenylethanol and 2-benzyl-1,2,3,4-tetrahydro-

isoquinoline.

Table 26. Screening of the DKR-ATH of 1a with various precatalysts<sup>a</sup>

Reaction scheme: *rac*-29a reacts with a catalyst (1.2 mol%), HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) in CH<sub>2</sub>Cl<sub>2</sub> at 30 °C for 24 h to yield 30a (major) and 31a (minor).

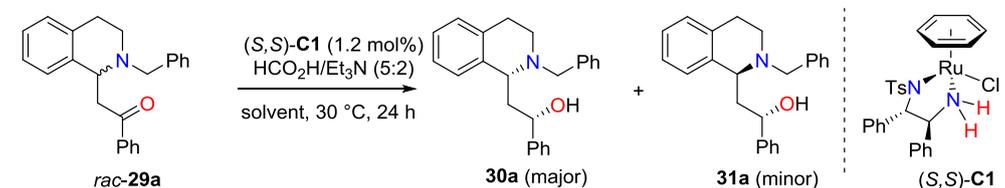
| Entry          | Cat.                     | Conv. (%) <sup>b</sup> | Yield (%) <sup>c</sup> | dr (30a:31a) <sup>b</sup> | ee (%) <sup>d</sup> |
|----------------|--------------------------|------------------------|------------------------|---------------------------|---------------------|
| 1              | <b>(<i>R,R</i>)-C2</b>   | 47                     | –                      | 76:24                     | 96 (–)/98 (–)       |
| 2 <sup>e</sup> | <b>(<i>R,R</i>)-C2</b>   | 64                     | –                      | 73:27                     | 99 (–)/99 (–)       |
| 3              | <b>(<i>S,S</i>)-C1</b>   | 97                     | 76                     | 68:32                     | 98 (+)/99 (+)       |
| 4              | <b>(<i>S,S</i>)-C3</b>   | 88                     | 68                     | 67:33                     | 99 (+)/99 (+)       |
| 5              | <b>(<i>R,R</i>)-C13a</b> | 96                     | 68                     | 52:48                     | 97 (–)/96 (–)       |
| 6              | <b>(<i>S,S</i>)-C11</b>  | 96                     | –                      | 49:51                     | 99 (+)/99 (+)       |
| 7              | <b>(<i>R,R</i>)-C84</b>  | 100                    | –                      | 47:53                     | 96 (–)/98 (–)       |

<sup>a</sup> Reaction conditions: **29a** (0.42 mmol), **Cat.** (1.2 mol%), HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) (2.75 equiv.), CH<sub>2</sub>Cl<sub>2</sub> (1.3 mL), 30 °C, 24 h. <sup>b</sup> Determined by <sup>1</sup>H NMR of the crude product after the ATH reaction. <sup>c</sup> Isolated yield for **30a:31a**. In case of unsatisfying conv. and/or dr, isolation of the reduced products was not attempted. <sup>d</sup> Determined by HPLC analysis using a chiral stationary phase. <sup>e</sup> 11.0 equiv. of HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) were used, reaction time was 40 h.

#### 4.2.2.2 Solvent screening

From the above results, we chose to carry on the optimization study with complex (*S,S*)-**C1** which showed the best compromise between high conversion and reasonable dr, and which led to excellent enantioselectivities for both reduced products **30a** and **31a**. We then explored the solvent effect on the ATH of compound **29a** by using the previous reaction conditions in the presence of catalyst (*S,S*)-**C1** (Table 27). When THF was used as a solvent instead of dichloromethane, the diastereoselectivity slightly improved (72:28 dr) but a lower yield was observed (Table 27, entries 1–2). On the other hand, full conversion was attained in a shorter time (3 h instead of 24 h) with MeOH, but an erosion of diastereoselectivity (52:48 dr) was observed and the aminoalcohols **30a:31a** were obtained with a lower yield because higher levels of by-products were formed in this case (Table 27, entry 3). Switching from dichloromethane to dichloroethane (DCE) did not change the outcome of the reaction (Table 27, entry 4).

**Table 27. Influence of the solvent <sup>a</sup>**



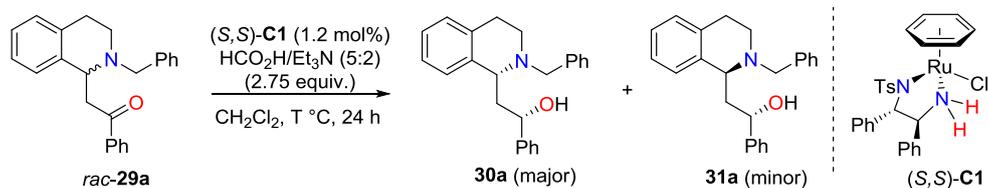
| Entry          | Solvent                         | Conv. (%) <sup>b</sup> | Yield (%) <sup>c</sup> | dr ( <b>30a:31a</b> ) <sup>b</sup> | ee (%) <sup>d</sup> |
|----------------|---------------------------------|------------------------|------------------------|------------------------------------|---------------------|
| 1              | CH <sub>2</sub> Cl <sub>2</sub> | 97                     | 76                     | 68:32                              | 98/99               |
| 2              | THF                             | 87                     | 67                     | 72:28                              | 98/99               |
| 3 <sup>e</sup> | CH <sub>3</sub> OH              | 100                    | 60 <sup>f</sup>        | 52:48                              | 99/99               |
| 4              | DCE                             | 97                     | 74                     | 68:32                              | 98/99               |

<sup>a</sup> Reaction conditions: **29a** (0.42 mmol), (*S,S*)-**C1** (1.2 mol%), HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) (2.75 equiv.), solvent (1.3 mL, 0.32 mol.L<sup>-1</sup>), 30 °C, 24 h. <sup>b</sup> Determined by <sup>1</sup>H NMR of the crude product after the ATH reaction. <sup>c</sup> Isolated yield for **30a:31a**. <sup>d</sup> Determined by HPLC analysis using a chiral stationary phase. <sup>e</sup> The reaction time was 3 h. <sup>f</sup> Yield determined by <sup>1</sup>H NMR of the crude product after the ATH reaction.

### 4.2.2.3 Influence of temperature and concentration

An increase of the reaction temperature to 40 °C had no beneficial effect for it only produced a higher proportion of by-products and hence a lower yield of the amino alcohols (Table 28, entry 2 *vs* entry 1). When the reaction was run at 0 °C, a slightly higher dr was obtained but at the expense of the reaction time which was prolonged to 110 h to ensure a conversion of 91% (Table 28, entry 3 *vs* entry 1). Lowering the reaction concentration from 0.32 to 0.21 mol·L<sup>-1</sup> had no impact on the reaction (Table 28, entry 4).

**Table 28. Influence of temperature and concentration**

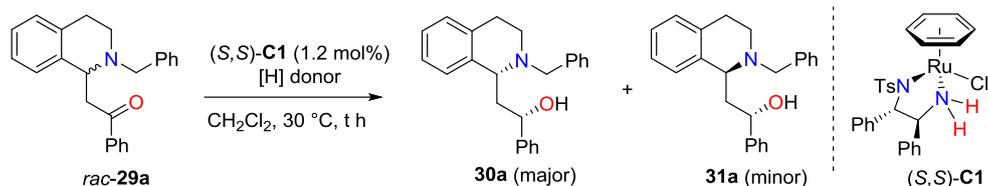


| Entry | Conc. [mol·L <sup>-1</sup> ] <sup>b</sup> | Temp. (°C) | t (h) | Conv. (%) <sup>c</sup> | Yield (%) <sup>d</sup> | dr<br>( <b>30a:31a</b> ) <sup>c</sup> | ee (%) <sup>e</sup> |
|-------|---|------------|-------|------------------------|------------------------|---------------------------------------|---------------------|
| 1     | 0.32                                      | 30         | 24    | 97                     | 76                     | 68:32                                 | 98/99               |
| 2     | 0.32                                      | 40         | 3     | 98                     | 65                     | 69:31                                 | 98/99               |
| 3     | 0.32                                      | 0          | 110   | 91                     | 73                     | 72:28                                 | 99/99               |
| 4     | 0.21                                      | 30         | 24    | 95                     | 70                     | 66:34                                 | 98/99               |

<sup>a</sup> Reaction conditions: **29a** (0.42 mmol), (*S,S*)-**C1** (1.2 mol%), HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) (2.75 equiv.), CH<sub>2</sub>Cl<sub>2</sub> (1.3 mL or 2.0 mL, 0.32 or 0.21 mol·L<sup>-1</sup>), certain temperature. <sup>b</sup> Reaction concentration = 1 M solution of substrate (1 mmol). <sup>c</sup> Determined by <sup>1</sup>H NMR of the crude product after the ATH reaction. <sup>d</sup> Isolated yield for **30a:31a**. <sup>e</sup> Determined by HPLC analysis using a chiral stationary phase.

### 4.2.2.4 Influence of the hydrogen source

By increasing the amount of HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) from 2.75 to 8.25 equiv., a full conversion was observed but with a slight loss of diastereoselectivity (Table 29, entries 1 and 2). Alternatively, variation of the ratio of formic acid to triethylamine from 5:2 to 1:5 or 1:1 was detrimental for the reaction both in terms of conversion and enantioselectivity (Table 29, entries 3 and 4). Finally, the use of HCO<sub>2</sub>H/DABCO (5:3) as the hydride source, did not allow significant improvement (Table 29, entry 5).

Table 29. Influence of the hydrogen source<sup>a</sup>

| Entry | [H] donor   | t (h) | Conv. (%) <sup>b</sup> | Yield (%) <sup>c</sup> | dr ( <b>30a</b> : <b>31a</b> ) <sup>b</sup> | ee (%) <sup>d</sup> |
|-------|---|-------|------------------------|------------------------|---|---------------------|
| 1     | HCO <sub>2</sub> H/Et <sub>3</sub> N (5:2)<br>2.75 equiv. | 24    | 97                     | 76                     | 68:32                                       | 98/99               |
| 2     | HCO <sub>2</sub> H/Et <sub>3</sub> N (5:2)<br>8.25 equiv. | 24    | 100                    | 79                     | 63:37                                       | 99/99               |
| 3     | HCO <sub>2</sub> H/Et <sub>3</sub> N (1:5)<br>4.0 equiv.  | 24    | 45                     | 23                     | 68:32                                       | 89/96               |
| 4     | HCO <sub>2</sub> H/Et <sub>3</sub> N (1:1)<br>2.0 equiv.  | 48    | 29                     | 19                     | 74:26                                       | 79/92               |
| 5     | HCO <sub>2</sub> H/DABCO (5:3)<br>1.0 equiv.              | 24    | 100                    | 75                     | 69:31                                       | 99/99               |

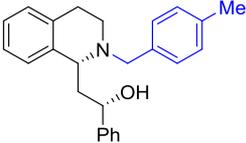
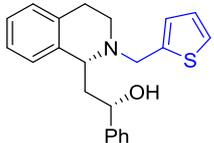
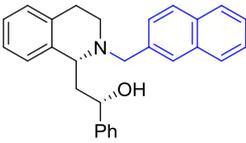
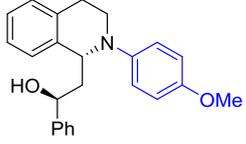
<sup>a</sup> Reaction conditions: **29a** (0.42 mmol), *(S,S)*-**C1** (1.2 mol%), HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) (2.75 equiv.), CH<sub>2</sub>Cl<sub>2</sub> (1.3 mL, 0.32 mol.L<sup>-1</sup>), 30 °C, 24 or 48 h. <sup>b</sup> Determined by <sup>1</sup>H NMR of the crude product after the ATH reaction. <sup>c</sup> Isolated yield for **30a**:**31a**. <sup>d</sup> Determined by HPLC analysis using a chiral stationary phase.

### 4.2.3 Substrate scope

In view of the above results, we set up the optimized reaction conditions as follows: complex *(S,S)*-**C1** (1.2 mol%), 2.75 equiv. of HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) as the hydrogen donor, in dichloromethane at 30 °C for 24 h. We then investigated the scope of the Ru-catalyzed ATH-DKR of tetrahydroisoquinoline-based β-amino ketones with a series of substrates **29a–q** previously prepared by redox-Mannich reactions (Table 30). Compounds bearing either electron-withdrawing or electron-donating substituents on the phenyl ring of the *N*-benzyl residue were reduced in good yields with excellent enantioselectivities and acceptable dr, of the same order as that of **29a** (Table 30, entries 1–8), with the exception of substrate **29d** having a more sterically demanding *o*-chlorobenzene substituent (Table 30, entry 4). The reaction was also tolerant to thienyl and naphthyl substituents instead of the benzene ring (Table 30, entries 9–10). However, the *(S,S)*-**C1**-catalyzed ATH of ketone **29k** bearing a *p*-MeO-benzene



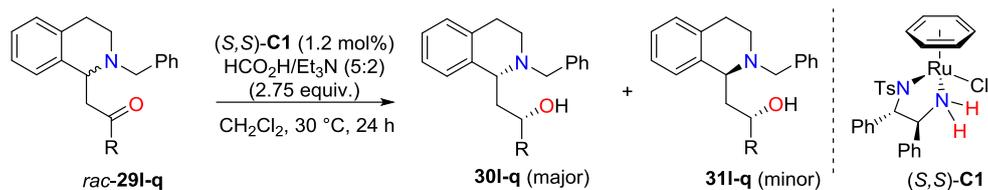
Part C: ATH of ketone derivatives via dynamic kinetic resolution

|    |            |   |                 |       |       |
|----|------------|---|-----------------|-------|-------|
| 8  | <b>30h</b> |  | 85              | 67:33 | 98/99 |
| 9  | <b>30i</b> |  | 61              | 70:30 | 99/99 |
| 10 | <b>30j</b> |  | 78              | 65:35 | 97/99 |
| 11 | <b>30k</b> |  | -- <sup>e</sup> | --    | --    |

<sup>a</sup> Reaction conditions: **29** (0.42 mmol), (*S,S*)-**C1** (1.2 mol%), HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) (2.75 equiv.), CH<sub>2</sub>Cl<sub>2</sub> (1.3 mL), 30 °C, 24 h. <sup>b</sup> Isolated yield for **30:31**. <sup>c</sup> Determined by <sup>1</sup>H NMR of the crude product after the ATH reaction. <sup>d</sup> Determined by HPLC analysis using a chiral stationary phase. <sup>e</sup> The ATH reaction only led to unidentified by-products.

Substitution on the ketone function (substrates **29l–q**) was investigated as well, and showed that either electron-donating groups such as methyl or methoxy, or electron-withdrawing groups such as fluoro or bromo, on the phenyl ring were well tolerated (Table 31, entries 1–4). A naphthyl group on the ketone had no effect on the outcome of the reaction (Table 31, entry 5) whereas a non-aromatic substituent such as a methyl group led to a lower enantiomeric excess of 81% (Table 31, entry 6).

Table 31. DKR/ATH of substrates bearing different substituents in ketone position



| Entry | Product 30 | Yield (%) <sup>b</sup> | dr (30:31) <sup>c</sup> | ee for 30/31(%) <sup>d</sup> |
|-------|------------|------------------------|-------------------------|------------------------------|
| 1     |            | 78                     | 64:36                   | 95/99                        |
| 2     |            | 71                     | 68:32                   | 98/98                        |
| 3     |            | 60                     | 69:31                   | 96/98                        |
| 4     |            | 79                     | 61:39                   | 98/99                        |
| 5     |            | 75                     | 63:37                   | 94/98                        |
| 6     |            | 65                     | 71:29                   | 81/99                        |

<sup>a</sup> Reaction conditions: **29** (0.42 mmol), (S,S)-C1 (1.2 mol%), HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) (2.75 equiv.), CH<sub>2</sub>Cl<sub>2</sub> (1.3 mL), 30 °C, 24 h. <sup>b</sup> Isolated yield for **30:31**. <sup>c</sup> Determined by <sup>1</sup>H NMR of the crude product after the ATH reaction. <sup>d</sup> Determined by HPLC analysis using a chiral stationary phase.

#### Absolute configuration assignment:

Acidic treatment of a diastereomerically pure sample of **30c** with hydrochloric acid allowed isolation of the corresponding salt **30c•HCl** as a single crystal. An

analytical sample of diastereomerically pure **30i** was also obtained as a single crystal. X-Ray analysis of **30c**•HCl and **30i** (Figure 12) allowed determination of their absolute configurations as (2*S*,4*S*). By analogy, we conjecture that the remainder of the ATH products **30** followed the same trend.

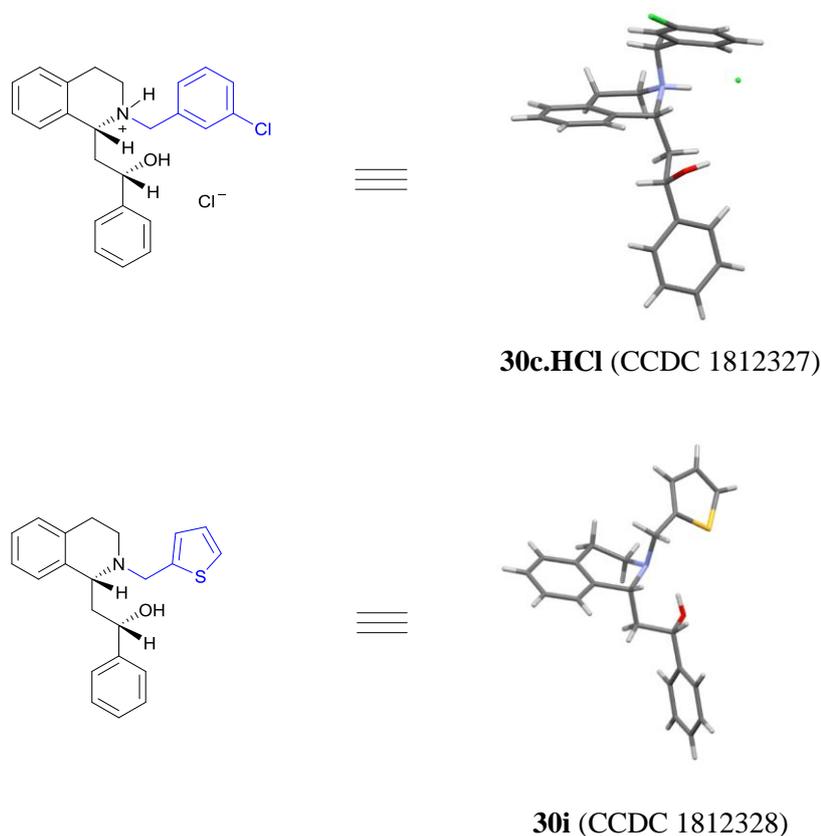
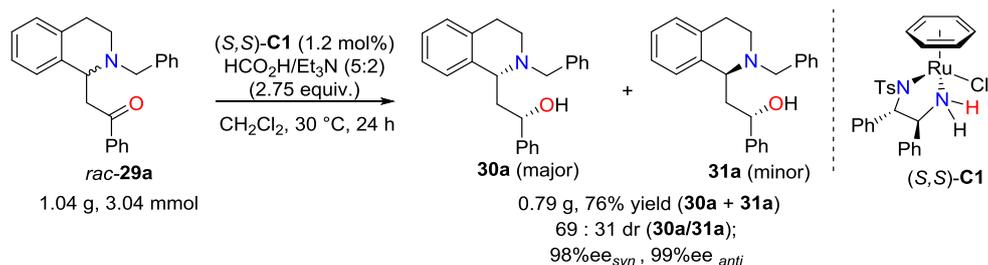


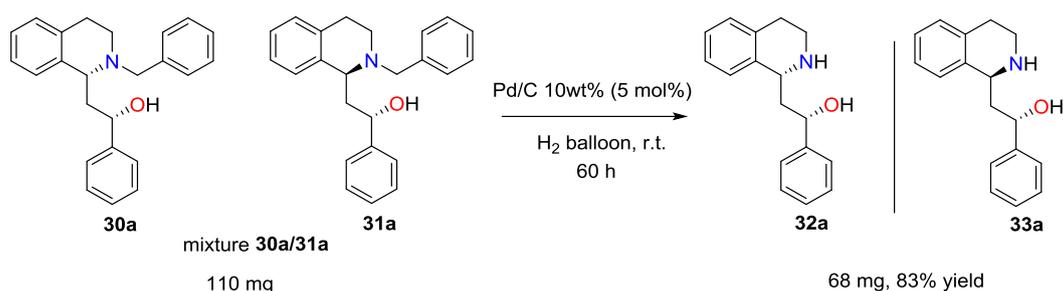
Figure 12

#### 4.2.4 Post-functionalization

To evaluate the practical application of this method, the reduction of **29a** was performed on a gram scale, and efficiently afforded the expected product (1.04 g, 76% yield, 69:31 dr, 98% ee for the *syn* product) (Scheme 183). Interestingly, the *N*-benzyl group could be readily removed from compound **30a/31a** (H<sub>2</sub> (1 atm), Pd/C 10%, MeOH, rt, 83% yield), thus allowing for the potential functionalization of the tetrahydroisoquinoline core (Scheme 184).



Scheme 183



Scheme 184

### 4.3 Conclusion

In summary, an efficient asymmetric synthesis of 2-(1,2,3,4-tetrahydro-1-isoquinolyl) ethanol derivatives, which act as *N*-methyl-D-aspartate (NMDA) receptor inhibitors, was developed by asymmetric reduction through a dynamic kinetic resolution process. This practical synthesis features the first application of Ru-catalyzed asymmetric transfer hydrogenation to establish enantiomerically enriched 1,3-aminoalcohol derivatives bearing the tetrahydroisoquinoline scaffold. The reaction proceeded under mild conditions, using a low catalyst loading of (*S,S*)-**C1** and HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) as the hydrogen source, delivering a variety of 2-(1,2,3,4-tetrahydro-1-isoquinolyl)ethanol derivatives with excellent enantioselectivities (up to 99% *ee*) for the *syn* products. Furthermore, the usefulness of this method was demonstrated by the efficient gram-scale reduction of **29a**.

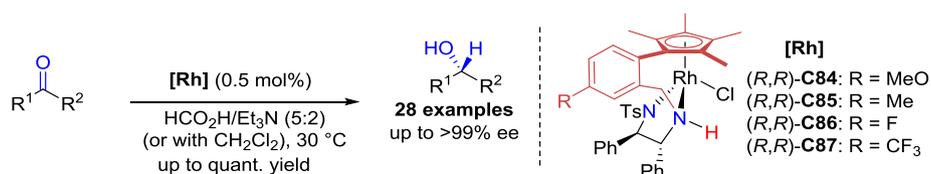


# **GENERAL CONCLUSION**

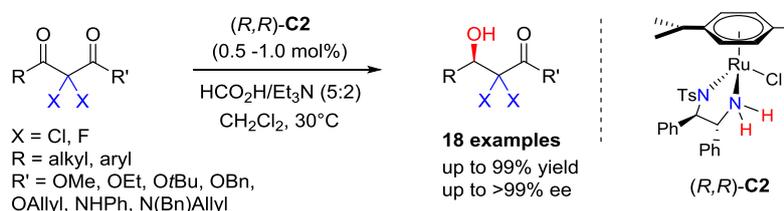


## General conclusion

In this thesis, with the aim at developing efficient catalysts for asymmetric transfer hydrogenation of functionalized ketones, we have succeeded in developing a new family of tethered rhodium complexes (*R,R*)-**C85**-**C87** bearing electron-donating and electron-withdrawing substituents at the *para* position on the phenyl tether. Evaluations of their catalytic activities and stereoselectivities in asymmetric transfer hydrogenation of a broad range of (hetero)aromatic ketones generally led to the corresponding chiral alcohols in high yields and high to excellent enantioselectivities. A comparative study demonstrated that electron-rich rhodium complex (*R,R*)-**C84** displayed a better catalytic activity than complexes (*R,R*)-**C23**, (*R,R*)-**C85**-**87** in the ATH of ketones (Scheme 185).<sup>272</sup>



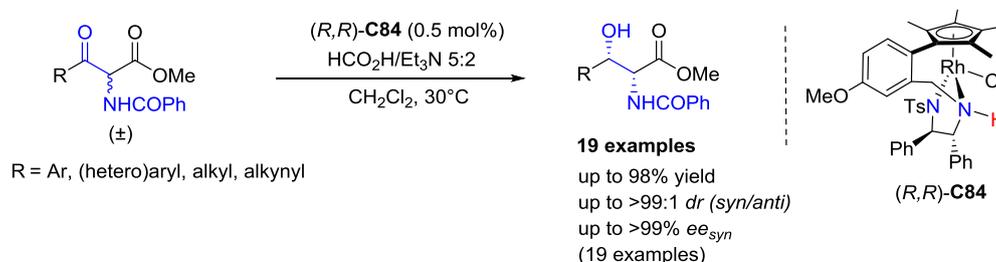
Because of the importance of halogenated compounds in medicinal chemistry, we have developed a new route to efficiently access enantiomerically enriched  $\alpha,\alpha$ -dichloro and  $\alpha,\alpha$ -difluoro  $\beta$ -hydroxy ester and amide derivatives through asymmetric transfer hydrogenation catalyzed by Noyori's catalyst (*R,R*)-**C2** under mild conditions (Scheme 186).<sup>273</sup>



<sup>272</sup> Zheng, L.-S.; Llopis, Q.; Echeverria, P.-G.; Féraud, C.; Guillamot, G.; Phansavath, P.; Ratovelomanana-Vidal, V. *J. Org. Chem.* **2017**, *82*, 5607.

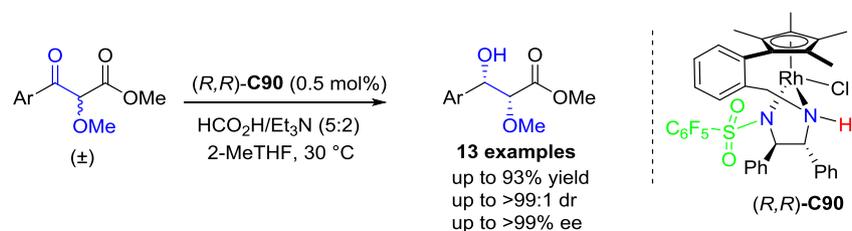
<sup>273</sup> Zheng, L.-S.; Phansavath, P.; Ratovelomanana-Vidal, V. *Org. Lett.* **2018**, *20*, 5107.

Unprecedented results were obtained using tethered Rh complex *(R,R)*-**C84** in the asymmetric transfer hydrogenation of mono-protected  $\alpha$ -amino  $\beta$ -ketoesters through a dynamic kinetic resolution process, delivering *syn*  $\alpha$ -amino- $\beta$ -hydroxy esters in high yields, high dr and excellent ee values (Scheme 187).<sup>274</sup>



Scheme 187

Based on the high performance of the tethered Rh complex *(R,R)*-**C84** in DKR/ATH of  $\alpha$ -amino  $\beta$ -ketoesters, we synthesized a new tethered Rh complex *(R,R)*-**C90** bearing a pentafluorobenzenesulfonyl DPEN ligand and evaluated its catalytic performance in DKR/ATH of  $\alpha$ -alkoxyl  $\beta$ -ketoesters to access the corresponding diol derivatives in high yields, high drs and excellent ees (Scheme 188).<sup>275</sup>



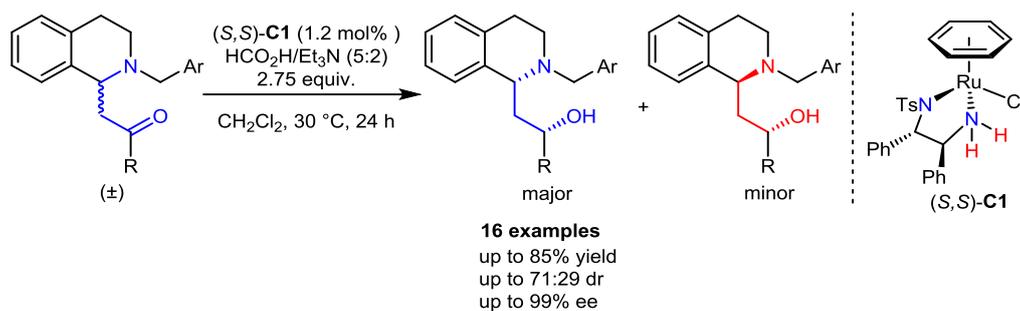
Scheme 188

Finally, an efficient asymmetric synthesis of 2-(1,2,3,4-tetrahydro-1-isoquinolyl) ethanol derivatives, which act as *N*-methyl-D-aspartate (NMDA) receptor inhibitors, was developed by asymmetric reduction through a dynamic kinetic resolution process. This practical synthesis features the first application of Ru-catalyzed asymmetric transfer

<sup>274</sup> Zheng, L.-S.; Ferard, C.; Phansavath, P.; Ratovelomanana-Vidal, V. *Chem. Commun.* **2018**, 54, 283.

<sup>275</sup> Unpublished results.

hydrogenation to establish enantiomerically enriched 1,3-aminoalcohol derivatives bearing the tetrahydroisoquinoline scaffold. The reaction proceeded under mild conditions, using a low catalyst loading of (*S,S*)-**C1** and HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) as the hydrogen source, delivering a variety of 2-(1,2,3,4-tetrahydro-1-isoquinolyl)ethanol derivatives with excellent enantioselectivities (up to 99% ee) for the *syn* products (Scheme 189).<sup>276</sup>



Scheme 189

<sup>276</sup> Zheng, L.-S.; Phansavath, P.; Ratovelomanana-Vidal, V. *Org. Chem. Front.* **2018**, *5*, 1366.



# **EXPERIMENTAL PART**



## Experimental part

### 1. General informations

#### 1.1 Purification of solvents and reagents

All reactions were performed under an atmosphere of argon. Reaction vessels were oven-dried, cooled under vacuum and flushed with argon before use.

Petroleum ether, ethyl acetate and toluene used for column chromatography were distilled under reduced pressure. THF, Et<sub>2</sub>O, CH<sub>2</sub>H<sub>2</sub>, toluene and DMF were dried over alumina columns in a solvent purification apparatus (Innovative Technologies). HPLC grade methanol and ethanol, and reagent grade hexane and cyclohexane were purchased and used without further purification. Every reagent was either purified following the methods described in the literature,<sup>277</sup> or used without further purification.

#### 1.2 Chromatography

Reactions were monitored by thin layer chromatography (TLC) using commercial silica-gel plates (Merck 60 F254). Spots were detected with UV light (254 nm) and revealed with KMnO<sub>4</sub>, Kagi-Mosher or Ninhydrin stain.<sup>278</sup> VWR Silica Gel 60 (40-63 μm) was employed for flash column chromatography using Still's method.<sup>279</sup>

#### 1.3 Analysis

Proton nuclear magnetic resonance (<sup>1</sup>H NMR) spectra were recorded using a Bruker AVANCE 300 (300 MHz) or a Bruker AVANCE 400 (400 MHz). Chemical shifts are reported in delta (δ) units part per million (ppm) relative to residual protiated solvent (7.26 ppm for

---

<sup>277</sup> Perrin, D. D.; Armarego, W. L. F. *Purification of laboratory chemicals*, Third Edition, Pergamon Press, Oxford, **1988**.

<sup>278</sup> KMnO<sub>4</sub> : Purple solution composed of potassium permanganate (1.5 g), potassium carbonate (10 g), NaOH (1.25 mL, 10wt%) and water (200 mL). Kagi-Mosher solution : rose red solution composed of *p*-anisaldehyde (3.7 mL), concentrated sulfuric acid (5 mL) in ethanol (135 mL). Ninhydrin solution : pale yellow solution composed of ninhydrin (1.5 g), *n*-butanol (100 mL) and acetic acid (3.0 mL).

<sup>279</sup> Still, W.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923

$\text{CDCl}_3$ , 2.50 ppm for  $d_6$ -DMSO, 7.16 ppm for  $\text{C}_6\text{D}_6$ , 2.05 ppm for acetone- $d_6$ ). Coupling constants are reported in Hertz (Hz). The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, brs = broad singlet, brd = broad doublet. Carbon-13 nuclear magnetic resonance ( $^{13}\text{C}$  NMR) spectra were recorded using a Bruker AVANCE 300 (75 MHz) or a Bruker AVANCE 400 (101 MHz). Chemical shifts are reported in delta ( $\delta$ ) units part per million (ppm) relative to the centre line of the triplet at 77.16 ppm for  $\text{CDCl}_3$ , the centre line of the septuplet at 39.52 ppm for  $d_6$ -DMSO, the centre line at 128.06 ppm for  $\text{C}_6\text{D}_6$ , the signal at 29.8 ppm for acetone- $d_6$ .  $^{13}\text{C}$  NMR experiments were routinely run with broadband decoupling. Fluorine-19 nuclear magnetic resonance ( $^{19}\text{F}$  NMR) was recorded using a Bruker AVANCE 300 (282 MHz) or a Bruker AVANCE 400 (376 MHz).

Mass spectra were recorded at the mass spectrometry laboratory in Chimie ParisTech using a Nermag R10-10C apparatus for chemical ionisation (CI) or electronic impact (EI), and API 3000 PE Sciex apparatus for electrospray (ESI) measurements. HRMS analyses were performed at the Sorbonne Université using a LTQ-Orbitrap (Thermo Fisher Scientific) apparatus.

Optical rotations were measured at 25 °C on a Perkin-Elmer 241 Polarimeter using a sodium lamp (589 nm) with spectrophotometric grade chloroform as a solvent.

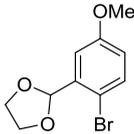
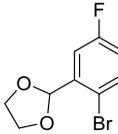
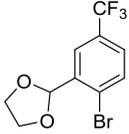
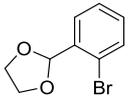
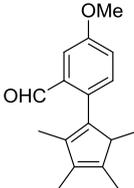
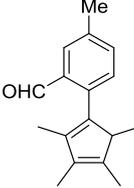
Supercritical Fluid Chromatography (SFC) measurements were run on a Berger Instruments apparatus equipped with chiral stationary phase Daicel Chiralcel OD-H and Chiralpak IA, IC, ID, AD-H and AS-H columns. HPLC grade methanol or isopropanol were used as a polar modifier. High Performance Liquid Chromatography (HPLC) measurements were run on a Waters Instruments apparatus equipped with Chiralpak IA, IB, IC, ID, IE columns. HPLC grade hexane and isopropanol were used as eluents.

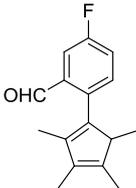
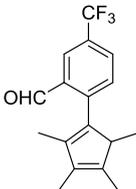
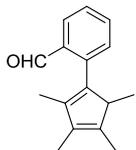
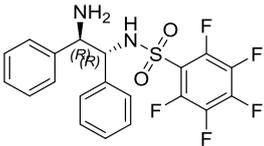
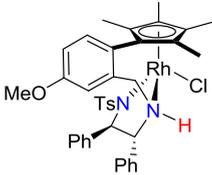
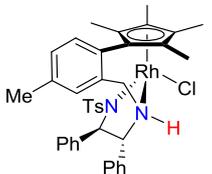
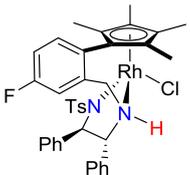
Melting point values were recorded on a Kofler bench.

X-ray diffraction studies were performed in the X-ray facility at the Sorbonne Université using a Bruker AXS Kapa-APEX II apparatus with a Cu source for absolute configuration determination.

## 2. Description of the synthesized products

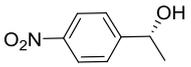
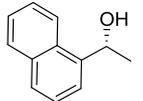
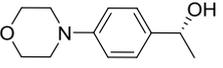
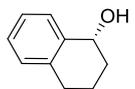
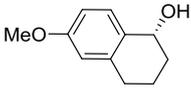
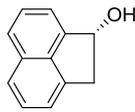
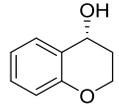
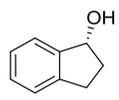
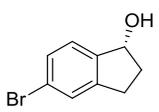
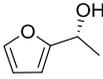
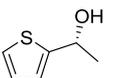
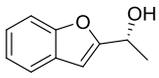
### 2.1 Index of synthesized products

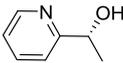
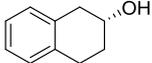
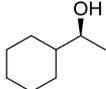
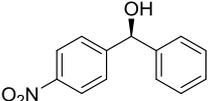
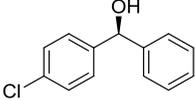
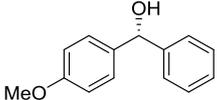
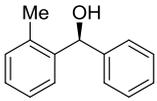
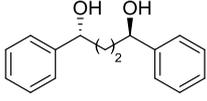
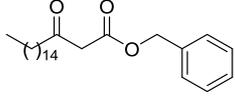
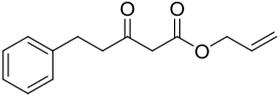
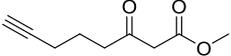
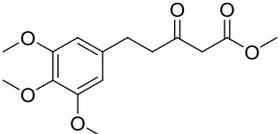
| No. | Structure   | Page |
|-----|---|------|
| 2a  |    | 231  |
| 2b  |    | 231  |
| 2c  |   | 232  |
| 2d  |  | 232  |
| 2e  |  | 233  |
| 3a  |  | 233  |
| 3b  |  | 234  |

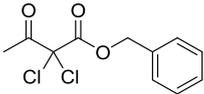
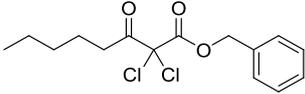
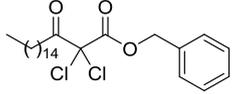
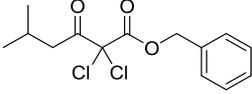
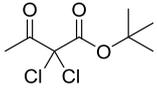
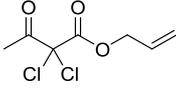
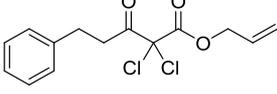
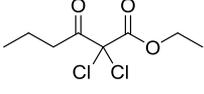
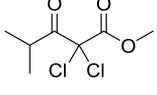
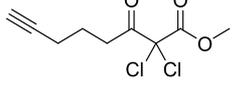
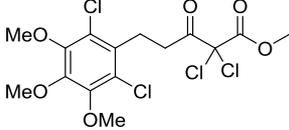
|                  |   |     |
|------------------|---|-----|
| <b>3c</b>        |    | 234 |
| <b>3d</b>        |    | 235 |
| <b>3e</b>        |    | 235 |
| <b>L42</b>       |   | 236 |
| <b>(R,R)-C84</b> |  | 237 |
| <b>(R,R)-C85</b> |  | 238 |
| <b>(R,R)-C86</b> |  | 239 |

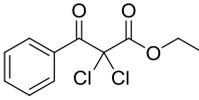
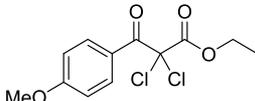
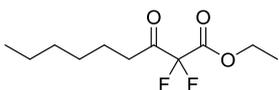
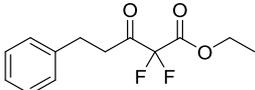
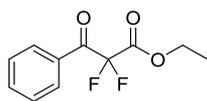
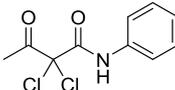
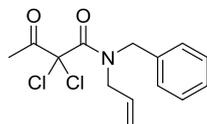
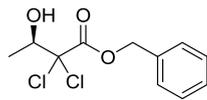
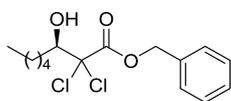
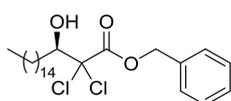
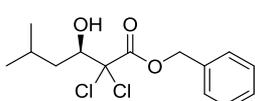
|                         |  |     |
|-------------------------|--|-----|
| <b>(<i>R,R</i>)-C87</b> |  | 240 |
| <b>(<i>R,R</i>)-C90</b> |  | 241 |
| <b>5a</b>               |  | 242 |
| <b>5b</b>               |  | 242 |
| <b>5c</b>               |  | 243 |
| <b>5d</b>               |  | 243 |
| <b>5e</b>               |  | 243 |
| <b>5f</b>               |  | 244 |
| <b>5g</b>               |  | 244 |
| <b>5h</b>               |  | 244 |

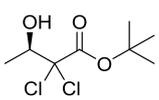
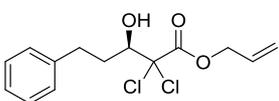
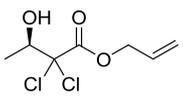
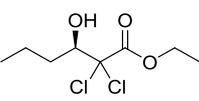
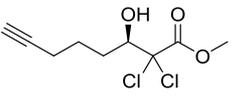
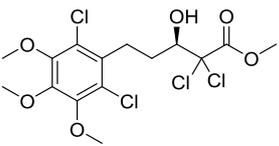
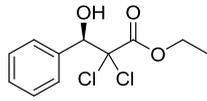
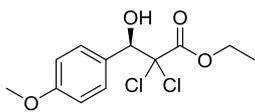
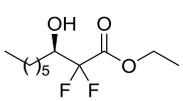
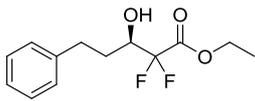
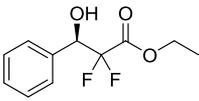
Experimental part

|    |   |     |
|----|---|-----|
| 5i |    | 245 |
| 5j |    | 245 |
| 5k |    | 245 |
| 5l |    | 246 |
| 5m |    | 246 |
| 5n |   | 246 |
| 5o |  | 247 |
| 5p |  | 247 |
| 5q |  | 247 |
| 7a |  | 248 |
| 7b |  | 248 |
| 7c |  | 248 |

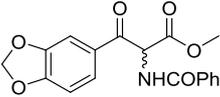
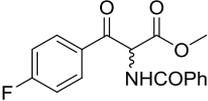
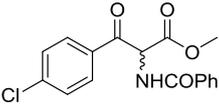
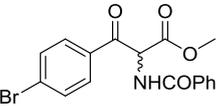
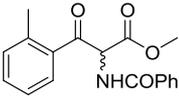
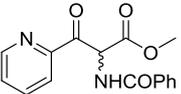
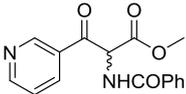
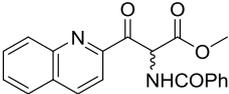
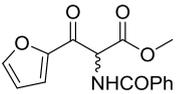
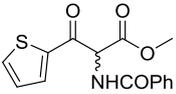
|     |   |     |
|-----|---|-----|
| 7d  |    | 249 |
| 7e  |    | 249 |
| 7f  |    | 249 |
| 9a  |    | 250 |
| 9b  |    | 250 |
| 9c  |   | 250 |
| 9d  |  | 251 |
| 11  |  | 251 |
| 12b |  | 253 |
| 12f |  | 254 |
| 12j |  | 254 |
| 12k |  | 255 |

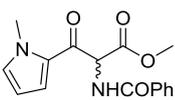
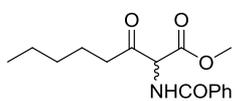
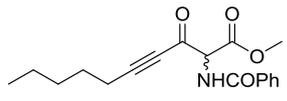
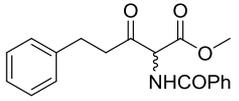
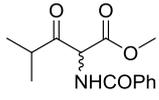
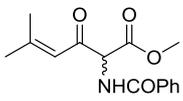
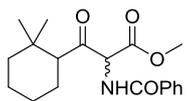
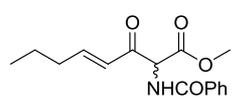
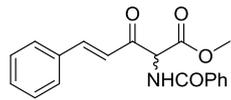
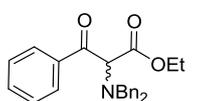
|     |   |     |
|-----|---|-----|
| 13a |    | 255 |
| 13b |    | 255 |
| 13c |    | 256 |
| 13d |    | 256 |
| 13e |    | 256 |
| 13f |  | 257 |
| 13g |  | 257 |
| 13h |  | 257 |
| 13i |  | 258 |
| 13j |  | 258 |
| 13k |  | 258 |

|            |   |     |
|------------|---|-----|
| <b>13l</b> |    | 259 |
| <b>13m</b> |    | 259 |
| <b>13n</b> |    | 259 |
| <b>13o</b> |    | 260 |
| <b>13p</b> |    | 260 |
| <b>13q</b> |  | 261 |
| <b>13r</b> |  | 261 |
| <b>14a</b> |  | 262 |
| <b>14b</b> |  | 263 |
| <b>14c</b> |  | 263 |
| <b>14d</b> |  | 264 |

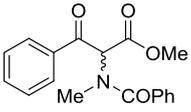
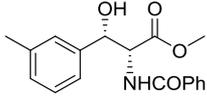
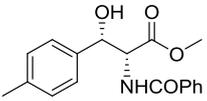
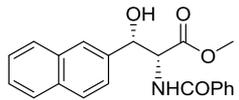
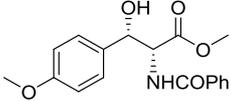
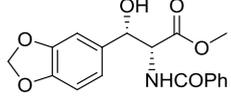
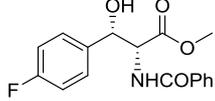
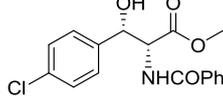
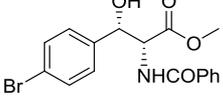
|     |   |     |
|-----|---|-----|
| 14e |    | 264 |
| 13f |    | 265 |
| 14g |    | 265 |
| 14h |    | 266 |
| 14j |    | 266 |
| 14k |   | 267 |
| 14l |  | 267 |
| 14m |  | 268 |
| 14n |  | 268 |
| 14o |  | 269 |
| 14p |  | 269 |

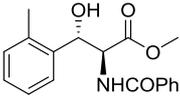
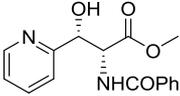
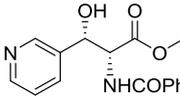
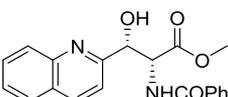
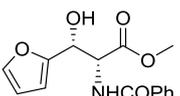
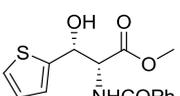
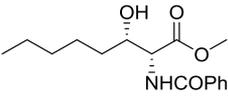
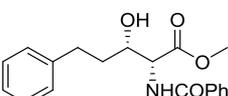
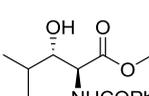
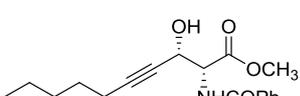


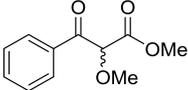
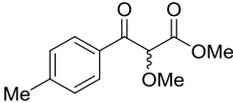
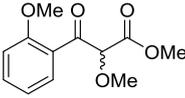
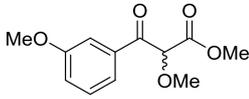
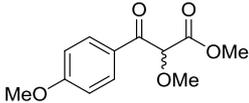
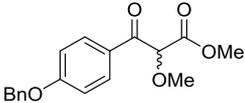
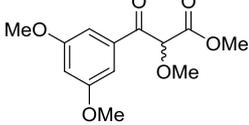
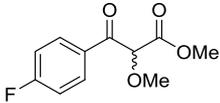
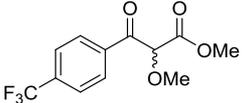
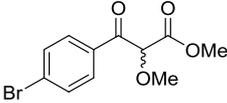
|     |   |     |
|-----|---|-----|
| 24f |    | 277 |
| 24g |    | 277 |
| 24h |    | 278 |
| 24i |    | 278 |
| 24j |   | 279 |
| 24k |  | 279 |
| 24l |  | 280 |
| 24m |  | 280 |
| 24n |  | 281 |
| 24o |  | 281 |

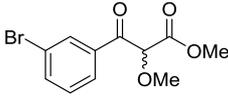
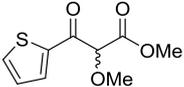
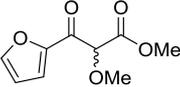
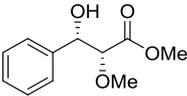
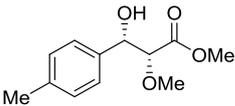
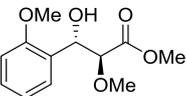
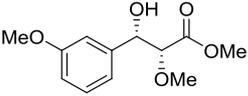
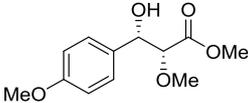
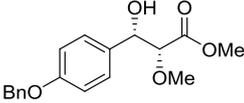
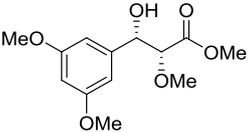
|     |   |     |
|-----|---|-----|
| 24p |    | 282 |
| 24q |    | 282 |
| 24r |    | 283 |
| 24s |    | 284 |
| 24t |   | 284 |
| 24u |  | 285 |
| 24v |  | 285 |
| 24w |  | 286 |
| 24x |  | 287 |
| 24y |  | 287 |

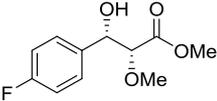
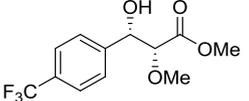
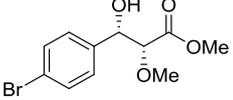
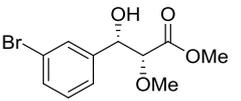
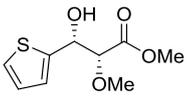
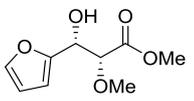
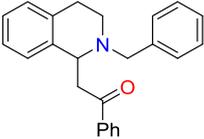
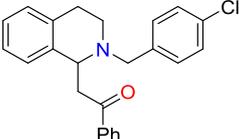
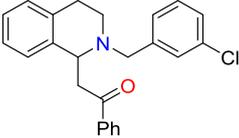
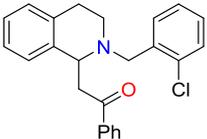
Experimental part

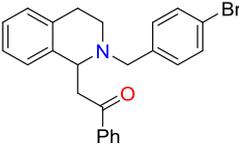
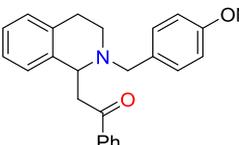
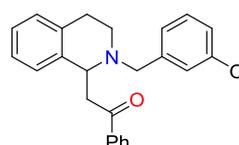
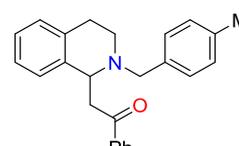
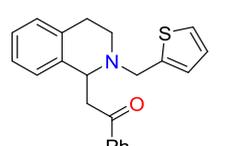
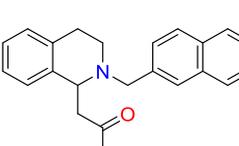
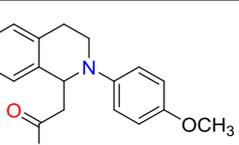
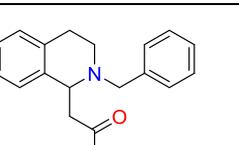
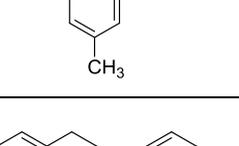
|     |   |     |
|-----|---|-----|
| 24z |    | 288 |
| 25a |    | 289 |
| 25b |    | 290 |
| 25c |    | 290 |
| 25d |   | 291 |
| 25e |  | 292 |
| 25f |  | 292 |
| 25g |  | 293 |
| 25h |  | 293 |
| 25i |  | 294 |

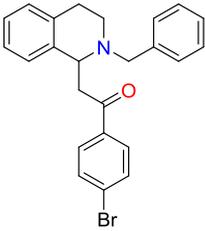
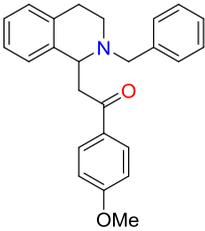
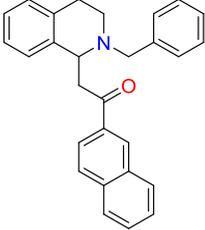
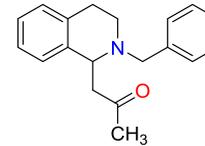
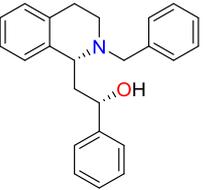
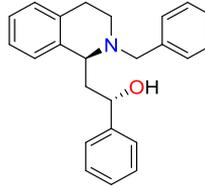
|     |   |     |
|-----|---|-----|
| 25j |    | 295 |
| 25k |    | 295 |
| 25l |    | 296 |
| 25m |    | 296 |
| 25o |   | 297 |
| 25o |  | 298 |
| 25q |  | 298 |
| 25r |  | 299 |
| 25s |  | 299 |
| 24t |  | 300 |

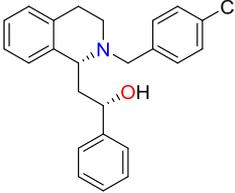
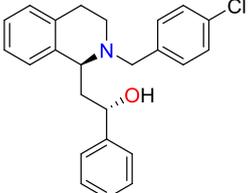
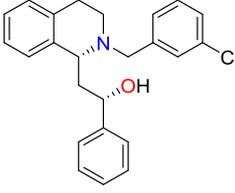
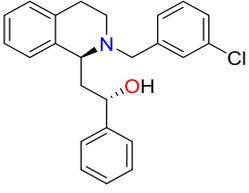
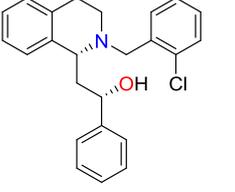
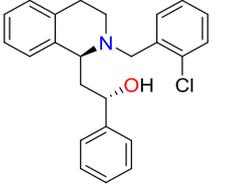
|     |   |     |
|-----|---|-----|
| 26a |    | 301 |
| 26b |    | 301 |
| 26c |    | 301 |
| 26d |    | 302 |
| 26e |   | 302 |
| 26f |  | 302 |
| 26g |  | 303 |
| 26h |  | 303 |
| 26i |  | 304 |
| 26j |  | 304 |

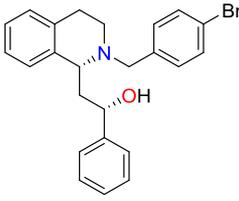
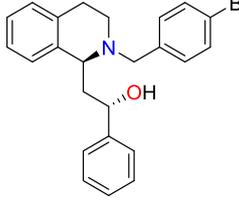
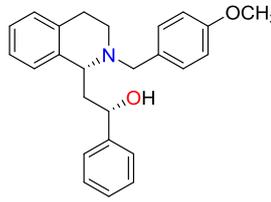
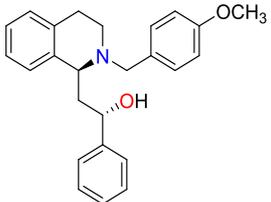
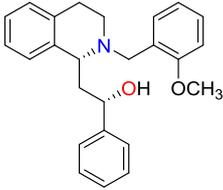
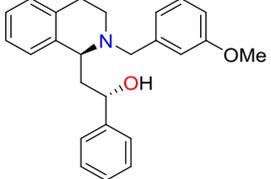
|            |   |     |
|------------|---|-----|
| <b>26k</b> |    | 304 |
| <b>26l</b> |    | 305 |
| <b>26m</b> |    | 305 |
| <b>27a</b> |    | 306 |
| <b>27b</b> |   | 307 |
| <b>28c</b> |  | 307 |
| <b>27d</b> |  | 308 |
| <b>27e</b> |  | 308 |
| <b>27f</b> |  | 309 |
| <b>27g</b> |  | 309 |

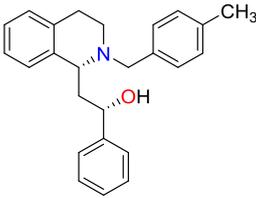
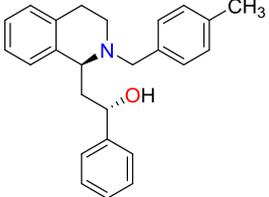
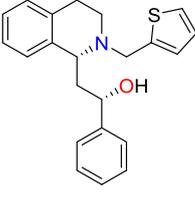
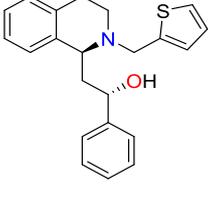
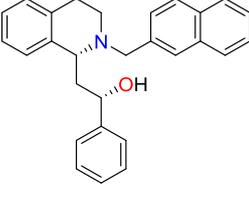
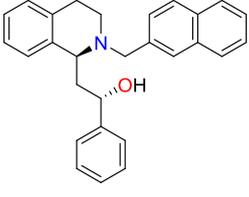
|     |   |     |
|-----|---|-----|
| 27h |    | 310 |
| 27i |    | 310 |
| 27j |    | 311 |
| 27k |    | 311 |
| 27l |   | 312 |
| 27m |  | 312 |
| 29a |  | 314 |
| 29b |  | 314 |
| 29c |  | 315 |
| 29d |  | 315 |

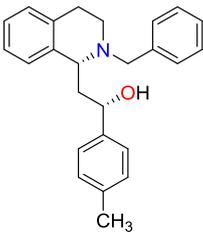
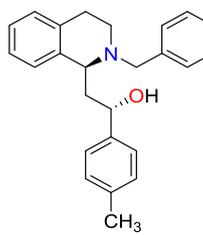
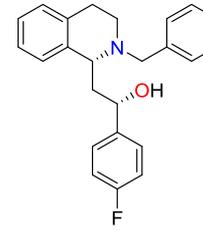
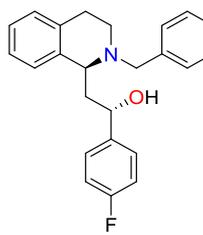
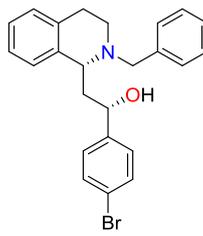
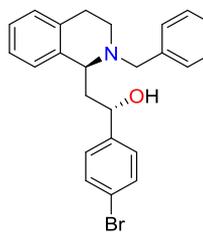
|            |   |     |
|------------|---|-----|
| <b>29e</b> |    | 316 |
| <b>29f</b> |    | 316 |
| <b>29g</b> |    | 317 |
| <b>29h</b> |    | 317 |
| <b>29i</b> |   | 318 |
| <b>29j</b> |  | 318 |
| <b>29k</b> |  | 319 |
| <b>29l</b> |  | 320 |
| <b>29m</b> |  | 320 |

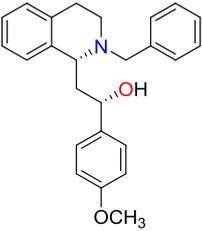
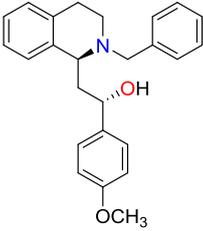
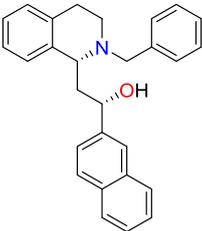
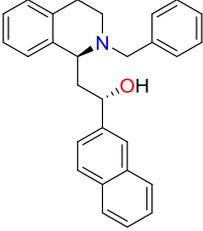
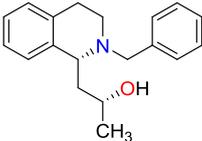
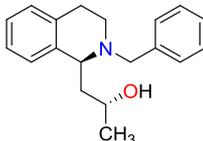
|                   |   |            |
|-------------------|---|------------|
| <p><b>29n</b></p> |    | <p>321</p> |
| <p><b>29o</b></p> |    | <p>321</p> |
| <p><b>29p</b></p> |    | <p>322</p> |
| <p><b>29q</b></p> |  | <p>322</p> |
| <p><b>30a</b></p> |  | <p>323</p> |
| <p><b>31a</b></p> |  | <p>323</p> |

|            |   |     |
|------------|---|-----|
| <b>30b</b> |    | 324 |
| <b>31b</b> |    | 324 |
| <b>30c</b> |    | 325 |
| <b>31c</b> |  | 325 |
| <b>30d</b> |  | 326 |
| <b>31d</b> |  | 326 |

|                   |   |            |
|-------------------|---|------------|
| <p><b>30e</b></p> |    | <p>327</p> |
| <p><b>31e</b></p> |    | <p>327</p> |
| <p><b>30f</b></p> |    | <p>328</p> |
| <p><b>31f</b></p> |  | <p>328</p> |
| <p><b>30g</b></p> |  | <p>329</p> |
| <p><b>31g</b></p> |  | <p>329</p> |

|            |   |     |
|------------|---|-----|
| <b>30h</b> |    | 330 |
| <b>31h</b> |    | 330 |
| <b>30i</b> |    | 331 |
| <b>31i</b> |  | 331 |
| <b>30j</b> |  | 332 |
| <b>31j</b> |  | 332 |

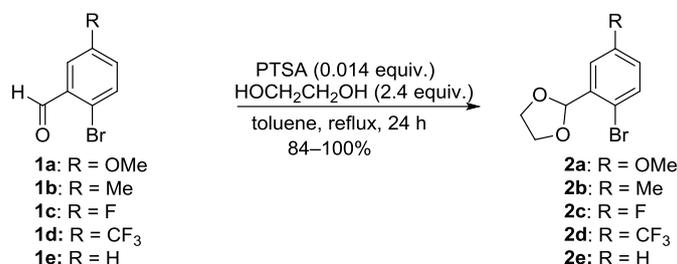
|                   |   |            |
|-------------------|---|------------|
| <p><b>30l</b></p> |    | <p>333</p> |
| <p><b>31l</b></p> |    | <p>333</p> |
| <p><b>30m</b></p> |    | <p>334</p> |
| <p><b>31m</b></p> |  | <p>334</p> |
| <p><b>30n</b></p> |  | <p>335</p> |
| <p><b>31n</b></p> |  | <p>335</p> |

|            |  |     |
|------------|--|-----|
| <b>30o</b> | <br><chem>COC1=CC=C(C=C1)CC[C@H]2CN(Cc3ccccc3)CC2</chem>        | 336 |
| <b>31o</b> | <br><chem>COC1=CC=C(C=C1)CC[C@@H]2CN(Cc3ccccc3)CC2</chem>       | 336 |
| <b>30p</b> | <br><chem>C1=CC=C2C=CC=CC2=C1CC[C@H]3CN(Cc4ccccc4)CC3</chem>    | 337 |
| <b>31p</b> | <br><chem>C1=CC=C2C=CC=CC2=C1CC[C@@H]3CN(Cc4ccccc4)CC3</chem> | 337 |
| <b>30q</b> | <br><chem>CC[C@H](O)CC[C@H]2CN(Cc3ccccc3)CC2</chem>           | 338 |
| <b>31q</b> | <br><chem>CC[C@@H](O)CC[C@@H]2CN(Cc3ccccc3)CC2</chem>         | 338 |

## 2.2 Description of the synthesis processes and detailed data

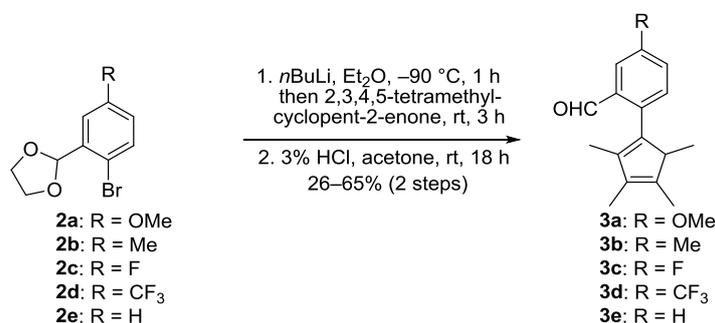
### Synthesis of complexes (*R,R*)-C84–C87, C90:

#### General procedure A: synthesis of compounds **2a–e**

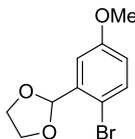


A mixture of 2-bromo-5-substituted-benzaldehyde **1** (1.0 equiv.), ethylene glycol (2.4 equiv.) and *p*-toluenesulfonic acid (0.014 equiv.) in toluene (0.5 mmol/mL) was refluxed in a Dean-Stark apparatus for 24 h. The cooled mixture was washed with H<sub>2</sub>O and brine. The organic layer was dried over MgSO<sub>4</sub>, filtered and concentrated. Purification of the residue by flash chromatography (SiO<sub>2</sub>, petroleum ether/EtOAc: 95/5) afforded **2** as a colorless oil.

#### General procedure B: synthesis of compounds **3a–e**



To a solution of **2** (1.0 equiv.) in Et<sub>2</sub>O (0.55 mmol/mL) was added dropwise *n*BuLi (2.5 M in hexane, 1.05 equiv.) at –90 °C. After 1 h at this temperature, 2,3,4,5-tetramethylcyclopent-2-enone (1.05 equiv.) was added dropwise and the reaction was allowed to warm to rt and stirred for 3 h. Toluene and water (30 mL/30 mL) were added and the aqueous layer was extracted with toluene. The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated to afford the crude alcohol. THF (140 mL), acetone (18 mL) and 3% aqueous HCl solution (60 mL) were added and the mixture was stirred overnight at rt. Toluene was added, the organic layer was washed with H<sub>2</sub>O then brine, dried over MgSO<sub>4</sub>, filtered and concentrated. The crude residue was purified by flash chromatography (SiO<sub>2</sub>, petroleum ether/EtOAc: 98/2) to give **3** as a bright yellow oil.

2-(2-bromo-5-methoxyphenyl)-1,3-dioxolane (**2a**)

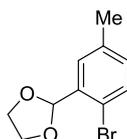
Chemical Formula: C<sub>10</sub>H<sub>11</sub>BrO<sub>3</sub>  
Exact Mass: 257.9892

Following the general procedure **A**, and starting from 2-bromo-5-methoxybenzaldehyde **1a** (5.0 g, 23.2 mmol), compound **2a** (6.1 g, quant. yield) was obtained as a colorless oil.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.44 (d, *J* = 8.8 Hz, 1H), 7.15 (d, *J* = 3.1 Hz, 1H), 6.78 (dd, *J* = 8.8, 3.1 Hz, 1H), 6.04 (s, 1H), 4.18–4.03 (m, 4H), 3.79 (s, 3H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 158.9, 137.3, 133.6, 116.6, 113.1, 112.9, 102.4, 65.4 (2C), 55.5.

MS (DCI/NH<sub>3</sub>): *m/z* = 259 [M + H]<sup>+</sup>

2-(2-bromo-5-methylphenyl)-1,3-dioxolane (**2b**)

Chemical Formula: C<sub>10</sub>H<sub>11</sub>BrO<sub>2</sub>  
Exact Mass: 241.9942

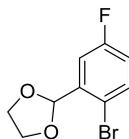
Following the general procedure **A**, and starting from 2-bromo-5-methylbenzaldehyde **1b** (4.2 g, 21.3 mmol), compound **2b** (4.8 g, 92%) was obtained as a colorless oil.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 7.52–7.32 (m, 2H), 7.03 (dd, *J* = 8.2, 2.3 Hz, 1H), 6.06 (s, 1H), 4.31–3.93 (m, 4H), 2.32 (s, 3H);

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ = 137.5, 136.2, 132.8, 131.6, 128.5, 119.7, 102.8, 65.6 (2C), 21.1.

MS (DCI/NH<sub>3</sub>): *m/z* = 244 [M+H]<sup>+</sup>.

2-(2-bromo-5-fluorophenyl)-1,3-dioxolane (**2c**)



Chemical Formula: C<sub>9</sub>H<sub>8</sub>BrFO<sub>2</sub>  
Exact Mass: 245.9692

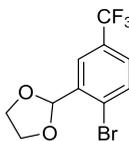
Following the general procedure **A**, and starting from 2-bromo-5-fluorobenzaldehyde **1c** (5.0 g, 25.0 mmol), compound **2c** (5.20 g, 84%) was obtained as a colorless oil.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 7.50 (dd, *J* = 8.8, 5.1 Hz, 1H), 7.32 (dd, *J* = 9.3, 3.1 Hz, 1H), 6.94 (ddd, *J* = 8.8, 7.8, 3.1 Hz, 1H), 6.03 (d, *J* = 1.3 Hz, 1H), 4.27–3.94 (m, 4H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ = 162.1 (d, *J*<sub>CF</sub> = 247.3 Hz), 139.1 (d, *J*<sub>CF</sub> = 6.2 Hz), 134.3 (d, *J*<sub>CF</sub> = 7.6 Hz), 117.8 (d, *J*<sub>CF</sub> = 22.7 Hz), 116.9 (d, *J*<sub>CF</sub> = 3.2 Hz), 115.2 (d, *J*<sub>CF</sub> = 24.4 Hz), 102.1, 65.6 (2C).

MS (DCI/NH<sub>3</sub>): *m/z* = 248 [M+H]<sup>+</sup>.

2-(2-bromo-5-(trifluoromethyl)phenyl)-1,3-dioxolane (**2d**)



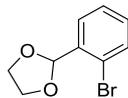
Chemical Formula: C<sub>10</sub>H<sub>8</sub>BrF<sub>3</sub>O<sub>2</sub>  
Exact Mass: 295.9660

Following the general procedure **A**, and starting from 2-bromo-5-trifluoromethylbenzaldehyde **1d** (5.0 g, 19.8 mmol), compound **2d** (5.85 g, 99%) was obtained as a colorless oil.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 8.00–7.78 (m, 1H), 7.78–7.62 (m, 1H), 7.47 (dt, *J* = 8.3, 1.5 Hz, 1H), 6.09 (s, 1H), 4.33–3.89 (m, 4H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ = 138.1, 133.7, 130.2 (q, *J*<sub>CF</sub> = 33.0 Hz), 127.2 (q, *J*<sub>CF</sub> = 3.9 Hz), 126.9, 125.0 (q, *J*<sub>CF</sub> = 3.6 Hz), 123.8 (q, *J*<sub>CF</sub> = 272.5 Hz), 102.0, 65.7 (2C).

MS (DCI/NH<sub>3</sub>): *m/z* = 299 [M+H]<sup>+</sup>.

2-(2-bromophenyl)-1,3-dioxolane (**2e**)

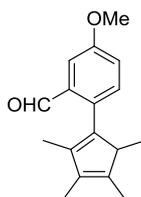
Chemical Formula: C<sub>9</sub>H<sub>9</sub>BrO<sub>2</sub>  
Exact Mass: 227.9786

Following the general procedure **A**, and starting from 2-bromobenzaldehyde **1e** (10.0 g, 19.8 mmol), compound **2e** (12.4g, quant.) was obtained as a colorless oil.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.62 – 7.55 (m, 2H), 7.37 – 7.31 (m, 1H), 7.25 – 7.19 (m, 1H), 6.10 (s, 1H), 4.19 – 4.04 (m, 4H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 136.8, 133.1, 130.7, 128.0, 127.6, 123.1, 102.8, 65.6 (2C).

MS (DCI/NH<sub>3</sub>): *m/z* = 229 [M+H]<sup>+</sup>.

2-(1,3-dioxolan-2-yl)-4-methoxybenzaldehyde (**3a**)

Chemical Formula: C<sub>17</sub>H<sub>20</sub>O<sub>2</sub>  
Exact Mass: 256.1463

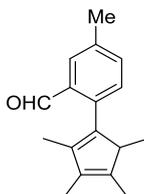
Following the general procedure **B**, and starting from **2a** (6.0 g, 23.2 mmol), compound **3a** (3.9 g, 65%) was obtained as a bright yellow oil.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 9.81 (br s, 1H), 7.44 (dd, *J* = 2.3, 0.8 Hz, 1H), 7.15–7.14 (m, 2H), 3.88 (s, 1H), 3.87 (s, 3H), 1.92 (s, 3H), 1.85 (s, 3H), 1.71 (s, 3H), 0.93 (d, *J* = 7.7 Hz, 3H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 192.9, 158.3, 141.8 (2C), 138.2, 135.3, 134.5, 132.0, 121.8 (2C), 109.0, 55.5 (2C), 14.2, 12.3, 11.9, 11.0.

MS (DCI/NH<sub>3</sub>): *m/z* = 257 [M + H]<sup>+</sup>.

2-(1,3-dioxolan-2-yl)-4-methylbenzaldehyde (**3b**)



Chemical Formula: C<sub>17</sub>H<sub>20</sub>O  
Exact Mass: 240.1514

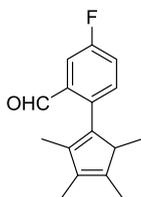
Following the general procedure **B**, and starting from **2b** (4.77 g, 19.6 mmol), compound **3b** (2.59 g, 55%) was obtained as a bright yellow oil.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 9.87 (br s, 1H), 7.90–7.66 (m, 1H), 7.40 (dd, *J* = 7.8, 2.0 Hz, 1H), 7.13 (d, *J* = 7.8 Hz, 1H), 3.20 (br s, 1H), 2.42 (s, 3H), 1.94 (s, 3H), 1.87 (s, 3H), 1.73 (s, 3H), 0.95 (d, *J* = 7.7 Hz, 3H);

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ = 193.2, 144.4, 141.9, 139.3, 138.8, 137.1, 136.5, 134.5, 134.4, 130.8, 127.3, 52.5, 21.0, 14.2, 12.4, 11.9, 11.1.

HRMS (ESI): *m/z* [M+Na]<sup>+</sup> calcd for C<sub>17</sub>H<sub>20</sub>ONa: 263.1406, found: 263.1408.

2-(1,3-dioxolan-2-yl)-4-fluorobenzaldehyde (**3c**)



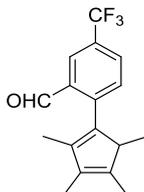
Chemical Formula: C<sub>16</sub>H<sub>17</sub>FO  
Exact Mass: 244.1263

Following the general procedure **B**, and starting from **2c** (5.2 g, 21 mmol), compound **3c** (2.50 g, 49%) was obtained as a bright yellow oil.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 9.80 (br s, 1H), 7.62 (dd, *J* = 8.9, 2.6 Hz, 1H), 7.37 – 7.16 (m, 2H), 3.18 (br s, 1H), 1.93 (s, 3H), 1.86 (s, 3H), 1.71 (s, 3H), 0.94 (d, *J* = 7.7 Hz, 3H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ = 191.9, 161.7 (d, *J*<sub>CF</sub> = 247.9 Hz), 145.1 (d, *J*<sub>CF</sub> = 19.4 Hz), 142.4, 139.9 (d, *J*<sub>CF</sub> = 14.0 Hz), 137.6, 136.2, 134.6, 132.8 (d, *J*<sub>CF</sub> = 6.5 Hz), 121.0 (d, *J*<sub>CF</sub> = 22.1 Hz), 113.1 (d, *J*<sub>CF</sub> = 22.0 Hz), 52.6, 14.2, 12.4, 12.0, 11.1.

HRMS (ESI): *m/z* [M+Na]<sup>+</sup> calcd for C<sub>16</sub>H<sub>17</sub>FONa: 267.1156, found: 267.1157.

2-(1,3-dioxolan-2-yl)-4-(trifluoromethyl)benzaldehyde (**3d**)

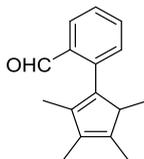
Chemical Formula: C<sub>17</sub>H<sub>17</sub>F<sub>3</sub>O  
Exact Mass: 294.1231

Following the general procedure **B**, and starting from **2d** (5.2 g, 17.5 mmol), compound **3d** (1.35 g, 26%) was obtained as a bright yellow oil.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 9.87 (br s, 1H), 8.30–8.10 (m, 1H), 7.79 (ddd, *J* = 8.1, 2.1, 0.8 Hz, 1H), 7.36 (d, *J* = 8.1 Hz, 1H), 3.26 (br s, 1H), 1.96 (s, 3H), 1.87 (s, 3H), 1.74 (s, 3H), 0.96 (d, *J* = 7.7 Hz, 3H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ = 191.6, 145.1, 143.5, 137.5, 134.9, 134.8, 131.7, 131.6, 129.6 (q, *J*<sub>CF</sub> = 3.2 Hz), 129.1 (q, *J*<sub>CF</sub> = 33.6 Hz), 124.6 (q, *J*<sub>CF</sub> = 3.7 Hz), 123.9 (q, *J*<sub>CF</sub> = 272.2 Hz), 52.5, 14.1, 12.6, 12.0, 11.1.

MS (DCI/NH<sub>3</sub>): *m/z* = 295 [M+H]<sup>+</sup>.

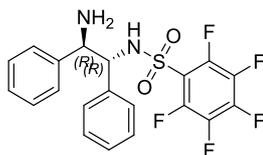
2-(2,3,4,5-tetramethylcyclopenta-1,3-dien-1-yl)benzaldehyde (**3e**)

Chemical Formula: C<sub>16</sub>H<sub>18</sub>O  
Exact Mass: 226.1358

Following the general procedure **B**, and starting from **2e** (6.0 g, 26.2 mmol), compound **3e** (3.6 g, 64%) was obtained as a bright yellow oil.

The analytical data were identical to those reported.<sup>41b</sup>

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.86 (s, 1H), 7.95 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.62 – 7.51 (m, 1H), 7.39 – (m, 1H), 7.22 (d, *J* = 7.9 Hz, 1H), 1.94 (s, 3H), 1.89 – 1.82 (m, 3H), 1.73 (s, 3H), 0.95 (d, *J* = 7.7 Hz, 3H).

***N*-(2-Amino-1,2-diphenyl-ethyl)-2,3,4,5,6-pentamethyl-benzene sulfonamide (**L42**)**

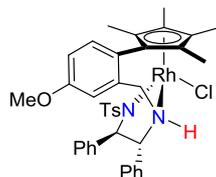
Chemical Formula: C<sub>20</sub>H<sub>15</sub>F<sub>5</sub>N<sub>2</sub>O<sub>2</sub>S  
Exact Mass: 442.0774

(*R,R*)-DPEN (0.5 g, 2.4 mmol) was dissolved in dichloromethane (20 mL) and the solution was cooled to 0 °C when triethylamine (0.4 mL, 2.88 mmol) was added followed by 2,3,4,5,6-pentamethylbenzenesulfonyl chloride (0.64 g, 2.4 mmol) in dichloromethane (5 mL). The reaction was allowed to stay at rt and was stirred overnight. The mixture was washed with water (10 mL) and then the organic phase was separated, dried over dried MgSO<sub>4</sub> and evaporated under reduced pressure to afford the crude product which was purified by silica gel chromatography (1:1 % v/v ethyl acetate/hexane) to afford the product **L42** as a white solid (0.68 g, 64%). The analytical data were identical to those reported in the literature.<sup>280</sup>

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.39 – 7.16 (m, 11H), 4.70 (d, *J* = 3.5 Hz, 1H), 4.39 (d, *J* = 3.5 Hz, 1H), 2.42 (brs, 2H).

<sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ -135.43 (dp, *J* = 18.1, 7.0 Hz), -147.68 (tt, *J* = 21.1, 6.2 Hz), -159.49 (tt, *J* = 21.5, 6.0 Hz).

<sup>280</sup> Martins, J. E. D.; Wills, M. *Tetrahedron* **2009**, *65*, 5782.

Catalyst (*R,R*)-**C84**

Chemical Formula:  $C_{38}H_{40}ClN_2O_3RhS$   
Exact Mass: 742.1503

**Complex (*R,R*)-**C84**:** To a solution of compound **3a** (538 mg, 2.1 mmol) in dry MeOH (24 mL) was added (*R,R*)-TsDPEN (900 mg, 2.5 mmol) followed by the addition of 700 mg of molecular sieves (4 Å) and 2 drops of glacial acetic acid. The mixture was stirred at rt for 5 h then  $NaBH_3CN$  (170 mg, 2.7 mmol) was added and the reaction was stirred overnight at rt. After removal of the molecular sieves and evaporation of MeOH, the residue was dissolved in EtOAc (40 mL). The organic layer was washed with saturated  $NaHCO_3$  then brine, dried over  $MgSO_4$ , filtered and concentrated. Purification of the residue by flash chromatography ( $SiO_2$ , pentane/EtOAc: 9/1 to 8/2) afforded the diamine (786 mg, 60%) as a white solid. To a solution of the diamine (740 mg, 1.22 mmol) in MeOH (28 mL) was added  $RhCl_3 \cdot H_2O$  (255 mg, 1.22 mmol) and the reaction mixture was heated under reflux for 23 h.  $Et_3N$  (0.34 mL, 2.44 mmol) was then added and the mixture was refluxed for a further 20 h and concentrated. The residue was triturated with  $H_2O$  and the solid was filtered, washed with  $H_2O$  and dried under vacuum. Purification of the black solid by flash chromatography ( $SiO_2$ , EtOAc/cyclohexane: 1/1 to EtOAc/MeOH: 95/5) afforded (*R,R*)-**C84** (455 mg, 50%) as an orange solid.<sup>168</sup> Mp: >260 °C (decomposition),  $R_f = 0.51$  ( $CH_2Cl_2/MeOH = 9/1$ , UV,  $KMnO_4$ ).  $[\alpha]_D^{25} = -154.4$  ( $c = 0.12$ ,  $CHCl_3$ ).

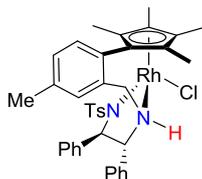
**IR** (neat): 2360, 2339, 1608, 1513, 1489, 1455, 1397, 1372, 1277, 1239, 1131, 1098, 1086, 1040, 1023, 940, 895, 812, 796, 766, 700, 682, 661, 646, 635, 622, 606  $cm^{-1}$ .

**$^1H$  NMR** (400 MHz,  $CDCl_3$ ):  $\delta$  7.37 (d,  $J = 8.5$  Hz, 1H), 7.27 (d,  $J = 8.6$  Hz, 2H), 7.19–7.16 (m, 3H), 7.02 (dd,  $J = 8.4, 2.5$  Hz, 1H), 6.73 (d,  $J = 8.0$  Hz, 2H), 6.70 (d,  $J = 7.3$  Hz, 2H), 6.59 (t,  $J = 7.8$  Hz, 2H), 6.48 (d,  $J = 7.4$  Hz, 2H), 6.42 (br d,  $J = 2.4$  Hz, 2H), 4.98 (d,  $J = 12.4$  Hz, 1H), 4.32 (d,  $J = 11.0$  Hz, 1H), 4.22 (dd,  $J = 14.0, 2.9$  Hz, 1H), 3.73 (s, 3H), 3.60 (d,  $J = 14.0$  Hz, 1H), 3.26 (t,  $J = 12.4$  Hz, 1H), 2.17 (s, 3H), 2.09 (s, 3H), 1.97 (s, 3H), 1.83 (s, 3H), 1.54 (s, 3H).

**$^{13}C$  NMR** (100 MHz,  $CDCl_3$ ):  $\delta$  160.2, 142.3, 139.0, 138.6, 137.5, 135.7, 131.2, 128.8, 128.7, 127.9, 127.7, 127.1, 126.2, 118.6, 117.0, 115.0, 106.4 (d,  $J_{CRh} = 6.6$  Hz), 99.2 (d,  $J_{CRh} = 6.6$  Hz), 97.0 (d,  $J_{CRh} = 8.8$  Hz), 88.7 (d,  $J_{CRh} = 9.5$  Hz), 80.6 (d,  $J_{CRh} = 8.0$  Hz), 75.9, 69.8, 55.5, 52.5, 21.3, 10.8, 10.7, 10.4, 8.3.

**HRMS** (ESI/ion trap):  $m/z$   $[M - Cl]^+$  calcd for  $C_{38}H_{40}N_2O_3RhS$  707.1809, found 707.1813.

Catalyst (*R,R*)-**C85**



Chemical Formula:  $C_{38}H_{40}ClN_2O_2RhS$   
Exact Mass: 726.1554

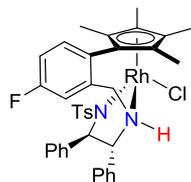
**Complex (*R,R*)-**C85**:** Following the general procedure described for (*R,R*)-**C84**, and starting from **3b** (546 mg, 2.3 mmol), complex (*R,R*)-**C85** (590 mg, 36%, 2 steps) was obtained as an orange solid. mp 274 °C (decomposition).  $R_f$  0.58 ( $CH_2Cl_2/MeOH:9/1$ , UV,  $KMnO_4$ ).  $[\alpha]_D^{25} = -112$  ( $c$  0.15,  $CHCl_3$ ).

**IR** (neat): 1456, 1277, 1133, 1107, 1085, 1036, 1021, 938, 894, 809, 751, 701, 682, 670, 661, 647, 601  $cm^{-1}$ .

**$^1H$  NMR** (400 MHz,  $CDCl_3$ ):  $\delta = 7.39$ – $7.23$  (m, 5H),  $7.23$ – $7.06$  (m, 3H),  $6.81$ – $6.66$  (m, 5H),  $6.59$  (dd,  $J = 8.2, 7.1$  Hz, 2H),  $6.48$  (d,  $J = 7.6$  Hz, 2H),  $4.99$  (d,  $J = 12.8$  Hz, 1H),  $4.30$  (d,  $J = 11.0$  Hz, 1H),  $4.20$  (dd,  $J = 14.0, 3.3$  Hz, 1H),  $3.62$  (d,  $J = 14.0$  Hz, 1H),  $3.25$  (dd,  $J = 12.8, 10.9$  Hz, 1H),  $2.29$  (s, 3H),  $2.17$  (s, 3H),  $2.09$  (s, 3H),  $1.98$  (s, 3H),  $1.82$  (s, 3H),  $1.54$  (s, 3H).

**$^{13}C$  NMR** (100 MHz,  $CDCl_3$ ):  $\delta = 142.2, 139.9, 139.1, 138.7, 135.9, 135.8, 132.4, 130.3, 129.8, 128.7, 127.9, 127.8, 127.0, 126.2, 123.9, 106.3$  (d,  $J_{CRh} = 6.1$  Hz),  $99.5$  (d,  $J_{CRh} = 7.0$  Hz),  $97.2$  (d,  $J_{CRh} = 9.0$  Hz),  $88.2$  (d,  $J_{CRh} = 9.2$  Hz),  $80.9$  (d,  $J_{CRh} = 8.6$  Hz),  $75.9, 69.9, 52.2, 21.3, 21.2, 10.8, 10.6, 10.4, 8.3$ .

**HRMS** (ESI):  $m/z$   $[M-Cl]^+$  calcd for  $C_{38}H_{40}N_2O_2RhS$ : 691.1860, found: 691.1870.

Catalyst (*R,R*)-**C86**

Chemical Formula:  $C_{37}H_{37}ClFN_2O_2RhS$   
Exact Mass: 730.1303

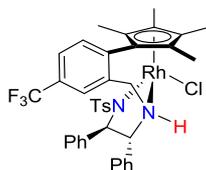
**Complex (*R,R*)-**C86**:** Following the general procedure described for (*R,R*)-**C84**, and starting from **3c** (555 mg, 2.3 mmol), complex (*R,R*)-**C86** (297 mg, 19%, 2 steps) was obtained as an orange solid. mp 280 °C (decomposition).  $R_f$  0.55 ( $CH_2Cl_2/MeOH:9/1$ , UV,  $KMnO_4$ ).  $[\alpha]_D^{25} = -151$  ( $c$  0.14,  $CHCl_3$ ).

**IR** (neat): 1736, 1608, 1585, 1511, 1492, 1455, 1373, 1275, 1235, 1216, 1158, 1132, 1023, 940, 894, 868, 852, 842, 811, 793, 779, 757, 730, 699, 677, 657, 645, 636, 607  $cm^{-1}$ .

**$^1H$  NMR** (400 MHz,  $CDCl_3$ ):  $\delta$  = 7.45 (dd,  $J$  = 8.5, 5.5 Hz, 1H), 7.33–7.10 (m, 7H), 6.74 (d,  $J$  = 8.0 Hz, 3H), 6.71–6.55 (m, 4H), 6.48 (d,  $J$  = 7.3 Hz, 2H), 5.04 (d,  $J$  = 12.8 Hz, 1H), 4.32 (d,  $J$  = 10.9 Hz, 1H), 4.22 (d,  $J$  = 14.2 Hz, 1H), 3.64 (d,  $J$  = 14.3 Hz, 1H), 3.34–3.13 (m, 1H), 2.17 (s, 3H), 2.10 (s, 3H), 1.98 (s, 3H), 1.83 (s, 3H), 1.55 (s, 3H).

**$^{13}C$  NMR** (100 MHz,  $CDCl_3$ ):  $\delta$  = 162.8 (d,  $J_{CF}$  = 251.3 Hz), 142.1, 139.2, 138.7 (d,  $J_{CF}$  = 7.7 Hz), 138.4, 135.4, 131.9 (d,  $J_{CF}$  = 8.4 Hz), 129.0, 128.9, 128.6, 127.9, 127.7, 127.1, 127.0, 126.3, 123.1 (d,  $J_{CF}$  = 3.2 Hz), 118.7 (d,  $J_{CF}$  = 22.3 Hz), 116.8 (d,  $J_{CF}$  = 21.4 Hz), 106.5 (d,  $J_{CRh}$  = 6.4 Hz), 99.9 (d,  $J_{CRh}$  = 7.0 Hz), 96.0 (d,  $J_{CRh}$  = 9.2 Hz), 88.2 (d,  $J_{CRh}$  = 9.5 Hz), 81.1 (d,  $J_{CRh}$  = 8.5 Hz), 76.3, 69.9, 52.2, 21.3, 10.8, 10.6, 10.4, 8.3.

**HRMS** (ESI):  $m/z$   $[M-Cl]^+$  calcd for  $C_{37}H_{37}FN_2O_2RhS$ : 695.1609, found: 695.1616.

Catalyst (*R,R*)-**C87**

Chemical Formula:  $C_{38}H_{37}ClF_3N_2O_2RhS$   
Exact Mass: 780.1271

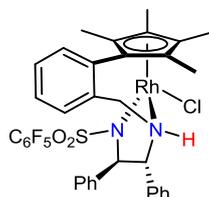
**Complex (*R,R*)-**C87**:** Following the general procedure described for (*R,R*)-**C84**, and starting from **3d** (656 mg, 2.23 mmol), compound (*R,R*)-**87** (310 mg, 18%, 2 steps) was obtained as an orange solid. mp 284 °C (decomposition).  $R_f$  0.56 ( $CH_2Cl_2/MeOH:9/1$ , UV,  $KMnO_4$ ).  $[\alpha]_D^{25} = -172$  ( $c$  0.14,  $CHCl_3$ ).

**IR** (neat): 2359, 2341, 1329, 1275, 1168, 1132, 1082, 938, 906, 896, 881, 870, 808, 791, 766, 756, 713, 699, 687, 679, 671, 659, 641, 622, 614, 605  $cm^{-1}$ .

**$^1H$  NMR** (400 MHz,  $CDCl_3$ ):  $\delta = 7.78$  (d,  $J = 8.0$  Hz, 1H), 7.63 (d,  $J = 8.0$  Hz, 1H), 7.25 (d,  $J = 8.2$  Hz, 2H), 7.23–7.09 (m, 4H), 6.73 (d,  $J = 8.0$  Hz, 2H), 6.76–6.66 (m, 3H), 6.65–6.54 (m, 2H), 6.47 (d,  $J = 7.6$  Hz, 2H), 5.04 (d,  $J = 12.7$  Hz, 1H), 4.35 (d,  $J = 10.9$  Hz, 1H), 4.26 (dd,  $J = 14.0, 3.3$  Hz, 1H), 3.73 (d,  $J = 14.1$  Hz, 1H), 3.19 (dd,  $J = 12.7, 10.9$  Hz, 1H), 2.17 (s, 3H), 2.10 (s, 3H), 1.98 (s, 3H), 1.83 (s, 3H), 1.56 (s, 3H).

**$^{13}C$  NMR** (100 MHz,  $CDCl_3$ ):  $\delta = 141.9, 139.2, 138.1, 137.0, 135.1, 131.8$  (q,  $J_{CF} = 33.2$  Hz), 131.5, 131.3, 130.7, 129.1, 128.9, 128.6, 128.6 (q,  $J_{CF} = 3.2$  Hz), 127.8, 127.6, 127.1, 126.5 (q,  $J_{CF} = 3.2$  Hz), 126.3, 123.3 (q,  $J_{CF} = 272.7$  Hz), 106.5 (d,  $J_{CRh} = 6.3$  Hz), 100.1 (d,  $J_{CRh} = 7.0$  Hz), 95.5 (d,  $J_{CRh} = 9.2$  Hz), 87.8 (d,  $J_{CRh} = 9.1$  Hz), 81.4 (d,  $J_{CRh} = 8.4$  Hz), 76.4, 69.5, 52.1, 21.2, 10.6, 10.5, 10.3, 8.2.

**HRMS** (ESI):  $m/z$   $[M-Cl]^+$  calcd for  $C_{38}H_{37}F_3N_2O_2RhS$ : 745.1577, found: 745.1585.

Catalyst (*R,R*)-**C90**

Chemical Formula: C<sub>36</sub>H<sub>31</sub>ClF<sub>5</sub>N<sub>2</sub>O<sub>2</sub>RhS  
Exact Mass: 788.0770

To a solution of compound **3e** (271 mg, 1.2 mmol) in dry MeOH (24 mL) was added (*R,R*)-C<sub>6</sub>F<sub>5</sub>SO<sub>2</sub>DPEN **L42** (442 mg, 1.0 mmol) followed by the addition of 500 mg of molecular sieves (4 Å) and 1 drops of glacial acetic acid. The mixture was stirred at rt for 20 h, then NaBH<sub>3</sub>CN (81.7 mg, 1.3 mmol) was added, and the reaction was stirred at rt for 18 h. After removal of the molecular sieves and evaporation of MeOH, the residue was dissolved in EtOAc (20 mL). The organic layer was washed with saturated NaHCO<sub>3</sub> and then brine, dried over MgSO<sub>4</sub>, filtered, and concentrated. Purification of the residue by flash chromatography (SiO<sub>2</sub>, pentane/EtOAc = 9/1 to 8/2) afforded the diamine (465 mg, 71%) as a white solid. To a solution of the diamine (440 mg, 0.674 mmol) in MeOH (15 mL) was added RhCl<sub>3</sub> · H<sub>2</sub>O (177 mg, 0.674 mmol), and the reaction mixture was heated under reflux using an oil bath for 22 h. Et<sub>3</sub>N (190 μL, 1.348 mmol) was then added, and the mixture was refluxed for a further 20 h and concentrated. The residue was triturated with H<sub>2</sub>O, and the solid was filtered, washed with H<sub>2</sub>O, and dried under vacuum. Purification of the black solid by flash chromatography (SiO<sub>2</sub>, EtOAc/Petrol ether = 1 : 1 – 2 : 1) afforded (*R,R*)-**C90** (311 mg, 58.5%) as an orange solid.  $[\alpha]_{25}^D = -41.4^\circ$  ( $c = 1.0$ , CHCl<sub>3</sub>).

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.57 – 7.35 (m, 4H), 7.23 – 7.14 (m, 3H), 6.94 – 6.70 (m, 7H), 5.00 (d,  $J = 12.3$  Hz, 1H), 4.45 (d,  $J = 11.0$  Hz, 1H), 4.22 (dd,  $J = 13.9, 2.8$  Hz, 1H), 3.72 (d,  $J = 14.1$  Hz, 1H), 3.39 – 3.31 (m, 1H), 2.01 (s, 3H), 1.96 (s, 3H), 1.89 (s, 3H), 1.48 (s, 3H).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 145.2 (m, br), 142.7 (m, br), 140.2 (m, br) 138.3, 138.1 (m, br), 135.7 (m, br), 135.5, 134.9, 131.7, 130.0, 129.9, 129.1, 128.0, 127.3, 127.1, 126.6, 121.3 (t,  $J_{CF} = 15.5$  Hz), 107.7 (d,  $J_{CRh} = 6.5$  Hz), 100.8 (d,  $J_{CRh} = 7.0$  Hz), 97.4 (d,  $J_{CRh} = 9.3$  Hz), 90.0 (d,  $J_{CRh} = 9.1$  Hz), 79.8 (d,  $J_{CRh} = 9.2$  Hz), 76.8, 75.5, 69.0, 52.1, 10.6, 10.4, 10.2, 8.1.

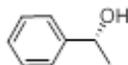
**<sup>19</sup>F NMR** (376 MHz, CDCl<sub>3</sub>) δ 135.9 (d,  $J = 22.5$  Hz), 154.0 (t,  $J = 21.0$  Hz), 163.7 (t,  $J = 19.5$  Hz).

**HRMS** (ESI):  $m/z$  [M+H]<sup>+</sup> calcd for C<sub>36</sub>H<sub>32</sub>ClF<sub>5</sub>N<sub>2</sub>O<sub>2</sub>RhS: 789.0848, found 789.1256.

**General procedure for the ATH of ketones with complexes (*R,R*)-C84-C87**

To a round-bottom tube containing complex (*R,R*)-C84-C87 (0.004 mmol, 0.5 mol%) was added at room temperature, an HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) azeotropic mixture (430 μL, 7.2 mmol) and 3 vacuum/argon cycles were used to insure an inert atmosphere. The orange mixture was stirred for 10–15 min before the ketone (0.8 mmol) was added. The reaction mixture was stirred at 24–30 °C until the starting material was consumed as determined by TLC, then the reaction mixture was purified by filtration through a pad of silica gel using pentane/EtOAc (8/2). The filtrate was concentrated under vacuum to give the reduced product. Enantiomeric excess was determined by SFC (Chiralpak OD-H and Chiralpak AD-H, AS-H, IA, IC or ID) or HPLC (Chiralpak IB, IC, ID column) analysis.

**(*R*)-1-phenylethanol (**5a**)**

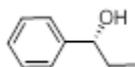


Pale yellow oil, 96 mg, 98% yield;  $[\alpha]_{\text{D}}^{20} +45.5$  ( $c$  1.0, CHCl<sub>3</sub>, 98% *ee*), lit. :<sup>168</sup>  $[\alpha]_{\text{D}}^{26} +45.4$  ( $c$  0.5, CHCl<sub>3</sub>, 98% *ee*);

**HPLC:** Daicel Chiralpak IB column (0.46 x 25 cm), hexane/*i*PrOH 95:5, 1.0 mL/min,  $\lambda = 215$  nm,  $t_{\text{R}}$ : 7.38 min (*R*), 8.04 min (*S*).

**MS** (DCI/NH<sub>3</sub>):  $m/z = 140$  [M+NH<sub>4</sub>]<sup>+</sup>.

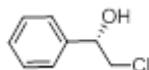
**(*R*)-1-Phenylpropan-1-ol (**5b**)**



Pale yellow oil, 98 mg, 90% yield;  $[\alpha]_{\text{D}}^{25} +45.0$  ( $c$  1.0, CHCl<sub>3</sub>, 98% *ee*), lit. :<sup>121</sup>  $[\alpha]_{\text{D}}^{20} +44.5$  ( $c$  1.0, CHCl<sub>3</sub>, 97% *ee*);

**SFC:** Daicel Chiralpak OD-H column (0.46 x 25 cm), *sc*CO<sub>2</sub>/MeOH 95:5, 4.0 mL/min, P = 150 bar,  $\lambda = 215$  nm,  $t_{\text{R}}$ : 2.07 min (*R*), 2.44 min (*S*).

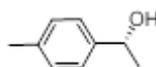
**MS** (DCI/NH<sub>3</sub>):  $m/z = 154$  [M+NH<sub>4</sub>]<sup>+</sup>.

**(S)-2-Chloro-1-phenylethan-1-ol (5c)**

Colorless oil, 119 mg, 95% yield;  $[\alpha]_{\text{D}}^{25} +56.0$  ( $c$  1.09,  $\text{CHCl}_3$ , 95% *ee*), lit. :<sup>281</sup>  $[\alpha]_{\text{D}}^{20} +57.8$  ( $c$  1.0,  $\text{CHCl}_3$ , 96.6% *ee*);

**SFC:** Daicel Chiralpak OD-H column (0.46 x 25 cm), *sc*CO<sub>2</sub>/MeOH 95:5, 4.0 mL/min, P = 150 bar,  $\lambda$  = 215 nm,  $t_{\text{R}}$ : 2.52 min (*S*), 3.38 min (*R*).

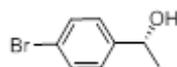
**MS** (DCI/NH<sub>3</sub>):  $m/z$  = 174 [M+NH<sub>4</sub>]<sup>+</sup>.

**(R)-1-(*p*-Tolyl)ethan-1-ol (5d)**

Pale yellow oil, 109 mg, 100% yield;  $[\alpha]_{\text{D}}^{25} +53.0$  ( $c$  0.94,  $\text{CHCl}_3$ , 98% *ee*), lit. :<sup>282</sup>  $[\alpha]_{\text{D}}^{20} +55.4$  ( $c$  1.01,  $\text{CHCl}_3$ , 98.7% *ee*);

**HPLC:** Daicel Chiralpak ID column (0.46 x 25 cm), hexane/*i*PrOH 97:3, 0.5 mL/min,  $\lambda$  = 215 nm,  $t_{\text{R}}$ : 18.77 min (*R*), 19.97 min (*S*).

**MS** (DCI/NH<sub>3</sub>):  $m/z$  = 119 [M+H-H<sub>2</sub>O]<sup>+</sup>.

**(R)-1-(4-Bromophenyl)ethan-1-ol (5e)**

Colorless oil, 159 mg, 99% yield;  $[\alpha]_{\text{D}}^{25} +35.0$  ( $c$  1.17,  $\text{CHCl}_3$ , 96% *ee*), lit. :<sup>283</sup>  $[\alpha]_{\text{D}}^{22} +34.8$  ( $c$  1.03,  $\text{CHCl}_3$ , 97% *ee*);

**HPLC:** Daicel Chiralpak IB column (0.46 x 25 cm), hexane/*i*PrOH 95:5, 0.5 mL/min,  $\lambda$  = 215 nm,  $t_{\text{R}}$ : 15.09 min (*S*), 15.83 min (*R*).

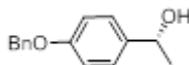
**MS** (DCI/NH<sub>3</sub>):  $m/z$  = 202 [M+NH<sub>4</sub>-H<sub>2</sub>O]<sup>+</sup>.

<sup>281</sup> Rowan, A. S.; Moody, T. S.; Howard, R. M.; Underwood, T. J.; Miskelly, I. R.; He, Y.; Wang, B. *Tetrahedron: Asymmetry* **2013**, *24*, 1369.

<sup>282</sup> Guo, J.; Chen, J.; Lu, Z. *Chem. Commun.* **2015**, *51*, 5725.

<sup>283</sup> Krane Thvedt, T. H.; Kristensen, T. E.; Sundby, E.; Hansen, T.; Hoff, B. H. *Tetrahedron: Asymmetry* **2011**, *22*, 2172.

(*R*)-1-(4-(Benzyloxy)phenyl)ethan-1-ol (**5f**)

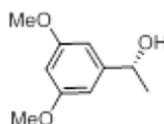


White solid, 182 mg, 100% yield;;  $[\alpha]_{\text{D}}^{25} +33.0$  (*c* 1.09, CHCl<sub>3</sub>, 99% *ee*), lit.<sup>284</sup> :  $[\alpha]_{\text{D}}^{25} -31.8$  (*c* 1.2, CHCl<sub>3</sub>, >99% *ee*, (*S*)-isomer);

**SFC**: Daicel Chiralpak OD-H column (0.46 x 25 cm), *sc*CO<sub>2</sub>/MeOH 98:2, 2.0 mL/min, P = 150 bar,  $\lambda = 215$  nm, *t<sub>R</sub>*: 39.24 min (*S*), 42.59 min (*R*).

**MS** (DCI/NH<sub>3</sub>): *m/z* = 211 [M+H–H<sub>2</sub>O]<sup>+</sup>.

(*R*)-1-(3,5-Dimethoxyphenyl)ethan-1-ol (**5g**)

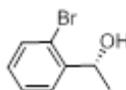


Colorless oil, 144 mg, 99% yield;  $[\alpha]_{\text{D}}^{25} +31.0$  (*c* 0.95, CHCl<sub>3</sub>, 96% *ee*), lit.<sup>285</sup>  $[\alpha]_{\text{D}}^{20} -32.7$  (*c* 2.0, CHCl<sub>3</sub>, 97% *ee*, (*S*)-isomer);

**SFC**: Daicel Chiralpak OD-H column (0.46 x 25 cm), *sc*CO<sub>2</sub>/MeOH 95:5, 4.0 mL/min, P = 150 bar,  $\lambda = 215$  nm, *t<sub>R</sub>*: 3.11 min (*R*), 3.49 min (*S*).

**MS** (DCI/NH<sub>3</sub>): *m/z* = 183 [M+H]<sup>+</sup>.

(*R*)-1-(2-Bromophenyl)ethan-1-ol (**5h**)



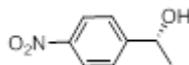
Colorless oil, 142 mg, 88% yield;  $[\alpha]_{\text{D}}^{25} +40.0$  (*c* 0.99, CHCl<sub>3</sub>, 64% *ee*), lit.<sup>281</sup>  $[\alpha]_{\text{D}}^{24} +32.7$  (*c* 0.8, CHCl<sub>3</sub>, 64% *ee*);

**SFC**: Daicel Chiralpak ID column (0.46 x 25 cm), *sc*CO<sub>2</sub>/MeOH 90:10, 4.0 mL/min, P = 150 bar,  $\lambda = 215$  nm, *t<sub>R</sub>*: 1.27 min (*R*), 1.50 min (*S*).

**MS** (DCI/NH<sub>3</sub>): *m/z* = 218 [M+NH<sub>4</sub>]<sup>+</sup>.

<sup>284</sup> Kamal, A.; Sandbhor, M.; Ramana, K. V. *Tetrahedron: Asymmetry* **2002**, *13*, 815.

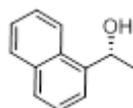
<sup>285</sup> Wettergren, J.; Bøgevig, A.; Portier, M.; Adolffsson, H. *Adv. Synth. Catal.* **2006**, *348*, 1277.

**(R)-1-(4-Nitrophenyl)ethan-1-ol (5i)**

Yellow oil, 132 mg, 99% yield;  $[\alpha]_{\text{D}}^{22} +34.9$  ( $c$  1.0,  $\text{CHCl}_3$ , 88%  $ee$ ); lit. :<sup>286</sup>  $[\alpha]_{\text{D}}^{23} +33.7$  ( $c$  1.0,  $\text{CHCl}_3$ , 85%  $ee$ );

**SFC:** Daicel Chiralpak AS-H column (0.46 x 25 cm),  $sc\text{CO}_2/\text{MeOH}$  95/5, 2.0 mL/min,  $P = 100$  bar,  $\lambda = 215$  nm,  $t_{\text{R}}$ : 6.30 min ( $R$ ), 7.33 min ( $S$ ).

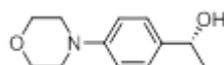
**MS** (DCI/ $\text{NH}_3$ ):  $m/z = 185$   $[\text{M}+\text{NH}_4]^+$ .

**(R)-1-(Naphthalen-1-yl)ethan-1-ol (5j)**

Colorless oil, 135 mg, 98% yield;  $[\alpha]_{\text{D}}^{20} +46.6$  ( $c$  1.0,  $\text{CHCl}_3$ , 85%  $ee$ ), lit. :<sup>287</sup>  $[\alpha]_{\text{D}}^{22} +55.1$  ( $c$  1.0,  $\text{CHCl}_3$ , 92%  $ee$ );

**SFC:** Daicel Chiralpak OD-H column (0.46 x 25 cm),  $sc\text{CO}_2/\text{MeOH}$  95:5, 4.0 mL/min,  $P = 150$  bar,  $\lambda = 215$  nm,  $t_{\text{R}}$ : 7.65 min ( $S$ ), 11.48 min ( $R$ ).

**MS** (DCI/ $\text{NH}_3$ ):  $m/z = 155$   $[\text{M}+\text{H}-\text{H}_2\text{O}]^+$ .

**(R)-1-(4-Morpholinophenyl)ethan-1-ol (5k)**

White solid, 164 mg, 99% yield;  $[\alpha]_{\text{D}}^{22} + 43.9$  ( $c$  1.16,  $\text{CHCl}_3$ , 99%  $ee$ ); lit. :<sup>288</sup>  $[\alpha]_{\text{D}}^{25} + 45.9$  ( $c$  1.0,  $\text{CHCl}_3$ , 93%  $ee$ );

**HPLC:** Daicel Chiralpak IC column (0.46 x 25 cm), hexane/ $i$ PrOH 90:10, 1.0 mL/min,  $\lambda = 215$  nm,  $t_{\text{R}}$ : 24.81 min ( $S$ ), 31.01 min ( $R$ ).

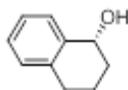
**MS** (DCI/ $\text{NH}_3$ ):  $m/z = 208$   $[\text{M}+\text{H}]^+$ .

<sup>286</sup> Li, J.; Li, X.; Ma, Y.; Wu, J.; Wang, F.; Xiang, J.; Zhu, J.; Wang, Q.; Deng, J. *RSC Adv.* **2013**, *3*, 1825.

<sup>287</sup> Cheng, Y.-N.; Wu, H.-L.; Wu, P.-Y.; Shen, Y.-Y.; Uang, B.-J. *Chem. Asian J.* **2012**, *7*, 2921.

<sup>288</sup> Inagaki, T.; Phong, L. T.; Furuta, A.; Ito, J.; Nishiyama, H. *Chem. Eur. J.* **2010**, *16*, 3090.

(*R*)-1,2,3,4-Tetrahydro-1-naphthol (**5l**)

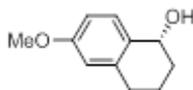


Colorless oil, 141 mg, 100% yield;  $[\alpha]_{\text{D}}^{25} -30.0$  ( $c$  0.94,  $\text{CHCl}_3$ , 99% *ee*), lit. :<sup>294</sup>  $[\alpha]_{\text{D}}^{30} -30.7$  ( $c$  1.02,  $\text{CHCl}_3$ , 99.2 % *ee*);

**SFC:** Daicel Chiralpak OD-H column (0.46 x 25 cm),  $sc\text{CO}_2/\text{MeOH}$  95:5, 3.0 mL/min,  $P = 150$  bar,  $\lambda = 215$  nm,  $t_{\text{R}}$ : 3.80 (*S*), 4.20 min (*R*).

**MS** (DCI/ $\text{NH}_3$ ):  $m/z = 131$   $[\text{M}+\text{H}-\text{H}_2\text{O}]^+$ .

(*R*)-6-Methoxy-1,2,3,4-tetrahydro-1-naphthol (**5m**)

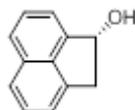


Colorless oil, 165 mg, 100% yield;  $[\alpha]_{\text{D}}^{25} -22.0$  ( $c$  0.92,  $\text{CHCl}_3$ , >99% *ee*), lit. :<sup>289</sup>  $[\alpha]_{\text{D}}^{21} -17.2$  ( $c$  1.19,  $\text{CHCl}_3$ , 92% *ee*);

**SFC:** Daicel Chiralpak AD-H column (0.46 x 25 cm),  $sc\text{CO}_2/\text{MeOH}$  90:10, 3.0 mL/min,  $P = 150$  bar,  $\lambda = 215$  nm,  $t_{\text{R}}$ : 5.37 min (*S*), 6.23 min (*R*).

**MS** (DCI/ $\text{NH}_3$ ):  $m/z = 161$   $[\text{M}+\text{H}-\text{H}_2\text{O}]^+$ .

(*R*)-1,2-Dihydroacenaphthylen-1-ol (**5n**)



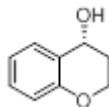
White solid, 129 mg, 95% yield;  $[\alpha]_{\text{D}}^{25} -1.4$  ( $c$  0.92,  $\text{CHCl}_3$ , 98% *ee*), lit. :<sup>290</sup>  $[\alpha]_{\text{D}}^{20} -1.4$  ( $c$  0.5,  $\text{CHCl}_3$ , 98.2% *ee*);

**SFC:** Daicel Chiralpak OD-H column (0.46 x 25 cm),  $sc\text{CO}_2/i\text{PrOH}$  93:7, 4.0 mL/min,  $P = 150$  bar,  $\lambda = 215$  nm,  $t_{\text{R}}$ : 8.17 min (*S*), 8.99 min (*R*).

**MS** (DCI/ $\text{NH}_3$ ):  $m/z = 153$   $[\text{M}+\text{H}-\text{H}_2\text{O}]^+$ .

<sup>289</sup> Ohkuma, T.; Hattori, T.; Ooka, H.; Inoue, T.; Noyori, R. *Org. Lett.* **2004**, *6*, 2681.

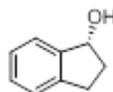
<sup>290</sup> Merabet-Khelassi, M.; Houiene, Z.; Aribi-Zouioueche, L.; Riant, O. *Tetrahedron: Asymmetry* **2012**, *23*, 828.

**(R)-Chroman-4-ol (5o)**

White solid, 120 mg, 100% yield;  $[\alpha]_{\text{D}}^{25} +68.0$  ( $c$  0.93,  $\text{CHCl}_3$ , >99%  $ee$ ), lit.  $^{281} [\alpha]_{\text{D}}^{20} +66.9$  ( $c$  1.0,  $\text{CHCl}_3$ , 99.1%  $ee$ );

**SFC:** Daicel Chiralpak AD-H column (0.46 x 25 cm),  $sc\text{CO}_2/\text{MeOH}$  97:3, 3.0 mL/min,  $P = 150$  bar,  $\lambda = 215$  nm,  $t_{\text{R}}$ : 10.59 min ( $S$ ), 11.25 min ( $R$ ).

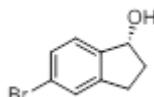
**MS** (DCI/ $\text{NH}_3$ ):  $m/z = 133$   $[\text{M}+\text{H}-\text{H}_2\text{O}]^+$ .

**(R)-2,3-Dihydro-1H-inden-1-ol (5p)**

White solid, 107 mg, 100% yield;  $[\alpha]_{\text{D}}^{25} -33.0$  ( $c$  0.85,  $\text{CHCl}_3$ , >99%  $ee$ ), lit.  $^{291} [\alpha]_{\text{D}}^{22} = +29.3$  ( $c = 0.967$ ,  $\text{CHCl}_3$ , > 99%  $ee$ );

**HPLC:** Daicel Chiralpak IB column (0.46 x 25 cm), hexane/ $i$ PrOH 98:2, 1.0 mL/min,  $\lambda = 215$  nm,  $t_{\text{R}}$ : 14.86 ( $S$ ), 16.43 min ( $R$ ).

**MS** (DCI/ $\text{NH}_3$ ):  $m/z = 117$   $[\text{M}+\text{H}-\text{H}_2\text{O}]^+$ .

**(R)-5-Bromo-2,3-dihydro-1H-inden-1-ol (5q)**

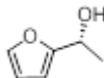
White solid, 170 mg, 100% yield;  $[\alpha]_{\text{D}}^{25} -16.0$  ( $c$  0.92,  $\text{CHCl}_3$ , >99%  $ee$ ), lit.  $^{86a} [\alpha]_{\text{D}}^{25} +15.8$  ( $c$  1.0,  $\text{CHCl}_3$ , 98.1%  $ee$ , ( $S$ )-isomer);

**SFC:** Daicel Chiralpak AD-H column (0.46 x 25 cm),  $sc\text{CO}_2/\text{MeOH}$  90:10, 3.0 mL/min,  $P = 150$  bar,  $\lambda = 215$  nm,  $t_{\text{R}}$ : 5.92 ( $S$ ), 8.21 min ( $R$ ).

**MS** (DCI/ $\text{NH}_3$ ):  $m/z = 195$   $[\text{M}+\text{H}-\text{H}_2\text{O}]^+$ .

<sup>291</sup> Brown, M. K.; Blewett, M. M.; Colombe, J. R.; Corey, E. J. *J. Am. Chem. Soc.* **2010**, *132*, 11165.

(*R*)-1-(2-Furyl)ethanol (**7a**)

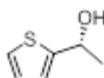


Colorless oil, 89 mg, 99% yield;  $[\alpha]_{\text{D}}^{25} +20.0$  ( $c$  0.79,  $\text{CHCl}_3$ , >99% *ee*), lit. :<sup>292</sup>  $[\alpha]_{\text{D}}^{25} +20.7$  ( $c$  1.0,  $\text{CHCl}_3$ , 99% *ee*);

**HPLC**: Daicel Chiralpak IC column (0.46 x 25 cm), hexane/*i*PrOH 95:5, 1.0 mL/min,  $\lambda = 215$  nm,  $t_{\text{R}}$ : 9.17 min (*S*), 9.90 min (*R*).

**MS** (DCI/ $\text{NH}_3$ ):  $m/z = 95$   $[\text{M}+\text{H}-\text{H}_2\text{O}]^+$ .

(*R*)-1-(2-Thienyl)ethanol (**7b**)

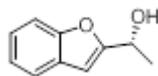


Colorless oil, 102 mg, 100% yield;  $[\alpha]_{\text{D}}^{25} +23.0$  ( $c$  0.91,  $\text{CHCl}_3$ , 99% *ee*), lit. :<sup>128</sup>  $[\alpha]_{\text{D}}^{20} +21.6$  ( $c$  1.0,  $\text{CHCl}_3$ , 98% *ee*);

**SFC**: Daicel Chiralpak ID column (0.46 x 25 cm), *sc* $\text{CO}_2$ /MeOH 93:7, 3.0 mL/min,  $P = 150$  bar,  $\lambda = 215$  nm,  $t_{\text{R}}$ : 2.07 min (*R*), 2.35 min (*S*).

**MS** (DCI/ $\text{NH}_3$ ):  $m/z = 111$   $[\text{M}+\text{H}-\text{H}_2\text{O}]^+$ .

(*R*)-1-(Benzofuran-2-yl)ethanol (**7c**)



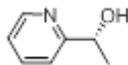
White solid, 129 mg, 100% yield;  $[\alpha]_{\text{D}}^{25} +18.0$  ( $c = 0.88$ ,  $\text{CHCl}_3$ , 97% *ee*), lit. :<sup>293</sup>  $[\alpha]_{\text{D}}^{23} +18$  ( $c$  3.0,  $\text{CHCl}_3$ , 96% *ee*);

**HPLC**: Daicel Chiralpak ID column (0.46 x 25 cm), hexane/*i*PrOH 95:5, 1.0 mL/min,  $\lambda = 215$  nm,  $t_{\text{R}}$ : 9.48 min (*R*), 10.11 min (*S*).

**MS** (DCI/ $\text{NH}_3$ ):  $m/z = 145$   $[\text{M}+\text{H}-\text{H}_2\text{O}]^+$ .

<sup>292</sup> Hara, P.; Turcu, M.-C.; Sundell, R.; Toşa, M.; Paizs, C.; Irimie, F.-D.; Kanerva, L. T. *Tetrahedron: Asymmetry* **2013**, *24*, 142.

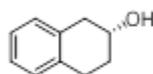
<sup>293</sup> Stepanenko, V.; De Jesús, M.; Correa, W.; Bermúdez, L.; Vázquez, C.; Guzmán, I.; Ortiz-Marciales, M. *Tetrahedron: Asymmetry* **2009**, *20*, 2659.

**(R)-1-(2-Pyridyl)ethanol (7d)**

Pale yellow oil, 98 mg, 100% yield;  $[\alpha]_{\text{D}}^{25} +21.0$  (*c* 0.99,  $\text{CHCl}_3$ , 96 % *ee*), lit. :<sup>294</sup>  $[\alpha]_{\text{D}}^{20} +26.6$  (*c* 1.0,  $\text{CHCl}_3$ , 97.3% *ee*);

**HPLC:** Daicel Chiralpak ID column (0.46 x 25 cm), hexane/*i*PrOH 95:5, 1.0 mL/min,  $\lambda = 215$  nm,  $t_{\text{R}}$ : 15.23 min (*S*), 17.10 min (*R*).

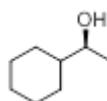
**MS** (DCI/ $\text{NH}_3$ ):  $m/z = 124$   $[\text{M}+\text{H}]^+$ .

**(R)-1,2,3,4-Tetrahydro-2-naphthol (7e)**

Pale yellow oil, 119 mg, 100% yield;  $[\alpha]_{\text{D}}^{25} +53.0$  (*c* 0.88,  $\text{CHCl}_3$ , 81% *ee*), lit. :<sup>295</sup>  $[\alpha]_{\text{D}}^{23} = +52.7$  (*c* 0.37,  $\text{CHCl}_3$ , 88% *ee*);

**SFC:** Daicel Chiralpak AD-H column (0.46 x 25 cm), *sc* $\text{CO}_2$ /*i*PrOH 90:10, 3.0 mL/min, *P* = 150 bar,  $\lambda = 215$  nm,  $t_{\text{R}}$ : 4.76 min (*S*), 5.19 min (*R*).

**MS** (DCI/ $\text{NH}_3$ ):  $m/z = 166$   $[\text{M}+\text{NH}_4]^+$ .

**(S)-1-Cyclohexylethanol (7f)**

Colorless oil, 80 mg, 100% yield;  $[\alpha]_{\text{D}}^{25} +2.1$  (*c* 3.5,  $\text{CHCl}_3$ , 94% *ee*), lit. :<sup>296</sup>  $[\alpha]_{\text{D}}^3 +3.51$  (*c* 3.1,  $\text{CHCl}_3$ , 95% *ee*);

**HPLC:** (determined on the benzoate derivative), Daicel Chiralpak ID column (0.46 x 25 cm), hexane/*i*PrOH 97:3, 0.5 mL/min,  $\lambda = 215$  nm,  $t_{\text{R}}$ : 8.87 min (*S*), 9.37 min (*R*).

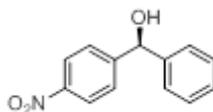
**MS** (DCI/ $\text{NH}_3$ ):  $m/z = 146$   $[\text{M}+\text{NH}_4]^+$ .

<sup>294</sup> Bigler, R.; Mezzetti, A. *Org. Process Res. Dev.* **2016**, *20*, 253.

<sup>295</sup> Soni, R.; Collinson, J.-M.; Clarkson, G. C.; Wills, M. *Org. Lett.* **2011**, *13*, 4304.

<sup>296</sup> Li, G.; W. Kabalka, G. *J. Organomet. Chem.* **1999**, *581*, 66.

(*S*)-(4-Nitrophenyl)(phenyl)methanol (**9a**)

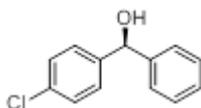


White solid, 169 mg, 92% yield;  $[\alpha]_{\text{D}}^{22} + 70.0$  ( $c$  1.0,  $\text{CHCl}_3$ , 83%  $ee$ ); lit. :<sup>297</sup>  $[\alpha]_{\text{D}}^{22} + 71.0$  ( $c$  0.27,  $\text{CHCl}_3$ , 92%  $ee$ );

**HPLC**: Daicel Chiralpak IA column (0.46 x 25 cm), hexane/<sup>*i*</sup>PrOH 90:10, 1.0 mL/min,  $\lambda = 254$  nm,  $t_{\text{R}}$ : 12.17 min (*R*), 14.49 min (*S*).

**MS** (DCI/ $\text{NH}_3$ ):  $m/z = 247$   $[\text{M}+\text{NH}_4]^+$ .

(*S*)-(4-Chlorophenyl)(phenyl)methanol (**9b**)

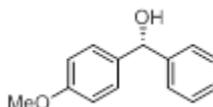


White solid, 173 mg, 99% yield;  $[\alpha]_{\text{D}}^{22} + 10.9$  ( $c$  2.0,  $\text{CHCl}_3$ , 50%  $ee$ ); lit. :<sup>297</sup>  $[\alpha]_{\text{D}}^{20} + 8.0$  ( $c$  1.51,  $\text{CHCl}_3$ , 48%  $ee$ );

**HPLC**: Daicel Chiralpak IA column (0.46 x 25 cm), hexane/<sup>*i*</sup>PrOH 95:5, 1.0 mL/min,  $\lambda = 254$  nm,  $t_{\text{R}}$ : 12.92 min (*R*), 14.01 min (*S*).

**MS** (DCI/ $\text{NH}_3$ ):  $m/z = 201$   $[\text{M}+\text{H}-\text{H}_2\text{O}]^+$ .

(*R*)-(4-Methoxyphenyl)(phenyl)methanol (**9c**)

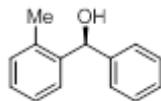


White solid, 123 mg, 72% yield;  $[\alpha]_{\text{D}}^{22} + 2.1$  ( $c$  1.65,  $\text{CHCl}_3$ , 9%  $ee$ ); lit. :<sup>297</sup>  $[\alpha]_{\text{D}}^{20} + 1.5$  ( $c$  1.08,  $\text{CHCl}_3$ , 5%  $ee$ );

**HPLC**: Daicel Chiralpak IA column (0.46 x 25 cm), hexane/<sup>*i*</sup>PrOH 90:10, 0.8 mL/min,  $\lambda = 254$  nm,  $t_{\text{R}}$ : 13.37 min (*R*), 14.37 min (*S*).

**MS** (DCI/ $\text{NH}_3$ ):  $m/z = 197$   $[\text{M}+\text{H}-\text{H}_2\text{O}]^+$ .

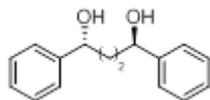
<sup>297</sup> Yamamoto, Y.; Kurihara, K.; Miyaura, N. *Angew. Chem. Int. Ed.* **2009**, *48*, 4414.

**(R)-(4-Methoxyphenyl)(phenyl)methanol (9d)**

White solid, 103 mg, 65% yield;  $[\alpha]_{\text{D}}^{22} +8.2$  (*c* 2.0,  $\text{CHCl}_3$ , 99% *ee*); lit.  $^{111} [\alpha]_{\text{D}}^{20} +7.3$  (*c* 0.735,  $\text{CHCl}_3$ , 98% *ee*);

**HPLC:** Daicel Chiralpak IC column (0.46 x 25 cm), hexane/ *i*PrOH = 98:2, 0.6 mL/min,  $\lambda = 254$  nm,  $t_{\text{R}}$ : 28.8 min (*S*), 32.6 min (*R*).

**MS** (DCI/ $\text{NH}_3$ ):  $m/z = 181$   $[\text{M}+\text{H}-\text{H}_2\text{O}]^+$ .

**(1*R*,4*R*)-1,4-Diphenylbutan-1,4-diol (11)**

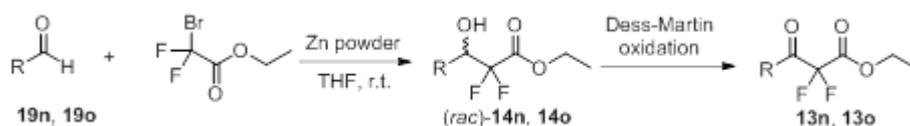
White solid, 186 mg, 96% yield;  $[\alpha]_{\text{D}}^{25} +51.0$  (*c* 1.1,  $\text{CHCl}_3$ , >99% *ee*), lit.  $^{298} [\alpha]_{\text{D}}^{25} +58$  (*c* 1.02,  $\text{CHCl}_3$ , 99% *ee*);

**SFC:** Daicel Chiralcel OD-H column (0.46 x 25 cm), *sc* $\text{CO}_2$ /MeOH 95:5, 4 mL/min, *P* = 150 bar,  $\lambda = 215$  nm,  $t_{\text{R}}$ : 22.13 min (*R,R*), 25.69 min (*meso*), 28.08 min (*S,S*).

**MS** (DCI/ $\text{NH}_3$ ):  $m/z = 242$   $[\text{M}+\text{H}-\text{H}_2\text{O}]^+$ .

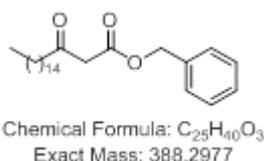
<sup>298</sup> Aldous, D. J.; Dutton, W. M.; Steel, P. G. *A Tetrahedron: Asymmetry* **2000**, *11*, 2455.



**General procedure E:**

**Step1:** To a solution of aldehyde (1.0 eq) and ethyl bromodifluoroacetate (1.5 eq) in THF was added zinc powder (1.5 eq) at room temperature in small portions. The reaction was monitored by TLC. After completion, the reaction was quenched with satd.  $\text{NH}_4\text{Cl}$  and filtered through a short pad of celite. The filtrate was concentrated to remove THF. The resulting mixture was extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 30 mL), the combined organic layers were washed with brine, dried ( $\text{MgSO}_4$ ), filtered and concentrated under reduced pressure. Purification of the residue by flash column chromatography afforded the alcohol.

**Step 2:** To the purified alcohol (1.0 eq) in  $\text{CH}_2\text{Cl}_2$ , was added Dess-Martin periodinane (1.2 eq) at 0 °C. After completion of the reaction monitored by TLC (0.5 ~1 h), the mixture was quenched with satd.  $\text{NaHCO}_3$  and extracted with  $\text{CH}_2\text{Cl}_2$ . The combined organic layers were washed with brine, dried ( $\text{MgSO}_4$ ), filtered and concentrated under reduced pressure. Purification of the residue by flash column chromatography afforded the pure keto ester.

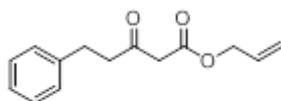
**Benzyl 3-oxoheptadecanoate (12b)**


Meldrum's acid (1.95 g, 13.5 mmol) was dissolved in THF (30 mL) at 0 °C in a dried 500 mL round bottom flask. Dry pyridine (2.97 mL, 36.8 mmol) was added drop-wise to the reaction mixture, and the reaction was allowed to stir for 1.5 h at 0 °C. Hexadecanoyl chloride (3.73 mL, 12.3 mmol) was then added to the reaction mixture dropwise over a 20 min period, and the reaction was allowed to stir for 1 h at 0 °C. The reaction mixture was then allowed to warm to room temperature for 1 h and concentrated. The red syrup was redissolved in benzyl alcohol (3.8 mL, 36.8 mmol) and 30 mL toluene, and the solution was refluxed for 3 h, allowed to cool to room temperature, and concentrated. The crude, red oil was purified via flash chromatography (ethyl acetate/hexane, 1/4) to yield **12b** as a pale yellow oil (1.6 g, 35% yield).

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.36 (d,  $J$  = 3.4 Hz, 5H), 5.17 (s, 2H), 3.48 (s, 2H), 2.50 (t,  $J$  = 7.4 Hz, 2H), 1.58 – 1.54 (m, 2H), 1.25 (d,  $J$  = 3.4 Hz, 24H), 0.88 (t,  $J$  = 6.8 Hz, 3H).

**$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$  202.9, 167.2, 135.5, 128.7 (2C), 128.5 (2C), 128.4, 67.2, 49.4, 43.2, 32.1, 29.8 (8C), 29.4, 29.1, 23.6, 22.8, 14.3.

Allyl 3-oxo-5-phenylpentanoate (**12f**)



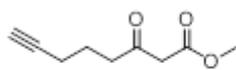
Chemical Formula: C<sub>14</sub>H<sub>16</sub>O<sub>3</sub>  
Exact Mass: 232.1099

Following the procedure of benzyl 3-oxoheptadecanoate, product **12f** was obtained as a pale yellow oil (1.4g, 49% yield).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.31 – 7.26 (m, 2H), 7.22 – 7.17 (m, 3H), 5.90 (ddt, *J* = 16.3, 10.5, 5.8 Hz, 1H), 5.36 – 5.24 (m, 2H), 4.62 (dt, *J* = 5.9, 1.2 Hz, 2H), 3.46 (s, 2H), 2.96 – 2.85 (m, 4H).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 201.7, 166.8, 140.6, 131.6, 128.6 (2C), 128.4 (2C), 126.3, 119.0, 66.1, 49.4, 44.6, 29.5.

Methyl 3-oxooct-7-ynoate (**12j**)

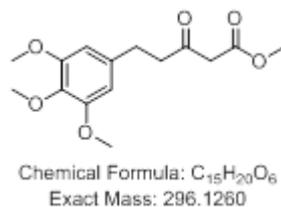


Chemical Formula: C<sub>9</sub>H<sub>12</sub>O<sub>3</sub>  
Exact Mass: 168.0786

To a solution of 5-hexenoic acid (1.68 g, 15 mmol) in THF (40 mL) was added CDI (2.92 g, 18 mmol) at room temperature and the mixture was stirred under Ar for 1 hour. Then mono-methyl malonate potassium salt (3.5 g, 22.5 mmol) and MgCl<sub>2</sub> (1.71 g, 18 mmol) were added to the above solution. The resulting mixture was stirred at room temperature overnight. It was then quenched with aqueous HCl (1.0 N) and was extracted with EtOAc (3 x 20 mL). The combined organic phases were washed with brine, and dried (MgSO<sub>4</sub>). Solvent was removed under reduced pressure and the residue was purified by flash chromatography to give desired product **12j** (2.02 g, 80% yield).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.77 (s, 3H), 3.50 (s, 2H), 2.73 (t, *J* = 7.1 Hz, 1H), 2.27 (td, *J* = 6.8, 2.6 Hz, 2H), 1.99 (t, *J* = 2.6 Hz, 2H), 1.85 (m, 2H).

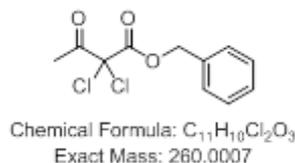
<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 202.2, 167.7, 83.4, 69.4, 52.5, 49.3, 41.5, 22.0, 17.7.

Methyl 3-oxo-5-(3,4,5-trimethoxyphenyl)pentanoate (**12k**)

Following the above procedure, 3-(3,4,5-trimethoxyphenyl)propanoic acid (2.4 g, 10 mmol), THF (30 mL), CDI (1.95 g, 12 mmol), mono-methyl malonate potassium salt (2.34 g, 15 mmol), MgCl<sub>2</sub> (1.14 g, 12 mmol) were used to provide product **12k** (2.42 g, 82% yield).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 6.39 (s, 2H), 3.84 (s, 6H), 3.81 (s, 3H), 3.72 (s, 3H), 3.45 (s, 2H), 2.90 – 2.80 (m, 4H).

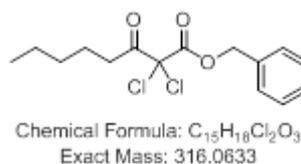
<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 201.9, 167.6, 153.4 (2C), 136.5, 136.4, 105.3 (2C), 61.0, 56.2, 52.6 (2C), 49.4, 44.8, 30.0.

Benzyl 2,2-dichloro-3-oxobutanoate (**13a**)

Synthesized according to general procedure C: **13a** (4.4 g, 98% yield), colorless oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.39 – 7.36 (m, 5H), 5.32 (s, 2H), 2.44 (s, 3H).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 191.3, 163.3, 134.0, 129.1, 128.9 (2C), 128.5 (2C), 82.0, 70.1, 23.5.

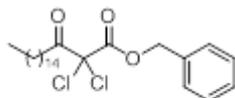
Benzyl 2,2-dichloro-3-oxooctanoate (**13b**)

Synthesized according to general procedure D: **13b** (340 mg, 45% yield, two steps), colorless oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.40 – 7.34 (m, 5H), 5.31 (s, 2H), 2.73 (t, *J* = 7.3 Hz, 2H), 1.62 (quint, *J* = 7.4 Hz, 2H), 1.34 – 1.17 (m, 4H), 0.87 (t, *J* = 7.0 Hz, 3H).

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  194.1, 163.5, 134.1, 129.1, 128.8 (2C), 128.6 (2C), 82.1, 70.0, 35.9, 31.0, 24.0, 22.4, 14.0.

Benzyl 2,2-dichloro-3-oxoheptadecanoate (**13c**)



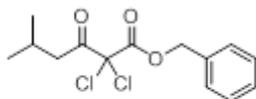
Chemical Formula:  $\text{C}_{25}\text{H}_{38}\text{Cl}_2\text{O}_3$   
Exact Mass: 456.2198

Synthesized according to general procedure C: **13c** (1.02 g, 85% yield), colorless oil.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.40 – 7.35 (m, 5H), 5.31 (s, 2H), 2.73 (t,  $J = 7.3$  Hz, 2H), 1.63 – 1.60 (m, 2H), 1.26 – 1.24 (m, 24H), 0.88 (t,  $J = 6.8$  Hz, 3H).

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  194.2, 163.5, 134.1, 129.1, 128.9 (2C), 128.6 (2C), 82.1, 70.0, 36.0, 32.1, 29.8 (5C), 29.7, 29.55, 29.52, 29.4, 28.9, 24.3, 22.8, 14.3.

Benzyl 2,2-dichloro-5-methyl-3-oxohexanoate (**13d**)



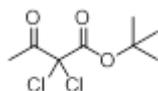
Chemical Formula:  $\text{C}_{14}\text{H}_{18}\text{Cl}_2\text{O}_3$   
Exact Mass: 302.0476

Synthesized according to general procedure D: **13d** (496 mg, 51% yield, two steps), colorless oil.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.38 – 7.35 (s, 5H), 5.32 (s, 2H), 2.62 (d,  $J = 6.8$  Hz, 2H), 2.19 (hept,  $J = 6.7$  Hz, 1H), 0.91 (d,  $J = 6.7$  Hz, 6H).

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  193.3, 163.5, 134.1, 129.1, 128.8 (2C), 128.6 (2C), 82.2, 70.0, 44.4, 24.7, 22.2 (2C).

*tert*-Butyl 2,2-dichloro-3-oxobutanoate (**13e**)



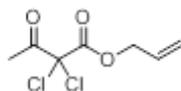
Chemical Formula:  $\text{C}_9\text{H}_{12}\text{Cl}_2\text{O}_3$   
Exact Mass: 226.0163

Synthesized according to general procedure C: **13e** (2.0 g, 88% yield), colorless oil.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.46 (s, 3H), 1.53 (s, 9H).

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  191.5, 162.0, 86.5, 82.9, 27.6 (3C), 23.8.

Allyl 2,2-dichloro-3-oxobutanoate (**13f**)



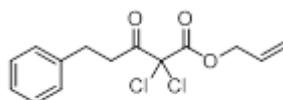
Chemical Formula:  $\text{C}_7\text{H}_8\text{Cl}_2\text{O}_3$   
Exact Mass: 209.9850

Synthesized according to general procedure C: **13f** (1.58 g, 75% yield), colorless oil.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  5.93 (ddt,  $J = 16.4, 10.6, 5.8$  Hz, 1H), 5.45 – 5.39 (m, 1H), 5.36 – 5.32 (m, 1H), 4.79 (d,  $J = 5.8$  Hz, 2H), 2.50 (s, 3H).

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  191.5, 163.2, 130.2, 120.4, 81.9, 68.8, 23.6.

Allyl 2,2-dichloro-3-oxo-5-phenylpentanoate (**13g**)



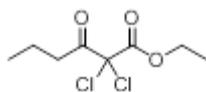
Chemical Formula:  $\text{C}_{14}\text{H}_{14}\text{Cl}_2\text{O}_3$   
Exact Mass: 300.0320

Synthesized according to general procedure C: **13g** (0.68 g, 66% yield), colorless oil.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.30 (t,  $J = 7.2$  Hz, 2H), 7.24 – 7.19 (m, 3H), 5.95 – 5.83 (m, 1H), 5.40 (dq,  $J = 17.2, 1.4$  Hz, 1H), 5.33 (dd,  $J = 10.4, 1.1$  Hz, 1H), 4.73 (dt,  $J = 5.9, 1.2$  Hz, 2H), 3.18 – 3.14 (m, 2H), 3.00 (t,  $J = 7.5$  Hz, 2H).

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  193.4, 163.2, 139.9, 130.2, 128.8 (2C), 128.5 (2C), 126.7, 120.5, 81.9, 68.8, 37.9, 30.4.

Ethyl 2,2-dichloro-3-oxohexanoate (**13h**)



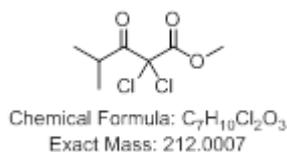
Chemical Formula:  $\text{C}_8\text{H}_{12}\text{Cl}_2\text{O}_3$   
Exact Mass: 226.0163

Synthesized according to general procedure C: **13h** (1.73 g, 95% yield), colorless oil.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  4.36 (q,  $J = 7.1$  Hz, 2H), 2.80 (t,  $J = 7.2$  Hz, 2H), 1.72 (sext,  $J = 7.3$  Hz, 2H), 1.34 (t,  $J = 7.1$  Hz, 3H), 0.96 (t,  $J = 7.4$  Hz, 3H).

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  194.2, 163.6, 82.1, 64.7, 37.8, 17.9, 14.0, 13.5.

Methyl 2,2-dichloro-4-methyl-3-oxopentanoate (**13i**)

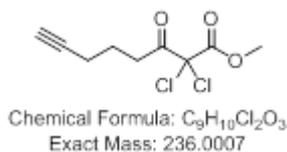


Synthesized according to general procedure C: **13i** (1.33 g, 78% yield), colorless oil.

$^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  3.92 (s, 3H), 3.29 (hept,  $J = 6.7$  Hz, 1H), 1.26 (d,  $J = 6.7$  Hz, 6H).

$^{13}C$  NMR (101 MHz,  $CDCl_3$ )  $\delta$  198.5, 164.2, 82.0, 55.0, 35.8, 21.1 (2C).

Methyl 2,2-dichloro-3-oxooct-7-ynoate (**13j**)

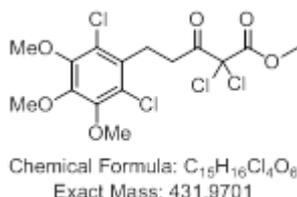


Synthesized according to general procedure C: **13j** (1.58 g, 74% yield), colorless oil.

$^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  3.91 (s, 3H), 2.99 (t,  $J = 7.1$  Hz, 2H), 2.27 (t,  $J = 6.8$  Hz, 2H), 1.99 (s, 1H), 1.90 (quint,  $J = 6.9$  Hz, 2H).

$^{13}C$  NMR (101 MHz,  $CDCl_3$ )  $\delta$  193.9, 164.0, 83.0, 81.7, 69.7, 55.1, 34.5, 23.0, 17.6.

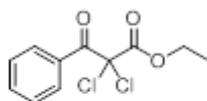
Methyl 2,2-dichloro-3-oxo-5-(3,4,5-trimethoxyphenyl)pentanoate (**13k**)



Synthesized according to general procedure C: **13k** (0.68 g, 66% yield), white solid, mp 50 °C.

$^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  3.94 (s, 3H), 3.93 (s, 3H), 3.90 (s, 6H), 3.29 – 3.25 (m, 2H), 3.07 – 3.03 (m, 2H).

$^{13}C$  NMR (101 MHz,  $CDCl_3$ )  $\delta$  193.0, 164.0, 149.4 (2C), 146.9, 131.5, 124.2 (2C), 81.7, 61.5, 61.3 (2C), 55.2, 34.3, 26.8.

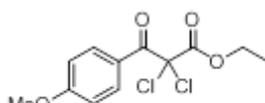
Ethyl 2,2-dichloro-3-oxo-3-phenylpropanoate (**13l**)

Chemical Formula: C<sub>11</sub>H<sub>10</sub>Cl<sub>2</sub>O<sub>3</sub>  
Exact Mass: 260.0007

Synthesized according to general procedure C: **13l** (0.9 g, 69% yield), colorless oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.05 – 8.02 (m, 2H), 7.64 – 7.60 (m, 1H), 7.50 – 7.46 (m, 2H), 4.31 (q, *J* = 7.1 Hz, 2H), 1.18 (t, *J* = 7.1 Hz, 3H).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 183.3, 164.1, 134.3, 130.9, 130.1 (2C), 128.7 (2C), 82.0, 64.8, 13.7.

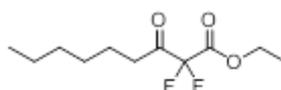
Ethyl 2,2-dichloro-3-(4-methoxyphenyl)-3-oxopropanoate (**13m**)

Chemical Formula: C<sub>12</sub>H<sub>12</sub>Cl<sub>2</sub>O<sub>4</sub>  
Exact Mass: 290.0113

Synthesized according to general procedure C: **13m** (0.62 g, 43% yield), colorless oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.06 – 8.02 (m, 2H), 6.96 – 6.91 (m, 2H), 4.32 (q, *J* = 7.1 Hz, 2H), 3.89 (s, 3H), 1.21 (t, *J* = 7.1 Hz, 3H).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 182.0, 164.4 (2C), 132.8 (2C), 123.4, 114.0 (2C), 82.3, 64.7, 55.7, 13.8.

Ethyl 2,2-difluoro-3-oxononanoate (**13n**)

Chemical Formula: C<sub>11</sub>H<sub>18</sub>F<sub>2</sub>O<sub>3</sub>  
Exact Mass: 236.1224

Synthesized according to general procedure E: **13n** (0.61 g, 63% yield, two steps), colorless oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 4.39 (q, *J* = 7.1 Hz, 2H), 2.75 (t, *J* = 7.2 Hz, 2H), 1.70 – 1.63 (m, 2H), 1.37 (t, *J* = 7.1 Hz, 3H), 1.34 – 1.23 (m, 6H), 0.91 (t, *J* = 6.6 Hz, 3H).

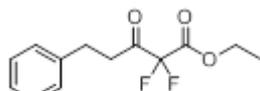
<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 197.6 (t, *J*<sub>CF</sub> = 28.0 Hz), 161.6 (t, *J*<sub>CF</sub> = 30.6 Hz), 108.3 (t, *J*<sub>CF</sub>

## Experimental part

= 264.0 Hz), 63.8, 36.8, 31.5, 28.6, 22.6 (2C), 14.1, 14.0.

$^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$  -113.9.

### Ethyl 2,2-difluoro-3-oxo-5-phenylpentanoate (**13o**)



Chemical Formula:  $\text{C}_{13}\text{H}_{14}\text{F}_2\text{O}_3$   
Exact Mass: 256.0911

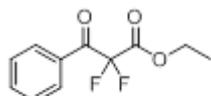
Synthesized according to general procedure E: **13o** (1.31 g, 59% yield, two steps), colorless oil.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.32 – 7.28 (m, 2H), 7.24 – 7.18 (m, 3H), 4.33 (q,  $J = 7.1$  Hz, 2H), 3.10 – 3.05 (m, 2H), 2.99 – 2.95 (m, 2H), 1.32 (t,  $J = 7.1$  Hz, 3H).

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  196.6 (t,  $J_{\text{CF}} = 28.2$  Hz), 161.3 (t,  $J_{\text{CF}} = 30.7$  Hz), 139.8, 128.7 (2C), 128.4 (2C), 126.6, 108.3 (t,  $J_{\text{CF}} = 264.0$  Hz), 63.9, 38.5, 28.5, 13.9.

$^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$  -113.9.

### Ethyl 2,2-difluoro-3-oxo-3-phenylpropanoate (**13p**)



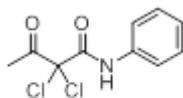
Chemical Formula:  $\text{C}_{11}\text{H}_{10}\text{F}_2\text{O}_3$   
Exact Mass: 228.0598

Following a reported procedure,<sup>299</sup> **13p** (0.246 g, 36% yield), colorless oil.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.09 – 8.07 (m, 2H), 7.70 – 7.66 (m, 1H), 7.55 – 7.51 (m, 2H), 4.39 (q,  $J = 7.1$  Hz, 2H), 1.32 (t,  $J = 7.1$  Hz, 3H).

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  185.6 (t,  $J_{\text{CF}} = 27.5$  Hz), 161.9 (t,  $J_{\text{CF}} = 30.6$  Hz), 135.2, 131.1, 130.0 (2C), 129.1 (2C), 109.90 (t,  $J_{\text{CF}} = 264.6$  Hz), 63.9, 13.9.

<sup>299</sup> Stavber, G.; Stavber, S. *Adv. Synth. Catal.* **2010**, 352, 2838.

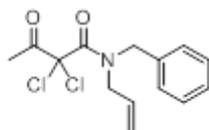
2,2-dichloro-3-oxo-*N*-phenylbutanamide (**13q**)

Chemical Formula: C<sub>10</sub>H<sub>9</sub>Cl<sub>2</sub>NO<sub>2</sub>  
Exact Mass: 245.0010

**Synthesized according to general procedure C: 13q** (2.3 g, 93% yield), white solid, m.p. < 48 °C.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 8.35 (s, 1H), 7.55 (d, *J* = 8.0 Hz, 2H), 7.41 – 7.37 (m, 2H), 7.25 – 7.21 (m, 1H), 2.55 (s, 3H).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 191.7, 161.0, 136.0, 129.3 (2C), 126.0, 120.5 (2C), 83.2, 24.5.

*N*-allyl-*N*-benzyl-2,2-dichloro-3-oxobutanamide (**13r**)

Chemical Formula: C<sub>14</sub>H<sub>15</sub>Cl<sub>2</sub>NO<sub>2</sub>  
Exact Mass: 299.0480

**Synthesized according to general procedure D: 13r** (714 mg, 65% yield, two steps), colorless oil.

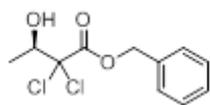
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>, at this temperature, two rotamers (A: major; B: minor) in 60:40 ratio are visible) δ 7.44 – 7.20 (m, 5H) [A + B], 5.90 [A] (ddt, *J* = 16.3, 11.7, 6.0 Hz, 1 H), 5.74 [B] (ddt, *J* = 16.2, 11.1, 5.8 Hz, 1H), 5.39 [A] (d, *J* = 9.7 Hz, 1H), 5.29 [A] (d, *J* = 17.2 Hz, 1H), 5.24 [B] (d, *J* = 10.3 Hz, 1H), 5.14 [B] (d, *J* = 17.1 Hz, 1H), 4.97 [B] (s, 2H), 4.62 [A] (s, 2H), 4.25 [A] (d, *J* = 5.9 Hz, 2H), 3.89 [B] (d, *J* = 5.6 Hz, 2H), 2.56 [B] (s, 3H), 2.53 [A] (s, 3H).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>, major rotamer) δ 190.2, 163.7, 135.8, 132.1, 128.9 (2C), 128.0 (2C), 127.9, 120.1, 83.8, 50.3, 48.3, 25.56;

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>, minor rotamer) δ 190.2, 163.8, 135.1, 130.8, 128.9 (2C), 128.1, 127.5 (2C), 118.5, 83.6, 51.4, 48.2, 25.64.

## General procedure for the synthesis of 14a–14h and 14j–14r by ATH.

A round-bottomed tube equipped with a balloon of argon was charged with the corresponding dihalogeno  $\beta$ -keto ester (or dihalo  $\beta$ -keto amide) **13** (1.0 mmol [or 0.6 mmol]) and the [RuCl(*p*-cymene)(*R,R*-TsDPEN)] complex (0.005 mmol, 0.5 mol% [or 0.006 mmol, 1.0 mol%]). The mixture was subjected to three vacuum/argon cycles before degassed dichloromethane (5 mL [or 3 mL]) was added. The mixture was stirred at room temperature for 3–5 min, then HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) azeotropic mixture (168  $\mu$ L, 2.0 mmol, 2.0 equiv. [or 101  $\mu$ L, 1.2 mmol, 2.0 eq]) was added dropwise and the reaction was heated at 30 °C. After complete consumption of the starting material (monitored by TLC or <sup>1</sup>H NMR), the catalyst was removed through a short pad of silica gel (petroleum ether/ethyl acetate 4:1 to 3:1). The filtrate was concentrated under vacuum to give the crude product. The conversion was determined by <sup>1</sup>H NMR analysis of the crude product. After purification of the crude product by flash column chromatography, the enantiomeric excess was determined by SFC or HPLC analysis (CHIRALPAK IA, IB, ID, IE).

Benzyl (*R*)-2,2-dichloro-3-hydroxybutanoate (**14a**)

Chemical Formula: C<sub>11</sub>H<sub>12</sub>Cl<sub>2</sub>O<sub>3</sub>  
Exact Mass: 262.0163

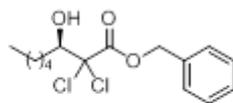
Colorless oil, 152 mg, 96% yield, > 99% ee. [ $\alpha$ ]<sub>D</sub><sup>25</sup> = -7.1 (*c* 1.0, CHCl<sub>3</sub>).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.43 – 7.33 (m, 5H), 5.32 (s, 2H), 4.53 – 4.43 (m, 1H), 2.61 (d, *J* = 7.2 Hz, 1H), 1.44 (d, *J* = 6.2 Hz, 3H).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  165.8, 134.4, 128.9, 128.8 (2C), 128.2 (2C), 87.2, 73.6, 69.4, 17.2.

**SFC:** Chiralpak IA-H, *sc*CO<sub>2</sub>/*i*PrOH 96/4, 3.0 mL/min, P = 150 bar,  $\lambda$  = 215 nm, *t*<sub>R</sub> = 8.86 min (major), *t*<sub>R</sub> = 9.86 min.

**HRMS** (ESI/ion trap): *m/z* [M+Na]<sup>+</sup> calcd for C<sub>11</sub>H<sub>12</sub>Cl<sub>2</sub>O<sub>3</sub>Na 285.0061, found 285.0057.

Benzyl (*R*)-2,2-dichloro-3-hydroxyoctanoate (**14b**)

Chemical Formula: C<sub>15</sub>H<sub>20</sub>Cl<sub>2</sub>O<sub>3</sub>  
Exact Mass: 318.0789

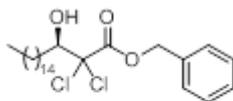
Colorless oil, 134 mg, 70% yield, >99% ee.  $[\alpha]_{\text{D}}^{25} = +13.4$  (*c* 1.01, CHCl<sub>3</sub>).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.40 – 7.35 (m, 5H), 5.36, 5.28 (ABq,  $J_{AB} = 13.5$  Hz, 2H), 4.21 (ddd,  $J = 9.3, 7.4, 1.9$  Hz, 1H), 2.44 (d,  $J = 7.4$  Hz, 1H), 1.84 – 1.74 (m, 1H), 1.59 (m, 2H), 1.43 – 1.23 (m, 5H), 0.89 (t,  $J = 6.8$  Hz, 3H).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  165.8, 134.4, 128.91, 128.85 (2C), 128.3 (2C), 87.3, 77.5, 69.4, 31.6, 31.2, 25.7, 22.6, 14.1.

**SFC:** Chiralpak IA-H, *sc*CO<sub>2</sub>/*i*PrOH 96/4, 3.0 mL/min, P = 150 bar,  $\lambda = 215$  nm,  $t_{\text{R}} = 12.44$  min,  $t_{\text{R}} = 14.67$  min (major).

**HRMS** (ESI/ion trap):  $m/z$  [M+Na]<sup>+</sup> calcd for C<sub>15</sub>H<sub>20</sub>Cl<sub>2</sub>O<sub>3</sub>Na 341.0687, found 341.0682.

Benzyl (*R*)-2,2-dichloro-3-hydroxyheptadecanoate (**14c**)

Chemical Formula: C<sub>25</sub>H<sub>40</sub>Cl<sub>2</sub>O<sub>3</sub>  
Exact Mass: 458.2355

White solid, m.p. < 48 °C. 204 mg, 90% yield, 98% ee.  $[\alpha]_{\text{D}}^{25} = +9.8$  (*c* 1.0, CHCl<sub>3</sub>).

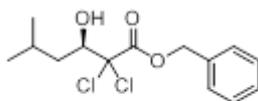
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.39 – 7.37 (m, 5H), 5.36, 5.28 (ABq,  $J_{AB} = 13.0$  Hz, 2H), 4.23 – 4.19 (m, 1H), 2.44 (d,  $J = 7.4$  Hz, 1H), 1.83 – 1.76 (m, 1H), 1.64 – 1.50 (m, 2H), 1.26 (br s, 25H), 0.88 (t,  $J = 6.6$  Hz, 3H).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  165.8, 134.4, 128.91, 128.85 (2C), 128.3 (2C), 87.3, 77.5, 69.4, 32.1, 31.3, 29.8 (6C), 29.7, 29.6, 29.51, 29.46, 26.0, 22.8, 14.3.

**HPLC:** Chiralpak IB, Hexane/*i*PrOH 97/3, 1.0 mL/min,  $\lambda = 215$  nm,  $t_{\text{R}} = 7.81$  min,  $t_{\text{R}} = 9.48$  min (major).

**MS (ESI):**  $m/z = 476$  [M + NH<sub>4</sub>]<sup>+</sup>.

Benzyl (*R*)-2,2-dichloro-3-hydroxy-5-methylhexanoate (**14d**)



Chemical Formula: C<sub>14</sub>H<sub>18</sub>Cl<sub>2</sub>O<sub>3</sub>  
Exact Mass: 304.0633

White solid, m.p. 54 °C, 47.6 mg, 26% yield, >99% ee.  $[\alpha]_D^{25} = +16.0$  (*c* 1.01, CHCl<sub>3</sub>).

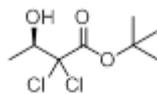
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.40 – 7.34 (m, 5H), 5.42, 5.26 (ABq, *J*<sub>AB</sub> = 13.7 Hz, 2H), 4.29 (ddd, *J* = 9.6, 7.4, 2.3 Hz, 1H), 2.45 (d, *J* = 7.3 Hz, 1H), 1.92 – 1.82 (m, 1H), 1.60 – 1.48 (m, 2H), 0.96 (d, *J* = 6.7 Hz, 3H), 0.91 (d, *J* = 6.6 Hz, 3H).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 165.8, 134.4, 128.93, 128.86 (2C), 128.4 (2C), 87.5, 75.9, 69.4, 40.2, 24.8, 23.8, 21.6.

**SFC**: Chiralpak IA-H, *sc*CO<sub>2</sub>/*i*PrOH 96/4, 3.0 mL/min, P = 150 bar, λ = 215 nm, *t*<sub>R</sub> = 7.98 min, *t*<sub>R</sub> = 8.94 min (major).

**HRMS** (ESI/ion trap): *m/z* [M+Na]<sup>+</sup> calcd for C<sub>14</sub>H<sub>18</sub>Cl<sub>2</sub>O<sub>3</sub>Na 327.0531, found 327.0526.

*tert*-Butyl (*R*)-2,2-dichloro-3-hydroxybutanoate (**14e**)



Chemical Formula: C<sub>8</sub>H<sub>14</sub>Cl<sub>2</sub>O<sub>3</sub>  
Exact Mass: 228.0320

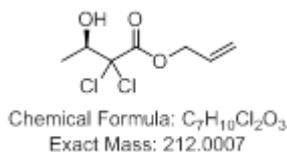
White solid, m.p. < 50 °C, 192 mg, 84% yield, 99% ee.  $[\alpha]_D^{25} = -7.3$  (*c* 1.0, CHCl<sub>3</sub>).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 4.41 (quint, *J* = 6.3 Hz, 1H), 2.68 (d, *J* = 7.0 Hz, 1H), 1.54 (s, 9H), 1.43 (d, *J* = 6.2 Hz, 3H).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 164.7, 88.1, 85.5, 73.6, 27.7, 17.4 (3C).

**HPLC**: Chiralpak IE, Hexane/*i*PrOH 98/2, 1.0 mL/min, λ = 215 nm, *t*<sub>R</sub> = 10.05 min, *t*<sub>R</sub> = 13.36 min (major).

**HRMS** (ESI/ion trap): *m/z* [M+Na]<sup>+</sup> calcd for C<sub>8</sub>H<sub>14</sub>Cl<sub>2</sub>O<sub>3</sub>Na 251.0218, found 251.0213.

Allyl (*R*)-2,2-dichloro-3-hydroxybutanoate (**14f**)

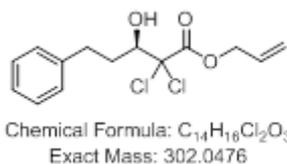
Colorless oil, 158 mg, 74% yield, >99% ee.  $[\alpha]_{\text{D}}^{25} = -7.0$  (*c* 1.06, CHCl<sub>3</sub>).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  5.95 (ddt, *J* = 17.1, 10.5, 5.7 Hz, 1H), 5.44 (dq, *J* = 17.2, 1.4 Hz, 1H), 5.33 (dq, *J* = 10.5, 1.1 Hz, 1H), 4.78 (dt, *J* = 5.7, 1.3 Hz, 2H), 4.64 – 4.34 (m, 1H), 2.65 (d, *J* = 7.2 Hz, 1H), 1.46 (d, *J* = 6.2 Hz, 3H).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  165.7, 130.5, 119.8, 87.1, 73.6, 68.2, 17.2.

HPLC: Chiralpak IB, Hexane/*i*PrOH 98/2, 1.0 mL/min,  $\lambda$  = 215 nm, *t<sub>R</sub>* = 10.80 min (major), *t<sub>R</sub>* = 14.30 min.

**HRMS** (ESI/ion trap): *m/z* [M+Na]<sup>+</sup> calcd for C<sub>7</sub>H<sub>10</sub>Cl<sub>2</sub>O<sub>3</sub>Na 234.9905, found 234.9900.

Allyl (*R*)-2,2-dichloro-3-hydroxy-5-phenylpentanoate (**14g**)

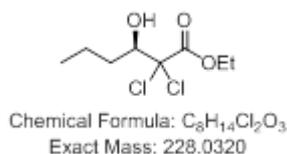
Colorless oil, 147 mg, 78% yield, > 99% ee.  $[\alpha]_{\text{D}}^{25} = +28.0$  (*c* 1.02, CHCl<sub>3</sub>).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.33 – 7.28 (m, 2H), 7.24 – 7.19 (m, 3H), 5.92 (ddt, *J* = 16.5, 11.0, 5.7 Hz, 1H), 5.42 (d, *J* = 17.2 Hz, 1H), 5.32 (d, *J* = 10.5 Hz, 1H), 4.76 (d, *J* = 5.7 Hz, 2H), 4.23 (ddd, *J* = 9.6, 7.0, 1.7 Hz, 1H), 2.98 (ddd, *J* = 14.1, 9.4, 4.9 Hz, 1H), 2.75 (dt, *J* = 13.9, 8.4 Hz, 1H), 2.64 (d, *J* = 7.0 Hz, 1H), 2.25 – 2.16 (m, 1H), 1.97 (dtd, *J* = 14.2, 9.6, 4.9 Hz, 1H).  
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  165.6, 141.1, 130.4, 128.56 (2C), 128.52 (2C), 126.3, 119.9, 86.7, 76.6, 68.2, 32.7, 31.9.

SFC: Chiralpak IA-H, *sc*CO<sub>2</sub>/*i*PrOH 96/4, 3.0 mL/min, P = 150 bar,  $\lambda$  = 215 nm, *t<sub>R</sub>* = 12.14 min, *t<sub>R</sub>* = 14.87 min (major).

**HRMS** (ESI/ion trap): *m/z* [M+Na]<sup>+</sup> calcd for C<sub>14</sub>H<sub>16</sub>Cl<sub>2</sub>O<sub>3</sub>Na 325.0374, found 325.0370.

Ethyl (*R*)-2,2-dichloro-3-hydroxyhexanoate (**14h**)



Colorless oil, 100 mg, 72% yield, >99% ee.  $[\alpha]_D^{25} = +15.5$  (*c* 1.03, CHCl<sub>3</sub>).

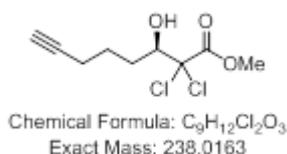
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 4.36 (q, *J* = 7.1 Hz, 2H), 4.22 (ddd, *J* = 9.3, 7.4, 1.8 Hz, 1H), 2.50 (d, *J* = 7.3 Hz, 1H), 1.87 – 1.78 (m, 1H), 1.71 – 1.55 (m, 2H), 1.50 – 1.42 (m, 1H), 1.37 (t, *J* = 7.1 Hz, 3H), 0.98 (t, *J* = 7.2 Hz, 3H).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 166.0, 87.2, 77.2, 64.1, 33.2, 19.2, 13.9 (2C).

HPLC: Chiralpak IB, Hexane/<sup>i</sup>PrOH 98/2, 1.0 mL/min, λ = 215 nm, *t*<sub>R</sub> = 8.37 min, *t*<sub>R</sub> = 9.11 min (major).

HRMS (ESI/ion trap): *m/z* [M+Na]<sup>+</sup> calcd for C<sub>8</sub>H<sub>14</sub>Cl<sub>2</sub>O<sub>3</sub>Na 251.0218, found 251.0213.

Methyl (*R*)-2,2-dichloro-3-hydroxyoct-7-ynoate (**14j**)



Colorless oil, 109 mg, 76% yield, > 99% ee.  $[\alpha]_D^{25} = +18.5$  (*c* 1.05, CHCl<sub>3</sub>).

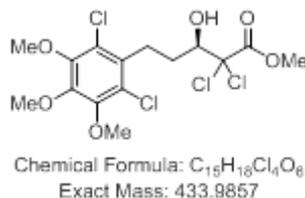
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 4.29 – 4.22 (m, 1H), 3.92 (s, 3H), 2.59 (d, *J* = 7.3 Hz, 1H), 2.29 (td, *J* = 6.7, 2.6 Hz, 2H), 2.10 – 2.01 (m, 1H), 1.98 (t, *J* = 2.6 Hz, 1H), 1.92 – 1.82 (m, 1H), 1.78 – 1.64 (m, 2H).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 166.5, 86.6, 83.8, 77.0, 69.1, 54.7, 30.0, 24.8, 18.2.

HPLC: Chiralpak IE, Hexane/<sup>i</sup>PrOH 95/5, 1.0 mL/min, λ = 215 nm, *t*<sub>R</sub> = 10.25 min, *t*<sub>R</sub> = 12.48 min (major).

HRMS (ESI/ion trap): *m/z* [M+Na]<sup>+</sup> calcd for C<sub>9</sub>H<sub>12</sub>Cl<sub>2</sub>NaO<sub>3</sub> 261.0061, found 261.0057.

Methyl (*R*)-2,2-dichloro-5-(2,6-dichloro-3,4,5-trimethoxyphenyl)-3-hydroxypentanoate  
(**14k**)



Colorless oil, 127 mg, 48% yield, 98% ee.  $[\alpha]_D^{25} = +12.6$  (*c* 1.03, CHCl<sub>3</sub>).

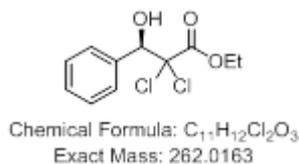
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 4.33 (ddd, *J* = 9.6, 7.7, 1.6 Hz, 1H), 3.92 (s, 3H), 3.91 (s, 3H), 3.90 (s, 6H), 3.27 (ddd, *J* = 13.0, 11.3, 5.0 Hz, 1H), 3.02 (ddd, *J* = 13.2, 11.0, 5.5 Hz, 1H), 2.65 (d, *J* = 7.6 Hz, 1H), 2.19 – 2.11 (m, 1H), 1.84 (ddd, *J* = 13.9, 10.1, 5.6 Hz, 1H).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 166.3, 149.2 (2C), 146.5, 133.1, 124.2 (2C), 86.5, 77.5, 61.5, 61.3 (2C), 54.7, 29.9, 28.4.

**HPLC**: Chiralpak IA, Hexane/*i*PrOH 95/5, 1.0 mL/min, λ = 215 nm, *t<sub>R</sub>* = 9.93 min, *t<sub>R</sub>* = 11.62 min (major).

**HRMS** (ESI/ion trap): *m/z* [M+Na]<sup>+</sup> calcd for C<sub>15</sub>H<sub>18</sub>Cl<sub>4</sub>O<sub>6</sub>Na 456.9755, found 456.9750.

Ethyl (*R*)-2,2-dichloro-3-hydroxy-3-phenylpropanoate (**14l**)



Colorless oil, 79 mg, 50% yield, 70% ee.  $[\alpha]_D^{25} = -11.3$  (*c* 1.0, CHCl<sub>3</sub>).

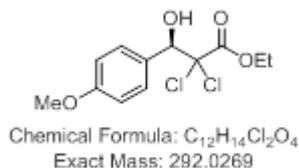
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.56 – 7.51 (m, 2H), 7.40 – 7.36 (m, 3H), 5.42 (d, *J* = 5.2 Hz, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 3.31 (d, *J* = 5.1 Hz, 1H), 1.36 (t, *J* = 7.1 Hz, 3H).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 166.1, 135.6, 129.3, 129.0 (2C), 127.9 (2C), 86.1, 78.8, 64.4, 13.9.

**HPLC**: Chiralpak IE, Hexane/*i*PrOH 90/10, 1.0 mL/min, λ = 215 nm, *t<sub>R</sub>* = 7.13 min, *t<sub>R</sub>* = 8.34 min (major).

**HRMS** (ESI/ion trap): *m/z* [M+Na]<sup>+</sup> calcd for C<sub>11</sub>H<sub>12</sub>Cl<sub>2</sub>O<sub>3</sub>Na 285.0061, found 285.0057.

Ethyl (*R*)-2,2-dichloro-3-hydroxy-3-(4-methoxyphenyl)propanoate (**14m**)



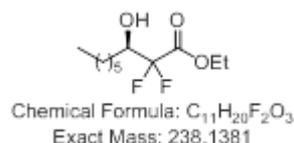
Colorless oil, 59 mg, 33.5% yield, 71% ee.  $[\alpha]_D^{25} = -9.5$  (*c* 1.07, CHCl<sub>3</sub>).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.48 – 7.44 (m, 2H), 6.92 – 6.88 (m, 2H), 5.38 (d, *J* = 5.1 Hz, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 3.82 (s, 3H), 3.20 (d, *J* = 5.1 Hz, 1H), 1.36 (t, *J* = 7.1 Hz, 3H).  
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  166.1, 160.2, 130.2 (2C), 127.7, 113.3 (2C), 86.6, 78.5, 64.3, 55.4, 13.9.

**HPLC**: Chiralpak IE, Hexane/*i*PrOH 94/6, 1.0 mL/min,  $\lambda$  = 254 nm, *t<sub>R</sub>* = 18.37 min, *t<sub>R</sub>* = 19.11 min (major).

**HRMS** (ESI/ion trap): *m/z* [M+Na]<sup>+</sup> calcd for C<sub>12</sub>H<sub>14</sub>Cl<sub>2</sub>O<sub>4</sub>Na 315.0167, found 315.0163.

Ethyl (*R*)-2,2-difluoro-3-hydroxynonanoate (**14n**)



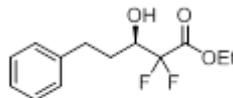
Colorless oil, 143 mg, 99% yield, 98% ee.  $[\alpha]_D^{25} = +19.7$  (*c* 1.11, CHCl<sub>3</sub>).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  4.36 (q, *J* = 7.1 Hz, 2H), 4.07 – 3.97 (m, 1H), 1.96 (d, *J* = 6.0 Hz, 1H), 1.71 – 1.49 (m, 4H), 1.37 (t, *J* = 7.1 Hz, 3H), 1.33 – 1.25 (m, 6H), 0.89 (t, *J* = 6.6 Hz, 3H).

**<sup>19</sup>F NMR** (376 MHz, CDCl<sub>3</sub>)  $\delta$  -115.0 (dd, *J* = 264.5, 7.4 Hz), -122.4 (dd, *J* = 264.5, 14.9 Hz).  
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  163.9 (t, *J<sub>CF</sub>* = 32.0 Hz), 115.4 (t, *J<sub>CF</sub>* = 255.4 Hz), 71.8 (t, *J<sub>CF</sub>* = 26.1 Hz), 63.2, 31.7, 29.3, 29.1, 25.3, 22.7, 14.1, 14.0.

**HPLC**: Chiralpak ID, Hexane/*i*PrOH 98/2, 1.0 mL/min,  $\lambda$  = 215 nm, *t<sub>R</sub>* = 8.90 min, *t<sub>R</sub>* = 10.02 min (major).

**HRMS** (ESI/ion trap): *m/z* [M+Na]<sup>+</sup> calcd for C<sub>11</sub>H<sub>20</sub>F<sub>2</sub>O<sub>3</sub>Na 261.1278, found 261.1274.

Ethyl (*R*)-2,2-difluoro-3-hydroxy-5-phenylpentanoate (**14o**)

Chemical Formula: C<sub>13</sub>H<sub>16</sub>F<sub>2</sub>O<sub>3</sub>  
Exact Mass: 258.1068

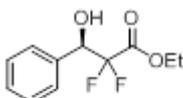
Colorless oil, 153 mg, 99% yield, 98% ee.  $[\alpha]_D^{25} = +31.9$  (*c* 1.0, CHCl<sub>3</sub>).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.32 – 7.28 (m, 2H), 7.23 – 7.20 (m, 3H), 4.34 (q, *J* = 7.1 Hz, 2H), 4.09 – 3.95 (m, 1H), 2.93 (ddd, *J* = 14.1, 9.1, 5.2 Hz, 1H), 2.74 (dt, *J* = 13.9, 8.3 Hz, 1H), 2.07 (d, *J* = 7.1 Hz, 1H), 2.05 – 1.97 (m, 1H), 1.89 (m, 1H), 1.34 (t, *J* = 7.1 Hz, 3H).

**<sup>19</sup>F NMR** (376 MHz, CDCl<sub>3</sub>)  $\delta$  –114.88 (dd, *J* = 266.0, 7.6 Hz), –121.89 (dd, *J* = 266.0, 14.5 Hz).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  163.7 (t, *J*<sub>CF</sub> = 31.8 Hz), 140.9, 128.7 (2C), 128.6 (2C), 126.4, 114.7 (t, *J*<sub>CF</sub> = 262.0 Hz), 71.1 (t, *J*<sub>CF</sub> = 26.2 Hz), 63.3, 31.3, 30.8, 14.0.

**SFC**: Chiralpak IA-H, *sc*CO<sub>2</sub>/*i*PrOH 96/4, 3.0 mL/min, *P* = 150 bar,  $\lambda$  = 215 nm, *t*<sub>R</sub> = 5.06 min, *t*<sub>R</sub> = 5.94 min (major).

Ethyl (*R*)-2,2-difluoro-3-hydroxy-3-phenylpropanoate (**14p**)

Chemical Formula: C<sub>11</sub>H<sub>12</sub>F<sub>2</sub>O<sub>3</sub>  
Exact Mass: 230.0755

Colorless oil, 136.7 mg, 99% yield, 56% ee.  $[\alpha]_D^{25} = -6.8$  (*c* 1.0, CHCl<sub>3</sub>), [Lit.<sup>300</sup>  $[\alpha]_D^{24} = -13.4$  (*c* 1.29, CHCl<sub>3</sub>, 97% ee)].

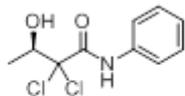
**<sup>1</sup>H NMR** (400 MHz, Chloroform-*d*)  $\delta$  7.46 – 7.40 (m, 2H), 7.41 – 7.38 (m, 3H), 5.18 (ddd, *J* = 15.3, 7.9, 5.3 Hz, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 2.62 (d, *J* = 5.3 Hz, 1H), 1.29 (t, *J* = 7.1 Hz, 3H).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  163.7 (t, *J*<sub>CF</sub> = 31.7 Hz), 134.6, 129.3 (2C), 128.5, 127.8 (2C), 113.9 (dd, *J*<sub>CF</sub> = 259.2, 254.2 Hz), 73.8 (dd, *J*<sub>CF</sub> = 27.5, 24.6 Hz), 63.3, 13.9.

**HPLC**: Chiralpak IC, Hexane/*i*PrOH 90/10, 1.0 mL/min,  $\lambda$  = 215 nm, *t*<sub>R</sub> = 5.70 min (major), *t*<sub>R</sub> = 7.09 min.

<sup>300</sup> Iseki, K.; Kuroki, Y.; Asada, D.; Takahashi, M.; Kishimoto, S.; Kobayashi, Y. *Tetrahedron* **1997**, *53*, 10271.

(*R*)-2,2-dichloro-3-hydroxy-*N*-phenylbutanamide (**14q**)



Chemical Formula: C<sub>10</sub>H<sub>11</sub>Cl<sub>2</sub>NO<sub>2</sub>  
Exact Mass: 247.0167

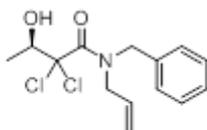
White solid, m.p. 78 °C, 230 mg, 93% yield, 98.5% ee.  $[\alpha]_D^{25} = -11.9$  (*c* 1.02, CHCl<sub>3</sub>).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 8.44 (s, 1H), 7.55 (d, *J* = 7.7 Hz, 2H), 7.39 (t, *J* = 7.9 Hz, 2H), 7.21 (t, *J* = 7.4 Hz, 1H), 4.64 (quint, *J* = 6.1 Hz, 1H), 3.39 (d, *J* = 5.0 Hz, 1H), 1.50 (d, *J* = 6.2 Hz, 3H).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 164.1, 136.3 (2C), 129.3, 125.8, 120.6 (2C), 88.8, 73.2, 17.1. HPLC: Chiralpak IB, Hexane/*i*PrOH 90/10, 1.0 mL/min, λ = 215 nm, *t<sub>R</sub>* = 7.29 min (major), *t<sub>R</sub>* = 8.06 min.

**HRMS** (ESI/ion trap): *m/z* [M+Na]<sup>+</sup> calcd for C<sub>10</sub>H<sub>11</sub>Cl<sub>2</sub>NO<sub>2</sub>Na 270.0065, found 270.0061.

(*R*)-*N*-allyl-*N*-benzyl-2,2-dichloro-3-hydroxybutanamide (**14r**)



Chemical Formula: C<sub>14</sub>H<sub>17</sub>Cl<sub>2</sub>NO<sub>2</sub>  
Exact Mass: 301.0636

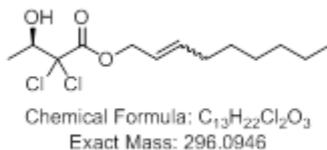
Colorless oil, 179.5 mg, 99% yield, 98% ee.  $[\alpha]_D^{25} = +19.7$  (*c* 1.11, CHCl<sub>3</sub>).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>, at this temperature, two rotamers (A: major; B: minor) in 60:40 ratio are visible) δ 7.40 – 7.25[A+B] (m, 4H), 7.23 – 7.16 [A+B] (m, 1H), 5.91 [A] (ddt, *J* = 16.5, 11.9, 6.0 Hz, 1H), 5.72 [B] (ddt, *J* = 15.9, 10.6, 5.5 Hz, 1H), 5.34 [A] (d, *J* = 10.2 Hz, 1H), 5.25 [A] (d, *J* = 17.2 Hz, 1H), 5.19 [B] (d, *J* = 10.5 Hz, 1H), 5.15 [B] (d, *J* = 16.3 Hz, 1H), 5.09 [A] (d, *J* = 18.0 Hz, 1H), 5.00 [B] (d, *J* = 16.1 Hz, 1H), 4.69 – 4.55 [A+B] (m, 2H), 4.50 – 4.30 [A+B] (m, 2H), 3.96 – 3.79 [A+B] (m, 1H), 1.50 [A+B] (d, *J* = 6.1 Hz, 3H).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>, at this temperature, two rotamers (A: major; B: minor) are visible) δ 166.7 [A+B]; 136.0 [A], 135.6 [B]; 132.5 [A], 131.1 [B]; 128.9 [A+B] (2C); 128.0 [B], 127.7 [A]; 127.6 [A+B] (2C); 119.9 [A], 117.9 [B]; 85.6 [A], 85.5 [B]; 74.2 [A+B]; 52.1 [B], 51.2 [A]; 48.5 [A+B]; 16.3 [A+B].

**HPLC**: Chiralpak IE, Hexane/*i*PrOH 98/2, 1.0 mL/min, λ = 215 nm, *t<sub>R</sub>* = 15.79 min, *t<sub>R</sub>* = 18.88 min (major).

**HRMS** (ESI/ion trap): *m/z* [M+Na]<sup>+</sup> calcd for C<sub>14</sub>H<sub>17</sub>Cl<sub>2</sub>NO<sub>2</sub>Na 324.0534, found 324.0530.

**(Z/E)-non-2-en-1-yl (R)-2,2-dichloro-3-hydroxybutanoate (20)**

In a round-bottom tube, charged with Grubbs II catalyst (17 mg, 0.02 mmol) under an argon atmosphere, was added a solution of allyl (*R*)-2,2-dichloro-3-hydroxybutanoate (**14e**, 43 mg, 0.2 mmol) and 1-octene (63  $\mu$ L, 0.4 mmol) in degassed DCM (2 mL). The mixture was heated to reflux until the conversion was complete as indicated by TLC (24 h). The solvent was removed under vacuum and the residue was purified by flash column chromatography with silica gel (petroleum ether/EtOAc, 20:1 to 15:1) to give compound **20** (40 mg, 67% yield, *Z/E* = 1/5.8) as a colorless oil.

**(Z)-non-2-en-1-yl (R)-2,2-dichloro-3-hydroxybutanoate (20)**

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  5.80 – 5.72 (m, 2 H), 4.83 (d, *J* = 6.9 Hz, 2H), 4.47 (quint, *J* = 6.4 Hz, 1H), 2.67 – 2.64 (m, 1H), 2.17 – 2.13 (m, 2H), 1.45 (d, *J* = 6.2 Hz, 3H), 1.40 – 1.28 (m, 8H), 0.88 (t, *J* = 6.6 Hz, 3H).

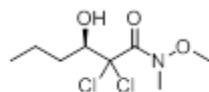
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  165.8, 137.8, 121.5, 87.2, 73.6, 63.7, 29.4, 29.0, 28.5, 27.8, 22.6, 17.2, 14.2.

**(E)-non-2-en-1-yl (R)-2,2-dichloro-3-hydroxybutanoate (20)**

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  5.88 (dt, *J* = 14.3, 6.6 Hz, 1H), 5.59 (dt, *J* = 13.9, 6.0 Hz, 1H), 4.72 (d, *J* = 6.5 Hz, 2H), 4.47 (quint, *J* = 6.4 Hz, 1H), 2.66 (d, *J* = 6.9 Hz, 1H), 2.07 (q, *J* = 7.4, 6.9 Hz, 2H), 1.45 (d, *J* = 6.2 Hz, 3H), 1.40 – 1.28 (m, 8H), 0.88 (t, *J* = 6.6 Hz, 3H).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  165.8, 138.9, 122.1, 87.2, 73.6, 68.7, 32.4, 31.8, 28.9, 28.8, 22.7, 17.2, 14.2.

**HRMS** (ESI/ion trap): *m/z* [M+Na]<sup>+</sup> calcd for C<sub>13</sub>H<sub>22</sub>Cl<sub>2</sub>O<sub>3</sub>Na 319.0844, found 319.0839.

**(R)-2,2-dichloro-3-hydroxy-N-methoxy-N-methylhexanamide (21)**

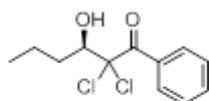
Chemical Formula: C<sub>8</sub>H<sub>15</sub>Cl<sub>2</sub>NO<sub>3</sub>  
Exact Mass: 243.0429

To a solution of *N,O*-dimethylhydroxylamine hydrochloride (0.87 g, 8.9 mmol) in THF (15 mL) was added <sup>t</sup>PrMgCl (2.0 M in THF, 8.9 mL, 17.8 mmol) at –30 °C. The cooling bath was removed for 10 min, then the mixture was cooled again to –30 °C, and a solution of ethyl (*R*)-2,2-dichloro-3-hydroxyhexanoate (**14h**, > 99% ee, 204 mg, 0.89 mmol) in THF (3 mL) was added. The reaction mixture was stirred at –30 °C for 1 h, then warmed to room temperature for 30 min, quenched by satd. NH<sub>4</sub>Cl (10 mL), and extracted with <sup>t</sup>Pr<sub>2</sub>O (3 x 20 mL). The combined extracts were dried (Mg<sub>2</sub>SO<sub>4</sub>), filtered and concentrated. Purification of the residue by flash column chromatography (petroleum ether/EtOAc 12:1 to 8:1) gave **21** (185 mg, 85% yield) as a colorless oil, [α]<sub>D</sub><sup>25</sup> = –34.3 (*c* 1.8, CHCl<sub>3</sub>).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 4.25 (ddd, *J* = 9.5, 4.1, 1.9 Hz, 1H), 3.82 (s, 3H), 3.78 (s, 1H), 3.36 (s, 3H), 1.92 – 1.84 (m, 1H), 1.75 – 1.62 (m, 2H), 1.51 – 1.40 (m, 1H), 0.98 (t, *J* = 7.3 Hz, 3H).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 165.6, 84.6, 77.3, 60.9, 34.9, 32.2, 19.4, 14.0.

HRMS (ESI/ion trap): *m/z* [M+Na]<sup>+</sup> calcd for C<sub>8</sub>H<sub>15</sub>Cl<sub>2</sub>NO<sub>3</sub>Na 266.0327, found 266.0323.

**(R)-2,2-dichloro-3-hydroxy-1-phenylhexan-1-one (22)**

Chemical Formula: C<sub>12</sub>H<sub>14</sub>Cl<sub>2</sub>O<sub>2</sub>  
Exact Mass: 260.0371

To a solution of **21** (49 mg, 0.2 mmol) in THF (1 mL) was added PhMgCl (2.0 M in THF, 0.5 mL, 1.0 mmol) at 0 °C. The reaction mixture was stirred at this temperature for 3 h, quenched with satd. NH<sub>4</sub>Cl (10 mL) and extracted with <sup>t</sup>Pr<sub>2</sub>O (3 x 20 mL). The combined extracts were washed with brine, dried (MgSO<sub>4</sub>), filtered and concentrated. Purification of the residue by flash column chromatography (petroleum ether/EtOAc 15:1) afforded **22** (28 mg, 54% yield) as a colorless oil, [α]<sub>D</sub><sup>25</sup> = –13.7 (*c* 0.8, CHCl<sub>3</sub>).

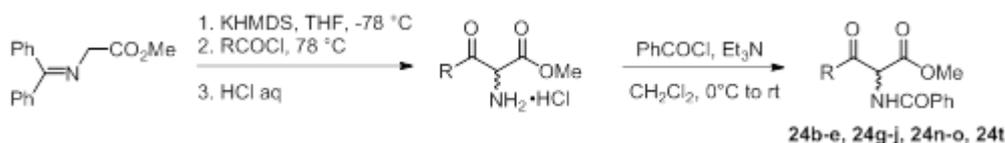
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.29 (dt, *J* = 8.6, 1.6 Hz, 2H), 7.64 – 7.59 (m, 1H), 7.51 – 7.46 (m, 2H), 4.40 (ddd, *J* = 9.7, 5.0, 1.9 Hz, 1H), 3.13 (dd, *J* = 5.1, 1.8 Hz, 1H), 2.00 – 1.92 (m, 1H), 1.80 – 1.68 (m, 2H), 1.53 – 1.47 (m, 1H), 1.01 (t, *J* = 7.4 Hz, 3H).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 190.3, 134.1, 132.0, 131.2 (2C), 128.3 (2C), 88.2, 76.7, 32.7,

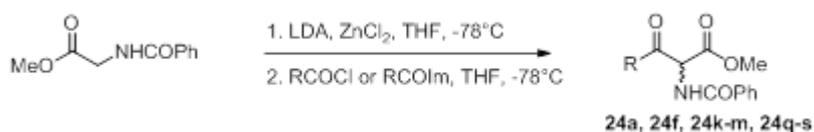
19.4, 14.1.

HRMS (ESI/ion trap):  $m/z$   $[M+Na]^+$  calcd for  $C_{12}H_{14}Cl_2O_2Na$  283.0269, found 283.0264.

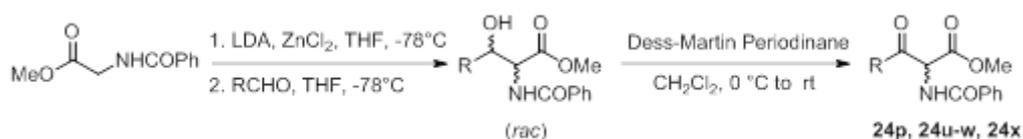
**General procedure for preparation of  $\alpha$ -amido- $\beta$ -keto esters (24a-z)**

**General procedure F:**

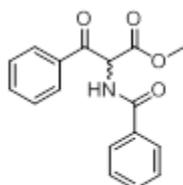
To a  $-78$  °C solution of benzophenone Schiff base (1.0 equiv) in THF (0.6 M) was added KHMDS (1 M in THF, 1.0 equiv), and the resulting mixture was stirred for 1 h at  $-78$  °C. The mixture was then added to a  $-78$  °C pre-cooled solution of acyl chloride in THF (0.2 M) and stirred at  $-78$  °C for 1 h, followed by a careful in situ 3.0 M HCl acid hydrolysis (30 mL). The mixture was concentrated under vacuum, and the resulting  $\alpha$ -amino- $\beta$ -keto ester hydrochloride salt was purified by filtration over a short pad of silica gel using  $CH_2Cl_2/MeOH$  (9:1) as eluent. After concentration under vacuum, the residue was taken up in EtOAc and filtered. Then the purified  $\alpha$ -amino- $\beta$ -keto ester hydrochloride salt was treated with benzoyl chloride (1.1 eq) in the presence of  $Et_3N$  (3.0 eq.) in  $CH_2Cl_2$  (0.3 M) at 0 °C and the reaction mixture was allowed to stir for 2.5 h at rt before it was quenched with sat.  $NH_4Cl$  and extracted with  $Et_2O$ . The combined organic layers were dried ( $MgSO_4$ ), the solvent was evaporated under vacuum, and the crude product was purified by flash chromatography on silica gel (cyclohexane/EtOAc) to give the desired  $\alpha$ -amido- $\beta$ -keto ester.

**General procedure G:**

To a  $-78$  °C solution of diisopropylamine (3.3 equiv) in THF (10 mL) was added  $n$ -BuLi (2.5 M in hexanes, 3.0 equiv). The solution was stirred for 10 min before the cooling bath was removed and the solution was stirred further for 10 min. In a two-neck round-bottom flask containing dried  $ZnCl_2$  (1.2 equiv) and  $N$ -benzoylglycine methyl ester (7.5 mmol, 1 equiv) was added THF (50 mL). The mixture was cooled to  $-78$  °C before the above prepared LDA solution was added slowly. The resulting solution was stirred for 1.5 h at  $-78$  °C, the acyl halide or imidazolide (1.1 equiv) was added, and the reaction mixture was allowed to stir at  $-78$  °C for 1–2 h before it was quenched with sat.  $NH_4Cl$  and extracted with  $Et_2O$ . The combined organic layers were dried ( $MgSO_4$ ), the solvent was evaporated under vacuum, and the crude product was purified by flash chromatography on silica gel (cyclohexane/EtOAc) to give the desired  $\alpha$ -amido- $\beta$ -keto ester.

**General procedure H:**

To a  $-78\text{ }^{\circ}\text{C}$  solution of diisopropylamine (3.3 equiv) in THF (10 mL) was added *n*-BuLi (2.5 M in hexanes, 3.0 equiv). The solution was stirred for 10 min before the cooling bath was removed and the solution was stirred further for 10 min. In a two-neck round-bottom flask containing dried  $\text{ZnCl}_2$  (1.2 equiv) and protected glycine *N*-benzoylglycine methyl ester (7.5 mmol, 1 equiv) was added THF (50 mL). The mixture was cooled to  $-78\text{ }^{\circ}\text{C}$  before the above prepared LDA solution was added slowly. The resulting solution was stirred for 1.5 h at  $-78\text{ }^{\circ}\text{C}$ , the aldehyde (1.1 equiv) was added, and the reaction mixture was allowed to stir for 1–2 h at  $-78\text{ }^{\circ}\text{C}$  before it was quenched with sat.  $\text{NH}_4\text{Cl}$  and extracted with  $\text{Et}_2\text{O}$ . The combined organic layers were dried ( $\text{MgSO}_4$ ), the solvent was evaporated under vacuum, and the crude product was purified by flash chromatography on silica gel (cyclohexane/ $\text{EtOAc}$ ) to give the corresponding (*rac*)- $\alpha$ -amido- $\beta$ -hydroxy ester. To a  $0\text{ }^{\circ}\text{C}$  solution of (*rac*)- $\alpha$ -amido- $\beta$ -hydroxy ester (1.0 eq.) in  $\text{CH}_2\text{Cl}_2$  (0.3 M) was added Dess-Martin periodinane (1.1–1.2 eq) in small portions. The reaction mixture was stirred at rt for 1 h, then quenched by sat.  $\text{NaHCO}_3$  and extracted with  $\text{CH}_2\text{Cl}_2$ . The combined organic layers were washed with sat.  $\text{NaCl}$ , dried ( $\text{MgSO}_4$ ), concentrated under vacuum, and the crude product was purified by flash chromatography on silica gel (cyclohexane/ $\text{EtOAc}$ ) to give the desired  $\alpha$ -amido- $\beta$ -keto ester.

Methyl 2-benzoylamino-3-oxo-3-phenylpropanoate (**24a**)

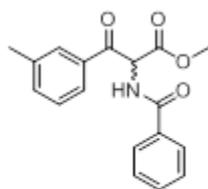
Chemical Formula:  $\text{C}_{17}\text{H}_{15}\text{NO}_4$   
Exact Mass: 297.1001

Synthesized according to general procedure **G**: 2.14 g (72% yield), white solid, m.p.  $140\text{ }^{\circ}\text{C}$ ;

$^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.20–8.17 (m, 2H), 7.93–7.81 (m, 2H), 7.73–7.61 (m, 1H), 7.58–7.42 (m, 6H), 6.41 (d,  $J = 7.3\text{ Hz}$ , 1H), 3.74 (s, 3H);

$^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ )  $\delta$  191.6, 167.3, 167.0, 134.7, 134.2, 133.2, 132.2, 129.7 (2C), 129.0 (2C), 128.8 (2C), 127.4 (2C), 58.5, 53.4.

**MS** (ESI):  $m/z = 298$  [ $\text{M} + \text{H}$ ] $^+$ .

Methyl 2-benzoylamino-3-oxo-3-(m-tolyl)propanoate (**24b**)

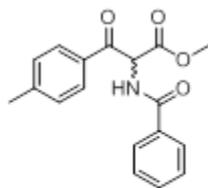
Chemical Formula: C<sub>18</sub>H<sub>17</sub>NO<sub>4</sub>  
Exact Mass: 311.1158

Synthesized according to general procedure **F**: 1.2 g (24% yield), white solid, m.p. 90 °C;

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 8.0–7.98 (m, 2H), 7.93–7.83 (m, 2H), 7.59–7.37 (m, 6H), 6.40 (d, *J* = 7.3 Hz, 1H), 3.74 (s, 3H), 2.44 (s, 3H);

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 191.8, 167.4, 167.0, 139.0, 135.6, 134.3, 133.4, 132.3, 130.2, 128.9, 128.8 (2C), 127.5 (2C), 127.1, 58.5, 53.4, 21.5.

**MS** (ESI): *m/z* = 312 [M + H]<sup>+</sup>.

Methyl 2-benzoylamino-3-oxo-3-(p-tolyl)propanoate (**24c**)

Chemical Formula: C<sub>18</sub>H<sub>17</sub>NO<sub>4</sub>  
Exact Mass: 311.1158

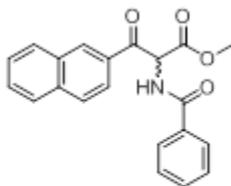
Synthesized according to general procedure **F**: 1.2 g (32% yield), white solid, m.p. 117 °C;

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 8.09 (d, *J* = 8.3 Hz, 2H), 7.92–7.82 (m, 2H), 7.59–7.41 (m, 4H), 7.37–7.29 (m, 2H), 6.38 (d, *J* = 7.4 Hz, 1H), 3.74 (s, 3H), 2.44 (s, 3H);

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 191.0, 167.5, 167.0, 146.0, 133.4, 132.2, 131.7, 129.9 (2C), 129.7 (2C), 128.8 (2C), 127.5 (2C), 58.4, 53.4, 21.9.

**MS** (ESI): *m/z* = 312 [M + H]<sup>+</sup>.

Methyl 2-benzoylamino-3-(naphthalen-2-yl)-3-oxopropanoate (**24d**)



Chemical Formula:  $C_{21}H_{17}NO_4$   
Exact Mass: 347.1158

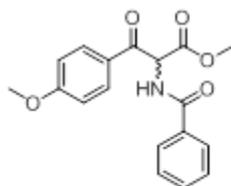
Synthesized according to general procedure **F**: 0.69 g (60% yield), white solid, m.p. 112 °C;

$^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.82 (s, 1H), 8.15 (dd,  $J = 8.7, 1.8$  Hz, 1H), 8.06 (d,  $J = 7.7$  Hz, 1H), 7.99–7.83 (m, 4H), 7.72–7.41 (m, 6H), 6.59 (d,  $J = 7.4$  Hz, 1H), 3.75 (s, 3H);

$^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ )  $\delta$  191.5, 167.5, 167.1, 136.4, 133.4, 132.6 (2C), 132.3, 131.6, 130.3, 129.6, 129.0, 128.8 (2C), 128.0, 127.5 (2C), 127.3, 124.5, 58.6, 53.5.

**MS** (ESI):  $m/z = 348$   $[\text{M} + \text{H}]^+$

Methyl 2-benzoylamino-3-(4-methoxyphenyl)-3-oxopropanoate (**24e**)



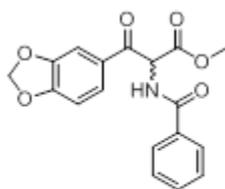
Chemical Formula:  $C_{18}H_{17}NO_5$   
Exact Mass: 327.1107

Synthesized according to general procedure **F**: 1.63 g (43% yield), white solid, m.p. 118 °C;

$^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.21–8.17 (m, 2H), 7.95–7.81 (m, 2H), 7.61–7.39 (m, 4H), 7.07–6.94 (m, 2H), 6.35 (d,  $J = 7.4$  Hz, 1H), 3.90 (s, 3H), 3.74 (s, 3H);

$^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ )  $\delta$  189.6, 167.6, 167.0, 164.9, 133.4, 132.3 (2C), 132.1, 128.7 (2C), 127.4 (2C), 127.0, 114.3 (2C), 58.2, 55.7, 53.3.

**MS** (ESI):  $m/z = 328$   $[\text{M} + \text{H}]^+$ .

Methyl 2-benzoylamino-3-(benzo[d][1,3]dioxol-5-yl)-3-oxopropanoate (**24f**)

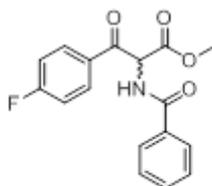
Chemical Formula:  $C_{18}H_{15}NO_8$   
Exact Mass: 341.0899

Prepared according to general procedure **G**: 1.2 g (70% yield), white solid, m.p. 78 °C;

$^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.94–7.79 (m, 3H), 7.58 (d,  $J = 1.8$  Hz, 1H), 7.57–7.49 (m, 2H), 7.49–7.42 (m, 2H), 6.91 (d,  $J = 8.3$  Hz, 1H), 6.31 (d,  $J = 7.4$  Hz, 1H), 6.07 (s, 2H), 3.74 (s, 3H);

$^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ )  $\delta$  189.4, 167.5, 166.9, 153.3, 148.6, 133.3, 132.2, 128.8 (3C), 127.4 (2C), 127.0, 109.0, 108.4, 102.3, 58.3, 53.4.

**MS** (ESI):  $m/z = 342$   $[\text{M} + \text{H}]^+$ .

Methyl 2-benzoylamino-3-(4-fluorophenyl)-3-oxopropanoate (**24g**)

Chemical Formula:  $C_{17}H_{14}FNO_4$   
Exact Mass: 315.0907

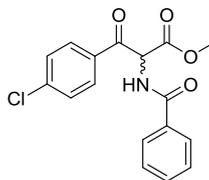
Synthesized according to general procedure **F**: 0.34 g (9% yield), white solid, m.p. 124 °C;

$^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.32–8.17 (m, 2H), 7.89–7.80 (m, 2H), 7.60–7.39 (m, 4H), 7.25–7.15 (m, 2H), 6.37 (d,  $J = 7.3$  Hz, 1H), 3.76 (s, 3H);

$^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ )  $\delta$  190.2, 167.2, 167.0, 166.8 (d,  $^1J_{CF} = 256.1$  Hz), 133.2, 132.7 (d,  $^3J_{CF} = 9.6$  Hz, 2C), 132.4, 130.7 (d,  $^4J_{CF} = 2.4$  Hz), 128.9 (2C), 127.5 (2C), 116.3 (d,  $^2J_{CF} = 22.1$  Hz, 2C), 58.4, 53.6.

**MS** (ESI):  $m/z = 316$   $[\text{M} + \text{H}]^+$ .

Methyl 2-benzoylamino-3-(4-chlorophenyl)-3-oxopropanoate (**24h**)



Chemical Formula: C<sub>17</sub>H<sub>14</sub>ClNO<sub>4</sub>  
Exact Mass: 331.0611

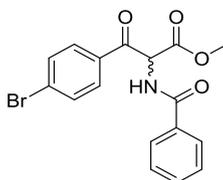
Synthesized according to general procedure **F**: 0.32 g (25% yield), white solid, m.p. 118 °C;

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.13 (d, *J* = 8.5 Hz, 2H), 7.94–7.78 (m, 2H), 7.62–7.37 (m, 6H), 6.36 (d, *J* = 7.3 Hz, 1H), 3.75 (s, 3H);

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 190.7, 167.2, 167.0, 141.4, 133.1, 132.7, 132.4, 131.1 (2C), 129.4 (2C), 128.8 (2C), 127.5 (2C), 58.5, 53.6.

MS (ESI): *m/z* = 332 [M + H]<sup>+</sup>.

Methyl 2-benzoylamino-3-(4-bromophenyl)-3-oxopropanoate (**24i**)



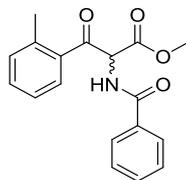
Chemical Formula: C<sub>17</sub>H<sub>14</sub>BrNO<sub>4</sub>  
Exact Mass: 375.0106

Synthesized according to general procedure **F**: 0.685 g (57% yield), white solid, m.p. 124 °C;

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.07 (d, *J* = 8.6 Hz, 2H), 7.95–7.82 (m, 2H), 7.70 (d, *J* = 8.6 Hz, 2H), 7.62–7.40 (m, 4H), 6.37 (d, *J* = 7.3 Hz, 1H), 3.78 (s, 3H);

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 190.9, 167.1, 167.0, 133.1, 132.4 (4C), 131.2 (2C), 130.3, 128.9 (2C), 127.5 (2C), 58.5, 53.6.

MS (ESI): *m/z* = 376, 378 [M + H]<sup>+</sup>.

Methyl 2-benzoylamino-3-oxo-3-(*o*-tolyl)propanoate (**24j**)

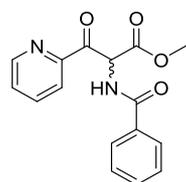
Chemical Formula: C<sub>18</sub>H<sub>17</sub>NO<sub>4</sub>  
Exact Mass: 311.1158

Synthesized according to general procedure **F**: 0.62 g (8% yield), white solid, m.p. 117 °C;

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.04 (d, *J* = 7.0 Hz, 1H), 7.93–7.81 (m, 2H), 7.59–7.41 (m, 5H), 7.40–7.27 (m, 2H), 6.27 (d, *J* = 7.0 Hz, 1H), 3.70 (s, 3H), 2.50 (s, 3H);

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 194.4, 167.4, 167.0, 139.9, 134.7, 133.3, 132.9, 132.2 (2C), 130.1, 128.8 (2C), 127.5 (2C), 126.1, 60.7, 53.3, 21.3.

MS (ESI): *m/z* = 312 [M + H]<sup>+</sup>.

Methyl 2-benzoylamino-3-oxo-3-(pyridin-2-yl)propanoate (**24k**)

Chemical Formula: C<sub>16</sub>H<sub>14</sub>N<sub>2</sub>O<sub>4</sub>  
Exact Mass: 298.0954

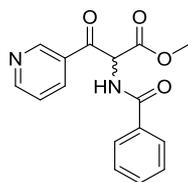
Prepared according to general procedure **G**: 1.02 g (35% yield), white solid, m.p. 102 °C;

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.75 (ddd, *J* = 4.7, 1.6, 0.9 Hz, 1H), 8.12 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.96–7.75 (m, 3H), 7.59–7.37 (m, 5H), 6.72 (d, *J* = 7.5 Hz, 1H), 3.74 (s, 3H);

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 192.4, 168.1, 166.8, 151.3, 149.2, 137.4, 133.4, 132.1, 128.7 (2C), 128.0, 127.4 (2C), 123.3, 58.0, 53.3.

MS (ESI): *m/z* = 299 [M + H]<sup>+</sup>.

Methyl 2-benzoylamino-3-oxo-3-(pyridin-3-yl)propanoate (**24l**)



Chemical Formula: C<sub>16</sub>H<sub>14</sub>N<sub>2</sub>O<sub>4</sub>  
Exact Mass: 298.0954

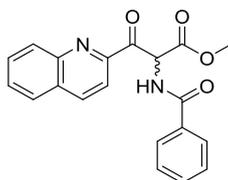
Prepared according to general procedure **G**: 0.6 g (20% yield), white solid, m.p. 93 °C;

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 9.37 (d, *J* = 1.7 Hz, 1H), 8.85 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.48–8.39 (m, 1H), 7.91–7.81 (m, 2H), 7.57–7.42 (m, 5H), 6.36 (d, *J* = 7.1 Hz, 1H), 3.77 (s, 3H);

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 191.1, 167.1, 166.8, 154.7, 150.9, 136.9, 133.0, 132.4, 130.1, 128.9 (2C), 127.5 (2C), 123.8, 58.8, 53.7.

MS (ESI): *m/z* = 299 [M + H]<sup>+</sup>.

Methyl 2-benzoylamino-3-oxo-3-(quinolin-2-yl)propanoate (**24m**)



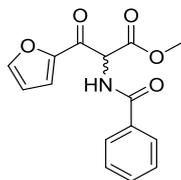
Chemical Formula: C<sub>20</sub>H<sub>16</sub>N<sub>2</sub>O<sub>4</sub>  
Exact Mass: 348.1110

Prepared according to general procedure **G**: 0.95 g (28% yield), white solid, m.p. 156 °C;

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.34 (d, *J* = 8.5 Hz, 1H), 8.23 (d, *J* = 8.5 Hz, 1H), 8.17 (d, *J* = 8.5 Hz, 1H), 7.93–7.79 (m, 4H), 7.73–7.69 (m, 1H), 7.61 (br d, *J* = 7.4 Hz, 1H), 7.55–7.41 (m, 3H), 6.87 (d, *J* = 7.7 Hz, 1H), 3.74 (s, 3H);

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 192.6, 168.4, 166.9, 150.7, 147.1, 137.6, 133.6, 132.1, 130.8, 130.6, 130.1, 129.4, 128.7 (2C), 127.9, 127.4 (2C), 119.0, 58.3, 53.3.

MS (ESI): *m/z* = 349 [M + H]<sup>+</sup>.

Methyl 2-benzoylamino-3-(furan-2-yl)-3-oxopropanoate (**24n**)

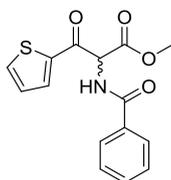
Chemical Formula: C<sub>15</sub>H<sub>13</sub>NO<sub>5</sub>  
Exact Mass: 287.0794

Synthesized according to general procedure **F**: 1.47 g (43% yield), white solid, m.p. 85 °C;

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.86 (dd, *J* = 5.3, 3.2 Hz, 2H), 7.76–7.68 (m, 1H), 7.63–7.35 (m, 5H), 6.64 (dd, *J* = 3.7, 1.7 Hz, 1H), 6.17 (d, *J* = 7.4 Hz, 1H), 3.79 (s, 3H);

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 179.4, 167.2, 167.0, 150.5, 148.6, 133.2, 132.3, 128.8 (2C), 127.5 (2C), 121.6, 113.1, 58.5, 53.5.

**MS** (ESI): *m/z* = 288 [M + H]<sup>+</sup>.

Methyl 2-benzoylamino-3-oxo-3-(thiophen-2-yl)propanoate (**24o**)

Chemical Formula: C<sub>15</sub>H<sub>13</sub>NO<sub>4</sub>S  
Exact Mass: 303.0565

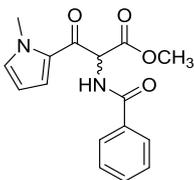
Synthesized according to general procedure **G**: 4.6 g (76% yield), white solid, m.p. 105 °C;

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 8.18 (dd, *J* = 3.9, 1.0 Hz, 1H), 7.87 (dd, *J* = 5.3, 3.2 Hz, 2H), 7.80 (dd, *J* = 4.9, 1.0 Hz, 1H), 7.60–7.39 (m, 4H), 7.22 (dd, *J* = 4.9, 4.0 Hz, 1H), 6.23 (d, *J* = 7.4 Hz, 1H), 3.79 (s, 3H);

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 183.8, 167.2, 167.0, 141.0, 136.6, 135.7, 133.2, 132.3, 128.9, 128.8 (2C), 127.5 (2C), 59.4, 53.6.

**MS** (ESI): *m/z* = 304 [M + H]<sup>+</sup>.

Methyl 2-benzamido-3-(1-methyl-1H-pyrrol-2-yl)-3-oxopropanoate (**24p**)



Chemical Formula: C<sub>16</sub>H<sub>16</sub>N<sub>2</sub>O<sub>4</sub>  
Exact Mass: 300.1110

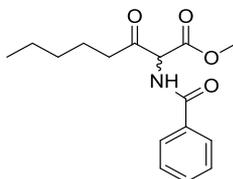
Synthesized according to general procedure **H**: 1.1 g (52% yield), white solid, m.p. 82 °C;

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.97 – 7.78 (m, 2H), 7.57 – 7.42 (m, 5H), 6.95 (s, 1H), 6.24 (dd, *J* = 4.3, 2.4 Hz, 1H), 6.07 (d, *J* = 7.4 Hz, 1H), 3.96 (s, 3H), 3.77 (s, 3H);

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 179.8, 168.1, 166.8, 133.7, 133.5, 132.0, 128.7 (2C), 128.2, 127.4 (2C), 123.2, 109.5, 58.8, 53.2, 37.8 ppm.

MS (ESI): *m/z* = 301 [M + H]<sup>+</sup>.

Methyl 2-benzoylamino-3-oxooctanoate (**24q**)



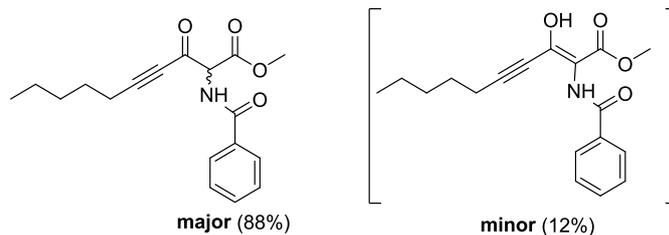
Chemical Formula: C<sub>16</sub>H<sub>21</sub>NO<sub>4</sub>  
Exact Mass: 291.1471

Synthesized according to general procedure **G**: 2.36g (52% yield), pale yellow oil;

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.89–7.78 (m, 2H), 7.58–7.40 (m, 3H), 7.33 (br d, *J* = 5.8 Hz, 1H), 5.44 (d, *J* = 6.5 Hz, 1H), 3.83 (s, 3H), 2.87–2.64 (m, 2H), 1.74–1.57 (m, 2H), 1.43–1.22 (m, 4H), 0.89 (t, *J* = 6.9 Hz, 3H);

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 201.3, 167.0, 166.9, 133.2, 132.2, 128.8 (2C), 127.4 (2C), 62.9, 53.4, 41.0, 31.2, 23.3, 22.5, 14.0.

MS (ESI): *m/z* = 292 [M + H]<sup>+</sup>.

Methyl 2- benzoylamino-3-oxodec-4-ynoate (**24r**)

Chemical Formula: C<sub>18</sub>H<sub>21</sub>NO<sub>4</sub>  
Exact Mass: 315.1471

Synthesized according to general procedure **H**: 0.61 g (58% yield), white solid, m.p. 106 °C.

**Keto form:**

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.89–7.80 (m, 2H), 7.58–7.41 (m, 3H), 7.33–7.25 (m, 1H), 5.51 (d, *J* = 6.7 Hz, 1H), 3.86 (s, 3H), 2.41 (t, *J* = 7.1 Hz, 2H), 1.62–1.53 (m, 2H), 1.46–1.22 (m, 4H), 0.88 (t, *J* = 7.1 Hz, 3H);

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 177.7, 166.8, 166.4, 133.2, 132.3, 128.8 (2C), 127.4 (2C), 101.3, 78.7, 64.6, 53.6, 31.1, 27.3, 22.2, 19.4, 13.9.

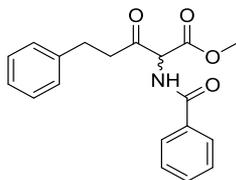
**Enol form:**

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 11.93 (s, 1H), 7.89–7.80 (m, 2H), 7.58–7.41 (m, 3H), 7.08 (br s, 1H), 3.78 (s, 3H), 2.33 (t, *J* = 7.0 Hz, 2H), 1.62–1.53 (m, 2H), 1.21–1.11 (m, 4H), 0.75 (t, *J* = 7.1 Hz, 3H);

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 170.7, 167.0, 154.9, 134.3, 132.0, 128.8 (2C), 127.4 (2C), 106.5, 103.5, 73.6, 52.5, 31.1, 27.7, 22.2, 19.7, 13.9.

MS (ESI): *m/z* = 316 [M + H]<sup>+</sup>.

Methyl 2-benzoylamino-3-oxo-5-phenylpentanoate (**24s**)



Chemical Formula: C<sub>19</sub>H<sub>19</sub>NO<sub>4</sub>  
Exact Mass: 325.1314

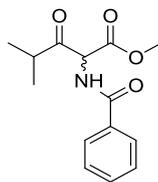
Synthesized according to general procedure **G**: 2.1 g (44% yield), white solid, m.p. 88 °C;

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.85–7.83 (m, 2H), 7.57–7.54 (m 1H), 7.50–7.42 (m, 2H), 7.33–7.14 (m, 6H), 5.44 (d, *J* = 6.4 Hz, 1H), 3.75 (s, 3H), 3.25–2.93 (m, 4H);

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 200.3, 167.0, 166.7, 140.3, 133.1, 132.3, 128.8 (2C), 128.7 (2C), 128.5 (2C), 127.4 (2C), 126.5, 63.0, 53.5, 42.6, 29.5.

MS (ESI): *m/z* = 326 [M + H]<sup>+</sup>.

Methyl 2-benzoylamino-4-methyl-3-oxopentanoate (**24t**)



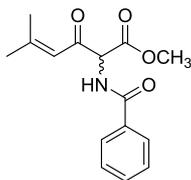
Chemical Formula: C<sub>14</sub>H<sub>17</sub>NO<sub>4</sub>  
Exact Mass: 263.1158

Synthesized according to general procedure **F**: 2.58 g (97% yield), white solid, m.p. 40 °C;

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.91–7.78 (m, 2H), 7.60–7.40 (m, 3H), 7.32 (br d, *J* = 5.9 Hz, 1H), 5.61 (d, *J* = 6.7 Hz, 1H), 3.82 (s, 3H), 3.13 (hept, *J* = 6.9 Hz, 1H), 1.25 (d, *J* = 6.9 Hz, 3H), 1.14 (d, *J* = 6.9 Hz, 3H);

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 205.2, 167.1, 166.9, 133.2, 132.2, 128.8 (2C), 127.4 (2C), 61.2, 53.4, 39.0, 19.0, 17.8.

MS (ESI): *m/z* = 264 [M + H]<sup>+</sup>.

Methyl 2-benzamido-5-methyl-3-oxohex-4-enoate (**24u**)

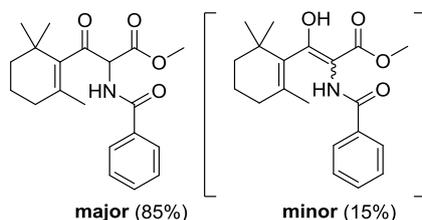
Chemical Formula: C<sub>15</sub>H<sub>17</sub>NO<sub>4</sub>  
Exact Mass: 275.1158

Synthesized according to general procedure **H**: Pale yellow oil; 0.75 g, 91% yield

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.87 – 7.84 (m, 2H), 7.54 – 7.38 (m, 4H), 6.45 – 6.38 (m, 1H), 5.38 (d, *J* = 6.3 Hz, 1H), 3.81 (s, 3H), 2.23 (d, *J* = 1.0 Hz, 3H), 1.99 (d, *J* = 1.1 Hz, 3H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 188.5, 167.5, 166.8, 162.9, 133.4, 132.1, 128.7 (2C), 127.4 (2C), 120.4, 63.5, 53.3, 28.4, 21.9.

MS (ESI): *m/z* = 276 [M + H]<sup>+</sup>.

Methyl 2-benzamido-3-oxo-3-(2,6,6-trimethylcyclohex-1-en-1-yl)propanoate (**24v**)

Chemical Formula: C<sub>20</sub>H<sub>25</sub>NO<sub>4</sub>  
Exact Mass: 343.1784

Synthesized according to general procedure **H**: Pale yellow oil, 0.85 g, 66% yield.

**Keto form:**

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.89 – 7.84 (m, 2H), 7.56 – 7.38 (m, 4H), 5.71 (d, *J* = 7.1 Hz, 1H), 3.79 (s, 3H), 2.11 – 1.96 (m, 2H), 1.76 – 1.65 (m, 2H), 1.62 (s, 3H), 1.50 – 1.40 (m, 2H), 1.28 (s, 3H), 0.94 (s, 3H);

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 199.4, 166.8, 166.7, 139.7, 136.4, 133.4, 132.1, 128.7 (2C), 127.4 (2C), 65.2, 53.1, 39.2, 33.7, 31.8, 29.3, 28.4, 21.8, 18.6.

**Enol form:**

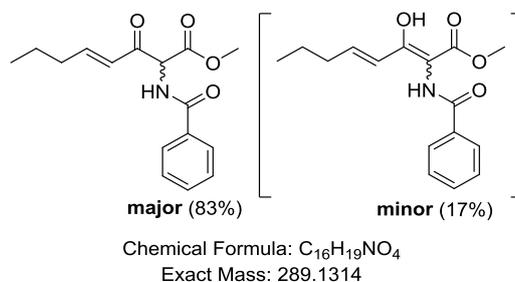
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 12.44 (s, 1H), 7.73 – 7.69 (m, 2H), 7.56 – 7.38 (m, 3H), 6.64 (s, 1H), 3.77 (s, 3H), 2.11 – 1.96 (m, 2H), 1.76 – 1.65 (m, 2H), 1.69 (s, 3H), 1.50 – 1.40 (m, 2H), 1.16 (s, 3H), 1.02 (s, 3H);

## Experimental part

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  173.6, 171.1, 165.3, 135.0, 134.8, 133.0, 131.7, 128.8 (2C), 127.1 (2C), 102.6, 52.3, 39.2, 34.5, 31.5, 29.3, 28.7, 21.3, 18.9.

MS (ESI):  $m/z = 344$   $[\text{M} + \text{H}]^+$ .

### Methyl (E)-2-benzamido-3-oxooct-4-enoate (**24w**)



Synthesized according to general procedure **H**: 0.9 g (78% yield), a colorless oil.

#### Keto form:

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.91 – 7.81 (m, 2H), 7.56 – 7.41 (m, 4H), 7.29 – 7.18 (m, 1H), 6.45 (dt,  $J = 15.7, 1.5$  Hz, 1H), 5.65 (d,  $J = 6.7$  Hz, 1H), 3.80 (s, 3H), 2.28 (qd,  $J = 7.2, 1.4$  Hz, 2H), 1.60 – 1.42 (m, 2H), 0.95 (t,  $J = 7.4$  Hz, 3H);

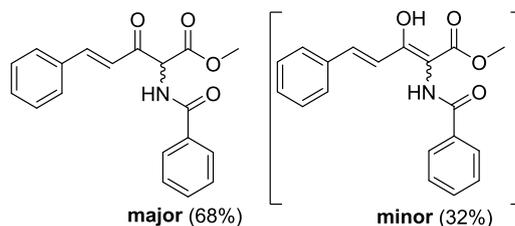
$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  189.4, 167.2, 166.9, 152.9, 133.3, 132.2, 128.8 (2C), 127.4 (2C), 126.4, 61.4, 53.4, 35.0, 21.3, 13.8 ppm.

#### Enol form:

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  12.23 (s, 1H), 7.91 – 7.81 (m, 2H), 7.56 – 7.41 (m, 3H), 7.01 (br s, 1H), 6.79 (dt,  $J = 14.5, 7.1$  Hz, 1H), 6.22 (dd,  $J = 15.5, 1.5$  Hz, 1H), 3.76 (s, 3H), 2.16 (qd,  $J = 7.2, 1.4$  Hz, 2H), 1.60 – 1.42 (m, 2H), 0.90 (t,  $J = 7.4$  Hz, 3H);

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  171.3, 168.0, 167.5, 143.9, 133.3, 132.2, 128.8 (2C), 127.4 (2C), 120.2, 99.2, 52.3, 35.2, 21.9, 13.8 ppm.

MS (ESI):  $m/z = 290$   $[\text{M} + \text{H}]^+$ .

Methyl (E)-2-benzamido-3-oxo-5-phenylpent-4-enoate (**24x**)

Chemical Formula: C<sub>19</sub>H<sub>17</sub>NO<sub>4</sub>  
Exact Mass: 323.1158

Synthesized according to general procedure **H**: 0.58 g (59% yield), white solid.

**Keto form:**

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.95 – 7.84 (m, 3H), 7.64 – 7.40 (m, 8H), 7.34 – 7.29 (m, 1H), 7.09 (d, *J* = 16.0 Hz, 1H), 5.76 (d, *J* = 6.7 Hz, 1H), 3.82 (s, 3H);

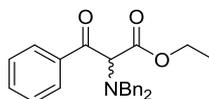
<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 189.3, 167.0, 166.8, 146.7, 133.9, 133.1, 132.1, 131.5, 129.1 (2C), 128.9 (2C), 128.6 (2C), 127.3 (2C), 121.8, 61.9, 53.3 ppm.

**Enol form:**

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 12.33 (s, 1H), 7.95 – 7.84 (m, 3H), 7.64 – 7.40 (m, 7H), 7.34 – 7.29 (m, 1H), 7.20 (br s, 1H), 6.87 (dd, *J* = 15.9, 1.6 Hz, 1H), 3.78 (s, 3H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 171.0, 167.6, 167.5, 138.9, 135.4, 134.0, 132.0, 129.6, 128.7 (4C), 127.9 (2C), 127.4 (2C), 117.4, 100.6, 52.3.

MS (ESI): *m/z* = 324 [M + H]<sup>+</sup>.

Ethyl 2-(dibenzylamino)-3-oxo-3-phenylpropanoate (**24y**)

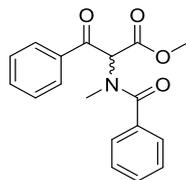
Chemical Formula: C<sub>25</sub>H<sub>25</sub>NO<sub>3</sub>  
Exact Mass: 387.1834

Synthesized according to general procedure **F**: 0.85 g (21% yield), a colorless oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.73 – 7.66 (m, 2H), 7.63 – 7.54 (m, 1H), 7.45 – 7.36 (m, 2H), 7.35 – 7.23 (m, 6H), 7.21 – 7.15 (m, 4H), 4.99 (s, 1H), 4.34 (d, *J* = 7.1 Hz, 2H), 3.96 (d, *J* = 13.7 Hz, 2H), 3.95 (d, *J* = 13.7 Hz, 2H), 3.91 (d, *J* = 13.7 Hz, 1H), 1.35 (t, *J* = 7.1 Hz, 3H).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 196.2, 169.7, 138.9 (2C), 135.7, 133.6, 129.4 (4C), 129.3 (2C), 128.4 (6C), 127.5 (2C), 67.6, 61.0, 55.5 (2C), 14.5.

Methyl 2-(N-methylbenzamido)-3-oxo-3-phenylpropanoate (**24z**)



Chemical Formula: C<sub>18</sub>H<sub>17</sub>NO<sub>4</sub>  
Exact Mass: 311.1158

Synthesized according to general procedure **G**: 1.7 g (78% yield), a colorless oil.

**Keto form:**

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.07 – 8.03 (m, 2H), 7.56 – 7.34 (m, 8H), 6.94 (s, 1H), 3.86 (s, 3H), 2.95 (s, 3H)

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 193.2, 172.0, 168.3, 134.8, 134.6 (2C), 130.3, 129.2 (2C), 128.8 (2C), 128.6 (2C), 127.1 (2C), 61.6, 52.8, 35.3.

**Enol form:**

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 12.61 (s, 1H), 7.69 – 7.63 (m, 3H), 7.56 – 7.34 (m, 2H), 7.26 – 7.22 (m, 1H), 7.17 – 7.10 (m, 2H), 6.92 – 6.89 (m, 2H), 3.87 (s, 3H), 3.25 (s, 3H)

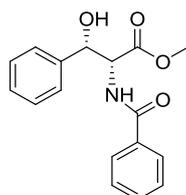
<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 172.3, 171.7, 169.8, 136.2, 132.5, 131.4, 129.6, 128.7 (2C), 128.0 (2C), 127.7 (2C), 126.5 (2C), 109.9, 52.6, 37.6.

MS (ESI):  $m/z = 312$  [M + H]<sup>+</sup>.

### General procedure for the synthesis of **25** via ATH

A round-bottom tube equipped with a balloon of argon was charged with the corresponding  $\alpha$ -amido  $\beta$ -keto ester **24** (0.8 mmol) and the rhodium complex (*R,R*)-**C84** (4.0  $\mu$ mol, 0.5 mol%). The solids were subjected to three vacuum/argon cycles before degassed CH<sub>2</sub>Cl<sub>2</sub> (1.6 mL) was added. The mixture was stirred at room temperature for 3–5 min, and the tube was transferred into an ice-water bath, before the HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) azeotropic mixture (134  $\mu$ L, 1.6 mmol, 2.0 equiv) was added dropwise. After complete consumption of the starting material (monitored by TLC or <sup>1</sup>H NMR), the reaction was quenched with sat. NaHCO<sub>3</sub>, and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were washed with brine, dried (MgSO<sub>4</sub>), filtered and concentrated under vacuum. The conversion and diastereomeric ratio were determined by <sup>1</sup>H NMR analysis of the crude product. After filtration of the crude product on silica gel (petroleum ether/ethyl acetate), the enantiomeric excess was determined by SFC or HPLC analysis (CHIRALCEL OD-H or CHIRALPAK IA, IB, IC or AD-H column)

### Methyl (2*R*,3*S*)-2-benzoylamino-3-hydroxy-3-phenylpropanoate (**25a**)



Chemical Formula: C<sub>17</sub>H<sub>17</sub>NO<sub>4</sub>  
Exact Mass: 299.1158

White solid, 223 mg, 93% yield, *syn/anti* = 92:8, *ee*<sub>*syn*</sub> > 99%;

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.77–7.61 (m, 2H), 7.55–7.44 (m, 1H), 7.44–7.20 (m, 7H), 6.94 (d, *J* = 8.6 Hz, 1H), 5.37 (t, *J* = 3.6 Hz, 1H), 5.06 (dd, *J* = 8.6, 3.1 Hz, 1H), 3.75 (s, 3H), 3.29 (d, *J* = 4.1 Hz, 1H);

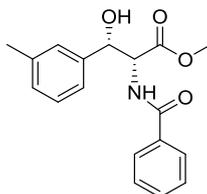
<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  171.2, 167.8, 139.8, 133.9, 131.9, 128.7 (2C), 128.6 (2C), 128.3, 127.2 (2C), 125.9 (2C), 73.9, 58.7, 52.8.

MS (ESI): *m/z* = 300 [M + H]<sup>+</sup>.

HRMS (ESI/ion trap): *m/z* [M + Na]<sup>+</sup> calcd for C<sub>17</sub>H<sub>17</sub>NNaO<sub>4</sub> 322.1055, found 322.1057.

SFC: Chiralpak AD-H, *sc*CO<sub>2</sub>/MeOH 85/15, 3.0 mL/min, P = 150 bar,  $\lambda$  = 215 nm, *t*<sub>R</sub> [*syn*-(*R,S*)] = 8.17 min (major), *t*<sub>R</sub> [*syn*-(*S,R*)] = 8.83 min, *t*<sub>R</sub> [*anti*] = 10.60 min, *t*<sub>R</sub> [*anti*] = 11.70 min.

Methyl (2*R*,3*S*)-2-benzoylamino-3-hydroxy-3-(*m*-tolyl)propanoate (**25b**)



Chemical Formula: C<sub>18</sub>H<sub>19</sub>NO<sub>4</sub>  
Exact Mass: 313.1314

Colorless oil, 246 mg, 98% yield, *syn/anti* = 93:7, *ee*<sub>*syn*</sub> > 99%;

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.71–7.62 (m, 2H), 7.55–7.44 (m, 1H), 7.43–7.37 (m, 2H), 7.24–7.17 (m, 3H), 7.11–7.01 (m, 1H), 6.91 (d, *J* = 8.5 Hz, 1H), 5.34 (t, *J* = 3.5 Hz, 1H), 5.03 (dd, *J* = 8.6, 3.1 Hz, 1H), 3.76 (s, 3H), 3.08 (d, *J* = 4.0 Hz, 1H), 2.31 (s, 3H);

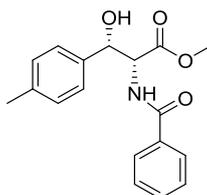
**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 171.2, 167.8, 139.7, 138.3, 134.0, 131.9, 129.1, 128.7 (2C), 128.5, 127.2 (2C), 126.7, 122.9, 74.0, 58.7, 52.8, 21.6.

**MS** (ESI): *m/z* = 314 [M + H]<sup>+</sup>.

**HRMS** (ESI/ion trap): *m/z* [M + Na]<sup>+</sup> calcd for C<sub>18</sub>H<sub>19</sub>NNaO<sub>4</sub> 336.1212, found 336.1214.

**SFC**: Chiralpak AD-H, *sc*CO<sub>2</sub>/MeOH 80/20, 4.0 mL/min, P = 150 bar, λ = 215 nm, *t<sub>R</sub>* [*syn*-(2*R*,3*S*)] = 2.43 min (major), *t<sub>R</sub>* [*anti*] = 4.32 min, *t<sub>R</sub>* [*syn*-(2*S*,3*R*)] = 4.82 min, *t<sub>R</sub>* [*anti*] = 6.37 min.

Methyl (2*R*,3*S*)-2-benzoylamino-3-hydroxy-3-(*p*-tolyl)propanoate (**25c**)



Chemical Formula: C<sub>18</sub>H<sub>19</sub>NO<sub>4</sub>  
Exact Mass: 313.1314

White solid, 241 mg, 96% yield, *syn/anti* = 93:7, *ee*<sub>*syn*</sub> > 99%, [α]<sub>D</sub><sup>20</sup> = +54.0 (*c* 1.06, CHCl<sub>3</sub>, purified *syn* compound);

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.71–7.66 (m, 2H), 7.54–7.44 (m, 1H), 7.44–7.35 (m, 2H), 7.27 (d, *J* = 8.1 Hz, 2H), 7.12 (d, *J* = 8.1 Hz, 2H), 6.93 (d, *J* = 8.7 Hz, 1H), 5.34 (t, *J* = 3.5 Hz, 1H), 5.03 (dd, *J* = 8.6, 3.1 Hz, 1H), 3.76 (s, 3H), 3.13 (d, *J* = 4.1 Hz, 1H), 2.30 (s, 3H);

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 171.2, 167.8, 137.9, 136.8, 133.9, 131.9, 129.3 (2C), 128.6 (2C),

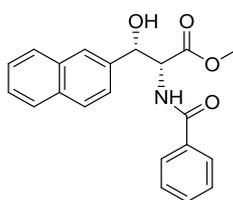
127.3 (2C), 125.8 (2C), 73.7, 58.6, 52.8, 21.2.

**MS** (ESI):  $m/z = 314 [M + H]^+$ .

**HRMS** (ESI/ion trap):  $m/z [M + Na]^+$  calcd for  $C_{18}H_{19}NNaO_4$  336.1212, found 336.1221.

**SFC**: Chiralpak AD-H,  $scCO_2/MeOH$  89/11, 3.0 mL/min, P = 150 bar,  $\lambda = 215$  nm,  $t_R$  [*syn*-(*R,S*)] = 8.77 min (major),  $t_R$  [*syn*-(*S,R*)] = 21.85 min,  $t_R$  [*anti*] = 24.07 min,  $t_R$  [*anti*] = 26.94 min.

Methyl (2*R*,3*S*)-2-benzoylamino-3-hydroxy-3-(naphthalen-2-yl)propanoate (**25d**)



Chemical Formula:  $C_{21}H_{19}NO_4$   
Exact Mass: 349.1314

White solid, 273 mg, 96% yield, *syn/anti* = 94:6,  $ee_{syn} > 99\%$ ,  $[\alpha]_D^{20} = +67.5$  ( $c$  1.01,  $CHCl_3$ , purified *syn* compound);

**$^1H$  NMR** (300 MHz,  $CDCl_3$ )  $\delta$  7.90–7.70 (m, 4H), 7.69–7.60 (m, 2H), 7.53–7.40 (m, 4H), 7.40–7.30 (m, 2H), 6.96 (br d,  $J = 8.8$  Hz, 1H), 5.53 (t,  $J = 3.5$  Hz, 1H), 5.17 (dd,  $J = 8.6, 3.2$  Hz, 1H), 3.76 (s, 3H), 3.32 (d,  $J = 4.1$  Hz, 1H);

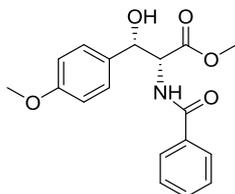
**$^{13}C$  NMR** (75 MHz,  $CDCl_3$ )  $\delta$  171.1, 168.0, 137.3, 133.7, 133.2 (2C), 131.8, 128.6 (2C), 128.4, 128.1, 127.8, 127.2 (2C), 126.3, 126.2, 125.0, 123.7, 73.8, 58.7, 52.8.

**MS** (ESI):  $m/z = 350 [M + H]^+$ .

**HRMS** (ESI/ion trap):  $m/z [M + Na]^+$  calcd for  $C_{21}H_{19}NNaO_4$  372.1212, found 372.1215.

**SFC**: Chiralpak AD-H,  $scCO_2/MeOH$  85/15, 4.0 mL/min, P = 100 bar,  $\lambda = 215$  nm,  $t_R$  [*syn*-(*R,S*)] = 8.80 min (major),  $t_R$  [*anti*] = 25.17 min,  $t_R$  [*syn*-(*S,R*)] = 28.70 min,  $t_R$  [*anti*] = 34.33 min.

Methyl (2*R*,3*S*)-2-benzoylamino-3-hydroxy-3-(4-methoxyphenyl)propanoate (**25e**)



Chemical Formula: C<sub>18</sub>H<sub>19</sub>NO<sub>5</sub>  
Exact Mass: 329.1263

White solid, 254 mg, 96% yield, *syn/anti* = 92:8, *ee*<sub>*syn*</sub> > 99%;

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.81–7.62 (m, 2H), 7.56–7.45 (m, 1H), 7.44–7.35 (m, 2H), 7.34–7.27 (m, 2H), 6.91 (d, *J* = 8.5 Hz, 1H), 6.88–6.77 (m, 2H), 5.31 (dd, *J* = 6.7, 3.4 Hz, 1H), 5.02 (dd, *J* = 8.6, 3.3 Hz, 1H), 3.77 (s, 3H), 3.76 (s, 3H), 3.04 (d, *J* = 3.6 Hz, 1H);

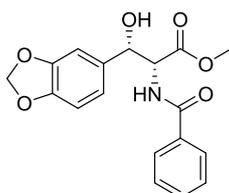
**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 171.2, 167.7, 159.6, 133.9, 131.9, 131.8, 128.7 (2C), 127.3 (2C), 127.2 (2C), 114.1 (2C), 73.7, 58.6, 55.4, 52.8.

**MS** (ESI): *m/z* = 330 [M + H]<sup>+</sup>.

**HRMS** (ESI/ion trap): *m/z* [M + Na]<sup>+</sup> calcd for C<sub>18</sub>H<sub>19</sub>NNaO<sub>5</sub> 352.1161, found 352.1163.

**HPLC**: Chiralpak IA, Hexane/*i*PrOH 90/10, 1.0 mL/min, λ = 215 nm, *t<sub>R</sub>* [*syn*-(*R,S*)] = 36.24 min (major), *t<sub>R</sub>* [*anti*] = 43.23 min, *t<sub>R</sub>* [*syn*-(*S,R*)] = 50.08 min, *t<sub>R</sub>* [*anti*] = 64.92 min.

Methyl (2*R*,3*S*)-2-benzoylamino-3-(benzo[d][1,3]dioxol-5-yl)-3-hydroxypropanoate (**25f**)



Chemical Formula: C<sub>18</sub>H<sub>17</sub>NO<sub>6</sub>  
Exact Mass: 343.1056

White solid, 236 mg, 86% yield, *syn/anti* = 91:9, *ee*<sub>*syn*</sub> > 99%;

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.74 (d, *J* = 8.2 Hz, 2H), 7.54–7.47 (m, 1H), 7.46–7.39 (m, 2H), 6.96–6.74 (m, 4H), 5.94 (s, 2H), 5.29 (t, *J* = 3.4 Hz, 1H), 5.01 (dd, *J* = 8.6, 3.1 Hz, 1H), 3.78 (s, 3H), 3.24 (br s, 1H);

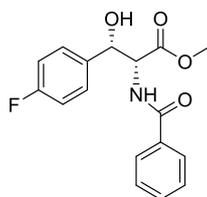
**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 171.1, 167.8, 148.0, 147.6, 133.8 (2C), 132.0, 128.7 (2C), 127.3 (2C), 119.4, 108.3, 106.5, 101.3, 73.8, 58.7, 52.8.

**MS** (ESI): *m/z* = 344 [M + H]<sup>+</sup>.

**HRMS** (ESI/ion trap):  $m/z$   $[M + Na]^+$  calcd for  $C_{18}H_{17}NNaO_6$  366.0954, found 366.0951.

**SFC**: Chiralpak IC,  $scCO_2/MeOH$  90/10, 4.0 mL/min,  $P = 150$  bar,  $\lambda = 215$  nm,  $t_R$  [ $syn-(S,R)$ ] = 4.89 min,  $t_R$  [ $syn-(R,S)$ ] = 6.19 min (major),  $t_R$  [ $anti$ ] = 7.01 min,  $t_R$  [ $anti$ ] = 7.74 min.

Methyl (2*R*,3*S*)-2-benzoylamino-3-(4-fluorophenyl)-3-hydroxypropanoate (**25g**)



Chemical Formula:  $C_{17}H_{16}FNO_4$   
Exact Mass: 317.1063

White solid, 250 mg, 98% yield,  $syn/anti = 92:8$ ,  $ee_{syn} > 99\%$ ,  $[\alpha]_D^{20} = +49.0$  ( $c$  0.95,  $CHCl_3$ , purified  $syn$  compound);

**$^1H$  NMR** (300 MHz,  $CDCl_3$ )  $\delta$  7.74–7.70 (m, 2H), 7.59–7.47 (m, 1H), 7.47–7.31 (m, 4H), 7.08–6.97 (m, 2H), 6.92 (d,  $J = 8.6$  Hz, 1H), 5.38 (t,  $J = 3.4$  Hz, 1H), 5.07 (dd,  $J = 8.7, 3.2$  Hz, 1H), 3.78 (s, 3H), 3.24 (d,  $J = 3.9$  Hz, 1H);

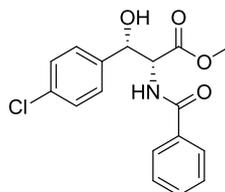
**$^{13}C$  NMR** (75 MHz,  $CDCl_3$ )  $\delta$  170.9, 168.0, 162.4 (d,  $^1J_{CF} = 246.3$  Hz), 135.8 (d,  $^4J_{CF} = 2.5$  Hz), 133.5, 132.0, 128.6 (2C), 127.6 (d,  $^3J_{CF} = 8.1$  Hz, 2C), 127.2 (2C), 115.3 (d,  $^2J_{CF} = 21.5$  Hz, 2C), 73.1, 58.7, 52.7.

**MS** (ESI):  $m/z = 318$   $[M + H]^+$ .

**HRMS** (ESI/ion trap):  $m/z$   $[M + Na]^+$  calcd for  $C_{17}H_{16}FNNaO_4$  340.0961, found 340.0963.

**SFC**: Chiralpak AD-H,  $scCO_2/MeOH$  85/15, 4.0 mL/min,  $P = 150$  bar,  $\lambda = 215$  nm,  $t_R$  [ $syn-(R,S)$ ] = 3.23 min (major),  $t_R$  [ $syn-(S,R)$ ] = 4.77 min,  $t_R$  [ $anti$ ] = 6.49 min,  $t_R$  [ $anti$ ] = 9.71 min.

Methyl (2*R*,3*S*)-2-benzoylamino-3-(4-chlorophenyl)-3-hydroxypropanoate (**25h**)



Chemical Formula:  $C_{17}H_{16}ClNO_4$   
Exact Mass: 333.0768

White solid, 254 mg, 95% yield,  $syn/anti = 93:7$ ,  $ee_{syn} > 99\%$ ,  $[\alpha]_D^{20} = +62.0$  ( $c$  1.18,  $CHCl_3$ , purified  $syn$  compound);

## Experimental part

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.65 (dd, *J* = 8.5, 1.1 Hz, 2H), 7.56–7.44 (m, 1H), 7.42–7.35 (m, 2H), 7.34–7.22 (m, 4H), 6.96 (d, *J* = 8.7 Hz, 1H), 5.34 (t, *J* = 3.4 Hz, 1H), 5.03 (dd, *J* = 8.8, 3.1 Hz, 1H), 3.74 (s, 3H), 3.62 (d, *J* = 4.1 Hz, 1H);

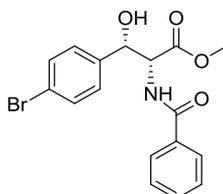
**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 170.9, 167.8, 138.4, 134.1, 133.6, 132.1, 128.8 (4C), 127.4 (2C), 127.2 (2C), 73.3, 58.5, 52.9.

**MS** (ESI): *m/z* = 334 [M + H]<sup>+</sup>.

**HRMS** (ESI/ion trap): *m/z* [M + Na]<sup>+</sup> calcd for C<sub>17</sub>H<sub>16</sub>ClNNaO<sub>4</sub> 356.0666, found 356.0667.

**SFC**: Chiralpak AD-H, *sc*CO<sub>2</sub>/MeOH 80/20, 4.0 mL/min, P = 150 bar, λ = 215 nm, *t<sub>R</sub>* [*syn*-(*R,S*)] = 2.85 min (major), *t<sub>R</sub>* [*syn*-(*S,R*)] = 4.52 min, *t<sub>R</sub>* [*anti*] = 7.59 min, *t<sub>R</sub>* [*anti*] = 10.57 min.

### Methyl (2*R*,3*S*)-2-benzoylamino-3-(4-bromophenyl)-3-hydroxypropanoate (**25i**)



Chemical Formula: C<sub>17</sub>H<sub>16</sub>BrNO<sub>4</sub>  
Exact Mass: 377.0263

White solid, 298 mg, 98% yield, *syn/anti* = 94:6, ee<sub>*syn*</sub> > 99%, [α]<sub>D</sub><sup>20</sup> = +62.2 (*c* 0.93, CHCl<sub>3</sub>, purified *syn* compound);

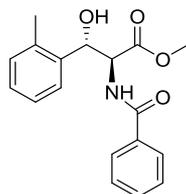
**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.72–7.64 (m, 2H), 7.55–7.35 (m, 5H), 7.31–7.21 (m, 2H), 6.87 (d, *J* = 8.7 Hz, 1H), 5.34 (t, *J* = 3.6 Hz, 1H), 5.06 (dd, *J* = 8.7, 3.1 Hz, 1H), 3.77 (s, 3H), 3.18 (d, *J* = 4.2 Hz, 1H);

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 170.9, 167.9, 139.0, 133.5, 132.1, 131.6 (2C), 128.7 (2C), 127.7 (2C), 127.2 (2C), 122.1, 73.2, 58.5, 52.9.

**MS** (ESI): *m/z* = 378, 380 [M + H]<sup>+</sup>.

**HRMS** (ESI/ion trap): *m/z* [M + Na]<sup>+</sup> calcd for C<sub>17</sub>H<sub>16</sub>BrNNaO<sub>4</sub> 400.0160, found 400.0168.

**SFC**: Chiralpak AD-H, *sc*CO<sub>2</sub>/MeOH 80/20, 4.0 mL/min, P = 150 bar, λ = 215 nm, *t<sub>R</sub>* [*syn*-(*R,S*)] = 3.56 min (major), *t<sub>R</sub>* [*syn*-(*S,R*)] = 5.92 min, *t<sub>R</sub>* [*anti*] = 9.55 min, *t<sub>R</sub>* [*anti*] = 12.47 min.

Methyl (2*R*,3*R*)-2-benzoylamino-3-hydroxy-3-(*o*-tolyl)propanoate (**25j**)

Chemical Formula: C<sub>18</sub>H<sub>19</sub>NO<sub>4</sub>  
Exact Mass: 313.1314

White solid, 175 mg, 70% yield, *syn/anti* = 12:88, *ee*<sub>*syn*</sub> > 99%, *ee*<sub>*anti*</sub> = 52%;

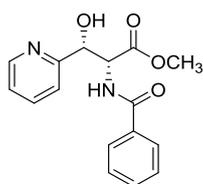
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.84–7.72 (m, 2H), 7.56–7.32 (m, 4H), 7.25–7.07 (m, 4H), 5.45 (t, *J* = 4.2 Hz, 1H), 5.09 (dd, *J* = 7.8, 3.7 Hz, 1H), 3.77–3.65 (m, 1H), 3.60 (s, 3H), 2.39 (s, 3H);

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 170.6, 167.8, 137.5, 135.0, 133.5, 132.2, 130.8, 128.8 (2C), 128.1, 127.3 (2C), 126.0, 125.9, 71.8, 57.6, 52.4, 19.1.

MS (ESI): *m/z* = 314 [M + H]<sup>+</sup>.

HRMS (ESI/ion trap): *m/z* [M + Na]<sup>+</sup> calcd for C<sub>18</sub>H<sub>19</sub>NNaO<sub>4</sub> 336.1212, found 336,1217.

HPLC: Chiralpak IB, Hexane/*i*PrOH 90/10, 0.8 mL/min, λ = 215 nm, *t*<sub>R</sub> [*anti*-(*R,R*)] = 15.09 min (major), *t*<sub>R</sub> [*anti*-(*S,S*)] = 17.77 min, *t*<sub>R</sub> [*syn*] = 20.39 min, *t*<sub>R</sub> [*syn*] = 32.13 min.

Methyl (2*R*,3*R*)-2-benzoylamino-3-hydroxy-3-(pyridin-2-yl)propanoate (**25k**)

Chemical Formula: C<sub>16</sub>H<sub>16</sub>N<sub>2</sub>O<sub>4</sub>  
Exact Mass: 300.1110

Pale yellow oil, 231mg; 96% yield, *syn/anti* = 97:3, *ee*<sub>*syn*</sub> > 99%, [α]<sub>D</sub><sup>20</sup> = +30.1 (*c* 1.22, CHCl<sub>3</sub>, purified *syn* compound);

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.48 (ddd, *J* = 4.9, 1.7, 1.0 Hz, 1H), 7.72 (td, *J* = 7.7, 1.7 Hz, 1H), 7.63–7.57 (m, 2H), 7.52–7.41 (m, 2H), 7.40–7.31 (m, 2H), 7.21 (ddd, *J* = 7.5, 4.9, 1.1 Hz, 1H), 6.94 (br d, *J* = 9.2 Hz, 1H), 5.64 – 4.86 (br s, 1H) 5.43 (d, *J* = 2.3 Hz, 1H), 5.31 (dd, *J* = 9.3, 2.2 Hz, 1H), 3.84 (s, 3H);

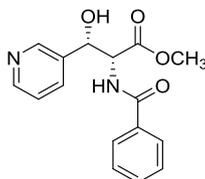
<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 170.8, 167.4, 157.1, 147.8, 137.3, 134.0, 131.8, 128.6 (2C), 127.1 (2C), 123.3, 121.1, 72.5, 57.2, 52.9.

MS (ESI): *m/z* = 301 [M + H]<sup>+</sup>.

**HRMS** (ESI/ion trap):  $m/z$   $[M + Na]^+$  calcd for  $C_{16}H_{16}N_2NaO_4$  323.1008, found 323.1012.

**HPLC**: Chiralpak IA, Hexane/*i*PrOH 80/20, 0.2 mL/min,  $\lambda = 215$  nm,  $t_R$  [*syn*-(*R,R*)] = 65.90 min (major),  $t_R$  [*anti*] = 80.95 min,  $t_R$  [*syn*-(*S,S*)] = 89.55 min,  $t_R$  [*anti*] = 99.49 min.

Methyl (2*R*,3*S*)-2-benzoylamino-3-hydroxy-3-(pyridin-3-yl)propanoate (**25l**)



Chemical Formula:  $C_{16}H_{16}N_2O_4$   
Exact Mass: 300.1110

Pale yellow solid, 151 mg; 63% yield, *syn/anti* = 87:13,  $ee_{syn} = 96\%$ ;

**$^1H$  NMR** (300 MHz,  $CDCl_3$ )  $\delta$  8.48–8.46 (m, 1H), 8.27–8.22 (m, 1H), 7.71–7.51 (m, 3H), 7.44–7.33 (m, 1H), 7.33–7.22 (m, 2H), 7.12 (dt,  $J = 8.2, 4.9$  Hz, 2H), 6.16–5.55 (br s, 1H), 5.36 (d,  $J = 2.5$  Hz, 1H), 4.99 (dd,  $J = 9.0, 2.7$  Hz, 1H), 3.61 (s, 3H);

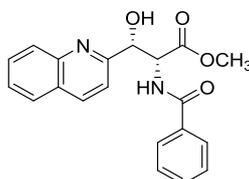
**$^{13}C$  NMR** (75 MHz,  $CDCl_3$ )  $\delta$  170.7, 167.9, 148.6, 147.4, 136.5, 134.4, 133.5, 132.0, 128.6 (2C), 127.2 (2C), 123.5, 71.4, 58.4, 52.8.

**MS** (ESI):  $m/z = 301$   $[M + H]^+$ .

**HRMS** (ESI/ion trap):  $m/z$   $[M + Na]^+$  calcd for  $C_{16}H_{16}N_2NaO_4$  323.1008, found 323.1014.

**SFC**: Chiralpak IA, *sc*CO<sub>2</sub>/MeOH 80/20, 4.0 mL/min, P = 150 bar,  $\lambda = 215$  nm,  $t_R$  [*syn*-(*S,R*)] = 2.23 min,  $t_R$  [*anti*] = 3.12 min,  $t_R$  [*anti*] = 4.79 min,  $t_R$  [*syn*-(*R,S*)] = 6.06 min.

Methyl (2*R*,3*R*)-2-benzoylamino-3-hydroxy-3-(quinolin-2-yl)propanoate (**25m**)



Chemical Formula:  $C_{20}H_{18}N_2O_4$   
Exact Mass: 350.1267

Pale yellow solid, 235 mg, 84% yield, *syn/anti* = 98:2,  $ee_{syn} > 99\%$ ,  $[\alpha]_D^{20} = -46.5$  ( $c$  1.05,  $CHCl_3$ , purified *syn* compound);

**$^1H$  NMR** (300 MHz,  $CDCl_3$ )  $\delta$  8.17 (d,  $J = 8.6$  Hz, 1H), 8.01 (d,  $J = 8.1$  Hz, 1H), 7.78 (d,  $J = 8.0$  Hz, 1H), 7.70–7.65 (m, 1H), 7.59–7.45 (m, 4H), 7.39–7.34 (m, 1H), 7.31–7.20 (m, 2H), 6.90 (br d,  $J = 9.0$  Hz, 1H), 5.75 (br s, 1H), 5.55 (d,  $J = 2.0$  Hz, 1H), 5.44 (dd,  $J = 9.3, 2.1$  Hz, 1H), 3.85 (s, 3H);

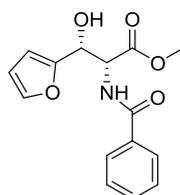
**$^{13}\text{C}$  NMR** (75 MHz,  $\text{CDCl}_3$ )  $\delta$  170.7, 167.4, 157.2, 146.1, 137.7, 133.8, 131.7, 130.1, 128.6, 128.5 (2C), 127.9, 127.8, 127.1 (2C), 126.9, 118.4, 72.9, 56.7, 52.9.

**MS** (ESI):  $m/z = 351$   $[\text{M} + \text{H}]^+$ .

**HRMS** (ESI/ion trap):  $m/z$   $[\text{M} + \text{Na}]^+$  calcd for  $\text{C}_{20}\text{H}_{18}\text{N}_2\text{NaO}_4$  373.1164, found 373.1166.

**SFC**: Chiralpak AD-H, *sc* $\text{CO}_2$ /MeOH 85/15, 3.0 mL/min,  $P = 150$  bar,  $\lambda = 215$  nm,  $t_R$  [*syn*-(*R,R*)] = 10.19 min (major),  $t_R$  [*anti*] = 15.99 min,  $t_R$  [*anti*] = 37.14 min,  $t_R$  [*syn*-(*S,S*)] = 40.50 min.

Methyl (2*R*,3*R*)-2-benzoylamino-3-(furan-2-yl)-3-hydroxypropanoate (**25n**)



Chemical Formula:  $\text{C}_{15}\text{H}_{15}\text{NO}_5$   
Exact Mass: 289.0950

White solid, 222 mg, 96% yield, *syn/anti* > 99:1,  $ee_{\text{syn}} > 99\%$ ,  $[\alpha]_{\text{D}}^{20} = -9.55$  ( $c$  1.11,  $\text{CHCl}_3$ );  
m.p. = 84 °C;

**$^1\text{H}$  NMR** (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.81–7.71 (m, 2H), 7.56–7.46 (m, 1H), 7.46–7.32 (m, 3H), 7.00 (br d,  $J = 8.5$  Hz, 1H), 6.37–6.32 (m, 1H), 6.30 (dd,  $J = 3.3, 1.8$  Hz, 1H), 5.35 (dd,  $J = 5.1, 3.1$  Hz, 1H), 5.20 (dd,  $J = 8.6, 3.1$  Hz, 1H), 3.79 (s, 3H), 3.37 (d,  $J = 5.4$  Hz, 1H);

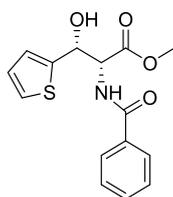
**$^{13}\text{C}$  NMR** (75 MHz,  $\text{CDCl}_3$ )  $\delta$  170.7, 167.8, 152.6, 142.8, 133.9, 132.0, 128.8 (2C), 127.3 (2C), 110.6, 107.6, 68.6, 56.4, 53.0.

**MS** (ESI):  $m/z = 290$   $[\text{M} + \text{H}]^+$ .

**HRMS** (ESI/ion trap):  $m/z$   $[\text{M} + \text{Na}]^+$  calcd for  $\text{C}_{15}\text{H}_{15}\text{NNaO}_5$  312.0848, found 312.0851.

**SFC**: Chiralpak OD-H, *sc* $\text{CO}_2$ /MeOH 95/5, 2.0 mL/min,  $P = 150$  bar,  $\lambda = 215$  nm,  $t_R$  [*syn*-(*R,R*)] = 10.54 min (major),  $t_R$  [*anti*] = 11.72 min,  $t_R$  [*anti*] = 12.76 min,  $t_R$  [*syn*-(*S,S*)] = 14.00 min.

Methyl (2*R*,3*R*)-2-benzoylamino-3-hydroxy-3-(thiophen-2-yl)propanoate (**25o**)



Chemical Formula: C<sub>15</sub>H<sub>15</sub>NO<sub>4</sub>S  
Exact Mass: 305.0722

White solid, 239 mg, 98% yield, *syn/anti* > 99:1, *ee*<sub>syn</sub> > 99%, [α]<sub>D</sub><sup>20</sup> = +33.5 (*c* 1.10, CHCl<sub>3</sub>);  
m.p. = 113 °C;

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.81–7.74 (m, 2H), 7.57–7.47 (m, 1H), 7.47–7.37 (m, 2H), 7.24 (dd, *J* = 5.0, 1.2 Hz, 1H), 7.07–7.02 (m, 2H), 6.95 (dd, *J* = 5.1, 3.6 Hz, 1H), 5.65 (dd, *J* = 3.5, 3.0 Hz, 1H), 5.13 (dd, *J* = 8.9, 2.7 Hz, 1H), 3.79 (s, 3H), 3.31 (d, *J* = 4.3 Hz, 1H);

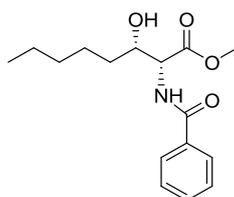
<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 170.8, 167.9, 143.1, 133.9, 132.1, 128.8 (2C), 127.4 (2C), 126.8, 125.9, 125.1, 70.7, 58.2, 53.0.

MS (ESI): *m/z* = 306 [M + H]<sup>+</sup>.

HRMS (ESI/ion trap): *m/z* [M + Na]<sup>+</sup> calcd for C<sub>15</sub>H<sub>15</sub>NNaO<sub>4</sub>S 328.0619, found 328.0623.

SFC: Chiralpak AD-H, *sc*CO<sub>2</sub>/MeOH 80/20, 4.0 mL/min, P = 150 bar, λ = 215 nm, *t<sub>R</sub>* [*syn*-(*R,R*)] = 2.97 min (major), *t<sub>R</sub>* [*syn*-(*S,S*)] = 3.73 min, *t<sub>R</sub>* [*anti*] = 5.26 min, *t<sub>R</sub>* [*anti*] = 5.86 min.

Methyl (2*R*,3*S*)-2-benzoylamino-3-hydroxyoctanoate (**25q**)



Chemical Formula: C<sub>16</sub>H<sub>23</sub>NO<sub>4</sub>  
Exact Mass: 293.1627

Colorless oil, 228 mg, 97% yield, *syn/anti* = 80:20, *ee*<sub>syn</sub> > 99%;

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.85–7.82 (m, 2H), 7.58–7.34 (m, 3H), 6.97–6.90 (m, 1H), 4.88 (dd, *J* = 8.9, 2.0 Hz, 1H), 4.28–4.18 (m, 1H), 3.78 (s, 3H), 2.50–2.30 (m, 1H), 1.64–1.11 (m, 8H), 0.89–0.85 (m, 3H);

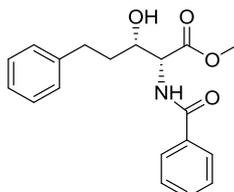
<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 172.0, 167.9, 134.0, 132.0, 128.8 (2C), 127.4 (2C), 72.3, 56.5, 52.8, 34.0, 31.7, 25.4, 22.7, 14.1.

**MS (ESI):**  $m/z = 294$   $[M + H]^+$ .

**HRMS (ESI/ion trap):**  $m/z$   $[M + Na]^+$  calcd for  $C_{16}H_{23}NNaO_4$  316.1525, found 316.1525.

**HPLC:** Chiralpak ID, Hexane/*i*PrOH 90/10, 1.0 mL/min,  $\lambda = 215$  nm,  $t_R$  [*syn*-(*R,S*)] = 29.68 min (major),  $t_R$  [*anti*] = 39.16 min,  $t_R$  [*anti*] = 45.74 min,  $t_R$  [*syn*-(*S,R*)] = 59.65 min.

Methyl (2*R*,3*S*)-2-benzoylamino-3-hydroxy-5-phenylpentanoate (**25r**)



Chemical Formula:  $C_{19}H_{21}NO_4$   
Exact Mass: 327.1471

White solid, 257 mg, 98% yield, *syn/anti* = 75:25,  $ee_{syn} > 99\%$ ;

**$^1H$  NMR** (300 MHz,  $CDCl_3$ )  $\delta$  7.87–7.78 (m, 2H), 7.57–7.48 (m, 1H), 7.48–7.38 (m, 2H), 7.32–7.23 (m, 2H), 7.22–7.12 (m, 3H), 6.97 (d,  $J = 8.7$  Hz, 1H), 4.94 (dd,  $J = 9.0, 2.2$  Hz, 1H), 4.30–4.20 (m, 1H), 3.77 (s, 3H), 2.95–2.65 (m, 2H), 2.46 (br d,  $J = 5.1$  Hz, 1H), 1.96–1.72 (m, 2H);

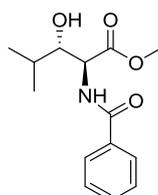
**$^{13}C$  NMR** (75 MHz,  $CDCl_3$ )  $\delta$  171.8, 168.0, 141.3, 133.8, 132.0, 128.7 (2C), 128.6 (4C) 127.3 (2C), 126.2, 71.6, 56.7, 52.8, 35.6, 32.0.

**MS (ESI):**  $m/z = 328$   $[M + H]^+$ .

**HRMS (ESI/ion trap):**  $m/z$   $[M + Na]^+$  calcd for  $C_{19}H_{21}NNaO_4$  350.1368, found 350.1369.

**SFC:** Chiralpak AD-H,  $scCO_2$ /MeOH 85/15, 3.0 mL/min,  $P = 150$  bar,  $\lambda = 215$  nm,  $t_R$  [*syn*-(*R,S*)] = 4.97 min (major),  $t_R$  [*anti*] = 14.08 min,  $t_R$  [*anti*] = 17.69 min,  $t_R$  [*syn*-(*S,R*)] = 23.07 min.

Methyl (2*S*,3*S*)-2-benzoylamino-3-hydroxy-4-methylpentanoate (**25s**)



Chemical Formula:  $C_{14}H_{19}NO_4$   
Exact Mass: 265.1314

Colorless oil, 153 mg, 72 % yield, *syn/anti* = 2:98,  $ee_{anti} = 99\%$ ,  $[\alpha]_D^{20} = -48.8$  ( $c$  1.15,  $CHCl_3$ , purified *anti* compound); Lit:<sup>[4]</sup>  $[\alpha]_D^{20} = -38$  ( $c$  0.038,  $CHCl_3$ , 99% ee);

## Experimental part

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.82–7.79 (m, 2H), 7.55–7.46 (m, 1H), 7.45–7.35 (m, 2H), 7.25 (d, *J* = 8.3 Hz, 1H), 4.95 (dd, *J* = 7.6, 3.4 Hz, 1H), 3.78 (s, 3H), 3.62–3.57 (m, 1H), 3.23 (d, *J* = 7.7 Hz, 1H), 1.84–1.68 (m, 1H), 1.01 (t, *J* = 6.3 Hz, 6H);

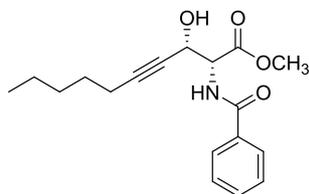
**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 171.5, 167.6, 133.6, 132.1, 128.7 (2C), 127.3 (2C), 78.9, 56.0, 52.6, 31.6, 19.2, 19.0.

**MS** (ESI): *m/z* = 266 [M + H]<sup>+</sup>.

**HRMS** (ESI/ion trap): *m/z* [M + Na]<sup>+</sup> calcd for C<sub>14</sub>H<sub>19</sub>NNaO<sub>4</sub> 288.1212, found 288.1216.

**SFC**: Chiralpak AD-H, scCO<sub>2</sub>/MeOH 92/8, 3.0 mL/min, P = 150 bar, λ = 215 nm, *t<sub>R</sub>* [*syn*] = 3.94 min, *t<sub>R</sub>* [*anti*-(*R,R*)] = 5.17 min (major), *t<sub>R</sub>* [*anti*-(*S,S*)] = 7.57 min, *t<sub>R</sub>* [*syn*] = 9.67 min.

### Methyl (2*R*,3*S*)-2-benzoylamino-3-hydroxydec-4-ynoate (**25t**)



Chemical Formula: C<sub>18</sub>H<sub>23</sub>NO<sub>4</sub>  
Exact Mass: 317.1627

Pale yellow oil, 218 mg, 86% yield, *syn/anti* = 99:1, ee<sub>*syn*</sub> > 99%, [α]<sub>D</sub><sup>20</sup> = –25.2 (*c* 1.07, CHCl<sub>3</sub>);

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.86–7.83 (m, 2H), 7.56–7.50 (m, 1H), 7.48–7.42 (m, 2H), 6.92 (br d, *J* = 8.7 Hz, 1H), 5.05 (dd, *J* = 8.6, 3.3 Hz, 1H), 4.96–4.86 (m, 1H), 3.82 (s, 3H), 2.87 (d, *J* = 6.2 Hz, 1H), 2.16 (td, *J* = 7.0, 1.9 Hz, 2H), 1.51–1.36 (m, 2H), 1.35–1.17 (m, 4H), 0.82 (t, *J* = 6.9 Hz, 3H);

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 170.3, 167.7, 133.9, 132.0, 128.7 (2C), 127.4 (2C), 88.0, 77.1, 63.4, 57.7, 52.9, 31.0, 28.2, 22.2, 18.7, 13.9.

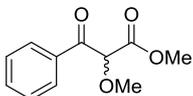
**MS** (ESI): *m/z* = 318 [M + H]<sup>+</sup>.

**HRMS** (ESI/ion trap): *m/z* [M + Na]<sup>+</sup> calcd for C<sub>18</sub>H<sub>23</sub>NNaO<sub>4</sub> 340.1525, found 340.1532.

**SFC**: Chiralpak AD-H, scCO<sub>2</sub>/MeOH 85/15, 3.0 mL/min, P = 150 bar, λ = 215 nm, *t<sub>R</sub>* [*syn*-(2*R*,3*S*)] = 2.46 min (major), *t<sub>R</sub>* [*anti*] = 5.25 min, *t<sub>R</sub>* [*anti*] = 8.05 min, *t<sub>R</sub>* [*syn*-(2*S*,3*R*)] = 11.39 min.

Substrates:  $\alpha$ -methoxyl - $\beta$ -keto esters (26a-m)

## Methyl 2-methoxy-3-oxo-3-phenylpropanoate (26a)



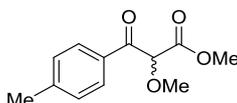
Chemical Formula: C<sub>11</sub>H<sub>12</sub>O<sub>4</sub>  
Exact Mass: 208.0736

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.08 – 8.05 (m, 2H), 7.63 – 7.58 (m, 1H), 7.50 – 7.46 (m, 2H), 4.95 (s, 1H), 3.78 (s, 3H), 3.53 (s, 3H).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  192.5, 168.1, 134.2, 134.1, 129.5 (2C), 128.8 (2C), 85.2, 58.8, 52.9.

**MS** (ESI) = 209 [M + H]<sup>+</sup>

## Methyl 2-methoxy-3-oxo-3-(p-tolyl)propanoate (26b)



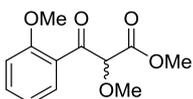
Chemical Formula: C<sub>12</sub>H<sub>14</sub>O<sub>4</sub>  
Exact Mass: 222.0892

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.97 (d, *J* = 8.1 Hz, 2H), 7.27 (d, *J* = 8.1 Hz, 2H), 4.93 (s, 1H), 3.76 (s, 3H), 3.52 (s, 3H), 2.41 (s, 3H).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>)  $\delta$  192.0, 168.2, 145.2, 131.7, 129.6 (2C), 129.5 (2C), 85.1, 58.7, 52.8, 21.8.

**MS** (ESI) = 223 [M + H]<sup>+</sup>

## Methyl 2-methoxy-3-(2-methoxyphenyl)-3-oxopropanoate (26c)



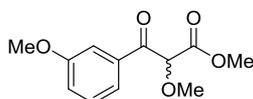
Chemical Formula: C<sub>12</sub>H<sub>14</sub>O<sub>5</sub>  
Exact Mass: 238.0841

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.79 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.55 – 7.46 (m, 1H), 7.07 – 7.01 (m, 1H), 6.96 (d, *J* = 8.4 Hz, 1H), 5.06 (s, 1H), 3.88 (s, 3H), 3.75 (s, 3H), 3.50 (s, 3H).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>)  $\delta$  194.3, 167.8, 158.9, 134.7, 131.2, 125.5, 121.2, 111.7, 86.6, 59.3, 55.4, 52.4.

MS (ESI) = 239 [M + H]<sup>+</sup>

Methyl 2-methoxy-3-(3-methoxyphenyl)-3-oxopropanoate (**26d**)



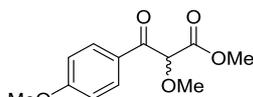
Chemical Formula: C<sub>12</sub>H<sub>14</sub>O<sub>5</sub>  
Exact Mass: 238.0841

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.67 (ddd, *J* = 7.7, 1.6, 1.0 Hz, 1H), 7.57 (dd, *J* = 2.5, 1.6 Hz, 1H), 7.40 – 7.35 (m, 1H), 7.15 (ddd, *J* = 8.3, 2.7, 1.0 Hz, 1H), 4.95 (s, 1H), 3.85 (s, 3H), 3.77 (s, 3H), 3.53 (s, 3H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 192.3, 168.1, 160.0, 135.5, 129.8, 122.2, 121.0, 113.4, 85.1, 58.8, 55.6, 52.9.

MS (ESI) = 239 [M + H]<sup>+</sup>

Methyl 2-methoxy-3-(4-methoxyphenyl)-3-oxopropanoate (**26e**)



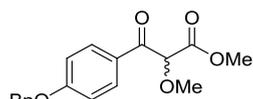
Chemical Formula: C<sub>12</sub>H<sub>14</sub>O<sub>5</sub>  
Exact Mass: 238.0841

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.07 (d, *J* = 8.9 Hz, 2H), 6.93 (d, *J* = 8.7 Hz, 2H), 4.90 (s, 1H), 3.87 (s, 3H), 3.76 (s, 3H), 3.51 (s, 3H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 190.8, 168.3, 164.4, 132.0 (2C), 127.2, 114.0 (2C), 85.3, 58.6, 55.6, 52.7

MS (ESI) = 239 [M + H]<sup>+</sup>

Methyl 3-(4-(benzyloxy)phenyl)-2-methoxy-3-oxopropanoate (**26f**)



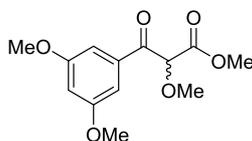
Chemical Formula: C<sub>18</sub>H<sub>18</sub>O<sub>5</sub>  
Exact Mass: 314.1154

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.07 (d, *J* = 9.0 Hz, 2H), 7.43 – 7.32 (m, 5H), 7.01 (d, *J* = 9.0 Hz, 2H), 5.13 (s, 2H), 4.90 (s, 1H), 3.76 (s, 3H), 3.51 (s, 3H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 190.9, 168.3, 163.5, 136.1, 132.1 (2C), 128.8 (2C), 128.4, 127.6 (2C), 127.4, 114.9 (2C), 85.3, 70.3, 58.7, 52.8.

MS (ESI) = 315 [M + H]<sup>+</sup>

Methyl 3-(3,5-dimethoxyphenyl)-2-methoxy-3-oxopropanoate (**26g**)



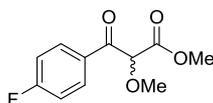
Chemical Formula: C<sub>13</sub>H<sub>16</sub>O<sub>6</sub>  
Exact Mass: 268.0947

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.21 (d, *J* = 2.3 Hz, 2H), 6.68 (t, *J* = 2.3 Hz, 1H), 4.92 (s, 1H), 3.82 (s, 6H), 3.77 (s, 3H), 3.53 (s, 3H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 192.1, 168.0, 161.0 (2C), 135.9, 107.1 (2C), 106.9, 85.0, 58.8, 55.7 (2C), 52.9.

MS (ESI) = 269 [M + H]<sup>+</sup>

Methyl 3-(4-fluorophenyl)-2-methoxy-3-oxopropanoate (**26h**)



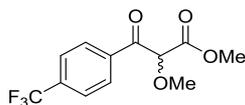
Chemical Formula: C<sub>11</sub>H<sub>11</sub>FO<sub>4</sub>  
Exact Mass: 226.0641

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.15 – 8.09 (m, 2H), 7.17 – 7.10 (m, 2H), 4.88 (s, 1H), 3.77 (s, 3H), 3.52 (s, 3H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 190.8, 167.9, 166.2 (d, *J*<sub>CF</sub> = 256.6 Hz), 132.3 (d, *J*<sub>CF</sub> = 9.5 Hz, 2C), 130.4 (d, *J*<sub>CF</sub> = 26.2 Hz), 115.9 (d, *J*<sub>CF</sub> = 21.9 Hz, 2C), 85.3, 58.7, 52.8.

MS (ESI) = 227 [M + H]<sup>+</sup>

Methyl 2-methoxy-3-oxo-3-(4-(trifluoromethyl)phenyl)propanoate (**26i**)



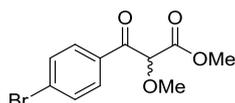
Chemical Formula: C<sub>12</sub>H<sub>11</sub>F<sub>3</sub>O<sub>4</sub>  
Exact Mass: 276.0609

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 8.19 – 8.17 (m, 2H), 7.75 – 7.71 (m, 2H), 4.91 (s, 1H), 3.78 (s, 3H), 3.54 (s, 3H).

**<sup>13</sup>C NMR** (75MHz, CDCl<sub>3</sub>) δ 191.8, 167.7, 136.8, 135.3 (q, *J*<sub>CF</sub> = 32.9 Hz), 130.0 (2C), 125.9 (q, *J*<sub>CF</sub> = 3.5 Hz, 2C), 123.4 (q, *J*<sub>CF</sub> = 272.7 Hz), 85.6, 59.1, 53.1.

**MS** (ESI) = 294 [M + NH<sub>4</sub>]<sup>+</sup>

Methyl 3-(4-bromophenyl)-2-methoxy-3-oxopropanoate (**26j**)



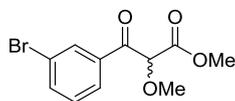
Chemical Formula: C<sub>11</sub>H<sub>11</sub>BrO<sub>4</sub>  
Exact Mass: 285.9841

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.96 – 7.92 (m, 2H), 7.63 – 7.59 (m, 2H), 4.87 (s, 1H), 3.77 (s, 3H), 3.52 (s, 3H).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 191.6, 167.9, 132.8, 132.2 (2C), 131.1 (2C), 129.6, 85.5, 58.9, 53.0.

**MS** (ESI) = 304 [M + NH<sub>4</sub>]<sup>+</sup>

Methyl 3-(3-bromophenyl)-2-methoxy-3-oxopropanoate (**26k**)

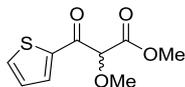


Chemical Formula: C<sub>11</sub>H<sub>11</sub>BrO<sub>4</sub>  
Exact Mass: 285.9841

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 8.18 (t, *J* = 1.7 Hz, 1H), 8.02 – 7.99 (m, 1H), 7.72 (ddd, *J* = 8.0, 2.0, 1.0 Hz, 1H), 7.34 (t, *J* = 7.9 Hz, 1H), 4.89 (s, 1H), 3.78 (s, 3H), 3.53 (s, 3H).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 191.3, 167.8, 137.0, 135.8, 132.4, 130.4, 128.2, 123.1, 85.2, 59.0, 53.0.

**MS** (ESI) = 304 [M + NH<sub>4</sub>]<sup>+</sup>

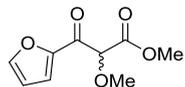
Methyl 2-methoxy-3-oxo-3-(thiophen-2-yl)propanoate (**26l**)

Chemical Formula: C<sub>9</sub>H<sub>10</sub>O<sub>4</sub>S  
Exact Mass: 214.0300

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 8.05 (dd, *J* = 3.9, 1.1 Hz, 1H), 7.73 (dd, *J* = 4.9, 1.1 Hz, 1H), 7.15 (dd, *J* = 4.9, 3.9 Hz, 1H), 4.80 (s, 1H), 3.78 (s, 3H), 3.54 (s, 3H).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 185.5, 167.5, 140.1, 135.6, 135.1, 128.5, 85.7, 58.7, 52.9.

**MS** (ESI) = 215 [M + H]<sup>+</sup>

methyl 3-(furan-2-yl)-2-methoxy-3-oxopropanoate (**26m**)

Chemical Formula: C<sub>9</sub>H<sub>10</sub>O<sub>5</sub>  
Exact Mass: 198.0528

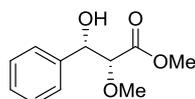
**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.67 (dd, *J* = 1.6, 0.7 Hz, 1H), 7.50 – 7.48 (m, 1H), 6.58 (dd, *J* = 3.6, 1.7 Hz, 1H), 4.81 (s, 1H), 3.78 (s, 3H), 3.53 (s, 3H).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 180.8, 167.5, 150.1, 147.9, 121.2, 112.8, 84.4, 59.0, 52.9.

**MS** (ESI) = 199 [M + H]<sup>+</sup>

**Typical procedure for rhodium complex (*R,R*)-C84-catalyzed ATH of  $\alpha$ -methoxyl - $\beta$ -keto esters **26****

A round-bottomed tube equipped with a balloon of argon was charged with the corresponding  $\alpha$ -methoxyl - $\beta$ -keto esters **26** (0.8 mmol) and the rhodium complex (*R,R*)-**C84** (0.0040 mmol, 0.5 mol%). The solids were subjected to three vacuum/argon cycles before anhydrous 2-MeTHF (4.0 mL) was added. The mixture was stirred at room temperature for 3-5 min, and the tube was transferred into 30 °C oil bath, before the HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) azeotropic mixture (134  $\mu$ L, 1.6 mmol, 2.0 equiv) was added dropwise. After complete consumption of the starting material (monitored by TLC or <sup>1</sup>H NMR), the reaction mixture was evaporated under vacuum, followed by quenched with sat. aq NaHCO<sub>3</sub>, extracted with CH<sub>2</sub>Cl<sub>2</sub>, the combined organic layers were washed with brine, dried (MgSO<sub>4</sub>), filtrated and concentrated under vacuum. The conversion and diastereomeric ratio were determined by <sup>1</sup>H NMR analysis of the crude product. After purification of the crude product, the enantiomeric excess was determined by SFC or HPLC analysis (Chiralcel OD-H or Chiralpak IA, IB, IC or AD-H column).

**Methyl (2*R*,3*S*)-3-hydroxy-2-methoxy-3-phenylpropanoate (**27a**)**

Chemical Formula: C<sub>11</sub>H<sub>14</sub>O<sub>4</sub>  
Exact Mass: 210.0892

Pale yellow oil, 156 mg, 93% yield, *syn* : *anti* = 97 : 3, *ee*<sub>*syn*</sub> >99%;

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.38 – 7.28 (m, 5H), 4.92 (t, *J* = 5.3 Hz, 1H), 3.91 (d, *J* = 5.6 Hz, 1H), 3.65 (s, 3H), 3.42 (s, 3H), 2.95 (d, *J* = 5.1 Hz, 1H).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  170.8, 139.2, 128.4 (2C), 128.3, 126.6 (2C), 85.4, 74.8, 59.0, 52.1.

MS (ESI): *m/z* = 228 [M + NH<sub>4</sub>]<sup>+</sup>

HPLC : Chiralpak IC, Hexane : *i*PrOH = 90 : 10, 1.0 mL/min,  $\lambda$  = 215 nm, *t*<sub>R</sub> [*anti*] = 12.13 min, *t*<sub>R</sub> [*anti*] = 14.15 min, *t*<sub>R</sub> [*syn*-(*S,R*)] = 18.80 min, *t*<sub>R</sub> [*syn*-(*R,S*)] = 27.83 min.

Methyl (2*R*,3*S*)-3-hydroxy-2-methoxy-3-(*p*-tolyl)propanoate (**27b**)

Pale yellow oil, 143 mg, 80% yield, *syn* : *anti* = 97 : 3, *ee<sub>syn</sub>* >99%;

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.18 (d, *J* = 8.1 Hz, 2H), 7.08 (d, *J* = 7.9 Hz, 2H), 4.81 (t, *J* = 5.3 Hz, 1H), 3.82 (d, *J* = 5.6 Hz, 1H), 3.58 (s, 3H), 3.35 (s, 3H), 2.83 (d, *J* = 4.8 Hz, 1H), 2.27 (s, 3H).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 170.9, 138.0, 136.2, 129.2 (2C), 126.5 (2C), 85.4, 74.6, 59.0, 52.1, 21.3.

ESI (*m/z*) = 242 [M + NH<sub>4</sub>]<sup>+</sup>

HPLC : Chiralpak IC, Hexane : *i*PrOH = 90 : 10, 1.0 mL/min, λ = 215 nm, *t<sub>R</sub>* [*anti*] = 14.36 min, *t<sub>R</sub>* [*anti*] = 18.39 min, *t<sub>R</sub>* [*syn*-(*S,R*)] = 25.26 min, *t<sub>R</sub>* [*syn*-(*R,S*)] = 32.34 min.

Methyl (2*S*,3*S*)-3-hydroxy-2-methoxy-3-(2-methoxyphenyl)propanoate (**28c**)

Pale yellow oil, 129 mg, 67% yield, *syn* : *anti* = 4 : 96, *ee<sub>anti</sub>* = 88%;

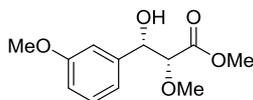
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.36 – 7.33 (m, 1H), 7.31 – 7.27 (m, 1H), 6.98 – 6.94 (m, 1H), 6.89 (d, *J* = 8.1 Hz, 1H), 5.19 (t, *J* = 5.9 Hz, 1H), 4.18 (d, *J* = 5.4 Hz, 1H), 3.87 (s, 3H), 3.64 (s, 3H), 3.39 (s, 3H), 3.23 (d, *J* = 6.4 Hz, 1H).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 170.9, 156.5, 129.1, 128.0, 127.2, 120.8, 110.4, 83.2, 71.1, 58.5, 55.5, 51.8.

MS (ESI): *m/z* = 258 [M + NH<sub>4</sub>]<sup>+</sup>

HPLC : Chiralpak ID, Hexane : *i*PrOH = 92 : 8, 1.0 mL/min, λ = 215 nm, *t<sub>R</sub>* [*syn*] = 27.67 min, *t<sub>R</sub>* [*anti*-(*R,R*)] = 30.06 min, *t<sub>R</sub>* [*syn*] = 45.96 min. *t<sub>R</sub>* [*anti*-(*S,S*)] = 54.14 min

Methyl (2*R*,3*S*)-3-hydroxy-2-methoxy-3-(3-methoxyphenyl)propanoate (**27d**)



Chemical Formula: C<sub>12</sub>H<sub>16</sub>O<sub>5</sub>  
Exact Mass: 240.0998

Pale yellow oil, 153 mg, 80% yield, *syn* : *anti* = 96 : 4, *ee*<sub>*syn*</sub> >99%;

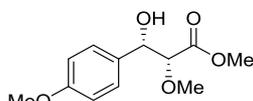
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.25 (t, *J* = 8.0 Hz, 1H), 6.95 – 6.91 (m, 2H), 6.84 (dd, *J* = 8.2, 1.9 Hz, 1H), 4.90 (t, *J* = 5.2 Hz, 1H), 3.90 (d, *J* = 5.4 Hz, 1H), 3.81 (s, 3H), 3.67 (s, 3H), 3.42 (s, 3H), 2.94 (d, *J* = 5.2 Hz, 1H).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 170.9, 159.8, 140.9, 129.5, 118.8, 113.9, 112.0, 85.3, 74.7, 59.1, 55.4, 52.2.

MS (ESI): *m/z* = 258 [M + NH<sub>4</sub>]<sup>+</sup>

SFC : Chiralpak AD-H, *sc*CO<sub>2</sub>/MeOH 92/8, 4.0 mL/min, P = 150 bar, λ = 215 nm, *t*<sub>R</sub> [*anti*] = 2.76 min, *t*<sub>R</sub> [*syn*-(*S,R*)] = 3.30 min, *t*<sub>R</sub> [*anti*] = 3.62 min, *t*<sub>R</sub> [*syn*-(*R,S*)] = 4.91 min.

Methyl (2*R*,3*S*)-3-hydroxy-2-methoxy-3-(4-methoxyphenyl)propanoate (**27e**)



Chemical Formula: C<sub>12</sub>H<sub>16</sub>O<sub>5</sub>  
Exact Mass: 240.0998

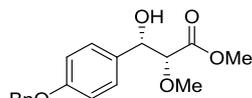
Pale yellow oil, 158 mg, 82% yield, *syn* : *anti* = 96 : 4, *ee*<sub>*syn*</sub> >99%;

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.33 – 7.25 (m, 2H), 6.92 – 6.83 (m, 2H), 4.85 (t, *J* = 6.0 Hz, 1H), 3.87 (d, *J* = 6.0 Hz, 1H), 3.80 (s, 3H), 3.64 (s, 3H), 3.43 (s, 3H), 2.90 (d, *J* = 4.6 Hz, 1H).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 170.9, 159.6, 131.1, 128.0 (2C), 113.9 (2C), 85.6, 74.5, 59.0, 55.4, 52.1.

MS (ESI): *m/z* = 258 [M + NH<sub>4</sub>]<sup>+</sup>

SFC : Chiralpak AD-H, *sc*CO<sub>2</sub>/MeOH 95/5, 3.0 mL/min, P = 150 bar, λ = 215 nm, *t*<sub>R</sub> [*syn*-(*S,R*)] = 5.49 min, *t*<sub>R</sub> [*anti*] = 6.38 min, *t*<sub>R</sub> [*anti*] = 6.86 min, *t*<sub>R</sub> [*syn*-(*R,S*)] = 7.45 min.

Methyl (2*R*,3*S*)-3-(4-(benzyloxy)phenyl)-3-hydroxy-2-methoxypropanoate (**27f**)

Chemical Formula: C<sub>18</sub>H<sub>20</sub>O<sub>5</sub>  
Exact Mass: 316.1311

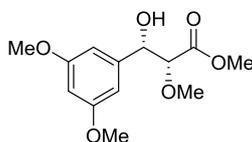
White solid, 233 mg, 92% yield, *syn* : *anti* = 97 : 3, *ee*<sub>*syn*</sub> >99%;

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.44 – 7.36 (m, 4H), 7.35 – 7.27 (m, 3H), 6.97 – 6.93 (m, 2H), 5.06 (s, 2H), 4.89 – 4.83 (m, 1H), 3.87 (d, *J* = 5.9 Hz, 1H), 3.63 (s, 3H), 3.43 (s, 3H), 2.92 (t, *J* = 3.7 Hz, 1H).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 170.9, 158.9, 137.0, 131.4, 128.7 (2C), 128.1, 128.0 (2C), 127.6 (2C), 114.9, 85.6, 74.5, 70.1, 59.0, 52.1.

MS (ESI): *m/z* = 334 [M + NH<sub>4</sub>]<sup>+</sup>

SFC : Chiralpak IC, *sc*CO<sub>2</sub>/*i*PrOH 92/8, 3.0 mL/min, P = 150 bar, λ = 215 nm, *t<sub>R</sub>* [*anti*] = 14.40 min, *t<sub>R</sub>* [*syn*-(*S,R*)] = 18.81 min, *t<sub>R</sub>* [*anti*] = 20.61 min, *t<sub>R</sub>* [*syn*-(*R,S*)] = 26.46 min.

Methyl (2*R*,3*S*)-3-(3,5-dimethoxyphenyl)-3-hydroxy-2-methoxypropanoate (**27g**)

Chemical Formula: C<sub>13</sub>H<sub>18</sub>O<sub>6</sub>  
Exact Mass: 270.1103

Pale yellow oil, 179 mg, 83% yield, *syn* : *anti* = 95 : 5, *ee*<sub>*syn*</sub> >99%;

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 6.53 (d, *J* = 2.2 Hz, 2H), 6.40 (t, *J* = 2.3 Hz, 1H), 4.86 (t, *J* = 5.0 Hz, 1H), 3.89 (d, *J* = 5.2 Hz, 1H), 3.79 (s, 6H), 3.69 (s, 3H), 3.42 (s, 3H), 2.91 (d, *J* = 5.1 Hz, 1H).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 170.8, 160.8 (2C), 141.8, 104.4 (2C), 100.2, 85.1, 74.6, 59.0, 55.4 (2C), 52.1.

MS (ESI): *m/z* = 288 [M + NH<sub>4</sub>]<sup>+</sup>

SFC : Chiralpak AD-H, *sc*CO<sub>2</sub>/MeOH 95/5, 2.0 mL/min, P = 150 bar, λ = 215 nm, *t<sub>R</sub>* [*anti*] = 10.38 min, *t<sub>R</sub>* [*syn*-(*S,R*)] = 13.74 min, *t<sub>R</sub>* [*anti*] = 14.82 min, *t<sub>R</sub>* [*syn*-(*R,S*)] = 18.95 min.

Methyl (2*R*,3*S*)-3-(4-fluorophenyl)-3-hydroxy-2-methoxypropanoate (**27h**)



Pale yellow oil, 124 mg, 68% yield, *syn* : *anti* = 98 : 2, *ee<sub>syn</sub>* >99%;

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.36 – 7.32 (m, 2H), 7.07 – 7.01 (m, 2H), 4.89 (t, *J* = 5.2 Hz, 1H), 3.85 (d, *J* = 5.8 Hz, 1H), 3.65 (s, 3H), 3.48 – 3.40 (m, 3H), 3.00 – 2.96 (m, 1H).

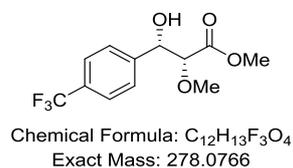
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 170.7, 162.7 (d, *J<sub>CF</sub>* = 246.4 Hz), 134.9, 128.4 (d, *J<sub>CF</sub>* = 8.2 Hz, 2C), 115.4 (d, *J<sub>CF</sub>* = 21.5 Hz, 2C), 85.3, 74.2, 59.0, 52.2.

**<sup>19</sup>F NMR** (376 MHz, CDCl<sub>3</sub>) δ -114.0.

**MS** (ESI): *m/z* = 246 [M + NH<sub>4</sub>]<sup>+</sup>

**HPLC** : Chiralpak IB, Hexane : *i*PrOH = 90 : 10, 0.2 mL/min, λ = 215 nm, *t<sub>R</sub>* [*anti*] = 37.38 min, *t<sub>R</sub>* [*anti*] = 41.79 min, *t<sub>R</sub>* [*syn*-(*S,R*)] = 44.52 min, *t<sub>R</sub>* [*syn*-(*R,S*)] = 47.61 min.

Methyl (2*R*,3*S*)-3-hydroxy-2-methoxy-3-(4-(trifluoromethyl)phenyl)propanoate (**27i**)



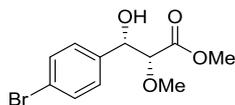
Pale yellow oil, 177 mg, 80% yield, *syn* : *anti* = 97 : 3, *ee<sub>syn</sub>* >99%;

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.62 (d, *J* = 8.2 Hz, 2H), 7.49 (d, *J* = 8.4 Hz, 2H), 4.99 (t, *J* = 5.3 Hz, 1H), 3.90 (d, *J* = 5.1 Hz, 1H), 3.69 (s, 3H), 3.42 (s, 3H), 3.06 (d, *J* = 5.6 Hz, 1H). **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 170.6, 143.4, 130.5 (q, *J<sub>CF</sub>* = 32.5 Hz), 127.0 (2C), 125.4 (q, *J<sub>CF</sub>* = 3.5 Hz 2C), 122.9 (q, *J<sub>CF</sub>* = 272 Hz), 84.7, 74.2, 59.2, 52.3.

**<sup>19</sup>F NMR** (376 MHz, CDCl<sub>3</sub>) δ -62.6.

**MS** (ESI): *m/z* = 296 [M + NH<sub>4</sub>]<sup>+</sup>

**HPLC** : Chiralpak IA, Hexane : *i*PrOH = 95 : 5, 1.0 mL/min, λ = 215 nm, *t<sub>R</sub>* [*anti*] = 13.56 min, *t<sub>R</sub>* [*syn*-(*R,S*)] = 14.91 min, *t<sub>R</sub>* [*syn*-(*S,R*)] = 18.39 min. *t<sub>R</sub>* [*anti*] = 23.92 min.

Methyl (2*R*,3*S*)-3-(4-bromophenyl)-3-hydroxy-2-methoxypropanoate (**27j**)

Chemical Formula: C<sub>11</sub>H<sub>13</sub>BrO<sub>4</sub>  
Exact Mass: 287.9997

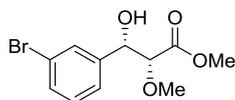
White solid, 190 mg, 82% yield, *syn* : *anti* = 97 : 3, *ee*<sub>*syn*</sub> >99%;

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.48 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 4.88 (t, *J* = 5.3 Hz, 1H), 3.85 (d, *J* = 5.4 Hz, 1H), 3.67 (s, 3H), 3.42 (s, 3H), 3.01 – 2.98 (br, 1H).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 170.6, 138.3, 131.6 (2C), 128.3 (2C), 122.2, 85.0, 74.2, 59.1, 52.2.

MS (ESI): *m/z* = 306 [M + NH<sub>4</sub>]<sup>+</sup>

HPLC : Chiralpak IA, Hexane : *i*PrOH = 95 : 5, 1.0 mL/min, λ = 215 nm, *t*<sub>R</sub> [*anti*] = 17.90 min, *t*<sub>R</sub> [*syn*-(*R,S*)] = 21.77 min, *t*<sub>R</sub> [*syn*-(*S,R*)] = 23.49 min. *t*<sub>R</sub> [*anti*] = 27.10 min

Methyl (2*R*,3*S*)-3-(3-bromophenyl)-3-hydroxy-2-methoxypropanoate (**27k**)

Chemical Formula: C<sub>11</sub>H<sub>13</sub>BrO<sub>4</sub>  
Exact Mass: 287.9997

Pale yellow oil, 157 mg, 68% yield, *syn* : *anti* = 99 : 1, *ee*<sub>*syn*</sub> >99%;

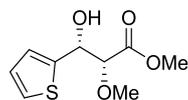
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.54 (s, 1H), 7.44 (d, *J* = 7.8 Hz, 1H), 7.28 (d, *J* = 7.8 Hz, 1H), 7.22 (t, *J* = 7.8 Hz, 1H), 4.89 (t, *J* = 5.3 Hz, 1H), 3.87 (d, *J* = 5.3 Hz, 1H), 3.69 (s, 3H), 3.42 (s, 3H), 3.02 – 2.98 (m, 1H).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 170.6, 141.7, 131.4, 130.0, 129.7, 125.2, 122.6, 84.9, 74.1, 59.1, 52.3.

MS (ESI): *m/z* = 306 [M + NH<sub>4</sub>]<sup>+</sup>

SFC : Chiralpak AD-H, *sc*CO<sub>2</sub>/MeOH 95/5, 5.0 mL/min, P = 150 bar, λ = 215 nm, *t*<sub>R</sub> [*anti*] = 6.68 min, *t*<sub>R</sub> [*syn*-(*S,R*)] = 7.29 min, *t*<sub>R</sub> [*anti*] = 8.90 min, *t*<sub>R</sub> [*syn*-(*R,S*)] = 13.10 min.

Methyl (2*R*,3*R*)-3-hydroxy-2-methoxy-3-(thiophen-2-yl)propanoate (**27l**)



Chemical Formula: C<sub>9</sub>H<sub>12</sub>O<sub>4</sub>S  
Exact Mass: 216.0456

Pale yellow oil, 157 mg, 91% yield, *syn* : *anti* > 99 : 1, *ee*<sub>*syn*</sub> >99%;

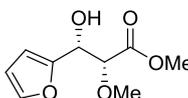
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.29 (dd, *J* = 5.0, 1.2 Hz, 1H), 7.03 (d, *J* = 3.4 Hz, 1H), 6.97 (dd, *J* = 5.0, 3.5 Hz, 1H), 5.22 (d, *J* = 4.5 Hz, 1H), 3.96 (d, *J* = 4.6 Hz, 1H), 3.74 (s, 3H), 3.51 (s, 3H), 2.96 (s, 1H).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 170.6, 142.6, 126.6, 125.9, 125.6, 84.6, 71.0, 59.3, 52.4.

MS (ESI): *m/z* = 234 [M + NH<sub>4</sub>]<sup>+</sup>

SFC : Chiralpak IC, *sc*CO<sub>2</sub>/*i*PrOH 90/10, 3.0 mL/min, P = 150 bar, λ = 215 nm, *t<sub>R</sub>* [*anti*] = 3.71 min, *t<sub>R</sub>* [*anti*] = 4.53 min, *t<sub>R</sub>* [*syn*-(*S,S*)] = 5.68 min, *t<sub>R</sub>* [*syn*-(*R,R*)] = 6.55 min.

Methyl (2*R*,3*R*)-3-(furan-2-yl)-3-hydroxy-2-methoxypropanoate (**27m**)



Chemical Formula: C<sub>9</sub>H<sub>12</sub>O<sub>5</sub>  
Exact Mass: 200.0685

Pale yellow oil, 136 mg, 86% yield, *syn* : *anti* = 99 : 1, *ee*<sub>*syn*</sub> >99%;

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.39 (t, *J* = 1.3 Hz, 1H), 6.35 (d, *J* = 1.4 Hz, 2H), 4.97 (dd, *J* = 7.2, 4.9 Hz, 1H), 4.13 (d, *J* = 4.9 Hz, 1H), 3.74 (s, 3H), 3.47 (s, 3H), 2.90 (d, *J* = 7.2 Hz, 1H).

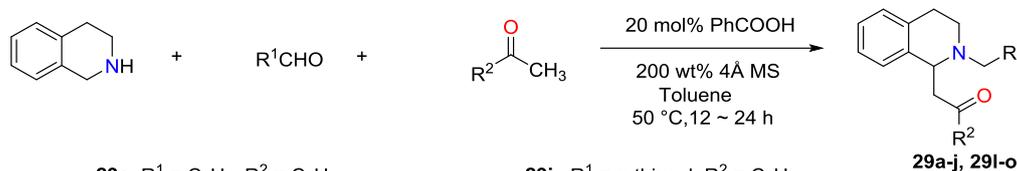
<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 170.6, 152.4, 142.5, 110.5, 107.9, 82.4, 69.0, 59.2, 52.4.

MS (ESI): *m/z* = 218 [M + NH<sub>4</sub>]<sup>+</sup>

SFC : Chiralpak IC, *sc*CO<sub>2</sub>/*i*PrOH 92/8, 3.0 mL/min, P = 150 bar, λ = 215 nm, *t<sub>R</sub>* [*anti*] = 4.29 min, *t<sub>R</sub>* [*syn*-(*S,S*)] = 5.27 min, *t<sub>R</sub>* [*anti*] = 6.33 min, *t<sub>R</sub>* [*syn*-(*R,R*)] = 8.15 min.

**Substrates: THIQ based  $\beta$ -amino ketones (29)**

**General procedure I :** preparation of THIQ based  $\beta$ -amino ketones



**29a:** R<sup>1</sup> = C<sub>6</sub>H<sub>5</sub>, R<sup>2</sup> = C<sub>6</sub>H<sub>5</sub>;

**29b:** R<sup>1</sup> = *p*-ClC<sub>6</sub>H<sub>4</sub>, R<sup>2</sup> = C<sub>6</sub>H<sub>5</sub>;

**29c:** R<sup>1</sup> = *m*-ClC<sub>6</sub>H<sub>4</sub>, R<sup>2</sup> = C<sub>6</sub>H<sub>5</sub>;

**29d:** R<sup>1</sup> = *o*-ClC<sub>6</sub>H<sub>4</sub>, R<sup>2</sup> = C<sub>6</sub>H<sub>5</sub>;

**29e:** R<sup>1</sup> = *p*-BrC<sub>6</sub>H<sub>4</sub>, R<sup>2</sup> = C<sub>6</sub>H<sub>5</sub>;

**29f:** R<sup>1</sup> = *p*-MeOIC<sub>6</sub>H<sub>4</sub>, R<sup>2</sup> = C<sub>6</sub>H<sub>5</sub>;

**29g:** R<sup>1</sup> = *m*-MeOC<sub>6</sub>H<sub>4</sub>, R<sup>2</sup> = C<sub>6</sub>H<sub>5</sub>;

**29h:** R<sup>1</sup> = *p*-MeC<sub>6</sub>H<sub>4</sub>, R<sup>2</sup> = C<sub>6</sub>H<sub>5</sub>;

**29i:** R<sup>1</sup> = *o*-thienyl, R<sup>2</sup> = C<sub>6</sub>H<sub>5</sub>;

**29j:** R<sup>1</sup> = 2-naphthyl, R<sup>2</sup> = C<sub>6</sub>H<sub>5</sub>;

**29l:** R<sup>1</sup> = C<sub>6</sub>H<sub>5</sub>, R<sup>2</sup> = *p*-MeC<sub>6</sub>H<sub>5</sub>;

**29m:** R<sup>1</sup> = C<sub>6</sub>H<sub>5</sub>, R<sup>2</sup> = *p*-FC<sub>6</sub>H<sub>5</sub>;

**29n:** R<sup>1</sup> = C<sub>6</sub>H<sub>5</sub>, R<sup>2</sup> = *p*-BrC<sub>6</sub>H<sub>5</sub>;

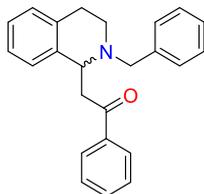
**29o:** R<sup>1</sup> = C<sub>6</sub>H<sub>5</sub>, R<sup>2</sup> = *p*-MeOC<sub>6</sub>H<sub>5</sub>;

**29p:** R<sup>1</sup> = C<sub>6</sub>H<sub>5</sub>, R<sup>2</sup> = 2-naphthyl;

**29q:** R<sup>1</sup> = C<sub>6</sub>H<sub>5</sub>, R<sup>2</sup> = CH<sub>3</sub>;

A 100 mL round-bottom flask was charged with 4Å molecular sieves (200 wt% of aldehyde), benzoic acid (2.4 mmol, 0.2 equiv), toluene (60 mL), the aldehyde (12.0 mmol, 1 equiv), aryl methyl ketones (18.0 mmol, 1.5 equiv) or acetone (3.0 equiv) and tetrahydroisoquinoline (THIQ) (18.0 mmol, 1.5 equiv). The mixture was stirred at 50 °C for 12 ~ 24 h at which time the aldehyde was consumed as detected by TLC analysis. The reaction mixture was allowed to cool to room temperature and filtered through a short pad of celite that was then rinsed with EtOAc (100 mL). The filtrate was washed with saturated aqueous NaHCO<sub>3</sub> (3 x 40 mL). The combined aqueous layers were extracted with EtOAc (3 x 40 mL), and the combined organic layers were washed with water (100 mL), brine (100 mL), and dried over anhydrous MgSO<sub>4</sub> or Na<sub>2</sub>SO<sub>4</sub>. Solvent was then removed under reduced pressure and the residue purified by silica gel chromatography. After column, the impurity was further purified under pressure (0.001 mbar), temperature (100 °C).

2-(2-benzyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-phenylethan-1-one (**29a**)



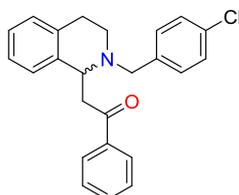
Chemical Formula: C<sub>24</sub>H<sub>23</sub>NO  
Exact Mass: 341.1780

Synthesized according to the general procedure **I**, 1.6 g (31% yield), pale yellow oil.

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.95 – 7.92 (m, 2H), 7.57 – 7.53 (m, 1H), 7.44 – 7.41 (m, 2H), 7.25 – 7.08 (m, 9H), 4.63 – 4.57 (m, 1H), 3.78, 3.67 (ABq, *J* = 13.4 Hz, 2H), 3.62 (dd, *J* = 15.7, 7.8 Hz, 1H), 3.24 – 3.13 (m, 2H), 2.99 (ddd, *J* = 16.5, 10.6, 5.6 Hz, 1H), 2.80 (ddd, *J* = 12.8, 5.8, 2.2 Hz, 1H), 2.62 – 2.54 (m, 1H);

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 199.1, 139.2, 138.4, 137.6, 134.5, 133.0, 129.3, 128.9 (2C), 128.7 (2C), 128.4 (2C), 128.2 (2C), 127.8, 127.0, 126.5, 126.2, 58.5, 58.1, 45.9, 42.4, 24.5.

2-(2-(4-chlorobenzyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-phenylethan-1-one (**29b**)

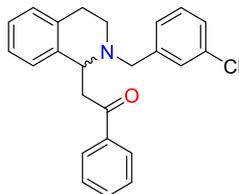


Chemical Formula: C<sub>24</sub>H<sub>22</sub>ClNO  
Exact Mass: 375.1390

Synthesized according to the general procedure **I**, 1.4 g (31% yield), pale yellow solid, m.p. 61 °C.

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.94 – 7.90 (m, 2H), 7.59 – 7.53 (m, 1H), 7.47 – 7.41 (m, 2H), 7.18 – 7.08 (m, 8H), 4.54 (dd, *J* = 8.3, 5.0 Hz, 1H), 3.72, 3.59 (ABq, *J* = 13.5 Hz, 2H), 3.57 (dd, *J* = 15.6, 8.4 Hz, 1H), 3.25 – 3.13 (m, 2H), 2.97 (ddd, *J* = 16.7, 10.8, 5.9 Hz, 1H), 2.78 (dddd, *J* = 13.4, 6.0, 2.1, 0.7 Hz, 1H), 2.57 (ddd, *J* = 16.9, 4.5, 2.1 Hz, 1H);

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 198.9, 138.0, 137.8, 137.5, 134.3, 133.1, 132.7, 130.2 (2C), 129.4, 128.7 (2C), 128.4 (4C), 127.8, 126.6, 126.3, 58.3, 57.3, 45.9, 42.5, 24.2.

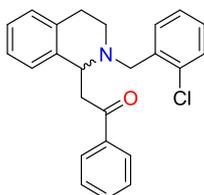
2-(2-(3-chlorobenzyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-phenylethan-1-one (**29c**)

Chemical Formula:  $C_{24}H_{22}ClNO$   
Exact Mass: 375.1390

Synthesized according to the general procedure **I**, 1.54 g (34% yield), pale yellow oil.

$^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  7.97 – 7.93 (m, 2H), 7.59 – 7.53 (m, 1H), 7.48 – 7.43 (m, 2H), 7.21 – 7.05 (m, 8H), 4.57 (dd,  $J = 8.1, 5.1$  Hz, 1H), 3.76 – 3.58 (m, 3H), 3.24 – 3.12 (m, 2H), 3.04 – 2.93 (m, 1H), 2.78 (ddd,  $J = 13.2, 5.6, 1.9$  Hz, 1H), 2.58 (ddd,  $J = 16.8, 4.6, 2.3$  Hz, 1H);

$^{13}C$  NMR (75 MHz,  $CDCl_3$ )  $\delta$  199.0, 141.5, 138.1, 137.6, 134.3, 134.2, 133.1, 129.5, 129.4, 128.9, 128.7 (2C), 128.3 (2C), 127.8, 127.3, 126.9, 126.6, 126.3, 58.6, 57.5, 45.8, 42.4, 24.2.

2-(2-(2-chlorobenzyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-phenylethan-1-one (**29d**)

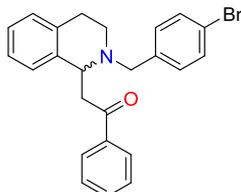
Chemical Formula:  $C_{24}H_{22}ClNO$   
Exact Mass: 375.1390

Synthesized according to the general procedure **I**, 1.3 g (35% yield), pale yellow oil.

$^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  7.94 – 7.91 (m, 2H), 7.57 – 7.51 (m, 1H), 7.46 – 7.40 (m, 2H), 7.36 – 7.33 (m, 1H), 7.28 – 7.23 (m, 1H), 7.18 – 7.10 (m, 6H), 4.62 (dd,  $J = 7.5, 5.5$  Hz, 1H), 3.94, 3.66 (dd,  $J = 14.4$  Hz, 2H), 3.62 (dd,  $J = 15.7, 7.9$  Hz, 1H), 3.28 – 3.15 (m, 2H), 3.12 – 3.00 (m, 1H), 2.86 – 2.79 (m, 1H), 2.65 – 2.58 (m, 1H);

$^{13}C$  NMR (75 MHz,  $CDCl_3$ )  $\delta$  199.0, 138.4, 137.6, 136.8, 134.4, 134.2, 133.0, 130.8, 129.3 (2C), 128.6 (2C), 128.4 (2C), 128.1, 127.7, 126.7, 126.5, 126.2, 58.7, 54.8, 45.8, 42.9, 24.8.

2-(2-(4-bromobenzyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-phenylethan-1-one (**29e**)



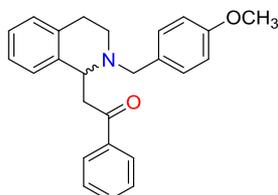
Chemical Formula: C<sub>24</sub>H<sub>22</sub>BrNO  
Exact Mass: 419.0885

Synthesized according to the general procedure **I**, 1.36 g (27% yield), pale yellow solid, m.p. 82 °C;

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.94 – 7.90 (m, 2H), 7.60 – 7.54 (m, 1H), 7.47 – 7.41 (m, 2H), 7.32 – 7.28 (m, 2H), 7.20 – 7.09 (m, 4H), 7.06 – 7.02 (m, 2H), 4.53 (dd, *J* = 8.4, 5.0 Hz, 1H), 3.71 – 3.52 (m, 3H), 3.26 – 3.13 (m, 2H), 3.03 – 2.91 (m, 1H), 2.82 – 2.75 (m, 1H), 2.57 (ddd, *J* = 16.8, 4.6, 2.1 Hz, 1H);

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 198.9, 138.3, 138.0, 137.4, 134.3, 133.1, 131.3 (2C), 130.6 (2C), 129.4, 128.7 (2C), 128.3 (2C), 127.8, 126.6, 126.3, 120.8, 58.3, 57.3, 45.9, 42.5, 24.2.

2-(2-(4-methoxybenzyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-phenylethan-1-one (**29f**)

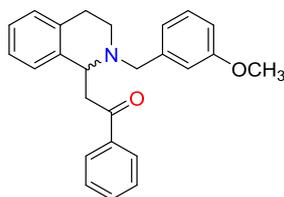


Chemical Formula: C<sub>25</sub>H<sub>25</sub>NO<sub>2</sub>  
Exact Mass: 371.1885

Synthesized according to the general procedure **I**, 0.98 g (22% yield), pale yellow oil.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.95 – 7.91 (m, 2H), 7.59 – 7.50 (m, 1H), 7.48 – 7.39 (m, 2H), 7.18 – 7.08 (m, 6H), 6.78 – 6.71 (m, 2H), 4.57 (dd, *J* = 7.7, 5.3 Hz, 1H), 3.78 (s, 3H), 3.70 – 3.53 (m, 3H), 3.22 – 3.12 (m, 2H), 2.97 (ddd, *J* = 16.9, 11.0, 6.0 Hz, 1H), 2.80 (ddd, *J* = 13.6, 6.3, 2.3 Hz, 1H), 2.56 (ddd, *J* = 16.8, 4.5, 2.4 Hz, 1H);

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 199.1, 158.8, 138.3, 137.6, 134.5, 132.9, 131.2 (2C), 130.0, 129.3 (2C), 128.7 (2C), 128.4, 127.8, 126.5, 126.2, 113.6 (2C), 58.3, 57.4, 55.4, 45.9, 42.3, 24.4.

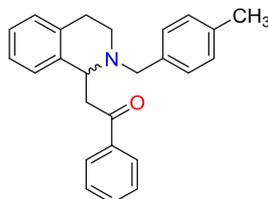
2-(2-(3-methoxybenzyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-phenylethan-1-one (**29g**)

Chemical Formula: C<sub>25</sub>H<sub>25</sub>NO<sub>2</sub>  
Exact Mass: 371.1885

Synthesized according to the general procedure **I**, 1.92 g (43% yield), pale yellow oil.

**<sup>1</sup>H NMR** (300 MHz, C<sub>6</sub>D<sub>6</sub>) 7.90 – 7.79 (m, 2H), 7.19 – 6.90 (m, 9H), 6.84 (d, *J* = 7.6 Hz, 1H), 6.75 – 6.71 (m, 1H), 4.75 (dd, *J* = 7.4, 5.3 Hz, 1H), 3.65, 3.55 (ABq, *J* = 13.5 Hz, 2H), 3.39 (dd, *J* = 16.0, 7.7 Hz, 1H), 3.34 (s, 3H), 3.01 – 2.87 (m, 2H), 2.75 (ddd, *J* = 16.1, 10.5, 5.8 Hz, 1H), 2.66 – 2.58 (m, 1H), 2.31 – 2.23 (m, 1H);

**<sup>13</sup>C NMR** (75 MHz, C<sub>6</sub>D<sub>6</sub>) δ 198.0, 160.4, 141.5, 139.0, 138.2, 134.7, 132.6, 129.4 (2C), 128.6 (2C), 128.5 (2C), 127.8, 126.5, 126.4, 121.3, 114.4, 113.3, 58.9, 58.3, 54.7, 45.8, 42.6, 24.9.

2-(2-(4-methylbenzyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-phenylethan-1-one (**29h**)

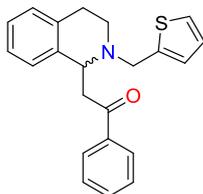
Chemical Formula: C<sub>25</sub>H<sub>25</sub>NO  
Exact Mass: 355.1936

Synthesized according to the general procedure **I**: 1.16 g (27% yield), pale yellow solid, m.p. 92 °C;

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.96 – 7.92 (m, 2H), 7.58 – 7.52 (m, 1H), 7.47 – 7.41 (m, 2H), 7.18 – 7.02 (m, 8H), 4.59 (dd, *J* = 7.6, 5.4 Hz, 1H), 3.73 – 3.56 (m, 3H), 3.22 – 3.13 (m, 2H), 3.09 – 2.93 (m, 1H), 2.80 (ddd, *J* = 7.8, 6.0, 2.2 Hz, 1H), 2.57 (ddd, *J* = 16.6, 4.5, 2.5 Hz, 1H), 2.31 (s, 3H);

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 199.2, 138.4, 137.7, 136.5, 136.1, 134.5, 132.9, 129.3, 128.9 (4C), 128.6 (2C), 128.4 (2C), 127.8, 126.5, 126.2, 58.4, 57.8, 45.9, 42.4, 24.5, 21.2.

phenyl-2-(2-(thiophen-2-ylmethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)ethan-1-one (**29i**)



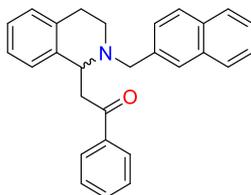
Chemical Formula: C<sub>22</sub>H<sub>21</sub>NOS  
Exact Mass: 347.1344

Synthesized according to the general procedure **I**: 1.21 g (29% yield), pale yellow oil.

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.97 – 7.93 (m, 2H), 7.58 – 7.52 (m, 1H), 7.48 – 7.41 (m, 2H), 7.18 – 7.08 (m, 5H), 6.88 (dd, *J* = 5.1, 3.4 Hz, 1H), 6.83 – 6.82 (m, 1H), 4.72 – 4.64 (m, 1H), 4.00 – 3.82 (m, 2H), 3.60 (dd, *J* = 16.0, 7.3 Hz, 1H), 3.24 – 3.15 (m, 2H), 3.03 – 2.87 (m, 2H), 2.65 – 2.58 (m, 1H);

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 199.0, 143.5, 138.2, 137.6, 134.3, 133.0, 129.3, 128.7 (2C), 128.4 (2C), 127.8, 126.5, 126.3, 126.2, 125.5, 125.0, 58.0, 52.8, 46.1, 42.8, 24.7.

2-(2-(naphthalen-2-ylmethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-phenylethan-1-one (**29j**)

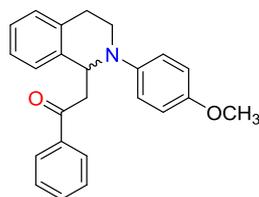


Chemical Formula: C<sub>28</sub>H<sub>25</sub>NO  
Exact Mass: 391.1936

Synthesized according to the general procedure **I**: 1.89 g (40% yield), pale yellow solid, m.p. 90 °C.

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.96 – 7.92 (m, 2H), 7.81 – 7.77 (m, 1H), 7.74 – 7.68 (m, 2H), 7.62 (s, 1H), 7.54 – 7.35 (m, 6H), 7.20 – 7.11 (m, 4H), 4.66 (dd, *J* = 8.0, 5.2 Hz, 1H), 3.94, 3.81 (ABq, *J* = 13.3 Hz, 2H), 3.66 (dd, *J* = 15.6, 8.1 Hz, 1H), 3.27 – 3.16 (m, 2H), 3.03 (ddd, *J* = 16.8, 11.0, 5.8 Hz, 1H), 2.84 (ddd, *J* = 13.1, 5.6, 1.9 Hz, 1H), 2.59 (ddd, *J* = 16.7, 4.4, 2.3 Hz, 1H);

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 199.1, 138.3, 137.6, 136.9, 134.5, 133.4, 132.9 (2C), 129.4, 128.6 (2C), 128.3 (2C), 127.9, 127.8 (2C), 127.7, 127.3 (2C), 126.5, 126.2, 125.9, 125.5, 58.7, 58.2, 45.9, 42.4, 24.4.

1-phenyl-2-(2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)ethan-1-one (**29k**)

Chemical Formula: C<sub>24</sub>H<sub>23</sub>NO<sub>2</sub>  
Exact Mass: 357.1729

A mixture of DDQ (10 mol%, 33.1 mg, 0.146 mmol), AIBN (24.0 mg, 0.0146 mmol), N-(4-methoxyphenyl) tetrahydroisoquinoline (350 mg, 1.46 mmol) and acetophenone (877 mg, 7.3 mmol) in MeOH (6 mL) were heated at 60 °C under oxygen atmosphere (oxygen balloon) for 24 h. The solvent was removed under vacuo, added water and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. Then, the crude product was purified by column chromatography on silica gel using ethyl acetate/hexane (1:20 – 1:10) to afford the desired product **29k** (220 mg) as a pale yellow solid in 42% yield.

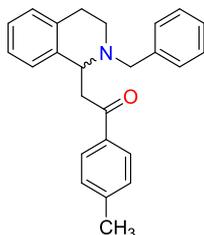
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.84 (d, *J* = 7.1 Hz, 2H), 7.54 – 7.49 (m, 1H), 7.43 – 7.37 (m, 2H), 7.20 – 7.08 (m, 4H), 6.94 (d, *J* = 8.6 Hz, 2H), 6.80 (d, *J* = 9.1 Hz, 2H), 5.54 (t, *J* = 5.4 Hz, 1H), 3.74 (s, 3H), 3.59 – 3.56 (m, 3H), 3.31 (dd, *J* = 16.3, 6.5 Hz, 1H), 3.09 (dt, *J* = 15.7, 7.8 Hz, 1H), 2.87 – 2.82 (m, 1H);

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 198.9, 153.2, 143.8, 138.7, 137.5, 134.4, 133.1, 129.0 (2C), 128.6 (2C), 128.2, 127.2, 126.8, 126.3, 118.0 (2C), 114.9 (2C), 56.4, 55.8, 45.1, 43.0, 27.4.

The spectral data are in agreement with those reported.<sup>301</sup>

<sup>301</sup> Y. Shen, M. Li, S. Wang, T. Zhan, Z. Tan, C.-C. Guo, *Chem. Commun.* **2009**, 953.

2-(2-benzyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-(p-tolyl)ethan-1-one (**29l**)



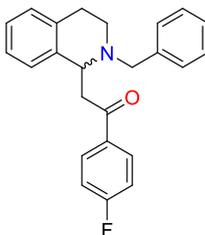
Chemical Formula: C<sub>25</sub>H<sub>25</sub>NO  
Exact Mass: 355.1936

Synthesized according to the general procedure **I**: 1.3 g (37% yield), pale yellow oil;

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.84 (d, *J* = 8.2 Hz, 2H), 7.26–7.11 (m, 11H), 4.60 (dd, *J* = 7.3, 5.8 Hz, 1H), 3.75 (d, *J* = 13.3 Hz, 1H), 3.68 (d, *J* = 13.3 Hz, 1H), 3.59 (dd, *J* = 15.7, 7.8 Hz, 1H), 3.23–3.12 (m, 2H), 3.04–2.93 (m, 1H), 2.80 (ddd, *J* = 12.8, 5.4, 2.2 Hz, 1H), 2.58 (ddd, *J* = 16.9, 4.4, 2.4 Hz, 1H), 2.42 (s, 3H);

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 198.7, 143.7, 139.3, 138.5, 135.2, 134.4, 129.4 (2C), 129.3, 128.9 (2C), 128.5 (2C), 128.2 (2C), 127.8, 127.0, 126.4, 126.1, 58.5, 58.0, 45.7, 42.4, 24.5, 21.8.

2-(2-benzyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-(4-fluorophenyl)ethan-1-one (**29m**)



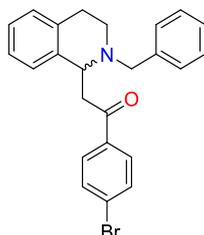
Chemical Formula: C<sub>24</sub>H<sub>22</sub>FNO  
Exact Mass: 359.1685

Synthesized according to the general procedure **I**: 1.4 g (39% yield), pale yellow oil;

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.96–7.90 (m, 2H), 7.20–7.06 (m, 11H), 4.54 (dd, *J* = 7.5, 5.6 Hz, 1H), 3.73 (d, *J* = 13.3 Hz, 1H), 3.62 (d, *J* = 13.3 Hz, 1H), 3.55 (dd, *J* = 15.4, 7.9 Hz, 1H), 3.24–3.11 (m, 2H), 3.05–2.94 (m, 1H), 2.85–2.78 (m, 1H), 2.61–2.53 (m, 1H);

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 197.5, 165.7 (d, *J*<sub>CF</sub> = 252.8 Hz), 139.1, 138.1, 134.4, 134.0 (d, *J*<sub>CF</sub> = 2.4 Hz), 131.0 (d, *J*<sub>CF</sub> = 9.2 Hz, 2C), 129.4, 128.9 (2C), 128.2 (2C), 127.8, 127.1, 126.6, 126.2, 115.7 (d, *J*<sub>CF</sub> = 21.8 Hz, 2C), 58.4, 58.0, 45.9, 42.5, 24.3;

**<sup>19</sup>F NMR** (282 MHz, CDCl<sub>3</sub>) δ –106.7.

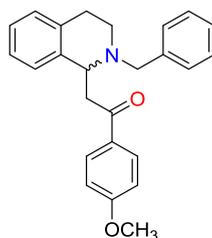
2-(2-benzyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-(4-bromophenyl)ethan-1-one (**29n**)

Chemical Formula:  $C_{24}H_{22}BrNO$   
Exact Mass: 419.0885

Synthesized according to the general procedure **I**: 1.4 g (39% yield), pale yellow oil;

$^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  7.77 (d,  $J = 8.6$  Hz, 2H), 7.56 (d,  $J = 8.5$  Hz, 2H), 7.23–7.07 (m, 9H), 4.52 (dd,  $J = 7.9, 5.5$  Hz, 1H), 3.73 (d,  $J = 13.2$  Hz, 1H), 3.65 (d,  $J = 13.2$  Hz, 1H), 3.53 (dd,  $J = 15.4, 8.2$  Hz, 1H), 3.25–3.10 (m, 2H), 3.05–2.94 (m, 1H), 2.82 (ddd,  $J = 13.1, 5.8, 2.0$  Hz, 1H), 2.57 (ddd,  $J = 16.4, 4.4, 2.0$  Hz, 1H).

$^{13}C$  NMR (75 MHz,  $CDCl_3$ )  $\delta$  198.1, 139.0, 137.9, 136.3, 134.4, 132.0 (2C), 129.9 (2C), 129.4, 128.9 (2C), 128.3 (2C), 128.1, 127.7, 127.1, 126.6, 126.2, 58.4, 58.0, 45.9, 42.5, 24.2.

2-(2-benzyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-(4-methoxyphenyl)ethan-1-one (**29o**)

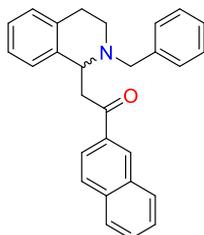
Chemical Formula:  $C_{25}H_{25}NO_2$   
Exact Mass: 371.1885

Synthesized according to the general procedure **I**: 1.48 g (40% yield), pale yellow oil;

$^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  7.93 (d,  $J = 8.8$  Hz, 2H), 7.26–7.12 (m, 9H), 6.91 (d,  $J = 8.8$  Hz, 2H), 4.62–4.57 (m, 1H), 3.88 (s, 3H), 3.76 (d,  $J = 13.4$  Hz, 1H), 3.69 (d,  $J = 13.4$  Hz, 1H), 3.57 (dd,  $J = 15.6, 7.5$  Hz, 1H), 3.24–3.10 (m, 2H), 2.99 (ddd,  $J = 16.4, 10.8, 5.5$  Hz, 1H), 2.84–2.77 (m, 1H), 2.63–2.55 (m, 1H);

$^{13}C$  NMR (75 MHz,  $CDCl_3$ )  $\delta$  197.6, 163.5, 139.3, 138.5, 134.4, 130.7, 130.6 (2C), 129.3, 128.9 (2C), 128.2 (2C), 127.8, 127.0, 126.4, 126.1, 113.8 (2C), 58.6, 58.1, 55.6, 45.5, 42.6.

2-(2-benzyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-(naphthalen-2-yl)ethan-1-one (**29p**)



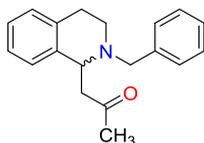
Chemical Formula: C<sub>28</sub>H<sub>25</sub>NO  
Exact Mass: 391.1936

Synthesized according to the general procedure **I**: 0.7 g (30% yield), pale yellow oil;

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.41 (s, 1H), 8.05 (dd, *J* = 8.7, 1.6 Hz, 1H), 7.93–7.88 (m, 3H), 7.64–7.52 (m, 2H), 7.21–7.11 (m, 9H), 4.66 (dd, *J* = 7.7, 5.5 Hz, 1H), 3.80–3.68 (m, 3H), 3.31 (dd, *J* = 15.6, 5.2 Hz, 1H), 3.26–3.20 (m, 1H), 3.01 (ddd, *J* = 16.7, 10.8, 5.9 Hz, 1H), 2.86–2.79 (m, 1H), 2.64–2.56 (m, 1H);

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 199.0, 139.2, 138.4, 135.7, 135.0, 134.5, 132.7, 130.0, 129.7, 129.4, 128.9 (2C), 128.52, 128.47, 128.2 (2C), 127.9, 127.8, 127.0, 126.8, 126.5, 126.2, 124.3, 58.6, 58.1, 46.0, 42.5, 24.5.

1-(2-benzyl-1,2,3,4-tetrahydroisoquinolin-1-yl)propan-2-one (**29q**)



Chemical Formula: C<sub>19</sub>H<sub>21</sub>NO  
Exact Mass: 279.1623

Synthesized according to the general procedure **I**: 0.32 g (6% yield), pale yellow oil.

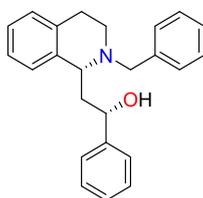
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.31 – 7.24 (m, 5H), 7.18 – 7.05 (m, 4H), 4.32 (dd, *J* = 6.8, 5.4 Hz, 1H), 3.77 – 3.67 (m, 2H), 3.21 – 3.11 (m, 1H), 3.03 – 2.92 (m, 2H), 2.83 (dd, *J* = 12.5, 6.1 Hz, 1H), 2.68 (dd, *J* = 15.1, 5.0 Hz, 1H), 2.55 (d, *J* = 17.3 Hz, 1H), 2.10 (s, 3H).;

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 207.5, 139.0, 137.6, 134.3, 129.4, 129.2 (2C), 128.4 (2C), 127.7, 127.3, 126.6, 126.3, 58.2, 57.8, 50.8, 42.3, 30.5, 23.9.

**General procedure for ruthenium complex (*S,S*)-C1 catalyzed ATH of THIQ-derived  $\beta$ -amino ketones (**29**)**

In a round-bottom tube, charged with complex (*S,S*)-C1 (5.0  $\mu$ mol, 0.012 equiv) was added under argon a solution of the ketone **29** (0.42 mmol, 1.0 equiv) in anhydrous  $\text{CH}_2\text{Cl}_2$  (1.3 mL), then  $\text{HCO}_2\text{H}/\text{NEt}_3$  (5:2) azeotropic mixture (97  $\mu\text{L}$ , 1.15 mmol, 2.75 equiv) was added dropwise. The mixture was stirred at 30  $^\circ\text{C}$  for 24 h, then filtered through a short pad of silica gel (ethyl acetate/petroleum ether: 1/4) and concentrated. The residue was purified by flash column chromatography (ethyl acetate/petroleum ether: 1/10 to 1/8) to afford compounds **30:31** as a mixture of diastereomers.

**(*S*)-2-((*R*)-2-benzyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-phenylethan-1-ol (**30a**)**

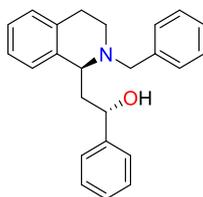


Chemical Formula:  $\text{C}_{24}\text{H}_{25}\text{NO}$   
Exact Mass: 343.1936

**$^1\text{H}$  NMR** (300 MHz,  $\text{CDCl}_3$ ) (*syn*)  $\delta$  7.59 (br s, 1H), 7.42–6.93 (m, 14H), 4.95 (d,  $J = 10.6$  Hz, 1H), 4.12 (dd,  $J = 11.8, 2.6$  Hz, 1H), 3.92, 3.84 (ABq,  $J = 12.9$  Hz, 2H), 3.60–3.47 (m, 1H), 3.17–2.99 (m, 2H), 2.55 (dd,  $J = 16.4, 4.8$  Hz, 1H), 2.23–2.11 (m, 1H), 1.90–1.83 (m, 1H);

**$^{13}\text{C}$  NMR** (75 MHz,  $\text{CDCl}_3$ ) (*syn*)  $\delta$  144.8, 137.7, 136.4, 133.2, 129.5, 129.4 (2C), 128.8 (2C), 128.3 (2C), 127.8, 127.1, 126.7, 126.5, 125.8 (2C), 125.5, 75.5, 62.2, 57.3, 44.6, 40.8, 21.5.

**(*S*)-2-((*S*)-2-benzyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-phenylethan-1-ol (**31a**)**



Chemical Formula:  $\text{C}_{24}\text{H}_{25}\text{NO}$   
Exact Mass: 343.1936

**$^1\text{H}$  NMR** (300 MHz,  $\text{CDCl}_3$ ) (*anti*)  $\delta$  7.59 (br s, 1H), 7.42–6.93 (m, 14H), 4.87 (dd,  $J = 6.5, 3.1$  Hz, 1H), 4.03–3.95 (m, 2H), 3.60–3.47 (m, 1H), 3.31 (ddd,  $J = 12.8, 7.9, 4.7$  Hz, 1H), 2.92–2.73 (m, 2H), 2.72–2.63 (m, 1H), 2.46 (ddd,  $J = 14.8, 8.1, 3.2$  Hz, 1H), 2.27–2.15 (m, 1H);

**$^{13}\text{C}$  NMR** (75 MHz,  $\text{CDCl}_3$ ) (*anti*)  $\delta$  145.4, 137.7, 136.6, 134.9, 129.3 (2C), 129.1, 128.8 (2C),

## Experimental part

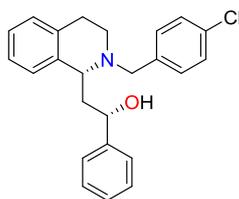
128.2 (2C), 127.8, 127.7, 126.7, 126.4, 125.8, 125.5 (2C), 72.3, 60.3, 58.3, 43.5, 42.2, 25.0.

Colourless oil, (**30a** + **31a**): 76% yield, dr (*syn/anti*) = 68/32, ee<sub>syn</sub> = 98%, ee<sub>anti</sub> = 99%.

**HRMS** (ESI/ion trap): *m/z* [M + H]<sup>+</sup> calcd for C<sub>24</sub>H<sub>26</sub>NO 344.2014, found 344.2016.

**HPLC** : Chiralpak IC, Hexane : *i*PrOH = 90:10, 1.0 mL/min, λ = 215 nm; t<sub>R</sub> (*anti*) 10.38 min, t<sub>R</sub> (*syn*) 13.94 min (major), t<sub>R</sub> (*syn*) 25.38 min (minor).

(*S*)-2-((*R*)-2-(4-chlorobenzyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-phenylethan-1-ol

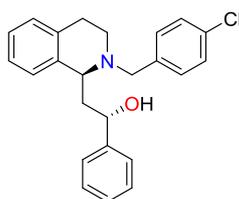


Chemical Formula: C<sub>24</sub>H<sub>24</sub>ClNO  
Exact Mass: 377.1546

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) (*syn*) δ 7.51–6.86 (m, 14H), 4.92 (d, *J* = 9.3 Hz, 1H), 4.11–4.01 (dd, *J* = 11.9, 2.9 Hz, 1H), 3.89, 3.78 (ABq, *J* = 12.9 Hz, 2H), 3.50 (d, *J* = 12.9 Hz, 1H), 3.16–2.95 (m, 2H), 2.56 (dd, *J* = 16.8, 4.8 Hz, 1H), 2.22–2.10 (m, 1H), 1.92–1.79 (m, 1H);

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 144.7, 136.2, 136.1, 133.6, 133.0, 130.7 (2C), 129.1, 129.0 (2C), 128.3 (2C), 127.4, 127.2, 126.7, 126.5, 125.7 (2C), 75.5, 62.2, 56.5, 44.6, 41.0, 21.5.

(*S*)-2-((*S*)-2-(4-chlorobenzyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-phenylethan-1-ol (**31b**)



Chemical Formula: C<sub>24</sub>H<sub>24</sub>ClNO  
Exact Mass: 377.1546

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) (*anti*) δ 7.67–6.74 (m, 14H), 4.86 (dd, *J* = 6.1, 3.1 Hz, 1H), 3.95–3.91 (m, 2H), 3.61–3.53 (m, 1H), 3.35–3.27 (m, 1H), 2.91–2.77 (m, 2H), 2.73–2.64 (m, 1H), 2.46 (ddd, *J* = 14.9, 8.3, 3.2 Hz, 1H), 2.25–2.15 (d, *J* = 11.4 Hz, 1H);

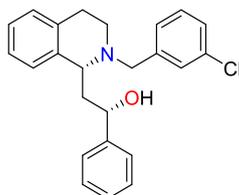
**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 145.1, 136.3, 134.7, 133.6, 133.0, 130.8 (2C), 129.4 (2C), 129.1, 128.2 (2C), 127.4, 127.2, 126.7, 126.5, 125.4 (2C), 72.2, 60.1, 57.5, 43.7, 42.1, 24.9.

Colourless oil, (**30b** + **31b**): 73% yield, dr (*syn/anti*) = 66/34, ee<sub>syn</sub> = 97%, ee<sub>anti</sub> = 99%.

**HRMS** (ESI/ion trap):  $m/z$   $[M + H]^+$  calcd for  $C_{24}H_{25}ClNO$  378.1624, found 378.1627.

**HPLC** : Chiralpak IC, Hexane :  $i$ PrOH = 90:10, 1.0 mL/min,  $\lambda$  = 215 nm;  $t_R$  (*anti*) 11.15 min,  $t_R$  (*syn*) 14.00 min (major),  $t_R$  (*syn*) 27.63 min (minor).

(*S*)-2-((*R*)-2-(3-chlorobenzyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-phenylethan-1-ol (**30c**)

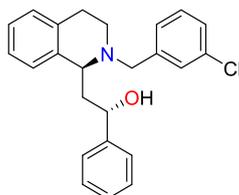


Chemical Formula:  $C_{24}H_{24}ClNO$   
Exact Mass: 377.1546

**$^1H$  NMR** (300 MHz,  $CDCl_3$ ) (*syn*)  $\delta$  7.42–6.94 (m, 14H), 4.96 (d,  $J$  = 10.5 Hz, 1H), 4.09 (dd,  $J$  = 11.7, 2.6 Hz, 1H), 3.98–3.81 (m, 2H), 3.61–3.49 (m, 1H), 3.15–2.99 (m, 2H), 2.58 (dd,  $J$  = 16.7, 4.8 Hz, 1H), 2.27–2.13 (m, 1H), 1.92–1.86 (m, 1H);

**$^{13}C$  NMR** (75 MHz,  $CDCl_3$ ) (*syn*)  $\delta$  144.7, 139.8, 136.1, 134.6, 133.0, 130.3, 129.5, 129.4, 128.4 (2C), 128.2, 128.0, 127.5, 127.3, 126.8, 126.6, 125.8 (2C), 75.5, 62.5, 56.8, 44.7, 40.9, 21.5.

(*S*)-2-((*S*)-2-(3-chlorobenzyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-phenylethan-1-ol (**31c**)



Chemical Formula:  $C_{24}H_{24}ClNO$   
Exact Mass: 377.1546

**$^1H$  NMR** (300 MHz,  $CDCl_3$ ) (*anti*)  $\delta$  7.42–6.94 (m, 14H), 4.88 (dd,  $J$  = 6.5, 3.1 Hz, 1H), 3.98–3.81 (m, 2H), 3.61–3.49 (m, 1H), 3.33 (ddd,  $J$  = 12.8, 7.9, 4.8 Hz, 1H), 2.93–2.76 (m, 2H), 2.74–2.66 (m, 1H), 2.53–2.42 (m, 1H), 2.27–2.13 (m, 1H);

**$^{13}C$  NMR** (75 MHz,  $CDCl_3$ ) (*anti*)  $\delta$  145.2, 139.8, 136.4, 134.7, 134.6, 130.2, 129.6, 129.1, 128.4 (2C), 128.0, 127.6, 127.5, 126.8, 126.6, 126.5, 125.4 (2C), 72.2, 60.2, 57.8, 43.7, 42.2, 25.0.

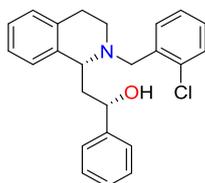
Colourless oil, (**30c** + **31c**): 70% yield, dr (*syn/anti*) = 66/34,  $ee_{syn}$  = 96%,  $ee_{anti}$  = 98%.

**HRMS** (ESI/ion trap):  $m/z$   $[M + H]^+$  calcd for  $C_{24}H_{25}ClNO$  378.1624, found 378.1626.

## Experimental part

**HPLC** : Chiralpak IB, Hexane : *i*PrOH = 90:10, 0.5 mL/min,  $\lambda$  = 215 nm;  $t_R$  (*anti*) 10.54 min,  $t_R$  (*anti*) 13.35 min,  $t_R$  (*syn*) 14.97 min (major),  $t_R$  (*syn*) 17.34 min (minor).

(*S*)-2-((*R*)-2-(2-chlorobenzyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-phenylethan-1-ol

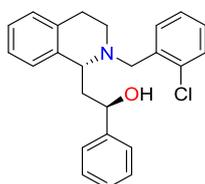


Chemical Formula: C<sub>24</sub>H<sub>24</sub>ClNO  
Exact Mass: 377.1546

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) (*syn*)  $\delta$  7.38–6.70 (m, 14H), 4.76 (dd,  $J$  = 5.2, 3.8 Hz, 1H), 4.01 (dd,  $J$  = 12.0, 2.9 Hz, 1H), 3.85–3.68 (m, 2H), 3.55–3.41 (m, 1H), 3.15–2.98 (m, 1H), 2.91–2.78 (m, 1H), 2.50 (dd,  $J$  = 16.0, 4.4 Hz, 1H), 2.11–1.97 (m, 1H), 1.77–1.70 (m, 1H);

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) (*syn*)  $\delta$  144.8, 136.5, 135.5, 135.2, 133.2, 131.6, 130.0, 129.2, 129.1, 128.3 (2C), 127.7, 127.1, 126.7, 126.5 (2C), 125.8, 125.4, 75.5, 62.0, 55.0, 44.2, 41.8, 22.0.

(*S*)-2-((*S*)-2-(2-chlorobenzyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-phenylethan-1-ol (**31d**)



Chemical Formula: C<sub>24</sub>H<sub>24</sub>ClNO  
Exact Mass: 377.1546

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) (*anti*)  $\delta$  7.38–6.70 (m, 14H), 4.66 (dd,  $J$  = 10.5, 1.2 Hz, 1H), 3.96 (d,  $J$  = 13.0 Hz, 1H), 3.85–3.68 (m, 2H), 3.38–3.31 (m, 1H), 3.15–2.98 (m, 1H), 2.92–2.77 (m, 1H), 2.71–2.61 (m, 1H), 2.44–2.35 (m, 1H), 2.11–1.97 (m, 1H);

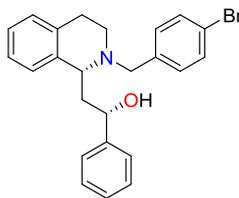
**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) (*anti*)  $\delta$  145.2, 136.6, 135.6, 135.3, 134.5, 131.7, 130.1, 129.4, 129.1, 128.3 (3C), 127.2, 127.0, 126.5 (2C), 125.8, 125.4, 72.2, 58.9, 54.4, 45.0, 42.4, 24.6.

Colourless oil, (**30d** + **31d**): 61% yield, dr (*syn/anti*) = 51/49, ee<sub>*syn*</sub> = 96%, ee<sub>*anti*</sub> = 98%.

**HRMS** (ESI/ion trap):  $m/z$  [M + H]<sup>+</sup> calcd for C<sub>24</sub>H<sub>25</sub>ClNO 378.1624, found 378.1630.

**HPLC** : Chiralpak IA, Hexane : *i*PrOH = 90:10, 0.5 mL/min,  $\lambda$  = 215 nm;  $t_R$  (*syn*) 15.19 min (minor),  $t_R$  (*syn*) 16.48 min (major),  $t_R$  (*anti*) 22.05 min (minor),  $t_R$  (*anti*) 27.42 min (major).

(*S*)-2-((*R*)-2-(4-bromobenzyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-phenylethan-1-ol  
(**30e**)

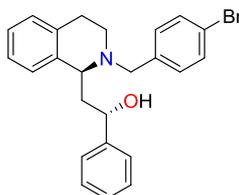


Chemical Formula: C<sub>24</sub>H<sub>24</sub>BrNO  
Exact Mass: 421.1041

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) (*syn*) δ 7.52–6.91 (m, 14H), 4.91 (d, *J* = 10.4 Hz, 1H), 4.06 (dd, *J* = 11.7, 2.7 Hz, 1H), 3.87, 3.76 (ABq, *J* = 12.9 Hz, 2H), 3.59–3.46 (m, 1H), 3.13–2.97 (m, 2H), 2.59–2.52 (m, 1H), 2.21–2.09 (m, 1H), 1.85 (dd, *J* = 12.6, 2.2 Hz, 1H);

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) (*syn*) δ 144.7, 136.8, 136.1, 133.0, 132.0 (2C), 131.1 (2C), 129.4, 128.3 (2C), 127.2, 126.8, 126.5, 125.7 (2C), 125.4, 121.7, 75.5, 62.2, 56.6, 44.6, 41.0, 21.5.

(*S*)-2-((*S*)-2-(4-bromobenzyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-phenylethan-1-ol (**31e**)



Chemical Formula: C<sub>24</sub>H<sub>24</sub>BrNO  
Exact Mass: 421.1041

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) (*anti*) δ 7.52–6.91 (m, 14H), 4.85 (dd, *J* = 6.3, 3.1 Hz, 1H), 3.92–3.87 (m, 2H), 3.59–3.46 (m, 1H), 3.35–3.26 (m, 1H), 2.90–2.72 (m, 2H), 2.71–2.63 (m, 1H), 2.50–2.40 (m, 1H), 2.24–2.14 (m, 1H);

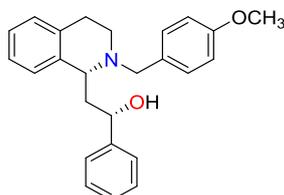
<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) (*anti*) δ 145.1, 136.8, 136.3, 134.6, 132.0 (2C), 131.2 (2C), 129.1, 128.2 (2C), 127.4, 126.8, 126.5, 125.7 (2C), 125.4, 121.7, 72.2, 60.0, 57.6, 43.7, 42.1, 24.9.

Colourless oil, (**30e** + **31e**): 75% yield, dr (*syn/anti*) = 67/33, ee<sub>*syn*</sub> = 98%, ee<sub>*anti*</sub> = 99%.

HRMS (ESI/ion trap): *m/z* [M + H]<sup>+</sup> calcd for C<sub>24</sub>H<sub>25</sub>BrNO 422.1119, found 422.1119.

HPLC : Chiralpak IC, Hexane : *i*PrOH = 90:10, 1.0 mL/min, λ = 215 nm; t<sub>R</sub> (*anti*) 11.12 min, t<sub>R</sub> (*syn*) 14.03 min (major), t<sub>R</sub> (*syn*) 30.17 min (minor).

(*S*)-2-((*R*)-2-(4-methoxybenzyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-phenylethan-1-ol  
(**30f**)

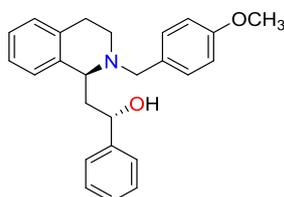


Chemical Formula: C<sub>25</sub>H<sub>27</sub>NO<sub>2</sub>  
Exact Mass: 373.2042

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) (*syn*) δ 7.60 (br s, 1H), 7.41–6.91 (m, 13H), 4.92 (d, *J* = 10.4 Hz, 1H), 4.13–4.07 (m, 1H), 3.85–3.76 (m, 2H), 3.83 (s, 3H), 3.59–3.45 (m, 1H), 3.15–2.99 (m, 2H), 2.53 (dd, *J* = 16.9, 5.0 Hz, 1H), 2.21–2.08 (m, 1H), 1.85 (dd, *J* = 14.6, 1.5 Hz, 1H);

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) (*syn*) δ 159.2, 144.9, 136.4, 133.3, 130.6 (2C), 129.8, 129.3, 128.3 (2C), 128.2, 127.1, 126.6, 126.4, 125.8 (2C), 114.2 (2C), 75.5, 61.9, 56.5, 55.4, 44.6, 40.8, 21.5.

(*S*)-2-((*S*)-2-(4-methoxybenzyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-phenylethan-1-ol  
(**31f**)



Chemical Formula: C<sub>25</sub>H<sub>27</sub>NO<sub>2</sub>  
Exact Mass: 373.2042

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) (*anti*) δ 7.60 (br s, 1H), 7.41–6.91 (m, 13H), 4.86 (dd, *J* = 6.1, 3.0 Hz, 1H), 3.96–3.91 (m, 2H), 3.85 (s, 3H), 3.59–3.45 (m, 1H), 3.30 (ddd, *J* = 12.2, 7.7, 4.3 Hz, 1H), 2.91–2.74 (m, 2H), 2.72–2.62 (m, 1H), 2.46–2.40 (m, 1H), 2.25–2.13 (m, 1H);

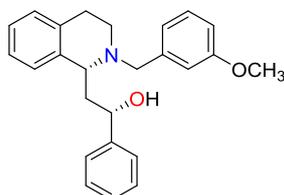
<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) (*anti*) δ 159.2, 145.4, 136.6, 135.0, 130.7 (2C), 129.7, 129.0, 128.3, 128.2 (2C), 127.4, 126.7, 126.4, 125.5 (2C), 114.2 (2C), 72.3, 60.0, 57.5, 55.4, 43.4, 42.1, 25.1.

Colourless oil, (**30f** + **31f**): 83% yield, dr (*syn/anti*) = 68/32, ee<sub>*syn*</sub> = 97%, ee<sub>*anti*</sub> = 99%.

HRMS (ESI/ion trap): *m/z* [M + H]<sup>+</sup> calcd for C<sub>25</sub>H<sub>28</sub>NO<sub>2</sub> 374.2120, found 374.2121.

HPLC : Chiralpak IA, Hexane : *i*PrOH = 90:10, 0.8 mL/min, λ = 215 nm; t<sub>R</sub> (*syn*) 11.58 min (major), t<sub>R</sub> (*syn*) 14.30 min (minor), t<sub>R</sub> (*anti*) 41.11 min.

(*S*)-2-((*R*)-2-(3-methoxybenzyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-phenylethan-1-ol  
(**30g**)

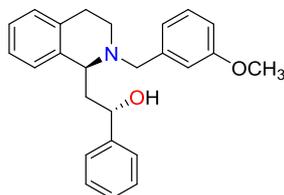


Chemical Formula: C<sub>25</sub>H<sub>27</sub>NO<sub>2</sub>  
Exact Mass: 373.2042

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) (*syn*) δ 7.62–6.81 (m, 14H), 4.94 (d, *J* = 9.5 Hz, 1H), 4.10 (dd, *J* = 11.9, 2.3 Hz, 1H), 4.01–3.77 (m, 2H), 3.83 (s, 3H) 3.61–3.45 (m, 1H), 3.17–3.00 (m, 2H), 2.61–2.50 (m, 1H), 2.23–2.10 (m, 1H), 1.85 (d, *J* = 15.1 Hz, 1H);

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) (*syn*) δ 160.0, 144.9, 139.4, 136.4, 133.2, 129.8, 129.4, 128.3 (2C), 127.2, 126.7, 126.5, 125.8 (2C), 125.5, 121.7, 114.6, 113.6, 75.5, 62.1, 57.3, 55.4, 44.7, 41.1, 21.6.

(*S*)-2-((*S*)-2-(3-methoxybenzyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-phenylethan-1-ol  
(**31g**)



Chemical Formula: C<sub>25</sub>H<sub>27</sub>NO<sub>2</sub>  
Exact Mass: 373.2042

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) (*anti*) δ 7.62–6.81 (m, 14H), 4.87 (dd, *J* = 6.6, 3.2 Hz, 1H), 4.01–3.77 (m, 2H), 3.86 (s, 3H), 3.61–3.45 (m, 1H), 3.36–3.27 (m, 1H), 2.92–2.77 (m, 2H), 2.72–2.67 (m, 1H), 2.49–2.40 (m, 1H), 2.26–2.15 (m, 1H);

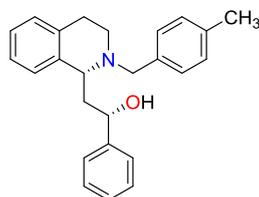
<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) (*anti*) 160.0, 145.4, 139.4, 136.6, 134.9, 129.8, 129.1, 128.2 (2C), 127.4, 126.7, 126.5, 125.8 (2C), 125.5, 121.7, 114.9, 113.3, 72.3, 60.3, 58.3, 55.4, 43.6, 42.3, 25.1.

Colourless oil, (**30g** + **31g**): 70% yield, dr (*syn/anti*) = 65/35, ee<sub>*syn*</sub> = 98%, ee<sub>*anti*</sub> = 99%.

HRMS (ESI/ion trap): *m/z* [M + H]<sup>+</sup> calcd for C<sub>25</sub>H<sub>28</sub>NO<sub>2</sub> 374.2120, found 374.2124.

HPLC : Chiralpak IC, Hexane : <sup>i</sup>PrOH = 90:10, 1.0 mL/min, λ = 215 nm; t<sub>R</sub> (*anti*) 11.74 min, t<sub>R</sub> (*syn*) 17.62 min (major), t<sub>R</sub> (*syn*) 27.27 min (minor).

(*S*)-2-((*R*)-2-(4-methylbenzyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-phenylethan-1-ol

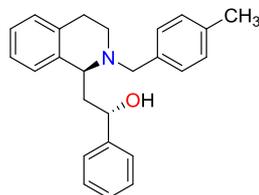


Chemical Formula: C<sub>25</sub>H<sub>27</sub>NO  
Exact Mass: 357.2093

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) (*syn*) δ 7.61 (br s, 1H), 7.41–6.92 (m, 13H), 4.94 (dd, *J* = 10.6, 1.5 Hz, 1H), 4.11 (dd, *J* = 11.8, 2.8 Hz, 1H), 3.88, 3.80 (ABq, *J* = 12.6 Hz, 2H), 3.57–3.45 (m, 1H), 3.16–2.99 (m, 2H), 2.59–2.49 (m, 1H), 2.38 (s, 3H), 2.22–2.09 (m, 1H), 1.89–1.82 (m, 1H);

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) (*syn*) δ 144.9, 137.4, 136.5, 134.7, 133.3, 129.5 (2C), 129.4 (2C), 128.3 (2C), 127.1, 126.7, 126.6, 126.4, 125.8 (2C), 125.5, 75.5, 62.1, 56.9, 44.6, 40.8, 21.5, 21.3.

(*S*)-2-((*S*)-2-(4-methylbenzyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-phenylethan-1-ol



Chemical Formula: C<sub>25</sub>H<sub>27</sub>NO  
Exact Mass: 357.2093

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) (*anti*) δ 7.61 (br s, 1H), 7.41–6.92 (m, 13H), 4.86 (dd, *J* = 6.4, 3.1 Hz, 1H), 3.98–3.92 (m, 2H), 3.57–3.45 (m, 1H), 3.31 (ddd, *J* = 12.7, 8.5, 4.6 Hz, 1H), 2.91–2.73 (m, 2H), 2.72–2.64 (m, 1H), 2.48–2.43 (m, 1H), 2.40 (s, 3H), 2.26–2.14 (m, 1H);

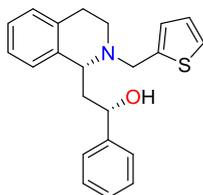
<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) (*anti*) δ 145.4, 137.4, 136.6, 134.9, 134.60, 129.5 (2C), 129.4 (2C), 129.0, 128.2 (2C), 127.4, 126.7, 126.4, 125.8 (2C), 125.5, 72.4, 60.2, 57.9, 43.4, 42.1, 25.0, 21.3.

Colourless oil, (**30h** + **31h**): 85% yield, dr (*syn/anti*) = 67/33, ee<sub>*syn*</sub> = 98%, ee<sub>*anti*</sub> = 99%.

HRMS (ESI/ion trap): *m/z* [M + H]<sup>+</sup> calcd for C<sub>25</sub>H<sub>28</sub>NO 358.2170, found 358.2172.

HPLC : Chiralpak ID, Hexane : *i*PrOH = 90:10, 1.0 mL/min, λ = 215 nm; t<sub>R</sub> (*syn*) 9.35 min (major), t<sub>R</sub> (*syn*) 10.51 min (minor), t<sub>R</sub> (*anti*) 22.34 min.

(*S*)-1-phenyl-2-((*R*)-2-(thiophen-2-ylmethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)ethan-1-ol  
(**30i**)

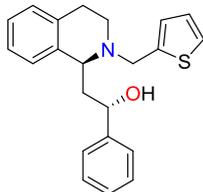


Chemical Formula: C<sub>22</sub>H<sub>23</sub>NOS  
Exact Mass: 349.1500

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) (*syn*) δ 7.43–6.92 (m, 13H), 5.01 (dd, *J* = 10.5, 1.4 Hz, 1H), 4.16 (dd, *J* = 11.8, 2.9 Hz, 1H), 4.12–3.90 (m, 2H), 3.56 (ddd, *J* = 15.6, 13.3, 5.1 Hz, 1H), 3.16–3.02 (m, 2H), 2.61–2.53 (m, 1H), 2.24–2.12 (m, 1H), 1.88 (ddd, *J* = 14.9, 3.1, 1.9 Hz, 1H);

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) (*syn*) δ 144.8, 141.4, 136.3, 133.1, 129.4, 128.3 (3C), 127.2, 126.8 (2C), 126.7, 126.5, 125.81 (2C), 125.77, 75.4, 62.0, 51.6, 44.9, 41.2, 21.5.

(*S*)-1-phenyl-2-((*S*)-2-(thiophen-2-ylmethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)ethan-1-ol  
(**31i**)



Chemical Formula: C<sub>22</sub>H<sub>23</sub>NOS  
Exact Mass: 349.1500

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) (*anti*) δ 7.43–6.92 (m, 13H), 4.89 (dd, *J* = 6.8, 3.0 Hz, 1H), 4.12–3.90 (m, 3H), 3.38–3.29 (m, 1H), 2.95–2.75 (m, 3H), 2.47–2.41 (m, 1H), 2.24–2.12 (m, 1H);

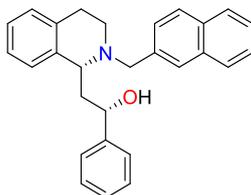
<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) (*anti*) δ 145.3, 140.8, 136.5, 134.8, 129.1, 128.4 (3C), 127.4, 126.8 (2C), 126.7, 126.5, 125.6 (3C), 72.2, 59.7, 52.2, 43.3, 42.4, 25.0.

Colourless oil, (**30i** + **31i**): 59% yield, dr (*syn/anti*) = 71/29, ee<sub>*syn*</sub> = 99%, ee<sub>*anti*</sub> = 99%.

HRMS (ESI/ion trap): *m/z* [M + H]<sup>+</sup> calcd for C<sub>22</sub>H<sub>24</sub>NOS 350.1578, found 350.1581.

HPLC : Chiralpak IC, Hexane : *i*PrOH = 90:10, 1.0 mL/min, λ = 215 nm; t<sub>R</sub> (*syn*) 13.89 min (minor), t<sub>R</sub> (*syn*) 18.01 min (major), t<sub>R</sub> (*anti*) 32.66 min.

(*S*)-2-((*R*)-2-(naphthalen-2-ylmethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-phenylethan-1-ol (**30j**)

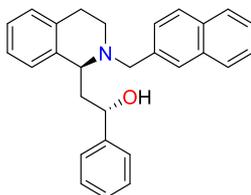


Chemical Formula: C<sub>28</sub>H<sub>27</sub>NO  
Exact Mass: 393.2093

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) (*syn*) δ 7.94–6.93 (m, 17H), 4.95–4.88 (m, 1H), 4.18–3.98 (m, 3H), 3.62–3.51 (m, 1H), 3.23–3.03 (m, 2H), 2.56 (dd, *J* = 16.8, 4.7 Hz, 1H), 2.27–2.12 (m, 1H), 1.89–1.83 (m, 1H);

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) (*syn*) δ 144.8, 136.4, 135.2, 133.4, 133.2, 133.1, 129.4, 128.8, 128.3 (4C), 127.9 (2C), 127.2 (2C), 126.7, 126.5, 126.3, 126.1, 125.8 (2C), 75.5, 62.1, 57.5, 44.7, 41.1, 21.6.

(*S*)-2-((*S*)-2-(naphthalen-2-ylmethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-phenylethan-1-ol (**31j**)



Chemical Formula: C<sub>28</sub>H<sub>27</sub>NO  
Exact Mass: 393.2093

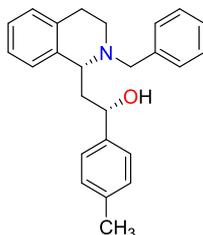
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) (*anti*) δ 7.94–6.93 (m, 17H), 4.95–4.88 (m, 1H), 4.18–3.98 (m, 2H), 3.70 (d, *J* = 12.9 Hz, 1H), 3.41–3.32 (m, 1H), 2.94–2.85 (m, 1H), 2.80–2.70 (m, 2H), 2.51–2.45 (m, 1H), 2.27–2.12 (m, 1H);

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) (*anti*) δ 145.3, 136.6, 134.8, 133.2, 133.1, 129.1, 128.8, 128.3 (4C), 128.4, 127.9, 127.5, 127.3, 127.2, 126.7, 126.5, 126.4, 126.1, 125.5 (2C), 72.4, 60.1, 58.4, 43.6, 42.2, 24.9.

Colourless oil, (**30j** + **31j**): 78% yield, dr (*syn/anti*) = 68/32, ee<sub>*syn*</sub> = 99%, ee<sub>*anti*</sub> = 99%.

HRMS (ESI/ion trap): *m/z* [M + H]<sup>+</sup> calcd for C<sub>28</sub>H<sub>28</sub>NO 394.2170, found 394.2173.

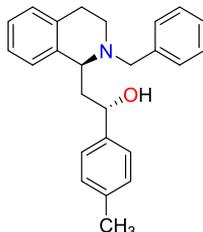
HPLC : Chiralpak IC, Hexane : *i*PrOH = 90:10, 1.0 mL/min, λ = 215 nm; t<sub>R</sub> (*syn*) 13.89 min (minor), t<sub>R</sub> (*syn*) 18.01 min (major), t<sub>R</sub> (*anti*) 32.66 min.

**(S)-2-((R)-2-benzyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-(p-tolyl)ethan-1-ol (301)**

Chemical Formula: C<sub>25</sub>H<sub>27</sub>NO  
Exact Mass: 357.2093

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) (*syn*) δ 7.55 (br s, 1H), 7.46–6.93 (m, 13H), 4.91 (d, *J* = 10.6 Hz, 1H), 4.10 (dd, *J* = 11.8, 2.7 Hz, 1H), 3.91, 3.83 (ABq, *J* = 12.6 Hz, 2H), 3.55–3.45 (m, 1H), 3.16–2.98 (m, 2H), 2.54 (dd, *J* = 16.6, 4.8 Hz, 1H), 2.32 (s, 3H), 2.27–2.09 (m, 1H), 1.88–1.81 (m, 1H).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) (*syn*) δ 141.9, 137.7, 136.7, 136.5, 133.2, 129.4 (2C), 129.3, 129.0 (2C), 128.8 (2C), 128.2, 127.7, 126.6, 126.4, 125.7 (2C), 75.4, 62.3, 57.3, 43.4, 40.8, 21.5, 21.2

**(S)-2-((S)-2-benzyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-(p-tolyl)ethan-1-ol (311)**

Chemical Formula: C<sub>25</sub>H<sub>27</sub>NO  
Exact Mass: 357.2093

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) (*anti*) δ 7.55 (br s, 1H), 7.46–6.93 (m, 13H), 4.84 (dd, *J* = 6.5, 2.9 Hz, 1H), 4.01 (d, *J* = 12.9 Hz, 1H), 3.96 (dd, *J* = 8.2, 2.8 Hz, 1H), 3.55–3.45 (m, 1H), 3.29 (ddd, *J* = 12.8, 8.0, 4.7 Hz, 1H), 2.91–2.72 (m, 2H), 2.70–2.62 (m, 1H), 2.48–2.37 (m, 1H), 2.36 (s, 3H), 2.27–2.09 (m, 1H);

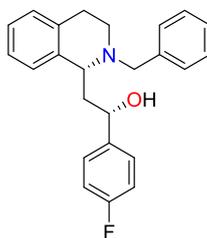
**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) (*anti*) δ 142.4, 137.7, 136.7, 136.2, 134.9, 129.5 (2C), 129.3, 129.0 (2C), 128.8 (2C), 127.7, 127.4, 126.4, 126.3, 125.4 (2C), 72.2, 60.4, 58.3, 44.7, 42.2, 25.0, 21.2.

Colourless oil, (**301** + **311**): 78% yield, dr (*syn/anti*) = 64/36, ee<sub>*syn*</sub> = 99%, ee<sub>*anti*</sub> = 95%.

**HRMS** (ESI/ion trap): *m/z* [M + H]<sup>+</sup> calcd for C<sub>25</sub>H<sub>28</sub>NO 358.2170, found 358.2173.

**HPLC** : Chiralpak IB, Hexane : *i*PrOH = 97:3, 0.5 mL/min, λ = 215 nm; t<sub>R</sub> (*anti*) 19.89 min, t<sub>R</sub> (*syn*) 23.40 min (major), t<sub>R</sub> (*syn*) 30.20 min (minor).

(S)-2-((R)-2-benzyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-(4-fluorophenyl)ethan-1-ol

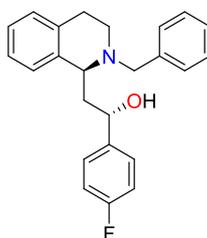


Chemical Formula: C<sub>24</sub>H<sub>24</sub>FNO  
Exact Mass: 361.1842

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) (*syn*) δ 7.48 (br s, 1H), 7.30–6.82 (m, 13H), 4.80 (d, *J* = 9.7 Hz, 1H), 3.99 (dd, *J* = 11.8, 2.6 Hz, 1H), 3.82, 3.71 (ABq, *J* = 12.8 Hz, 2H), 3.46–3.34 (m, 1H), 3.07–2.89 (m, 2H), 2.44 (dd, *J* = 16.4, 4.7 Hz, 1H), 2.08–1.95 (m, 1H), 1.74–1.68 (m, 1H);

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) (*syn*) δ 160.2 (*J* = 242.8 Hz), 140.7, 137.7, 136.2, 133.2, 129.6, 129.4 (2C), 128.8 (2C), 128.2, 127.8, 127.4, 127.3, 126.5 (2C), 115.0 (*J* = 21.1 Hz, 2C), 74.9, 62.1, 57.3, 44.7, 40.9, 21.5.

(S)-2-((S)-2-benzyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-(4-fluorophenyl)ethan-1-ol  
(**31m**)



Chemical Formula: C<sub>24</sub>H<sub>24</sub>FNO  
Exact Mass: 361.1842

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) (*anti*) δ 7.48 (br s, 1H), 7.30–6.82 (m, 13H), 4.71 (dd, *J* = 6.4, 2.9 Hz, 1H), 3.89 (d, *J* = 12.9 Hz, 1H), 3.87–3.84 (m, 1H), 3.46–3.34 (m, 1H), 3.21 (ddd, *J* = 12.6, 7.5, 5.0 Hz, 1H), 2.81–2.63 (m, 2H), 2.63–2.54 (m, 1H), 2.35–2.26 (m, 1H), 2.11–1.95 (m, 1H);

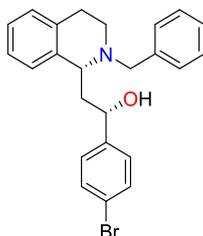
<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) (*anti*) δ 163.5 (*J*<sub>CF</sub> = 233.9 Hz), 141.1, 137.6, 136.4, 134.9, 129.4 (2C), 129.1, 128.8 (2C), 128.2, 127.8, 127.1, 127.0, 126.7 (2C), 115.0 (*J*<sub>CF</sub> = 21.1 Hz, 2C), 71.7, 60.1, 58.4, 44.0, 42.2, 25.3.

Colourless oil, (**30m** + **31m**): 71% yield, dr (*syn/anti*) = 68/32, ee<sub>*syn*</sub> = 98%, ee<sub>*anti*</sub> = 98%.

HRMS (ESI/ion trap): *m/z* [M + H]<sup>+</sup> calcd for C<sub>24</sub>H<sub>25</sub>FNO 362.1920, found 362.1923.

**HPLC (21:31):** Chiralpak IB, Hexane : *i*PrOH = 97:3, 0.5 mL/min,  $\lambda$  = 215 nm;  $t_R$  (*anti*) 18.05 min (minor),  $t_R$  (*anti*) 19.00 min (major),  $t_R$  (*syn*) 21.38 min (major),  $t_R$  (*syn*) 24.97 min (minor).

(*S*)-2-((*R*)-2-benzyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-(4-bromophenyl)ethan-1-ol

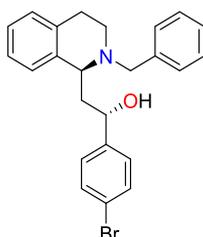


Chemical Formula: C<sub>24</sub>H<sub>24</sub>BrNO  
Exact Mass: 421.1041

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) (*syn*)  $\delta$  7.72 (br s, 1H), 7.45–6.90 (m, 13H), 4.88 (d,  $J$  = 10.2 Hz, 1H), 4.10 (dd,  $J$  = 11.7, 2.5 Hz, 1H), 3.91, 3.81 (ABq,  $J$  = 12.9 Hz, 2H), 3.56–3.43 (m, 1H), 3.16–3.09 (m, 2H), 2.55 (dd,  $J$  = 16.4, 4.7 Hz, 1H), 2.21–2.03 (m, 1H), 1.84–1.77 (m, 1H);

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) (*syn*)  $\delta$  143.9, 137.6, 136.1, 133.2, 131.4 (2C), 129.6, 129.4 (2C), 128.9 (2C), 128.2, 127.8, 127.5 (2C), 126.8, 126.5, 120.8, 74.9, 62.1, 57.2, 44.5, 40.9, 21.5.

(*S*)-2-((*S*)-2-benzyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-(4-bromophenyl)ethan-1-ol



Chemical Formula: C<sub>24</sub>H<sub>24</sub>BrNO  
Exact Mass: 421.1041

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) (*anti*)  $\delta$  7.72 (br s, 1H), 7.45–6.90 (m, 13H), 4.79 (dd,  $J$  = 6.2, 3.0 Hz, 1H), 3.98–3.92 (m, 2H), 3.56–3.43 (m, 1H), 3.37–3.33 (m, 1H), 2.92–2.77 (m, 2H), 2.73–2.66 (m, 1H), 2.49–2.38 (m, 1H), 2.21–2.03 (m, 1H);

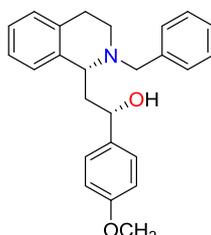
**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) (*anti*)  $\delta$  144.5, 137.6, 136.1, 134.8, 131.4 (2C), 129.4 (2C), 129.1, 128.9 (2C), 128.2, 127.8, 127.3 (2C), 126.8, 126.5, 120.3, 71.8, 59.9, 58.3, 43.9, 41.9, 25.0.

Colourless oil, (**30n** + **31n**): 60% yield, dr (*syn/anti*) = 69/31, ee<sub>*syn*</sub> = 96%, ee<sub>*anti*</sub> = 98%.

**HRMS** (ESI/ion trap):  $m/z$  [M + H]<sup>+</sup> calcd for C<sub>24</sub>H<sub>25</sub>BrNO 422.1119, found 422.1120.

**HPLC** : Chiralpak IB, Hexane : *i*PrOH = 97:3, 0.5 mL/min,  $\lambda$  = 215 nm;  $t_R$  (*anti*) 16.47 min (minor),  $t_R$  (*anti*) 18.53 min (major),  $t_R$  (*syn*) 19.67 min (major),  $t_R$  (*syn*) 23.50 min (minor).

(*S*)-2-((*R*)-2-benzyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-(4-methoxyphenyl)ethan-1-ol  
**(30o)**

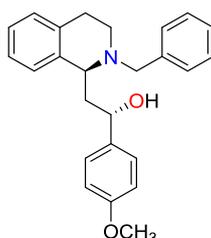


Chemical Formula: C<sub>25</sub>H<sub>27</sub>NO<sub>2</sub>  
Exact Mass: 373.2042

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) (*syn*)  $\delta$  7.43–7.25 (m, 8H), 7.20–7.13 (m, 3H), 7.06–7.03 (m, 1H), 6.91–6.85 (m, 2H), 4.92–4.89 (m, 1H), 4.10 (dd,  $J$  = 11.7, 2.5 z, 1H), 3.93–3.84 (m, 2H), 3.80 (s, 3H), 3.56–3.47 (m, 1H), 3.17–2.99 (m, 2H), 2.55 (dd,  $J$  = 16.7, 4.9 Hz, 1H), 2.25–2.11 (m, 1H), 1.87–1.80 (m, 1H).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) (*syn*)  $\delta$  158.8, 137.7, 137.2, 136.4, 133.2, 129.4 (2C), 129.3, 128.8 (2C), 128.2, 127.7, 126.9 (2C), 126.6, 126.4, 113.7 (2C), 75.1, 62.2, 57.2, 55.3, 44.7, 40.8, 21.5.

(*S*)-2-((*S*)-2-benzyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-(4-methoxyphenyl)ethan-1-ol  
**(31o)**



Chemical Formula: C<sub>25</sub>H<sub>27</sub>NO<sub>2</sub>  
Exact Mass: 373.2042

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) (*anti*)  $\delta$  7.43–7.25 (m, 8H), 7.20–7.13 (m, 3H), 6.97–6.94 (m, 1H), 6.91–6.85 (m, 2H), 4.83 (dd,  $J$  = 6.4, 2.8 Hz, 1H), 4.04–3.97 (m, 2H) 3.82 (s, 3H), 3.56–3.47 (m, 1H), 3.30 (ddd,  $J$  = 12.6, 7.7, 4.7 Hz, 1H), 2.92–2.74 (m, 2H), 2.71–2.63 (m, 1H), 2.42 (ddd,  $J$  = 14.8, 8.1, 3.1 Hz, 1H), 2.25–2.11 (m, 1H).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) (*anti*)  $\delta$  158.4, 137.6, 137.5, 136.6, 134.9, 129.5 (2C), 129.0, 128.8 (2C), 128.7, 127.4, 126.9 (2C), 126.6, 126.3, 113.7 (2C), 71.8, 60.3, 58.3, 55.3, 43.5, 42.2, 25.1.

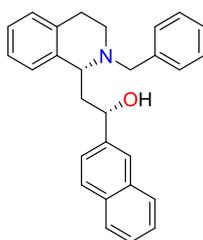
Sticky yellow oil, (**30o** + **31o**): 79% yield, dr (*syn/anti*) = 61/39, ee<sub>*syn*</sub> = 98%, ee<sub>*anti*</sub> = 99%.

**MS (ESI):**  $m/z = 374 [M + H]^+$ .

**HRMS (ESI/ion trap):**  $m/z [M + H]^+$  calcd for  $C_{25}H_{28}NO_2$  374.2120, found 374.2121.

**HPLC :** Chiralpak IE, Hexane :  $i$ PrOH = 95:5, 1.0 mL/min,  $\lambda = 215$  nm;  $t_R$  [*syn* – (*R,S*)] = 48.55 min,  $t_R$  [*syn* – (*S,R*)] = 52.45 min,  $t_R$  (*anti*) = 58.91 min,  $t_R$  (*anti*) = 90.98 min.

(*S*)-2-((*R*)-2-benzyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-(naphthalen-2-yl)ethan-1-ol

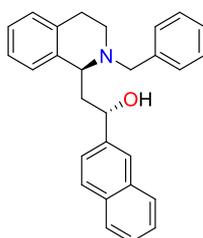


Chemical Formula:  $C_{28}H_{27}NO$   
Exact Mass: 393.2093

**$^1H$  NMR** (300 MHz,  $CDCl_3$ ) (*syn*)  $\delta$  7.92–7.81 (m, 5H), 7.54–7.34 (m, 8H), 7.22–6.93 (m, 4H), 5.13 (d,  $J = 9.3$  Hz, 1H), 4.18 (dd,  $J = 11.8, 2.7$  Hz, 1H), 3.95, 3.88 (ABq,  $J = 12.8$  Hz, 2H), 3.63–3.51 (m, 1H), 3.19–3.03 (m, 2H), 2.60–2.50 (m, 1H), 2.37–2.18 (m, 1H), 2.00–1.93 (m, 1H);

**$^{13}C$  NMR** (75 MHz,  $CDCl_3$ ) (*syn*)  $\delta$  142.3, 137.7, 136.3, 133.6, 133.2, 132.9, 129.5 (2C), 129.4, 128.8 (2C), 128.2, 128.1, 128.0, 127.8, 127.7, 126.7, 126.5, 125.9, 125.5, 124.3, 124.2, 75.6, 62.3, 57.3, 44.5, 40.7, 21.5.

(*S*)-2-((*S*)-2-benzyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-(naphthalen-2-yl)ethan-1-ol



Chemical Formula:  $C_{28}H_{27}NO$   
Exact Mass: 393.2093

**$^1H$  NMR** (300 MHz,  $CDCl_3$ ) (*anti*)  $\delta$  7.92–7.81 (m, 5H), 7.54–7.34 (m, 8H), 7.22–6.93 (m, 4H), 5.06 (dd,  $J = 6.1, 3.1$  Hz, 1H), 4.04–3.97 (m, 2H), 3.63–3.51 (m, 1H), 3.34 (ddd,  $J = 12.8, 7.9, 4.6$  Hz, 1H), 2.93–2.75 (m, 2H), 2.74–2.66 (m, 1H), 2.60–2.50 (m, 1H), 2.37–2.18 (m, 1H);

## Experimental part

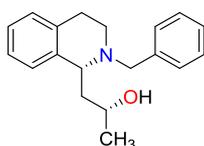
$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ) (*anti*)  $\delta$  142.8, 137.6, 136.5, 134.9, 133.6, 132.7, 129.5 (2C), 129.1, 128.8 (2C), 128.1 (2C), 128.0, 127.8, 127.4, 126.5, 126.4, 126.0, 125.5, 124.1, 124.0, 72.4, 60.5, 58.3, 43.4, 42.0, 25.0.

Colourless oil, (**30p** + **31p**): 75% yield, dr (*syn/anti*) = 63/37, ee<sub>syn</sub> = 94%, ee<sub>anti</sub> = 98%.

HRMS (ESI/ion trap):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{28}\text{H}_{28}\text{NO}$  394.2170, found 394.2173.

HPLC : Chiralpak IB, Hexane : *i*PrOH = 94:6, 0.7 mL/min,  $\lambda$  = 215 nm;  $t_R$  (*anti*) 14.63 min (minor),  $t_R$  (*syn*) 17.05 min (major),  $t_R$  (*anti*) 18.41 min (major),  $t_R$  (*syn*) 38.77 min (minor).

### (*R*)-1-((*R*)-2-benzyl-1,2,3,4-tetrahydroisoquinolin-1-yl)propan-2-ol (**30q**)

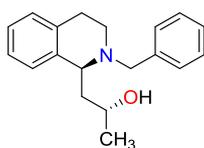


Chemical Formula:  $\text{C}_{19}\text{H}_{23}\text{NO}$   
Exact Mass: 281.1780

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ) (*syn*)  $\delta$  7.39–7.00 (m, 10H), 4.04–3.96 (m, 1H), 3.91 (dd,  $J$  = 12.0, 2.8 Hz, 1H), 3.79 (q,  $J$  = 12.7 Hz, 2H), 3.47–3.36 (m, 1H), 3.13–3.01 (m, 1H), 2.93 (dd,  $J$  = 14.0, 6.2 Hz, 1H), 2.51 (dd,  $J$  = 17.1, 4.9 Hz, 1H), 1.95–1.82 (m, 1H), 1.67–1.60 (m, 1H), 1.15 (d,  $J$  = 6.2 Hz, 3H);

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ) (*syn*)  $\delta$  137.8, 136.7, 133.2, 129.3 (3C), 128.7 (2C), 128.2, 127.6, 126.5, 126.4, 69.1, 62.1, 57.2, 43.8, 40.8, 23.5, 21.5.

### (*R*)-1-((*S*)-2-benzyl-1,2,3,4-tetrahydroisoquinolin-1-yl)propan-2-ol (**31q**)



Chemical Formula:  $\text{C}_{19}\text{H}_{23}\text{NO}$   
Exact Mass: 281.1780

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ) (*anti*)  $\delta$  7.37 – 7.03 (m, 9H), 6.23 (br s, 1H), 4.15 – 4.06 (m, 2H), 3.75 (dd,  $J$  = 10.4, 5.5 Hz, 1H), 3.48 (d,  $J$  = 12.8 Hz, 1H), 3.21 (dt,  $J$  = 11.7, 5.3 Hz, 1H), 2.83 – 2.77 (m, 2H), 2.58 – 2.50 (m, 1H), 2.05 – 2.01 (m, 2H), 1.10 (d,  $J$  = 6.3 Hz, 3H).

Colourless oil, (**30q** + **31q**): 65% yield, dr (*syn/anti*) = 71/29, ee<sub>syn</sub> = 81%, ee<sub>anti</sub> = 99%.

HRMS (ESI/ion trap):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{19}\text{H}_{24}\text{NO}$  282.1858, found 282.1861.

HPLC : Chiralpak IA, Hexane : *i*PrOH = 96 : 4, 0.6 mL/min,  $\lambda$  = 215 nm;  $t_R$  (*syn*) 14.29 min (major),  $t_R$  (*syn*) 17.17 min (minor),  $t_R$  (*anti*) 18.57 min.

# **PUBLICATIONS**



# Asymmetric Transfer Hydrogenation of (Hetero)arylketones with Tethered Rh(III)–*N*-(*p*-Tolylsulfonyl)-1,2-diphenylethylene-1,2-diamine Complexes: Scope and Limitations

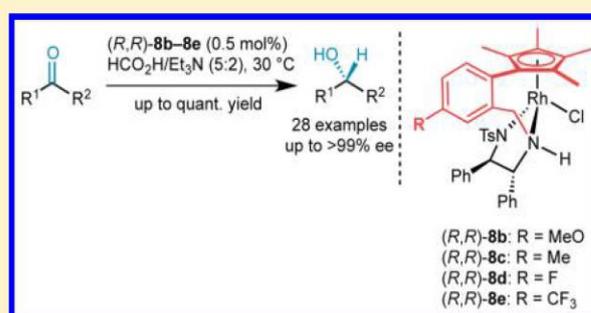
Long-Sheng Zheng,<sup>†</sup> Quentin Llopis,<sup>†</sup> Pierre-Georges Echeverria,<sup>†</sup> Charlène Férard,<sup>†</sup> Gérard Guillamot,<sup>‡</sup> Phannarath Phansavath,<sup>\*,†</sup> and Virginie Ratovelomanana-Vidal<sup>\*,†</sup>

<sup>†</sup>Institut de Recherche de Chimie Paris, PSL Research University, Chimie ParisTech-CNRS, 75005 Paris, France

<sup>‡</sup>PCAS, 23 rue Bossuet, Z.I. de la vigne aux Loups, 91160 Longjumeau, France

## Supporting Information

**ABSTRACT:** A series of new tethered Rh(III)/Cp\* complexes containing the *N*-(*p*-tolylsulfonyl)-1,2-diphenylethylene-1,2-diamine ligand have been prepared, characterized, and evaluated in the asymmetric transfer hydrogenation (ATH) of a wide range of (hetero)aryl ketones. The reaction was performed under mild conditions with the formic acid/triethylamine (5:2) system as the hydrogen source and provided enantiomerically enriched alcohols with good yields and high to excellent enantioselectivities. Although the nature of the substituents on the phenyl tethering ring did not alter the stereochemical outcome of the reaction, complexes bearing electron-donating groups exhibited a higher catalytic activity than those having electron-withdrawing groups. A scale-up of the ATH of 4-chromanone to the gram scale quantitatively delivered the reduced product with excellent enantioselectivity, demonstrating the potential usefulness of these new complexes.



## INTRODUCTION

Because enantiomerically pure alcohols are important synthetic building blocks in the manufacturing of pharmaceuticals, flavors, and fragrances, significant efforts have been made to develop efficient and atom-economical stereoselective processes for the synthesis of these compounds.<sup>1</sup> In this area, transition-metal-catalyzed asymmetric transfer hydrogenation (ATH) is one of the most powerful and useful methods for the generation of enantiomerically enriched secondary alcohols from the corresponding prochiral ketones, owing not only to its high performance in terms of activity and selectivity, but also to its operational simplicity.<sup>2</sup> Moreover, a variety of convenient, safe, and inexpensive non-H<sub>2</sub> hydrogen sources can be used for this reaction, typically 2-propanol, formic acid/triethylamine mixtures, or formate salts. Since the seminal report in 1995 by Noyori and Ikariya of the [RuCl( $\eta^6$ -arene)(*N*-TsDPEN)] complexes **1**<sup>3</sup> (named Noyori catalysts; TsDPEN = *N*-(*p*-tosylsulfonyl)-1,2-diphenylethylene-1,2-diamine), ruthenium-based catalysts have been widely used in the ATH of ketones and imines (Figure 1). Rhodium and iridium derivatives **2** and **3**, respectively, bearing Cp\* as a ligand in place of the benzene ring were also studied and successfully employed for these transformations.<sup>1a,2h,4</sup> Numerous investigations aimed at diversifying the ligands were undertaken to achieve more efficient catalytic performances, and various derivatives of the Noyori catalysts have been reported.<sup>2</sup> Notably, Wills et al. introduced a series of ruthenium complexes **4** and **5** bearing a tether between the  $\eta^6$ -arene and the diamine unit,<sup>5</sup> and developed the isoelectronic

Rh(III) derivatives **6**,<sup>6</sup> **7**,<sup>7</sup> and **8a**,<sup>8</sup> which proved effective for the asymmetric catalytic reduction of imines and functionalized ketones.

As part of our ongoing studies toward the development of efficient catalysts for the asymmetric reduction of unsaturated compounds,<sup>9</sup> we reported the synthesis and catalytic performances of the rhodium(III)–TsDPEN-based tethered catalyst **8b** bearing a methoxy group on the tethering phenyl ring (Figure 1).

This new complex showed a good catalytic behavior in the asymmetric transfer hydrogenation of ketones<sup>10</sup> and  $\alpha$ -amino  $\beta$ -keto ester hydrochlorides.<sup>11</sup> Following these initial reports, we now describe herein the synthesis, characterization, and evaluation of the novel Rh–TsDPEN-based tethered complexes **8c**–**8e** having electron-donating methyl and electron-withdrawing fluorine and trifluoromethyl substituents, respectively, on the 2-benzyl tether (Figure 1). To evaluate the electronic effect of the 2-benzyl tether substituent on the catalytic performance of the resulting complexes, a complete comparative study of the Wills complex **8a**<sup>8</sup> and complexes **8b**–**8e** in the ATH of a wide range of aromatic ketones is disclosed.

## RESULTS AND DISCUSSION

Novel complexes (*R,R*)-**8b**–**8e** were prepared from commercially available 2-bromo-5-methoxybenzaldehyde (**9**), 2-bromo-5-methylbenzaldehyde (**10**), 2-bromo-5-fluorobenzaldehyde

Received: February 23, 2017

Published: May 5, 2017

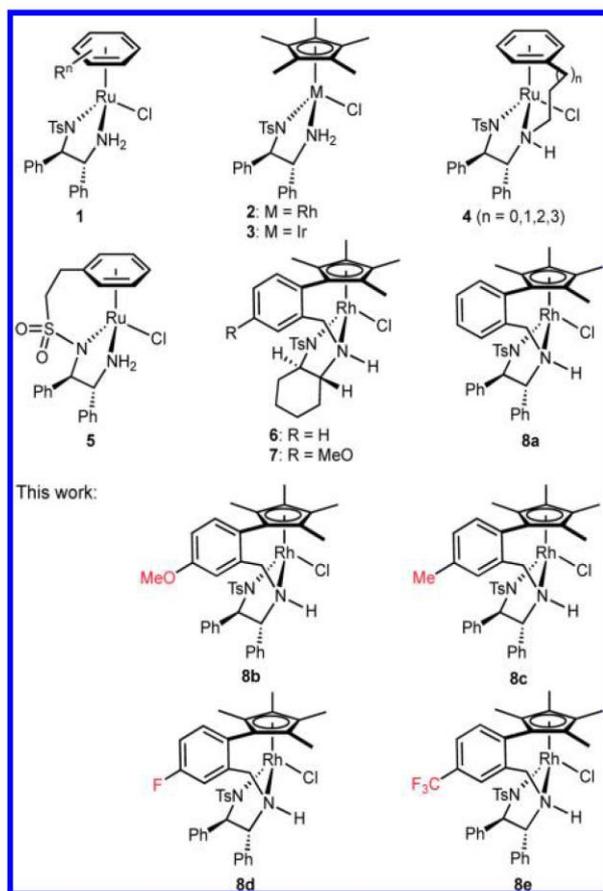
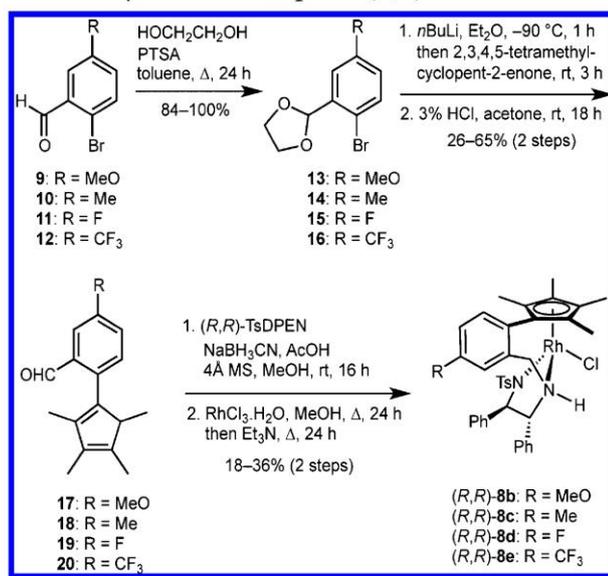


Figure 1. Transition-metal complexes used in ATH.

(11), and 2-bromo-5-(trifluoromethyl)benzaldehyde (12), which were protected as their 1,3-dioxolane derivatives 13–16 (Scheme 1).

### Scheme 1. Synthesis of Complexes (*R,R*)-8b–8e



Treatment of these compounds with *n*-BuLi followed by addition of 2,3,4,5-tetramethylcyclopent-2-enone furnished the corresponding alcohols, which were then subjected to 3% hydrochloric acid in acetone. The latter conditions led to both deprotection of the aldehyde function and dehydration of the tertiary alcohol, providing compounds 17–20. Subsequent reductive amination using (*R,R*)-TsDPEN in the presence of

sodium cyanoborohydride then delivered the corresponding diamines, and the targeted complexes (*R,R*)-8b–8e were obtained through heating the latter in refluxing methanol in the presence of rhodium(III) chloride followed by treatment with triethylamine. The four complexes were isolated after flash chromatography as orange solids and as single diastereomers, whereas their structures were confirmed by X-ray crystallographic analysis in the case of (*R,R*)-8b, (*R,R*)-8c, and (*R,R*)-8d (Figures 2–4).<sup>12</sup>

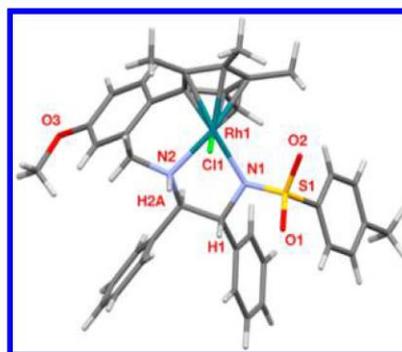


Figure 2. X-ray structure of complex (*R,R*)-8b.<sup>12</sup>

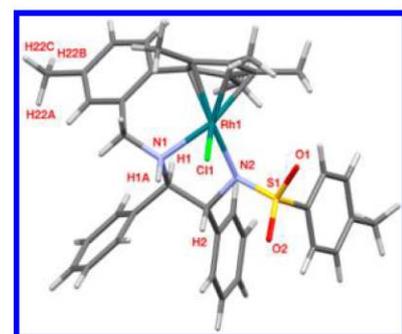


Figure 3. X-ray structure of complex (*R,R*)-8c.<sup>12</sup>

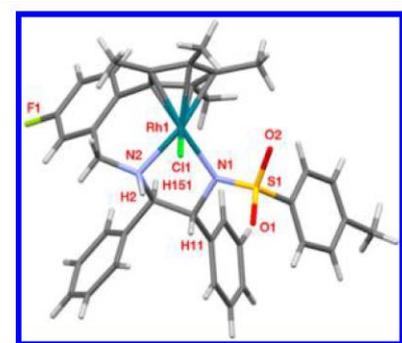
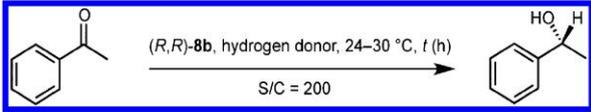


Figure 4. X-ray structure of complex (*R,R*)-8d.<sup>12</sup>

Evaluation of these complexes started with the ATH of acetophenone as the standard substrate using (*R,R*)-8b in combination with various hydrogen donor systems (Table 1). The reaction was carried out at 24–30 °C with 0.5 mol % of (*R,R*)-8b. A comparison of various hydrogen donor sources highlighted the choice of a formic acid/triethylamine (5:2) system in preference to sodium hypophosphite, ammonium formate, or an *i*-PrOH/*t*-BuOK system. Indeed, in the presence of a formic acid/triethylamine (5:2) system, a full conversion was attained within 5 h, and the reduced compound, (*R*)-1-phenylethanol, was obtained with a very high enantiomeric excess of 98% (entry 1). On the other hand, in the presence of sodium hypophosphite, the conversion dramatically decreased to

**Table 1. Optimization of the Reaction Conditions for the ATH of Acetophenone with (R,R)-8b<sup>a</sup>**


| entry | hydrogen donor  | t (h) | conversion <sup>b</sup> (%) | ee <sup>c</sup> (%) |
|-------|---|-------|-----------------------------|---------------------|
| 1     | HCO <sub>2</sub> H/Et <sub>3</sub> N (5:2) <sup>d</sup>         | 5     | 100                         | 98                  |
| 2     | NaH <sub>2</sub> PO <sub>2</sub> ·H <sub>2</sub> O <sup>e</sup> | 29    | 7                           |                     |
| 3     | HCO <sub>2</sub> NH <sub>4</sub> <sup>f</sup>                   | 29    | 53                          | 98                  |
| 4     | <i>i</i> -PrOH/ <i>t</i> -BuOK <sup>g</sup>                     | 29    |                             |                     |

<sup>a</sup>Reaction conditions: acetophenone (126  $\mu$ L, 1.08 mmol), (R,R)-8b (4 mg, 0.0054 mmol). <sup>b</sup>Determined by <sup>1</sup>H NMR of the crude product. <sup>c</sup>Determined by HPLC analysis. <sup>d</sup>A 580  $\mu$ L volume of HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2). <sup>e</sup>NaH<sub>2</sub>PO<sub>2</sub>·H<sub>2</sub>O (2.7 mmol), THF used as a solvent. <sup>f</sup>HCO<sub>2</sub>NH<sub>4</sub> (2.4 mmol), CH<sub>2</sub>Cl<sub>2</sub> used as a solvent. <sup>g</sup>*i*-PrOH (0.026 mmol) in *t*-BuOK (11 mL).

7% (entry 2). In the same manner, an unsatisfactory conversion of 53% was observed with ammonium formate (entry 3). Upon using the *i*-PrOH/*t*-BuOK system as the reducing agent, only degradation products were formed (entry 4). Finally, the optimized reaction conditions for the ATH of acetophenone with (R,R)-8b were set as follows: 0.5 mol % concentration of tethered Rh complex (R,R)-8b in neat HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) at 24–30 °C. With this optimized set of conditions in hand, and to establish the scope and limitations of the (R,R)-8b–8e-catalyzed ATH reaction, a series of aryl ketones were first examined (Table 2). A comparison with the rhodium complex (R,R)-8a<sup>8</sup> was carried out as well. It should be noted that, with the exception of four substrates (entries 1, 3, 10, and 11) indicated in Table 2, none of the ketones described in this paper have been previously reduced using the Wills complex (R,R)-8a so that the range of ketones has been consistently expanded in this comparative study.

Acetophenone underwent a faster reduction with (R,R)-8b and (R,R)-8c than with the other parent complexes (R,R)-8a, (R,R)-8d, and (R,R)-8e, excellent yields and enantioselectivities being observed in all cases (entry 1). The ATH of propiophenone proceeded similarly except for (R,R)-8e, which failed to afford complete conversion even after a prolonged reaction time of 96 h, and with a significantly higher catalytic activity observed for complexes (R,R)-8b and (R,R)-8c, which gave full conversions in only 6 h as compared to 22 h with (R,R)-8a (entry 2). On the other hand, 2-chloroacetophenone was readily reduced with all five complexes with ee values ranging from 95% to >99% (entry 3). The catalytic reduction of acetophenones bearing substituents in the para or meta positions of the phenyl ring led to high levels of stereoselectivity as well (entries 4–7), with a higher catalytic activity observed with (R,R)-8b and (R,R)-8c (entries 4 and 5), whereas complex (R,R)-8e led only to 62–64% conversions after 100–110 h of reaction for 4-(benzyloxy)acetophenone and 3,5-dimethoxyacetophenone (entries 6 and 7). In contrast, lower enantiofacial discriminations were observed for aryl ketones possessing an ortho substituent as for 2-bromoacetophenone (entry 8, 64–71% ee) and 1-acetonaphthone (entry 10, 78–85% ee). In both instances, compared to complex (R,R)-8a, slightly higher ee values could be attained with complexes (R,R)-8b, (R,R)-8c, and (R,R)-8d (entries 8 and 10). Whereas fair enantioselectivities were reached within a short reaction time for 4-nitroacetophenone (88% ee, entry 9), polycyclic aryl ketones afforded uniformly high enantioinductions with ee values ranging from

92% to >99% (entries 11–16). A gram-scale ATH of 4-chromanone was also carried out with complex (R,R)-8b under the standard conditions and furnished quantitatively the desired (R)-chroman-4-ol with the same enantiomeric purity (>99% ee, cf. entry 14).

Additionally, we studied the ATH of a highly electron-rich aryl ketone bearing a morpholine substituent in the para position. Although this challenging family of substrates was recently efficiently reduced through ATH with tethered ruthenium–TsDPEN catalysts,<sup>13</sup> no example of catalytic reduction with a rhodium catalyst has been reported to our knowledge. The use of complexes (R,R)-8a and (R,R)-8b under the defined standard conditions smoothly afforded the desired reduced compound in quantitative yield and with an excellent enantioselectivity (entry 17). It appears from this survey that complexes (R,R)-8a–8e exhibited comparable stereoselectivities, providing the corresponding alcohols with mainly high enantioselectivities for para- and meta-substituted ketones (ee values up to >99%), whereas lower enantioinductions were observed for the ortho-substituted compounds. Of note, a lower catalytic activity was displayed by complex (R,R)-8e, possessing an electron-withdrawing trifluoromethyl substituent, which generally required longer reaction times.

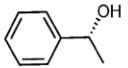
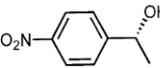
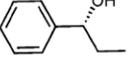
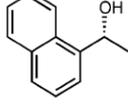
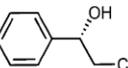
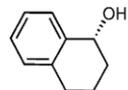
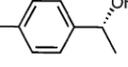
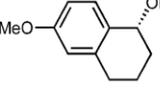
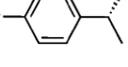
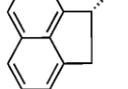
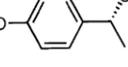
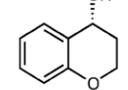
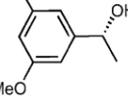
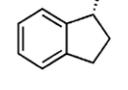
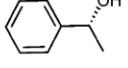
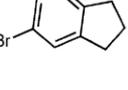
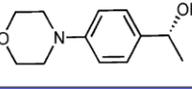
To test the substrate scope further, we next explored the (R,R)-8a–8e-mediated ATH of heteroaryl and alkyl ketones (Table 3). The former compounds underwent the catalytic reduction in good yields, with systematically high asymmetric inductions observed with all the examined tethered Rh(III)/Cp\* complexes, for (R)-1-(2-furyl)ethanol, (R)-1-(2-thienyl)ethanol, (1R)-1-(benzofuran-2-yl)ethanol, and (R)-1-(2-pyridyl)ethanol (entries 1–4). With regard to nonaromatic ketones,  $\beta$ -tetralone yielded moderate ee values (80–83%, entry 5), whereas high stereoselectivities were obtained for the ATH of acetylcyclohexane (entry 6, 93–95% ee), albeit lower ee values of 84 and 87% were respectively observed using parent tethered rhodium complexes.<sup>6,7</sup>

In addition, because the catalytic asymmetric reduction of unsymmetrical benzophenones has been less investigated,<sup>14</sup> we were keen to evaluate the catalytic performance of our new complexes in the ATH of these more challenging substrates wherein a catalyst has to discriminate structural differences in the two aromatic moieties (Scheme 2). Interestingly, the tethered Rh–TsDPEN complexes (R,R)-8a and (R,R)-8b operated efficiently under the standard reaction conditions, and 4-nitrobenzophenone underwent the ATH with satisfactory enantiomeric excesses of 84% and 83%, respectively (Scheme 2). On the other hand, the asymmetric transfer hydrogenation proceeded with low enantioinductions for 4-chlorobenzophenone and 4-methoxybenzophenone. Unsurprisingly, the highest stereoselectivity was observed with the ortho-substituted substrate 2-methylbenzophenone, which was converted into the corresponding alcohol in 99% ee.

The ATH reaction was also carried out with a 1,4-diaryl diketone (Scheme 3). Thus, 1,4-diphenyl-1,4-butanedione was successfully reduced with (R,R)-8b under the standard conditions, giving the corresponding (1R,4R)-1,4-diphenyl-1,4-butanediol with a very high *dl*/*meso* ratio (96:4) and an excellent enantioselectivity (>99% ee).

When the reaction was performed with (R,R)-8a, an incomplete conversion was observed even after a prolonged reaction time of 48 h (48% conversion, 41% isolated yield), whereas the stereochemical outcome remained unchanged. This compound is a precursor of (2R,5R)-diphenylpyrrolidine, which is commonly used in asymmetric organocatalytic reactions.<sup>15</sup>

Table 2. Asymmetric Transfer Hydrogenation of Aryl Ketones Mediated by Complexes (*R,R*)-**8a**–**8e**<sup>a</sup>

| Entry/ATH product <sup>b</sup>   | Cat. <b>8</b>          | Time [h] | Yield [%] <sup>c</sup> | ee [%] <sup>d</sup> | Entry/ATH product <sup>b</sup>  | Cat. <b>8</b>          | Time [h] | Yield [%] <sup>c</sup> | ee [%] <sup>d</sup> |
|--|------------------------|----------|------------------------|---------------------|---|------------------------|----------|------------------------|---------------------|
| 1<br>                 | <b>8a</b> <sup>e</sup> | 10       | 100                    | 98                  | 9<br>    | <b>8a</b>              | 1        | 99                     | 88                  |
|  | <b>8b</b>              | 5        | 99                     | 98                  |   | <b>8b</b>              | 0.5      | 99                     | 88                  |
|  | <b>8c</b>              | 8.5      | 99                     | 97                  |   | <b>8c</b>              | 1        | 99                     | 88                  |
|  | <b>8d</b>              | 22       | 97                     | 98                  |   | <b>8d</b>              | 0.5      | 99                     | 88                  |
|  | <b>8e</b>              | 24       | 99                     | 98                  |   | <b>8e</b>              | 2.5      | 99                     | 88                  |
| 2<br>                 | <b>8a</b>              | 22       | 90                     | 98                  | 10<br>   | <b>8a</b> <sup>e</sup> | 8        | 35                     | 80                  |
|  | <b>8b</b>              | 6        | 79                     | 97                  |   | <b>8b</b>              | 27       | 94                     | 82                  |
|  | <b>8c</b>              | 6        | 100                    | 97                  |   | <b>8c</b>              | 30       | 100                    | 84                  |
|  | <b>8d</b>              | 30       | 100                    | 97                  |   | <b>8d</b>              | 39       | 98                     | 85                  |
|  | <b>8e</b>              | 96       | (89)                   | 97                  |   | <b>8e</b>              | 110      | (68)                   | 78                  |
| 3 <sup>[f]</sup><br>  | <b>8a</b> <sup>e</sup> | 2        | 100                    | 99.6                | 11<br>   | <b>8a</b> <sup>e</sup> | 9        | 100                    | 99.9                |
|  | <b>8b</b>              | 1.5      | 99                     | 99                  |   | <b>8b</b>              | 7        | 92                     | >99                 |
|  | <b>8c</b>              | 1        | 93                     | 95                  |   | <b>8c</b>              | 9        | 100                    | >99                 |
|  | <b>8d</b>              | 4        | 95                     | 95                  |   | <b>8d</b>              | 39       | 98                     | >99                 |
|  | <b>8e</b>              | 5        | 88                     | 95                  |   | <b>8e</b>              | 24       | 100                    | 99                  |
| 4<br>                 | <b>8a</b>              | 22       | 100                    | 98                  | 12<br>   | <b>8a</b>              | 48       | 97                     | >99                 |
|  | <b>8b</b>              | 7        | 98                     | 98                  |   | <b>8b</b>              | 29       | 72                     | >99                 |
|  | <b>8c</b>              | 7        | 93                     | 97                  |   | <b>8c</b>              | 24       | 100                    | 99                  |
|  | <b>8d</b>              | 27       | 97                     | 98                  |   | <b>8d</b>              | 96       | (94)                   | 92                  |
|  | <b>8e</b>              | 96       | 90                     | 98                  |   | <b>8e</b>              | 96       | (81)                   | 99                  |
| 5<br>               | <b>8a</b>              | 22       | 97                     | 95                  | 13<br> | <b>8a</b>              | 24       | 62                     | 98                  |
|  | <b>8b</b>              | 3        | 99                     | 96                  |   | <b>8b</b>              | 5.5      | 95                     | 98                  |
|  | <b>8c</b>              | 24       | 99                     | 94                  |   | <b>8c</b>              | 22       | 100                    | 97                  |
|  | <b>8d</b>              | 30       | 99                     | 94                  |   | <b>8d</b>              | 22       | 100                    | 97                  |
|  | <b>8e</b>              | 96       | 91                     | 95                  |   | <b>8e</b>              | 55       | 76                     | 98                  |
| 6 <sup>g</sup><br>  | <b>8a</b>              | 22       | 100                    | 98                  | 14<br> | <b>8a</b>              | 6        | 100                    | 99                  |
|  | <b>8b</b>              | 23       | 97                     | 99                  |   | <b>8b</b>              | 4        | 100                    | >99                 |
|  | <b>8c</b>              | 39       | 100                    | 99                  |   | <b>8c</b>              | 4.5      | 100                    | >99                 |
|  | <b>8d</b>              | 48       | 84                     | 99                  |   | <b>8d</b>              | 10       | 100                    | >99                 |
|  | <b>8e</b>              | 110      | (64)                   | 98                  |   | <b>8e</b>              | 96       | 79                     | >99                 |
| 7<br>               | <b>8a</b>              | 7        | 99                     | 96                  | 15<br> | <b>8a</b>              | 7        | 97                     | >99                 |
|  | <b>8b</b>              | 2        | 90                     | 96                  |   | <b>8b</b>              | 5.5      | 100                    | >99                 |
|  | <b>8c</b>              | 2.5      | 100                    | 94                  |   | <b>8c</b>              | 5        | 100                    | >99                 |
|  | <b>8d</b>              | 72       | 100                    | 94                  |   | <b>8d</b>              | 7        | 100                    | >99                 |
|  | <b>8e</b>              | 100      | (62)                   | 96                  |   | <b>8e</b>              | 6.5      | 99                     | 99                  |
| 8<br>               | <b>8a</b>              | 22       | 88                     | 64                  | 16<br> | <b>8a</b>              | 23       | 95                     | 99                  |
|  | <b>8b</b>              | 27       | 98                     | 70                  |   | <b>8b</b>              | 22       | 79                     | >99                 |
|  | <b>8c</b>              | 30       | 99                     | 65                  |   | <b>8c</b>              | 4        | 100                    | >99                 |
|  | <b>8d</b>              | 88       | 93                     | 71                  |   | <b>8d</b>              | 6        | 100                    | >99                 |
|  | <b>8e</b>              | 110      | (82)                   | 66                  |   | <b>8e</b>              | 65       | 84                     | >99                 |
| 17 <sup>h</sup><br> | <b>8a</b>              | 30       | 99                     | 99                  | <b>8a</b>   | 30                     | 99       | 99                     |                     |
|  | <b>8b</b>              | 30       | 99                     | 99                  | <b>8b</b>   | 30                     | 99       | 99                     |                     |

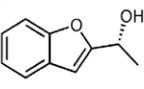
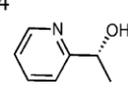
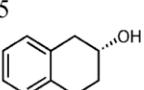
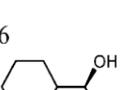
<sup>a</sup>Reaction conditions: ketone (0.8 mmol) in neat HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) (430 μL), (*R,R*)-**8a**–**8e** (0.004 mmol, 0.5 mol %), 24–30 °C. Except where indicated, complete conversions were observed. <sup>b</sup>Absolute configuration assigned by comparing the optical rotation with literature data and on the basis of the general trends in enantioselectivity observed for the Rh-catalyzed ATH of ketones. <sup>c</sup>Isolated yields after filtration through a short pad of silica gel. Values in parentheses refer to incomplete conversions. <sup>d</sup>Determined by HPLC or SFC analysis. <sup>e</sup>Results described by Wills et al.<sup>8</sup> Conversion is reported in place of yield. <sup>f</sup>Ethyl acetate was used as a cosolvent to allow solubilization of the reaction mixture. <sup>g</sup>Dichloromethane was used as a cosolvent to allow solubilization of the reaction mixture.

## CONCLUSION

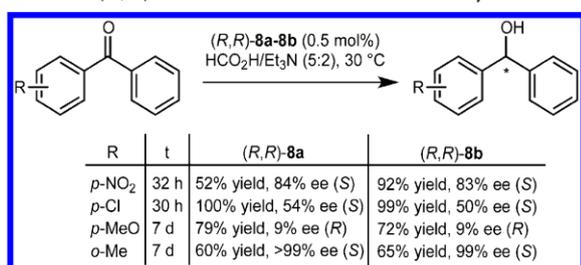
In conclusion, the synthesis, characterization, and evaluation of novel tethered Rh(III) complexes (*R,R*)-**8b**–**8e** having

electron-donating groups as well as electron-withdrawing substituents on the tethering phenyl ring were successfully accomplished. These new complexes showed high stability and

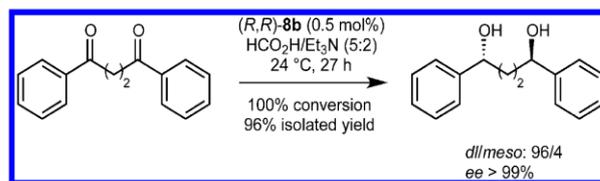
Table 3. (*R,R*)-**8a**–**8e**-Mediated ATH of Heteroaryl and Aliphatic Ketones<sup>a</sup>

| Entry/ATH product <sup>b</sup>   | Cat. <b>8</b> | Time [h] | Yield [%] <sup>c</sup> | ee [%] <sup>d</sup> |
|--|---------------|----------|------------------------|---------------------|
| 1<br>   | <b>8a</b>     | 5.5      | 82                     | 99                  |
|  | <b>8b</b>     | 5.5      | 100                    | 98                  |
|  | <b>8c</b>     | 8        | 100                    | >99                 |
|  | <b>8d</b>     | 27       | 92                     | >99                 |
|  | <b>8e</b>     | 24       | 85                     | 99                  |
| 2<br>   | <b>8a</b>     | 23       | 100                    | 99                  |
|  | <b>8b</b>     | 23       | 76                     | 98                  |
|  | <b>8c</b>     | 17       | 98                     | 99                  |
|  | <b>8d</b>     | 20       | 100                    | 99                  |
|  | <b>8e</b>     | 65       | 84                     | >99                 |
| 3<br>   | <b>8a</b>     | 5.5      | 100                    | 97                  |
|  | <b>8b</b>     | 3        | 100                    | 98                  |
|  | <b>8c</b>     | 3        | 100                    | 98                  |
|  | <b>8d</b>     | 3.5      | 100                    | 99                  |
|  | <b>8e</b>     | 6.5      | 100                    | 98                  |
| 4<br>   | <b>8a</b>     | 6        | 89                     | 97                  |
|  | <b>8b</b>     | 4.5      | 99                     | 94                  |
|  | <b>8c</b>     | 6.5      | 100                    | 96                  |
|  | <b>8d</b>     | 9        | 98                     | 99                  |
|  | <b>8e</b>     | 24       | 70                     | 96                  |
| 5<br>  | <b>8a</b>     | 24       | 53                     | 81                  |
|  | <b>8b</b>     | 3        | 96                     | 83                  |
|  | <b>8c</b>     | 3        | 100                    | 83                  |
|  | <b>8d</b>     | 27       | 100                    | 80                  |
|  | <b>8e</b>     | 30       | 89                     | 80                  |
| 6<br> | <b>8a</b>     | 22       | 71 <sup>e</sup>        | 94 <sup>f</sup>     |
|  | <b>8b</b>     | 7        | 68 <sup>e</sup>        | 95 <sup>f</sup>     |
|  | <b>8c</b>     | 7        | 73 <sup>e</sup>        | 93 <sup>f</sup>     |
|  | <b>8d</b>     | 30       | 72 <sup>e</sup>        | 94 <sup>f</sup>     |
|  | <b>8e</b>     | 24       | 58 <sup>e</sup>        | 94 <sup>f</sup>     |

<sup>a</sup>Reaction conditions: see Table 2. <sup>b</sup>Absolute configuration assigned by comparing the optical rotation with literature data. <sup>c</sup>Isolated yields after filtration through a pad of silica gel. <sup>d</sup>Determined by HPLC or SFC analysis. <sup>e</sup>Isolated yield (two steps) after conversion of the alcohol into the benzoyl ester. <sup>f</sup>Determined by HPLC on the related benzoyl ester.

Scheme 2. (*R,R*)-**8a**–**8b**-Mediated ATH of Diaryl Ketones

were easy to handle. As far as the synthesis, characterization, and applications of novel tethered Rh(III) complexes is concerned, a complete comparative study of the catalytic performances of complexes (*R,R*)-**8b**–**8e** was conducted. This study demonstrated that these complexes exhibited excellent activities for the asymmetric transfer hydrogenation of a wide range of functionalized ketones. In this survey, the catalytic performance of the Wills complex (*R,R*)-**8a** was also evaluated on a broad scope of

Scheme 3. (*R,R*)-**8b**-Mediated ATH of 1,4-Diphenyl-1,4-butanedione

new substrates. Selectivities obtained with complexes (*R,R*)-**8b**–**8e** were comparable to those obtained with (*R,R*)-**8a** or slightly higher in a few instances, and with a better catalytic activity observed in several cases. A wide range of (hetero)aryl ketones underwent the (*R,R*)-**8b**–**8e**-promoted ATH using formic acid/triethylamine with high levels of enantioselectivities under mild reaction conditions at a low catalyst loading. The scope of the prochiral ketones for the ATH promoted by tethered Rh–TsDPEN/Cp\* complexes has been consistently expanded, including notably unsymmetrical benzophenones, a highly electron-rich acetophenone bearing a morpholine substituent, and a highly electron-poor aryl ketone possessing a nitro substituent. Moreover, 1,4-diphenyl-1,4-butanedione was efficiently reduced upon using the Rh–TsDPEN complex (*R,R*)-**8b** into the enantiomerically pure 1,4-diphenyl-1,4-butanediol, a valuable intermediate in the preparation of the (*2R,5R*)-diphenylpyrrolidine organocatalyst. In addition, the ATH of 4-chromanone was performed with (*R,R*)-**8b** on the gram scale without a detrimental impact on the yield and the stereochemical outcome of the reaction, demonstrating the potential usefulness of these new complexes.

## EXPERIMENTAL SECTION

### Synthesis of Complexes (*R,R*)-**8b**–**8e**. Compound **13**.<sup>16</sup>

A mixture of 2-bromo-5-methoxybenzaldehyde (**9**) (5.0 g, 23.2 mmol), ethylene glycol (3.1 mL, 56.6 mmol), and *p*-toluenesulfonic acid (56 mg, 0.32 mmol) in toluene (40 mL) was refluxed in a Dean–Stark apparatus using an oil bath for 24 h. The cooled mixture was washed with H<sub>2</sub>O and brine. The organic layer was dried over MgSO<sub>4</sub>, filtered, and concentrated. Purification of the residue by flash chromatography (SiO<sub>2</sub>, petroleum ether/EtOAc = 95/5) afforded **13** (6.01 g, quantitative) as a colorless oil. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.44 (d, *J* = 8.8 Hz, 1H), 7.15 (d, *J* = 3.1 Hz, 1H), 6.78 (dd, *J* = 8.8, 3.1 Hz, 1H), 6.04 (s, 1H), 4.18–4.03 (m, 4H), 3.79 (s, 3H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 158.9, 137.3, 133.6, 116.6, 113.1, 112.9, 102.4, 65.4 (2C), 55.5. MS (DCI/NH<sub>3</sub>): *m/z* = 259 [M + H]<sup>+</sup>.

**Compound 14**.<sup>17</sup> Following the general procedure described for **13**, and starting from 2-bromo-5-methylbenzaldehyde (**10**) (4.2 g, 21.3 mmol), compound **14** (4.8 g, 92%) was obtained as a colorless oil. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.52–7.32 (m, 2H), 7.03 (dd, *J* = 8.2, 2.3 Hz, 1H), 6.06 (s, 1H), 4.31–3.93 (m, 4H), 2.32 (s, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 137.5, 136.2, 132.8, 131.6, 128.5, 119.7, 102.8, 65.6 (2C), 21.1. MS (DCI/NH<sub>3</sub>): *m/z* = 244 [M + H]<sup>+</sup>.

**Compound 15**.<sup>18</sup> Following the general procedure described for **13**, and starting from 2-fluoro-5-methylbenzaldehyde (**11**) (5.0 g, 25.0 mmol), compound **15** (5.2 g, 84%) was obtained as a colorless oil. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.50 (dd, *J* = 8.8, 5.1 Hz, 1H), 7.32 (dd, *J* = 9.3, 3.1 Hz, 1H), 6.94 (ddd, *J* = 8.8, 7.8, 3.1 Hz, 1H), 6.03 (d, *J* = 1.3 Hz, 1H), 4.27–3.94 (m, 4H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 162.1 (d, *J*<sub>CF</sub> = 247.3 Hz), 139.1 (d, *J*<sub>CF</sub> = 6.2 Hz), 134.3 (d, *J*<sub>CF</sub> = 7.6 Hz), 117.8 (d, *J*<sub>CF</sub> = 22.7 Hz), 116.9 (d, *J*<sub>CF</sub> = 3.2 Hz), 115.2 (d, *J*<sub>CF</sub> = 24.4 Hz), 102.1, 65.6 (2C). MS (DCI/NH<sub>3</sub>): *m/z* = 248 [M + H]<sup>+</sup>.

**Compound 16**.<sup>19</sup> Following the general procedure described for **13**, and starting from 2-bromo-5-(trifluoromethyl)benzaldehyde (**12**) (5.0 g, 19.8 mmol), compound **16** (5.8 g, 99%) was obtained as a colorless oil. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.00–7.78 (m, 1H), 7.78–7.62 (m, 1H), 7.47 (dt, *J* = 8.3, 1.5 Hz, 1H), 6.09 (s, 1H), 4.33–3.89 (m, 4H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 138.1, 133.7,

130.2 (q,  $J_{CF} = 33.0$  Hz), 127.2 (q,  $J_{CF} = 3.9$  Hz), 125.0 (q,  $J_{CF} = 3.6$  Hz), 123.8 (q,  $J_{CF} = 272.5$  Hz), 102.0, 65.7 (2C). MS (DCI/NH<sub>3</sub>):  $m/z = 299$  [M + H]<sup>+</sup>.

**Compound 17.**<sup>7</sup> To a solution of **13** (6.0 g, 23.2 mmol) in Et<sub>2</sub>O (42 mL) was added dropwise *n*-BuLi (9.7 mL, 2.5 M in hexane, 24.4 mmol) at -90 °C. After 1 h at this temperature, 2,3,4,5-tetramethylcyclopent-2-enone (3.7 mL, 24.4 mmol) was added dropwise and the reaction, was allowed to warm to rt and stirred for 3 h. Toluene and water (30 mL/30 mL) were added, and the aqueous layer was extracted with toluene. The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated to afford the crude alcohol. THF (140 mL), acetone (18 mL), and 3% aqueous HCl solution (60 mL) were added, and the mixture was stirred overnight at rt. Toluene was added, and the organic layer was washed with H<sub>2</sub>O and then brine, dried over MgSO<sub>4</sub>, filtered, and concentrated. The crude residue was purified by flash chromatography (SiO<sub>2</sub>, petroleum ether/EtOAc = 98/2) to give **17** (3.9 g, 65%) as a bright yellow oil. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 9.81 (br s, 1H), 7.44 (dd,  $J = 2.3, 0.8$  Hz, 1H), 7.15–7.14 (m, 2H), 3.88 (s, 1H), 3.87 (s, 3H), 1.92 (s, 3H), 1.85 (s, 3H), 1.71 (s, 3H), 0.93 (d,  $J = 7.7$  Hz, 3H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 192.9, 158.3, 141.8 (2C), 138.2, 135.3, 134.5, 132.0, 121.8 (2C), 109.0, 55.5 (2C), 14.2, 12.3, 11.9, 11.0. MS (DCI/NH<sub>3</sub>):  $m/z = 257$  [M + H]<sup>+</sup>.

**Compound 18.** Following the general procedure described for **17**, and starting from **14** (4.8 g, 19.6 mmol), compound **18** (2.6 g, 55%) was obtained as a bright yellow oil. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 9.87 (br s, 1H), 7.90–7.66 (m, 1H), 7.40 (dd,  $J = 7.8, 2.0$  Hz, 1H), 7.13 (d,  $J = 7.8$  Hz, 1H), 3.20 (br s, 1H), 2.42 (s, 3H), 1.94 (s, 3H), 1.87 (s, 3H), 1.73 (s, 3H), 0.95 (d,  $J = 7.7$  Hz, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 193.2, 144.4, 141.9, 139.3, 138.8, 137.1, 136.5, 134.5, 134.4, 130.8, 127.3, 52.5, 21.0, 14.2, 12.4, 11.9, 11.1. HRMS (ESI/ion trap):  $m/z$  [M + Na]<sup>+</sup> calcd for C<sub>17</sub>H<sub>20</sub>O<sub>2</sub>Na 263.1406, found 263.1408.

**Compound 19.** Following the general procedure described for **17**, and starting from **15** (5.2 g, 21.0 mmol), compound **23** (2.5 g, 49%) was obtained as a bright yellow oil. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 9.80 (br s, 1H), 7.62 (dd,  $J = 8.9, 2.6$  Hz, 1H), 7.37–7.16 (m, 2H), 3.18 (br s, 1H), 1.93 (s, 3H), 1.86 (s, 3H), 1.71 (s, 3H), 0.94 (d,  $J = 7.7$  Hz, 3H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 191.9, 161.7 (d,  $J_{CF} = 247.9$  Hz), 145.1 (d,  $J_{CF} = 19.4$  Hz), 142.4, 139.9 (d,  $J_{CF} = 14.0$  Hz), 137.6, 136.2, 134.6, 132.8 (d,  $J_{CF} = 6.5$  Hz), 121.0 (d,  $J_{CF} = 22.1$  Hz), 113.1 (d,  $J_{CF} = 22.0$  Hz), 52.6, 14.2, 12.4, 12.0, 11.1. HRMS (ESI/ion trap):  $m/z$  [M + Na]<sup>+</sup> calcd for C<sub>16</sub>H<sub>17</sub>FONa 267.1156, found 267.1157.

**Compound 20.** Following the general procedure described for **17**, and starting from **16** (5.2 g, 17.5 mmol), compound **20** (1.4 g, 26%) was obtained as a bright yellow oil. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 9.87 (br s, 1H), 8.30–8.10 (m, 1H), 7.79 (ddd,  $J = 8.1, 2.1, 0.8$  Hz, 1H), 7.36 (d,  $J = 8.1$  Hz, 1H), 3.26 (br s, 1H), 1.96 (s, 3H), 1.87 (s, 3H), 1.74 (s, 3H), 0.96 (d,  $J = 7.7$  Hz, 3H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 191.6, 145.1, 143.5, 137.5, 134.9, 134.8, 131.7, 131.6, 129.6 (q,  $J_{CF} = 3.2$  Hz), 129.1 (q,  $J_{CF} = 33.6$  Hz), 124.6 (q,  $J_{CF} = 3.7$  Hz), 123.9 (q,  $J_{CF} = 272.2$  Hz), 52.5, 14.1, 12.6, 12.0, 11.1. MS (DCI/NH<sub>3</sub>):  $m/z = 295$  [M + H]<sup>+</sup>. HRMS (APCI):  $m/z$  [M + H]<sup>+</sup> calcd for C<sub>17</sub>H<sub>18</sub>F<sub>3</sub>O 295.1304, found 295.1310.

**Complex (R,R)-8b.** To a solution of compound **17** (538 mg, 2.1 mmol) in dry MeOH (24 mL) was added (R,R)-TsDPEN (900 mg, 2.5 mmol) followed by the addition of 700 mg of molecular sieves (4 Å) and 2 drops of glacial acetic acid. The mixture was stirred at rt for 5 h, then NaBH<sub>3</sub>CN (170 mg, 2.7 mmol) was added, and the reaction was stirred overnight at rt. After removal of the molecular sieves and evaporation of MeOH, the residue was dissolved in EtOAc (40 mL). The organic layer was washed with saturated NaHCO<sub>3</sub> and then brine, dried over MgSO<sub>4</sub>, filtered, and concentrated. Purification of the residue by flash chromatography (SiO<sub>2</sub>, pentane/EtOAc = 9/1 to 8/2) afforded the diamine (786 mg, 60%) as a white solid. To a solution of the diamine (740 mg, 1.2 mmol) in MeOH (28 mL) was added RhCl<sub>3</sub>·H<sub>2</sub>O (255 mg, 1.2 mmol), and the reaction mixture was heated under reflux using an oil bath for 23 h. Et<sub>3</sub>N (340 μL, 2.4 mmol) was then added, and the mixture was refluxed for a further 20 h and concentrated. The residue was triturated with H<sub>2</sub>O, and the solid was filtered, washed with H<sub>2</sub>O, and dried under vacuum. Purification of the black solid by flash chromatography (SiO<sub>2</sub>, EtOAc/cyclohexane = 1/1 to EtOAc/MeOH = 95/5) afforded (R,R)-**8b** (455 mg, 50%) as an orange solid.

Mp: >260 °C dec.  $R_f = 0.51$  (CH<sub>2</sub>Cl<sub>2</sub>/MeOH = 9/1, UV, KMnO<sub>4</sub>).  $[\alpha]_D^{25} = -154.4$  ( $c = 0.12$ , CHCl<sub>3</sub>). IR (neat): 2360, 2339, 1608, 1513, 1489, 1455, 1397, 1372, 1277, 1239, 1131, 1098, 1086, 1040, 1023, 940, 895, 812, 796, 766, 700, 682, 661, 646, 635, 622, 606 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.37 (d,  $J = 8.5$  Hz, 1H), 7.27 (d,  $J = 8.6$  Hz, 2H), 7.19–7.16 (m, 3H), 7.02 (dd,  $J = 8.4, 2.5$  Hz, 1H), 6.73 (d,  $J = 8.0$  Hz, 2H), 6.70 (d,  $J = 7.3$  Hz, 2H), 6.59 (t,  $J = 7.8$  Hz, 2H), 6.48 (d,  $J = 7.4$  Hz, 2H), 6.42 (br d,  $J = 2.4$  Hz, 2H), 4.98 (d,  $J = 12.4$  Hz, 1H), 4.32 (d,  $J = 11.0$  Hz, 1H), 4.22 (dd,  $J = 14.0, 2.9$  Hz, 1H), 3.73 (s, 3H), 3.60 (d,  $J = 14.0$  Hz, 1H), 3.26 (t,  $J = 12.4$  Hz, 1H), 2.17 (s, 3H), 2.09 (s, 3H), 1.97 (s, 3H), 1.83 (s, 3H), 1.54 (s, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 160.2, 142.3, 139.0, 138.6, 137.5, 135.7, 131.2, 128.8, 128.7, 127.9, 127.7, 127.1, 126.2, 118.6, 117.0, 115.0, 106.4 (d,  $J_{CRh} = 6.6$  Hz), 99.2 (d,  $J_{CRh} = 6.6$  Hz), 97.0 (d,  $J_{CRh} = 8.8$  Hz), 88.7 (d,  $J_{CRh} = 9.5$  Hz), 80.6 (d,  $J_{CRh} = 8.0$  Hz), 75.9, 69.8, 55.5, 52.5, 21.3, 10.8, 10.7, 10.4, 8.3. HRMS (ESI/ion trap):  $m/z$  [M - Cl]<sup>+</sup> calcd for C<sub>38</sub>H<sub>40</sub>N<sub>2</sub>O<sub>3</sub>RhS 707.1809, found 707.1813.

**Complex (R,R)-8c.** Following the general procedure described for (R,R)-**8b**, and starting from **18** (546 mg, 2.3 mmol), complex (R,R)-**8c** (590 mg, 36%, 2 steps) was obtained as an orange solid. Mp: 274 °C dec.  $R_f = 0.58$  (CH<sub>2</sub>Cl<sub>2</sub>/MeOH = 9/1, UV, KMnO<sub>4</sub>).  $[\alpha]_D^{25} = -112$  ( $c = 0.15$ , CHCl<sub>3</sub>). IR (neat): 1456, 1277, 1133, 1107, 1085, 1036, 1021, 938, 894, 809, 751, 701, 682, 670, 661, 647, 601 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.39–7.23 (m, 5H), 7.23–7.06 (m, 3H), 6.81–6.66 (m, 5H), 6.59 (dd,  $J = 8.2, 7.1$  Hz, 2H), 6.48 (d,  $J = 7.6$  Hz, 2H), 4.99 (d,  $J = 12.8$  Hz, 1H), 4.30 (d,  $J = 11.0$  Hz, 1H), 4.20 (dd,  $J = 14.0, 3.3$  Hz, 1H), 3.62 (d,  $J = 14.0$  Hz, 1H), 3.25 (dd,  $J = 12.8, 10.9$  Hz, 1H), 2.29 (s, 3H), 2.17 (s, 3H), 2.09 (s, 3H), 1.98 (s, 3H), 1.82 (s, 3H), 1.54 (s, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 142.2, 139.9, 139.1, 138.7, 135.9, 135.8, 132.4, 130.3, 129.8, 128.7, 127.9, 127.8, 127.0, 126.2, 123.9, 106.3 (d,  $J_{CRh} = 6.1$  Hz), 99.5 (d,  $J_{CRh} = 7.0$  Hz), 97.2 (d,  $J_{CRh} = 9.0$  Hz), 88.2 (d,  $J_{CRh} = 9.2$  Hz), 80.9 (d,  $J_{CRh} = 8.6$  Hz), 75.9, 69.9, 52.2, 21.3, 21.2, 10.8, 10.6, 10.4, 8.3. HRMS (ESI/ion trap):  $m/z$  [M - Cl]<sup>+</sup> calcd for C<sub>38</sub>H<sub>40</sub>N<sub>2</sub>O<sub>3</sub>RhS 691.1860, found 691.1870.

**Complex (R,R)-8d.** Following the general procedure described for (R,R)-**8b**, and starting from **19** (555 mg, 2.3 mmol), complex (R,R)-**8d** (297 mg, 19%, 2 steps) was obtained as an orange solid. Mp: 280 °C dec.  $R_f = 0.55$  (CH<sub>2</sub>Cl<sub>2</sub>/MeOH = 9/1, UV, KMnO<sub>4</sub>).  $[\alpha]_D^{25} = -151$  ( $c = 0.14$ , CHCl<sub>3</sub>). IR (neat): 1736, 1608, 1585, 1511, 1492, 1455, 1373, 1275, 1235, 1216, 1158, 1132, 1023, 940, 894, 868, 852, 842, 811, 793, 779, 757, 730, 699, 677, 657, 645, 636, 607 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.45 (dd,  $J = 8.5, 5.5$  Hz, 1H), 7.33–7.10 (m, 7H), 6.74 (d,  $J = 8.0$  Hz, 3H), 6.71–6.55 (m, 4H), 6.48 (d,  $J = 7.3$  Hz, 2H), 5.04 (d,  $J = 12.8$  Hz, 1H), 4.32 (d,  $J = 10.9$  Hz, 1H), 4.22 (d,  $J = 14.2$  Hz, 1H), 3.64 (d,  $J = 14.3$  Hz, 1H), 3.34–3.13 (m, 1H), 2.17 (s, 3H), 2.10 (s, 3H), 1.98 (s, 3H), 1.83 (s, 3H), 1.55 (s, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 162.8 (d,  $J_{CF} = 251.3$  Hz), 142.1, 139.2, 138.7 (d,  $J_{CF} = 7.7$  Hz), 138.4, 135.4, 131.9 (d,  $J_{CF} = 8.4$  Hz), 129.0, 128.9, 128.6, 127.9, 127.7, 127.1, 127.0, 126.3, 123.1 (d,  $J_{CF} = 3.2$  Hz), 118.7 (d,  $J_{CF} = 22.3$  Hz), 116.8 (d,  $J_{CF} = 21.4$  Hz), 106.5 (d,  $J_{CRh} = 6.4$  Hz), 99.9 (d,  $J_{CRh} = 7.0$  Hz), 96.0 (d,  $J_{CRh} = 9.2$  Hz), 88.2 (d,  $J_{CRh} = 9.5$  Hz), 81.1 (d,  $J_{CRh} = 8.5$  Hz), 76.3, 69.9, 52.2, 21.3, 10.8, 10.6, 10.4, 8.3. HRMS (ESI/ion trap):  $m/z$  [M - Cl]<sup>+</sup> calcd for C<sub>37</sub>H<sub>37</sub>FN<sub>2</sub>O<sub>2</sub>RhS 695.1609, found 695.1616.

**Complex (R,R)-8e.** Following the general procedure described for (R,R)-**8b**, and starting from **20** (656 mg, 2.2 mmol), compound (R,R)-**8e** (310 mg, 18%, 2 steps) was obtained as an orange solid. Mp: 284 °C dec.  $R_f = 0.56$  (CH<sub>2</sub>Cl<sub>2</sub>/MeOH = 9/1, UV, KMnO<sub>4</sub>).  $[\alpha]_D^{25} = -172$  ( $c = 0.14$ , CHCl<sub>3</sub>). IR (neat): 2359, 2341, 1329, 1275, 1168, 1132, 1082, 938, 906, 896, 881, 870, 808, 791, 766, 756, 713, 699, 687, 679, 671, 659, 641, 622, 614, 605 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.78 (d,  $J = 8.0$  Hz, 1H), 7.63 (d,  $J = 8.0$  Hz, 1H), 7.25 (d,  $J = 8.2$  Hz, 2H), 7.23–7.09 (m, 4H), 6.73 (d,  $J = 8.0$  Hz, 2H), 6.76–6.66 (m, 3H), 6.65–6.54 (m, 2H), 6.47 (d,  $J = 7.6$  Hz, 2H), 5.04 (d,  $J = 12.7$  Hz, 1H), 4.35 (d,  $J = 10.9$  Hz, 1H), 4.26 (dd,  $J = 14.0, 3.3$  Hz, 1H), 3.73 (d,  $J = 14.1$  Hz, 1H), 3.19 (dd,  $J = 12.7, 10.9$  Hz, 1H), 2.17 (s, 3H), 2.10 (s, 3H), 1.98 (s, 3H), 1.83 (s, 3H), 1.56 (s, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 141.9, 139.2, 138.1, 137.0, 135.1, 131.8 (q,  $J_{CF} = 33.2$  Hz), 131.5, 131.3, 130.7, 129.1, 128.9, 128.6, 128.6 (q,  $J_{CF} = 3.2$  Hz), 127.8, 127.6, 127.1, 126.5 (q,  $J_{CF} = 3.2$  Hz), 126.3, 123.3 (q,  $J_{CF} = 272.7$  Hz), 106.5 (d,  $J_{CRh} = 6.3$  Hz), 100.1 (d,  $J_{CRh} = 7.0$  Hz), 95.5 (d,  $J_{CRh} = 9.2$  Hz),

87.8 (d,  $J_{\text{CRh}} = 9.1$  Hz), 81.4 (d,  $J_{\text{CRh}} = 8.4$  Hz), 76.4, 69.5, 52.1, 21.2, 10.6, 10.5, 10.3, 8.2. HRMS (ESI/ion trap):  $m/z$  [M - Cl]<sup>+</sup> calcd for C<sub>36</sub>H<sub>37</sub>F<sub>3</sub>N<sub>2</sub>O<sub>2</sub>RhS 745.1577, found 745.1585.

**General Procedure for the ATH of Ketones with Complexes (R,R)-8a–8e.** To a round-bottom tube containing complex (R,R)-8 (4 μmol, 0.5 mol %) was added at room temperature a HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) azeotropic mixture (430 μL, 7.2 mmol), and three vacuum/argon cycles were used to ensure an inert atmosphere. The orange mixture was stirred for 10–15 min before the ketone (0.8 mmol) was added. The reaction mixture was stirred at 24–30 °C until the starting material was consumed as determined by TLC, and then the reaction mixture was purified by filtration through a pad of silica gel using pentane/EtOAc (8:2). The filtrate was concentrated under vacuum to give the reduced product. Enantiomeric excess was determined by SFC (Chiralpak OD-H and Chiralpak AD-H, AS-H, IA, IC, or ID) or HPLC (Chiralpak IB, IC, or ID column) analysis.

**(R)-1-Phenylethanol.**<sup>8</sup> Yield: 96 mg, 98%. Pale yellow oil.  $[\alpha]_{\text{D}}^{20} = +45.5$  ( $c = 1.0$ , CHCl<sub>3</sub>, 98% ee), lit.<sup>8</sup>  $[\alpha]_{\text{D}}^{26} = +45.4$  ( $c = 0.5$ , CHCl<sub>3</sub>, 98% ee). Enantiomeric excess determined by HPLC analysis on a Daicel Chiralpak IB column (0.46 × 25 cm), hexane/*i*-PrOH = 95/5, 1.0 mL/min,  $\lambda = 215$  nm,  $t_{\text{R}} = 7.38$  min (R), 8.04 min (S). MS (DCI/NH<sub>3</sub>):  $m/z = 140$  [M + NH<sub>4</sub>]<sup>+</sup>.

**(R)-1-Phenylpropan-1-ol.**<sup>20</sup> Yield: 98 mg, 90%. Pale yellow oil.  $[\alpha]_{\text{D}}^{25} = +45$  ( $c = 1.0$ , CHCl<sub>3</sub>, 98% ee), lit.<sup>20</sup>  $[\alpha]_{\text{D}}^{20} = +44.5$  ( $c = 1.0$ , CHCl<sub>3</sub>, 97% ee). Enantiomeric excess determined by SFC analysis on a Daicel Chiralpak OD-H column (0.46 × 25 cm), scCO<sub>2</sub>/MeOH = 95/5, 4.0 mL/min,  $P = 150$  bar,  $\lambda = 215$  nm,  $t_{\text{R}} = 2.07$  min (R), 2.44 min (S). MS (DCI/NH<sub>3</sub>):  $m/z = 154$  [M + NH<sub>4</sub>]<sup>+</sup>.

**(S)-2-Chloro-1-phenylethan-1-ol.**<sup>21</sup> Yield: 119 mg, 95%. Colorless oil.  $[\alpha]_{\text{D}}^{25} = +56$  ( $c = 1.09$ , CHCl<sub>3</sub>, 95% ee), lit.<sup>21</sup>  $[\alpha]_{\text{D}}^{20} = +57.8$  ( $c = 1.0$ , CHCl<sub>3</sub>, 96.6% ee). Enantiomeric excess determined by SFC analysis on a Daicel Chiralpak OD-H column (0.46 × 25 cm), scCO<sub>2</sub>/MeOH = 95/5, 4.0 mL/min,  $P = 150$  bar,  $\lambda = 215$  nm,  $t_{\text{R}} = 2.52$  min (S), 3.38 min (R). MS (DCI/NH<sub>3</sub>):  $m/z = 174$  [M + NH<sub>4</sub>]<sup>+</sup>.

**(R)-1-(*p*-Tolyl)ethan-1-ol.**<sup>22</sup> Yield: 109 mg, 100%. Pale yellow oil.  $[\alpha]_{\text{D}}^{25} = +53$  ( $c = 0.94$ , CHCl<sub>3</sub>, 98% ee), lit.<sup>22</sup>  $[\alpha]_{\text{D}}^{20} = +55.4$  ( $c = 1.01$ , CHCl<sub>3</sub>, 98.7% ee). Enantiomeric excess determined by HPLC analysis on a Daicel Chiralpak ID column (0.46 × 25 cm), hexane/*i*-PrOH = 97/3, 0.5 mL/min,  $\lambda = 215$  nm,  $t_{\text{R}} = 18.77$  min (R), 19.97 min (S). MS (DCI/NH<sub>3</sub>):  $m/z = 119$  [M + H - H<sub>2</sub>O]<sup>+</sup>.

**(R)-1-(4-Bromophenyl)ethan-1-ol.**<sup>23</sup> Yield: 159 mg, 99%. Colorless oil.  $[\alpha]_{\text{D}}^{25} = +35$  ( $c = 1.17$ , CHCl<sub>3</sub>, 96% ee), lit.<sup>23</sup>  $[\alpha]_{\text{D}}^{22} = +34.8$  ( $c = 1.03$ , CHCl<sub>3</sub>, 97% ee). Enantiomeric excess determined by HPLC analysis on a Daicel Chiralpak IB column (0.46 × 25 cm), hexane/*i*-PrOH = 95/5, 0.5 mL/min,  $\lambda = 215$  nm,  $t_{\text{R}} = 15.09$  min (S), 15.83 min (R). MS (DCI/NH<sub>3</sub>):  $m/z = 202$  [M + NH<sub>4</sub> - H<sub>2</sub>O]<sup>+</sup>.

**(R)-1-(4-(Benzyloxy)phenyl)ethan-1-ol.**<sup>24</sup> Yield: 182 mg, 100%. White solid.  $[\alpha]_{\text{D}}^{25} = +33$  ( $c = 1.09$ , CHCl<sub>3</sub>, 99% ee), lit.<sup>24</sup>  $[\alpha]_{\text{D}}^{25} = -31.8$  ( $c = 1.2$ , CHCl<sub>3</sub>, > 99% ee, (S)-isomer). Enantiomeric excess determined by SFC analysis on a Daicel Chiralpak OD-H column (0.46 × 25 cm), scCO<sub>2</sub>/MeOH = 98/2, 2.0 mL/min,  $P = 150$  bar,  $\lambda = 215$  nm,  $t_{\text{R}} = 39.24$  min (S), 42.59 min (R). MS (DCI/NH<sub>3</sub>):  $m/z = 211$  [M + H - H<sub>2</sub>O]<sup>+</sup>.

**(R)-1-(3,5-Dimethoxyphenyl)ethan-1-ol.**<sup>25</sup> Yield: 144 mg, 99%. Colorless oil.  $[\alpha]_{\text{D}}^{25} = +31$  ( $c = 0.95$ , CHCl<sub>3</sub>, 96% ee), lit.<sup>25</sup>  $[\alpha]_{\text{D}}^{20} = -32.7$  ( $c = 2.0$ , CHCl<sub>3</sub>, 97% ee, (S)-isomer). Enantiomeric excess determined by SFC analysis on a Daicel Chiralpak OD-H column (0.46 × 25 cm), scCO<sub>2</sub>/MeOH = 95/5, 4.0 mL/min,  $P = 150$  bar,  $\lambda = 215$  nm,  $t_{\text{R}} = 3.11$  min (R), 3.49 min (S). MS (DCI/NH<sub>3</sub>):  $m/z = 183$  [M + H]<sup>+</sup>.

**(R)-1-(2-Bromophenyl)ethan-1-ol.**<sup>26</sup> Yield: 142 mg, 88%. Colorless oil.  $[\alpha]_{\text{D}}^{25} = +40$  ( $c = 0.99$ , CHCl<sub>3</sub>, 64% ee), lit.<sup>26</sup>  $[\alpha]_{\text{D}}^{24} = +32.7$  ( $c = 0.8$ , CHCl<sub>3</sub>, 64% ee). Enantiomeric excess determined by SFC analysis on a Daicel Chiralpak ID column (0.46 × 25 cm), scCO<sub>2</sub>/MeOH = 90/10, 4.0 mL/min,  $P = 150$  bar,  $\lambda = 215$  nm,  $t_{\text{R}} = 1.27$  min (R), 1.50 min (S). MS (DCI/NH<sub>3</sub>):  $m/z = 218$  [M + NH<sub>4</sub>]<sup>+</sup>.

**(R)-1-(4-Nitrophenyl)ethan-1-ol.**<sup>27</sup> Yield: 132 mg, 99%. Yellow oil.  $[\alpha]_{\text{D}}^{22} = +34.9$  ( $c = 1.0$ , CHCl<sub>3</sub>, 88% ee); lit.<sup>27</sup>  $[\alpha]_{\text{D}}^{25} = +33.7$  ( $c = 1.0$ , CHCl<sub>3</sub>, 85% ee). Enantiomeric excess determined by SFC analysis on a Daicel Chiralpak AS-H column (0.46 × 25 cm), scCO<sub>2</sub>/MeOH = 95/5,

2.0 mL/min,  $P = 100$  bar,  $\lambda = 215$  nm,  $t_{\text{R}} = 6.30$  min (R), 7.33 min (S). MS (DCI/NH<sub>3</sub>):  $m/z = 185$  [M + NH<sub>4</sub>]<sup>+</sup>.

**(R)-1-(Naphthalen-1-yl)ethan-1-ol.**<sup>28</sup> Yield: 135 mg, 98%. Colorless oil.  $[\alpha]_{\text{D}}^{20} = +46.6$  ( $c = 1.0$ , CHCl<sub>3</sub>, 85% ee), lit.<sup>28</sup>  $[\alpha]_{\text{D}}^{22} = +55.1$  ( $c = 1.0$ , CHCl<sub>3</sub>, 92% ee). Enantiomeric excess determined by SFC analysis on a Daicel Chiralpak OD-H column (0.46 × 25 cm), scCO<sub>2</sub>/MeOH = 95/5, 4.0 mL/min,  $P = 150$  bar,  $\lambda = 215$  nm,  $t_{\text{R}} = 7.65$  min (S), 11.48 min (R). MS (DCI/NH<sub>3</sub>):  $m/z = 155$  [M + H - H<sub>2</sub>O]<sup>+</sup>.

**(R)-1,2,3,4-Tetrahydro-1-naphthol.**<sup>5f</sup> Yield: 141 mg, 100%. Colorless oil.  $[\alpha]_{\text{D}}^{25} = -30$  ( $c = 0.94$ , CHCl<sub>3</sub>, 99% ee), lit.<sup>5f</sup>  $[\alpha]_{\text{D}}^{30} = -30.7$  ( $c = 1.02$ , CHCl<sub>3</sub>, 99.2% ee). Enantiomeric excess determined by SFC analysis on a Daicel Chiralpak OD-H column (0.46 × 25 cm), scCO<sub>2</sub>/MeOH = 95/5, 3.0 mL/min,  $P = 150$  bar,  $\lambda = 215$  nm,  $t_{\text{R}} = 3.80$  (S), 4.20 min (R). MS (DCI/NH<sub>3</sub>):  $m/z = 131$  [M + H - H<sub>2</sub>O]<sup>+</sup>.

**(R)-6-Methoxy-1,2,3,4-tetrahydro-1-naphthol.**<sup>29</sup> Yield: 165 mg, 100%. Colorless oil.  $[\alpha]_{\text{D}}^{25} = -22$  ( $c = 0.92$ , CHCl<sub>3</sub>, > 99% ee), lit.<sup>29</sup>  $[\alpha]_{\text{D}}^{21} = -17.2$  ( $c = 1.19$ , CHCl<sub>3</sub>, 92% ee). Enantiomeric excess determined by SFC analysis on a Daicel Chiralpak AD-H column (0.46 × 25 cm), scCO<sub>2</sub>/MeOH = 90/10, 3.0 mL/min,  $P = 150$  bar,  $\lambda = 215$  nm,  $t_{\text{R}} = 5.37$  min (S), 6.23 min (R). MS (DCI/NH<sub>3</sub>):  $m/z = 161$  [M + H - H<sub>2</sub>O]<sup>+</sup>.

**(R)-1,2-Dihydroacenaphthyl-1-ol.**<sup>30</sup> Yield: 129 mg, 95%. White solid.  $[\alpha]_{\text{D}}^{25} = -1.4$  ( $c = 0.92$ , CHCl<sub>3</sub>, 98% ee), lit.<sup>30,31</sup>  $[\alpha]_{\text{D}}^{20} = -1.4$  ( $c = 0.5$ , CHCl<sub>3</sub>, 98.2% ee). Enantiomeric excess determined by SFC analysis on a Daicel Chiralpak OD-H column (0.46 × 25 cm), scCO<sub>2</sub>/*i*-PrOH = 93/7, 4.0 mL/min,  $P = 150$  bar,  $\lambda = 215$  nm,  $t_{\text{R}} = 8.17$  min (S), 8.99 min (R). MS (DCI/NH<sub>3</sub>):  $m/z = 153$  [M + H - H<sub>2</sub>O]<sup>+</sup>.

**(R)-Chroman-4-ol.**<sup>21</sup> Yield: 120 mg, 100%. White solid.  $[\alpha]_{\text{D}}^{25} = +68$  ( $c = 0.93$ , CHCl<sub>3</sub>, > 99% ee), lit.<sup>21</sup>  $[\alpha]_{\text{D}}^{20} = +66.9$  ( $c = 1.0$ , CHCl<sub>3</sub>, 99.1% ee). Enantiomeric excess determined by SFC analysis on a Daicel Chiralpak AD-H column (0.46 × 25 cm), scCO<sub>2</sub>/MeOH = 97/3, 3.0 mL/min,  $P = 150$  bar,  $\lambda = 215$  nm,  $t_{\text{R}} = 10.59$  min (S), 11.25 min (R). MS (DCI/NH<sub>3</sub>):  $m/z = 133$  [M + H - H<sub>2</sub>O]<sup>+</sup>.

**(R)-2,3-Dihydro-1H-inden-1-ol.**<sup>2</sup> Yield: 107 mg, 100%. White solid.  $[\alpha]_{\text{D}}^{25} = -33$  ( $c = 0.85$ , CHCl<sub>3</sub>, > 99% ee), lit.<sup>21</sup>  $[\alpha]_{\text{D}}^{22} = +29.3$  ( $c = 0.967$ , CHCl<sub>3</sub>, > 99% ee, (S)-isomer). Enantiomeric excess determined by HPLC analysis on a Daicel Chiralpak IB column (0.46 × 25 cm), hexane/*i*-PrOH = 98/2, 1.0 mL/min,  $\lambda = 215$  nm,  $t_{\text{R}} = 14.86$  (S), 16.43 min (R). MS (DCI/NH<sub>3</sub>):  $m/z = 117$  [M + H - H<sub>2</sub>O]<sup>+</sup>.

**(R)-5-Bromo-2,3-dihydro-1H-inden-1-ol.**<sup>32</sup> Yield: 170 mg, 100%. White solid.  $[\alpha]_{\text{D}}^{25} = -16$  ( $c = 0.92$ , CHCl<sub>3</sub>, > 99% ee), lit.<sup>32</sup>  $[\alpha]_{\text{D}}^{25} = +15.8$  ( $c = 1.0$ , CHCl<sub>3</sub>, 98.1% ee, (S)-isomer). Enantiomeric excess determined by SFC analysis on a Daicel Chiralpak AD-H column (0.46 × 25 cm), scCO<sub>2</sub>/MeOH = 90/10, 3.0 mL/min,  $P = 150$  bar,  $\lambda = 215$  nm,  $t_{\text{R}} = 5.92$  (S), 8.21 min (R). MS (DCI/NH<sub>3</sub>):  $m/z = 195$  [M + H - H<sub>2</sub>O]<sup>+</sup>.

**(R)-1-(4-Morpholinophenyl)ethan-1-ol.**<sup>33</sup> Yield: 164 mg, 99%. White solid.  $[\alpha]_{\text{D}}^{22} = +43.9$  ( $c = 1.16$ , CHCl<sub>3</sub>, 99% ee); lit.<sup>33</sup>  $[\alpha]_{\text{D}}^{25} = +45.9$  ( $c = 1.0$ , CHCl<sub>3</sub>, 93% ee). Enantiomeric excess determined by HPLC analysis on a Daicel Chiralpak IC column (0.46 × 25 cm), hexane/*i*-PrOH = 90/10, 1.0 mL/min,  $\lambda = 215$  nm,  $t_{\text{R}} = 24.81$  min (S), 31.01 min (R). MS (DCI/NH<sub>3</sub>):  $m/z = 208$  [M + H]<sup>+</sup>.

**(R)-1-(2-Furyl)ethanol.**<sup>34</sup> Yield: 89 mg, 99%. Colorless oil.  $[\alpha]_{\text{D}}^{25} = +20.0$  ( $c = 0.79$ , CHCl<sub>3</sub>, > 99% ee), lit.<sup>34</sup>  $[\alpha]_{\text{D}}^{25} = +20.7$  ( $c = 1.0$ , CHCl<sub>3</sub>, 99% ee). Enantiomeric excess determined by HPLC analysis on a Daicel Chiralpak IC column (0.46 × 25 cm), hexane/*i*-PrOH = 95/5, 1.0 mL/min,  $\lambda = 215$  nm,  $t_{\text{R}} = 9.17$  min (S), 9.90 min (R). MS (DCI/NH<sub>3</sub>):  $m/z = 95$  [M + H - H<sub>2</sub>O]<sup>+</sup>.

**(R)-1-(2-Thienyl)ethanol.**<sup>35</sup> Yield: 102 mg, 100%. Colorless oil.  $[\alpha]_{\text{D}}^{25} = +23$  ( $c = 0.91$ , CHCl<sub>3</sub>, 99% ee), lit.<sup>35</sup>  $[\alpha]_{\text{D}}^{20} = +21.6$  ( $c = 1.0$ , CHCl<sub>3</sub>, 98% ee). Enantiomeric excess determined by SFC analysis on a Daicel Chiralpak ID column (0.46 × 25 cm), scCO<sub>2</sub>/MeOH = 93/7, 3.0 mL/min,  $P = 150$  bar,  $\lambda = 215$  nm,  $t_{\text{R}} = 2.07$  min (R), 2.35 min (S). MS (DCI/NH<sub>3</sub>):  $m/z = 111$  [M + H - H<sub>2</sub>O]<sup>+</sup>.

**(R)-1-(Benzofuran-2-yl)ethanol.**<sup>36</sup> Yield: 129 mg, 100%. White solid.  $[\alpha]_{\text{D}}^{25} = +18$  ( $c = 0.88$ , CHCl<sub>3</sub>, 97% ee), lit.<sup>36</sup>  $[\alpha]_{\text{D}}^{23} = +18$  ( $c = 3.0$ , CHCl<sub>3</sub>, 96% ee). Enantiomeric excess determined by HPLC analysis on a Daicel Chiralpak ID column (0.46 × 25 cm), hexane/*i*-PrOH = 95/5, 1.0 mL/min,  $\lambda = 215$  nm,  $t_{\text{R}} = 9.48$  min (R), 10.11 min (S). MS (DCI/NH<sub>3</sub>):  $m/z = 145$  [M + H - H<sub>2</sub>O]<sup>+</sup>.

(*R*)-1-(2-Pyridyl)ethanol.<sup>37</sup> Yield: 98 mg, 100%. Pale yellow oil.  $[\alpha]_{\text{D}}^{25} = +21$  ( $c = 0.99$ ,  $\text{CHCl}_3$ , 96% ee), lit.<sup>37</sup>  $[\alpha]_{\text{D}}^{20} = +26.6$  ( $c = 1.0$ ,  $\text{CHCl}_3$ , 97.3% ee). Enantiomeric excess determined by HPLC analysis on a Daicel Chiralpak ID column (0.46 × 25 cm), hexane/*i*-PrOH = 95/5, 1.0 mL/min,  $\lambda = 215$  nm,  $t_{\text{R}} = 15.23$  min (S), 17.10 min (R). MS (DCI/NH<sub>3</sub>):  $m/z = 124$   $[\text{M} + \text{H}]^+$ .

(*R*)-1,2,3,4-Tetrahydro-2-naphthol.<sup>5e</sup> Yield: 119 mg, 100%. Pale yellow oil.  $[\alpha]_{\text{D}}^{25} = +53$  ( $c = 0.88$ ,  $\text{CHCl}_3$ , 81% ee), lit.<sup>5e</sup>  $[\alpha]_{\text{D}}^{23} = +52.7$  ( $c = 0.37$ ,  $\text{CHCl}_3$ , 88% ee). Enantiomeric excess determined by SFC analysis on a Daicel Chiralpak AD-H column (0.46 × 25 cm),  $\text{scCO}_2$ /*i*-PrOH = 90/10, 3.0 mL/min,  $P = 150$  bar,  $\lambda = 215$  nm,  $t_{\text{R}} = 4.76$  min (S), 5.19 min (R). MS (DCI/NH<sub>3</sub>):  $m/z = 166$   $[\text{M} + \text{NH}_4]^+$ .

(*R*)-1-Cyclohexylethanol.<sup>38</sup> Yield: 80 mg, 100%. Colorless oil.  $[\alpha]_{\text{D}}^{25} = +2.1$  ( $c = 3.5$ ,  $\text{CHCl}_3$ , 94% ee), lit.<sup>38</sup>  $[\alpha]_{\text{D}}^{23} = +3.51$  ( $c = 3.1$ ,  $\text{CHCl}_3$ , 95% ee). Enantiomeric excess determined on the benzoate derivative by HPLC analysis on a Daicel Chiralpak ID column (0.46 × 25 cm), hexane/*i*-PrOH = 97/3, 0.5 mL/min,  $\lambda = 215$  nm,  $t_{\text{R}} = 8.87$  min (S), 9.37 min (R). MS (DCI/NH<sub>3</sub>):  $m/z = 146$   $[\text{M} + \text{NH}_4]^+$ .

(*S*)-(4-Nitrophenyl)(phenyl)methanol.<sup>39</sup> Yield: 169 mg, 92%. White solid.  $[\alpha]_{\text{D}}^{22} = +70.0$  ( $c = 1.0$ ,  $\text{CHCl}_3$ , 83% ee); lit.<sup>39</sup>  $[\alpha]_{\text{D}}^{22} = +71.0$  ( $c = 0.27$ ,  $\text{CHCl}_3$ , 92% ee). Enantiomeric excess determined by HPLC analysis on a Daicel Chiralpak IA column (0.46 × 25 cm), hexane/*i*-PrOH = 90/10, 1.0 mL/min,  $\lambda = 254$  nm,  $t_{\text{R}} = 12.17$  min (R), 14.49 min (S). MS (DCI/NH<sub>3</sub>):  $m/z = 247$   $[\text{M} + \text{NH}_4]^+$ .

(*S*)-(4-Chlorophenyl)(phenyl)methanol.<sup>39</sup> Yield: 173 mg, 99%. White solid.  $[\alpha]_{\text{D}}^{22} = +10.9$  ( $c = 2.0$ ,  $\text{CHCl}_3$ , 50% ee); lit.<sup>39</sup>  $[\alpha]_{\text{D}}^{20} = +8.0$  ( $c = 1.51$ ,  $\text{CHCl}_3$ , 48% ee). Enantiomeric excess determined by HPLC analysis on a Daicel Chiralpak IA column (0.46 × 25 cm), hexane/*i*-PrOH = 95/5, 1.0 mL/min,  $\lambda = 254$  nm,  $t_{\text{R}} = 12.92$  min (R), 14.01 min (S). MS (DCI/NH<sub>3</sub>):  $m/z = 201$   $[\text{M} + \text{H} - \text{H}_2\text{O}]^+$ .

(*R*)-(4-Methoxyphenyl)(phenyl)methanol.<sup>39</sup> Yield: 123 mg, 72%. White solid.  $[\alpha]_{\text{D}}^{22} = +2.1$  ( $c = 1.65$ ,  $\text{CHCl}_3$ , 9% ee); lit.<sup>39</sup>  $[\alpha]_{\text{D}}^{20} = +1.5$  ( $c = 1.08$ ,  $\text{CHCl}_3$ , 5% ee). Enantiomeric excess determined by HPLC analysis on a Daicel Chiralpak IA column (0.46 × 25 cm), hexane/*i*-PrOH = 90/10, 0.8 mL/min,  $\lambda = 254$  nm,  $t_{\text{R}} = 13.37$  min (R), 14.37 min (S). MS (DCI/NH<sub>3</sub>):  $m/z = 197$   $[\text{M} + \text{H} - \text{H}_2\text{O}]^+$ .

(*S*)-Phenyl(*o*-tolyl)methanol.<sup>40</sup> Yield: 103 mg, 65%. White solid.  $[\alpha]_{\text{D}}^{22} = +8.2$  ( $c = 2.0$ ,  $\text{CHCl}_3$ , 99% ee); lit.<sup>40</sup>  $[\alpha]_{\text{D}}^{20} = +7.3$  ( $c = 0.735$ ,  $\text{CHCl}_3$ , 98% ee). Enantiomeric excess determined by HPLC analysis on a Daicel Chiralpak IC column (0.46 × 25 cm), hexane/*i*-PrOH = 98/2, 0.6 mL/min,  $\lambda = 254$  nm,  $t_{\text{R}} = 28.8$  min (S), 32.6 min (R). MS (DCI/NH<sub>3</sub>):  $m/z = 181$   $[\text{M} + \text{H} - \text{H}_2\text{O}]^+$ .

(1*R*,4*R*)-1,4-Diphenylbutan-1,4-diol.<sup>41</sup> Yield: 186 mg, 96%. White solid.  $[\alpha]_{\text{D}}^{25} = +51$  ( $c = 1.1$ ,  $\text{CHCl}_3$ , >99% ee), lit.<sup>41</sup>  $[\alpha]_{\text{D}}^{25} = +58$  ( $c = 1.02$ ,  $\text{CHCl}_3$ , 99% ee). Enantiomeric excess determined by SFC analysis on a Daicel Chiralcel OD-H column (0.46 × 25 cm),  $\text{scCO}_2$ /MeOH = 95/5, 4 mL/min,  $P = 150$  bar,  $\lambda = 215$  nm,  $t_{\text{R}} = 22.13$  min (R,R), 25.69 min (meso), 28.08 min (S,S). MS (DCI/NH<sub>3</sub>):  $m/z = 242$   $[\text{M} + \text{H} - \text{H}_2\text{O}]^+$ .

## ■ ASSOCIATED CONTENT

### ● Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00436.

Crystallographic data for **8b** (CIF)

Crystallographic data for **8c** (CIF)

Crystallographic data for **8c** (CIF)

<sup>1</sup>H and <sup>13</sup>C NMR spectra of all compounds, HPLC and SFC chromatograms of the ATH products, and thermal ellipsoid plots for the crystal structures of **8b**–**8d** (PDF)

## ■ AUTHOR INFORMATION

### Corresponding Authors

\*E-mail: phannarath.phansavath@chimie-paristech.fr.

\*E-mail: virginie.vidal@chimie-paristech.fr.

### ORCID

Virginie Ratovelomanana-Vidal: 0000-0003-1167-1195

## Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

This work was supported by the CNRS (Centre National de la Recherche Scientifique) and MENESR (Ministère de l'Éducation Nationale, de l'Enseignement Supérieur et de la Recherche). We gratefully acknowledge the China Scholarship Council for a grant to L.Z. We also thank PCAS for a grant to Q.L. We thank Dr. Céline Fosse for the mass spectrometry analyses and Dr. Lise-Marie Chamoreau for the X-ray analyses.

## ■ REFERENCES

- (a) Bartoszewicz, A.; Ahlsten, N.; Martín-Matute, B. *Chem. - Eur. J.* **2013**, *19*, 7274–7302. (b) Ahn, Y.; Ko, S.-B.; Kim, M.-J.; Park, J. *Coord. Chem. Rev.* **2008**, *252*, 647–658.
- (a) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97–102. (b) Palmer, M. J.; Wills, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2045–2061. (c) Everaere, K.; Mortreux, A.; Carpentier, J.-F. *Adv. Synth. Catal.* **2003**, *345*, 67–77. (d) Gladiali, S.; Alberico, E. *Chem. Soc. Rev.* **2006**, *35*, 226–236. (e) Samec, J. S. M.; Bäckvall, J.-E.; Andersson, P. G.; Brandt, P. *Chem. Soc. Rev.* **2006**, *35*, 237–248. (f) Ikariya, T.; Blacker, A. *J. Acc. Chem. Res.* **2007**, *40*, 1300–1308. (g) Blacker, A. J. In *Handbook of Homogeneous Hydrogenation*; de Vries, J. G., Elsevier, C. J., Eds.; Wiley-VCH: Weinheim, Germany, 2007; pp 1215–1244. (h) Foubelo, F.; Nájera, C.; Yus, M. *Tetrahedron: Asymmetry* **2015**, *26*, 769–790. (i) Wang, D.; Astruc, D. *Chem. Rev.* **2015**, *115*, 6621–6686. (j) Echeverria, P.-G.; Ayad, T.; Phansavath, P.; Ratovelomanana-Vidal, V. *Synthesis* **2016**, *48*, 2523–2539.
- (a) Hashiguchi, S.; Fujii, A.; Takehara, J.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 7562–7563. (b) Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 2521–2522. (c) Haack, K.-J.; Hashiguchi, S.; Fujii, A.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 285–288. (d) Ikariya, T.; Murata, K.; Noyori, R. *Org. Biomol. Chem.* **2006**, *4*, 393–406.
- (a) Mashima, K.; Abe, T.; Tani, K. *Chem. Lett.* **1998**, *27*, 1199–1200. (b) Murata, K.; Ikariya, T.; Noyori, R. *J. Org. Chem.* **1999**, *64*, 2186–2187. (c) Cross, D. J.; Kenny, J. A.; Houson, I.; Campbell, L.; Walsgrove, T.; Wills, M. *Tetrahedron: Asymmetry* **2001**, *12*, 1801–1806. (d) Hamada, T.; Torii, T.; Izawa, K.; Noyori, R.; Ikariya, T. *Org. Lett.* **2002**, *4*, 4373–4376. (e) Hamada, T.; Torii, T.; Onishi, T.; Izawa, K.; Ikariya, T. *J. Org. Chem.* **2004**, *69*, 7391–7394. (f) Wu, X.; Vinci, D.; Ikariya, T.; Xiao, J. *Chem. Commun.* **2005**, 4447–4449.
- (a) Hannedouche, J.; Clarkson, G. J.; Wills, M. *J. Am. Chem. Soc.* **2004**, *126*, 986–987. (b) Hayes, A. M.; Morris, D. J.; Clarkson, G. J.; Wills, M. *J. Am. Chem. Soc.* **2005**, *127*, 7318–7319. (c) Cheung, F. K.; Lin, C.; Minissi, F.; Crivillé, A. L.; Graham, M. A.; Fox, D. J.; Wills, M. *Org. Lett.* **2007**, *9*, 4659–4662. (d) Soni, R.; Cheung, F. K.; Clarkson, G. C.; Martins, J. E. D.; Graham, M. A.; Wills, M. *Org. Biomol. Chem.* **2011**, *9*, 3290–3294. (e) Soni, R.; Collinson, J.-M.; Clarkson, G. C.; Wills, M. *Org. Lett.* **2011**, *13*, 4304–4307. (f) Soni, R.; Jolley, K. E.; Clarkson, G. J.; Wills, M. *Org. Lett.* **2013**, *15*, 5110–5113. (g) Nedden, H. G.; Zanotti-Gerosa, A.; Wills, M. *Chem. Rec.* **2016**, *16*, 2623–2643.
- (a) Matharu, D. S.; Morris, D. J.; Clarkson, G. J.; Wills, M. *Chem. Commun.* **2006**, 3232–3234.
- (a) Matharu, D. S.; Martins, J. E. D.; Wills, M. *Chem. - Asian J.* **2008**, *3*, 1374–1383.
- (a) Matharu, D. S.; Morris, D. J.; Kawamoto, A. M.; Clarkson, G. J.; Wills, M. *Org. Lett.* **2005**, *7*, 5489–5491.
- (a) Wu, Z.; Ayad, T.; Ratovelomanana-Vidal, V. *Org. Lett.* **2011**, *13*, 3782–3785. (b) Berhal, F.; Wu, Z.; Zhang, Z.; Ayad, T.; Ratovelomanana-Vidal, V. *Org. Lett.* **2012**, *14*, 3308–3311. (c) Cartigny, D.; Berhal, F.; Nagano, T.; Phansavath, P.; Ayad, T.; Genêt, J.-P.; Ohshima, T.; Mashima, K.; Ratovelomanana-Vidal, V. *J. Org. Chem.* **2012**, *77*, 4544–4556. (d) Wu, Z.; Perez, M.; Scalone, M.; Ayad, T.; Ratovelomanana-Vidal, V. *Angew. Chem., Int. Ed.* **2013**, *52*, 4925–4928. (e) Echeverria, P.-G.; Cornil, J.; Féraud, C.; Guérinot, A.; Cossy, J.; Phansavath, P.; Ratovelomanana-Vidal, V. *RSC Adv.* **2015**, *5*, 56815–56819.

- (f) Monnereau, L.; Cartigny, D.; Scalone, M.; Ayad, T.; Ratovelomanana-Vidal, V. *Chem. - Eur. J.* **2015**, *21*, 11799–11806. (g) Ayad, T.; Phansavath, P.; Ratovelomanana-Vidal, V. *Chem. Rec.* **2016**, *16*, 2750–2767.
- (10) Echeverria, P.-G.; Férard, C.; Phansavath, P.; Ratovelomanana-Vidal, V. *Catal. Commun.* **2015**, *62*, 95–99.
- (11) Llopis, Q.; Férard, C.; Guillaumot, G.; Phansavath, P.; Ratovelomanana-Vidal, V. *Synthesis* **2016**, *48*, 3357–3363.
- (12) CCDC-1517930, CCDC-1517928, and CCDC-1517929 contain the supplementary crystallographic data for complexes (R,R)-**8b**, (R,R)-**8c**, and (R,R)-**8d**, respectively. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).
- (13) Soni, R.; Hall, T. H.; Mitchell, B. P.; Owen, M. R.; Wills, M. *J. Org. Chem.* **2015**, *80*, 6784–6793.
- (14) Touge, T.; Nara, H.; Fujiwhara, M.; Kayaki, Y.; Ikariya, T. *J. Am. Chem. Soc.* **2016**, *138*, 10084–10087.
- (15) Halland, N.; Braunton, A.; Bachmann, S.; Marigo, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 4790–4791.
- (16) Porcs-Makkay, M.; Lukács, G.; Pandur, A.; Simig, G.; Volk, B. *Tetrahedron* **2014**, *70*, 286–293.
- (17) Bunce, R. A.; Harrison, T.; Nammalwar, B. *Heterocycl. Commun.* **2012**, *18*, 123–126.
- (18) Dell'Acqua, M.; Pirovano, V.; Confalonieri, G.; Arcadi, A.; Rossi, E.; Abbiati, G. *Org. Biomol. Chem.* **2014**, *12*, 8019–8030.
- (19) Pilgrim, B. S.; Gatland, A. E.; McTernan, C. T.; Procopiu, P. A.; Donohoe, T. *J. Org. Lett.* **2013**, *15*, 6190–6193.
- (20) Liu, W.-P.; Yuan, M.-L.; Yang, X.-H.; Li, K.; Xie, J.-H.; Zhou, Q.-L. *Chem. Commun.* **2015**, *51*, 6123–6125.
- (21) Rowan, A. S.; Moody, T. S.; Howard, R. M.; Underwood, T. J.; Miskelly, I. R.; He, Y.; Wang, B. *Tetrahedron: Asymmetry* **2013**, *24*, 1369–1381.
- (22) Guo, J.; Chen, J.; Lu, Z. *Chem. Commun.* **2015**, *51*, 5725–5727.
- (23) Krane Thvedt, T. H.; Kristensen, T. E.; Sundby, E.; Hansen, T.; Hoff, B. H. *Tetrahedron: Asymmetry* **2011**, *22*, 2172–2178.
- (24) Kamal, A.; Sandbhor, M.; Ramana, K. V. *Tetrahedron: Asymmetry* **2002**, *13*, 815–820.
- (25) Wettergren, J.; Bøgevig, A.; Portier, M.; Adolffson, H. *Adv. Synth. Catal.* **2006**, *348*, 1277–1282.
- (26) Martins, J. E. D.; Contreras Redondo, M. A.; Wills, M. *Tetrahedron: Asymmetry* **2010**, *21*, 2258–2264.
- (27) Li, J.; Li, X.; Ma, Y.; Wu, J.; Wang, F.; Xiang, J.; Zhu, J.; Wang, Q.; Deng, J. *RSC Adv.* **2013**, *3*, 1825–1834.
- (28) Cheng, Y.-N.; Wu, H.-L.; Wu, P.-Y.; Shen, Y.-Y.; Uang, B.-J. *Chem. - Asian J.* **2012**, *7*, 2921–2924.
- (29) Ohkuma, T.; Hattori, T.; Ooka, H.; Inoue, T.; Noyori, R. *Org. Lett.* **2004**, *6*, 2681–2683.
- (30) Merabet-Khelassi, M.; Houiene, Z.; Aribi-Zouiouche, L.; Riant, O. *Tetrahedron: Asymmetry* **2012**, *23*, 828–833.
- (31) Brown, M. K.; Blewett, M. M.; Colombe, J. R.; Corey, E. J. *J. Am. Chem. Soc.* **2010**, *132*, 11165–11170.
- (32) Kišić, A.; Stephan, M.; Mohar, B. *Adv. Synth. Catal.* **2015**, *357*, 2540–2546.
- (33) Inagaki, T.; Phong, L. T.; Furuta, A.; Ito, J.; Nishiyama, H. *Chem. - Eur. J.* **2010**, *16*, 3090–3096.
- (34) Hara, P.; Turcu, M.-C.; Sundell, R.; Toşa, M.; Paizs, C.; Irimie, F.-D.; Kanerva, L. T. *Tetrahedron: Asymmetry* **2013**, *24*, 142–150.
- (35) Tian, C.; Gong, L.; Meggers, E. *Chem. Commun.* **2016**, *52*, 4207–4210.
- (36) Stepanenko, V.; De Jesús, M.; Correa, W.; Bermúdez, L.; Vázquez, C.; Guzmán, I.; Ortiz-Marciales, M. *Tetrahedron: Asymmetry* **2009**, *20*, 2659–2665.
- (37) Bigler, R.; Mezzetti, A. *Org. Process Res. Dev.* **2016**, *20*, 253–261.
- (38) Li, G.; Kabalka, G. W. *J. Organomet. Chem.* **1999**, *581*, 66–69.
- (39) Yamamoto, Y.; Kurihara, K.; Miyaura, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 4414–4416.
- (40) Touge, T.; Nara, H.; Fujiwhara, M.; Kayaki, Y.; Ikariya, T. *J. Am. Chem. Soc.* **2016**, *138*, 10084–10087.
- (41) Aldous, D. J.; Dutton, W. M.; Steel, P. G. *Tetrahedron: Asymmetry* **2000**, *11*, 2455–2462.





Cite this: *Chem. Commun.*, 2018, 54, 283

Received 25th October 2017,  
Accepted 7th December 2017

DOI: 10.1039/c7cc08231b

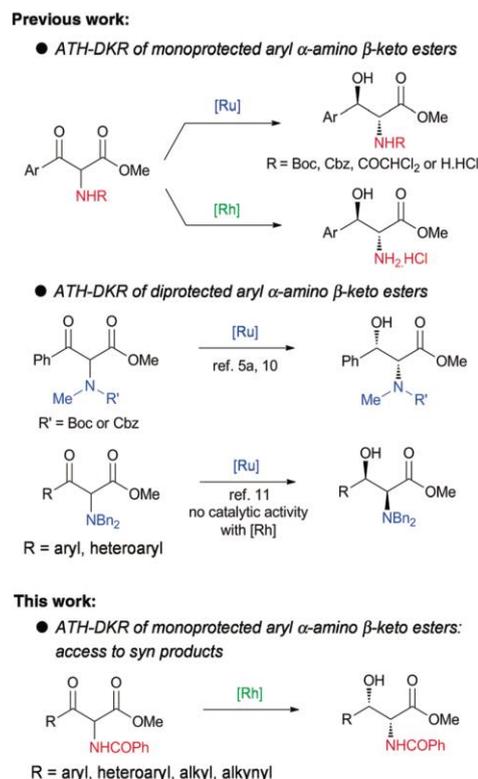
rsc.li/chemcomm

# Rhodium-mediated asymmetric transfer hydrogenation: a diastereo- and enantioselective synthesis of *syn*- $\alpha$ -amido $\beta$ -hydroxy esters†

Long-Sheng Zheng, Charlène Férard, Phannarath Phansavath\* and Virginie Ratovelomanana-Vidal \*

The preparation of *syn*  $\alpha$ -benzoylamido  $\beta$ -hydroxy esters through asymmetric transfer hydrogenation (ATH) with a tethered Rh(III)–DPEN complex *via* dynamic kinetic resolution (DKR) has been developed for the first time starting from  $\alpha$ -benzoylamido  $\beta$ -keto esters. A variety of  $\alpha$ -benzoylamido  $\beta$ -keto esters were converted under mild conditions into the corresponding *syn*  $\alpha$ -benzoylamino  $\beta$ -hydroxy esters with high yields (up to 98%) and diastereomeric ratios (up to >99:1 dr) as well as excellent enantioselectivities (up to >99% ee).

Because enantiomerically pure  $\beta$ -amino alcohols bearing two contiguous stereocenters are valuable building blocks in natural products and pharmaceuticals, and because they can be used as ligands in asymmetric catalysis, an efficient synthesis of these scaffolds is highly desirable. A straightforward and atom-economical access to such compounds involves the dynamic kinetic resolution (DKR) of racemic  $\alpha$ -amino  $\beta$ -keto ester derivatives that can be performed through either asymmetric hydrogenation (AH) or asymmetric transfer hydrogenation (ATH), to obtain the *syn* or *anti* reduced products.<sup>1</sup> However, although the DKR of  $\alpha$ -amido  $\beta$ -keto esters through asymmetric hydrogenation is now well established, the asymmetric transfer hydrogenation of these compounds is much less documented. Previous work in this field only focused on  $\beta$ -keto esters that were substituted with carbamate, 2,2-dichloro *N*-acetamido or amino hydrochloride functional groups in the  $\alpha$ -position to access the *anti* amino alcohol derivatives using either ruthenium<sup>2–8</sup> or rhodium<sup>9</sup> complexes (Scheme 1, previous work). On the other hand, scarce examples of the production of the *syn* compounds through Ru-catalyzed ATH have been described so far for *N*-diprotected compounds.<sup>5a,10,11</sup> We have previously observed this reversal of diastereoselectivity from *anti* to *syn* in the Ru<sup>7</sup> or



Scheme 1 ATH of  $\alpha$ -amino  $\beta$ -keto ester derivatives.

Rh-mediated<sup>9</sup> ATH of  $\alpha$ -amino  $\beta$ -keto ester hydrochlorides, bearing thienyl or furyl substituents on the ketone functional group. These results clearly indicate that the stereochemical outcome of the ATH of these  $\alpha$ -amino  $\beta$ -keto ester derivatives is highly dependent on the nature of the amino group as well as on the ketone substituent. As part of an ongoing program aimed at developing efficient methods for the asymmetric reduction of functionalized ketones,<sup>12</sup> we report herein an unprecedented *syn* diastereoselectivity obtained in the Rh-catalyzed DKR/ATH of *N*-monoprotected  $\alpha$ -amino  $\beta$ -keto esters, in this case,  $\alpha$ -benzoylamino  $\beta$ -keto esters (Scheme 1, this work). The novelty of this study resides in the use of a rhodium complex for the ATH-DKR

PSL Research University, Chimie ParisTech – CNRS, Institut de Recherche de Chimie Paris, 75005 Paris, France. E-mail: phannarath.phansavath@chimie-paristech.fr, virginie.vidal@chimie-paristech.fr

† Electronic supplementary information (ESI) available. CCDC 1581420–1581422. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c7cc08231b

of *N*-monoprotected  $\alpha$ -amino  $\beta$ -keto esters to access the corresponding *syn* products, as opposed to the work described by Wang and coworkers,<sup>11</sup> which involved the Ru-catalyzed ATH of *N*-diprotected compounds and for which rhodium and iridium complexes were inefficient.

We started our study with the racemic methyl 2-benzoyl-amino-3-oxo-3-phenylpropanoate **1a** as the standard substrate (Table 1). The initial asymmetric transfer hydrogenation experiments were carried out in CH<sub>2</sub>Cl<sub>2</sub> at 30 °C using ruthenium complexes (*R,R*)-**A**, (*S,S*)-**B** and (*R,R*)-**C** in the presence of a 5 : 2 HCO<sub>2</sub>H/Et<sub>3</sub>N azeotropic mixture as the hydrogen source, and afforded the corresponding *anti* amino alcohol derivatives as the major isomers albeit with low enantiomeric excesses (Table 1, entries 1–3). The sense of diastereoselectivity observed here was in agreement with the results reported previously for the ruthenium-catalyzed ATH of the parent  $\alpha$ -*N*-Boc or  $\alpha$ -*N*-Cbz  $\beta$ -keto ester compounds. To our surprise however, we found that with the tethered rhodium complex (*R,R*)-**D**,<sup>13,14</sup> the reaction proceeded smoothly within 5 h to deliver the reduced *syn* product (*R,S*)-**2a** in 90% yield with a good 86 : 14 dr and an excellent enantiomeric excess of >99% for the *syn* isomer (Table 1, entry 4). The absolute configuration of the reduced product **2a** was assigned as (2*R*,3*S*) by converting the diastereomerically pure *syn* **2a** into the known (1*S*,2*S*)-2-benzoylamino-1-phenyl-propane-1,3-diol and comparing the optical rotation value with the reported data ( $[\alpha]_{\text{D}}^{20} = +80.1$  (*c* 1.0, EtOH), lit.:<sup>15</sup>  $[\alpha]_{\text{D}} +94.6$  (*c* 1.0, EtOH)).<sup>16</sup> To our knowledge, this reversal of

diastereoselectivity from *anti* to *syn* provided by the use of a Rh complex has never been reported to date for the ATH of *N*-monoprotected  $\alpha$ -amino  $\beta$ -keto esters. The use of other solvents under otherwise identical conditions afforded similar results in terms of yields and stereoselectivities although the reaction time was longer in THF and *i*-PrOH (Table 1, entries 5–7). The neat reaction also led to an 86 : 14 dr and >99% ee (Table 1, entry 8). The stereochemical outcome of the transfer hydrogenation reaction was not altered by switching from (*R,R*)-**D** to (*R,R*)-**E**, (*R,R*)-**F** or (*R,R*)-**G**<sup>17</sup> bearing respectively, methyl, trifluoromethyl or fluoro groups on the aryl ring, even though the reactions required more time (Table 1, entries 9–11). Accordingly, we selected complex (*R,R*)-**D** as the pre-catalyst and CH<sub>2</sub>Cl<sub>2</sub> as the solvent for further studies (Table 2).

Performing the reaction at 30 °C with a catalyst loading of 0.1 mol% instead of 0.5 mol% resulted only in an extended reaction time without any noticeable effect on either the yield or stereoselectivity (Table 2, entries 1 and 2), whereas using a 1 : 1 HCO<sub>2</sub>H/Et<sub>3</sub>N azeotropic mixture rather than the 5 : 2 system led to incomplete conversion after 24 h of reaction (Table 2, entry 3). The temperature effect was then investigated, and the reaction was run at 18 °C, affording a slightly higher diastereomeric ratio of 89 : 11 (Table 2, entry 4). A satisfying 92 : 8 dr was attained at a temperature of 0 °C after either 47 h (Table 2, entry 5) or 94 h with a catalyst loading of 0.2 mol% (Table 2, entry 6). Finally, maintaining a 0.5 mol% catalyst loading, a variation of the initial concentration of  $\alpha$ -amido  $\beta$ -keto ester from 0.2 to 0.4 and 0.5 M showed a decrease of the reaction time from 47 h to 34 h and 28 h, respectively (Table 2, entries 5, 7 and 8). Accordingly, the optimized reaction conditions were set as follows: 0.5 mol% of (*R,R*)-**D**, a 5 : 2 HCO<sub>2</sub>H/Et<sub>3</sub>N azeotropic mixture as the hydrogen source, CH<sub>2</sub>Cl<sub>2</sub> as the solvent (0.5 M), and a reaction temperature of 0 °C. With these conditions in hand, we next investigated the scope of the reaction and a series of variously substituted  $\alpha$ -benzoylamino  $\beta$ -keto esters were subjected to the ATH.

Table 1 Catalyst and solvent screening<sup>a</sup>

| Entry           | Catalyst | Solvent                                      | Time (h) | Yield (%) | dr ( <i>syn/anti</i> ) <sup>b</sup> | ee <sub>syn</sub> <sup>c</sup> (%) |
|-----------------|----------|--|----------|-----------|-------------------------------------|------------------------------------|
| 1               | <b>A</b> | CH <sub>2</sub> Cl <sub>2</sub>              | 96       | 96        | 15 : 85                             | 28 <sup>d</sup>                    |
| 2               | <b>B</b> | CH <sub>2</sub> Cl <sub>2</sub> <sup>e</sup> | 7        | 95        | 10 : 90                             | 36 <sup>d</sup>                    |
| 3               | <b>C</b> | CH <sub>2</sub> Cl <sub>2</sub> <sup>e</sup> | 9        | 94        | 8 : 92                              | 25 <sup>d</sup>                    |
| 4               | <b>D</b> | CH <sub>2</sub> Cl <sub>2</sub>              | 5        | 90        | 86 : 14                             | >99                                |
| 5               | <b>D</b> | CH <sub>3</sub> CN                           | 4.5      | 86        | 87 : 13                             | >99                                |
| 6               | <b>D</b> | THF  | 23       | 89        | 87 : 13                             | >99                                |
| 7               | <b>D</b> | <i>i</i> -PrOH                               | 28       | 88        | 83 : 17                             | >99                                |
| 8 <sup>f</sup>  | <b>D</b> | —  | 4        | 87        | 86 : 14                             | >99                                |
| 9               | <b>E</b> | CH <sub>2</sub> Cl <sub>2</sub>              | 7        | 89        | 86 : 14                             | >99                                |
| 10              | <b>F</b> | CH <sub>2</sub> Cl <sub>2</sub>              | 7        | 88        | 86 : 14                             | >99                                |
| 11 <sup>f</sup> | <b>G</b> | —  | 20       | 93        | 84 : 16                             | >99                                |

<sup>a</sup> Conditions: 0.8 mmol of **1a**, 0.5 mol% of precatalyst, 134  $\mu$ L of HCO<sub>2</sub>H/Et<sub>3</sub>N (5 : 2) in 4 mL of solvent at 30 °C. Complete conversions in all cases. <sup>b</sup> Determined by <sup>1</sup>H NMR of the crude product. <sup>c</sup> Determined by SFC analysis. <sup>d</sup> ee of the *anti* compound. <sup>e</sup> 1.6 mL of solvent was used. <sup>f</sup> Neat reaction.

Table 2 Catalyst loading and temperature screening<sup>a</sup>

| Entry          | Catalyst (mol%) | <i>c</i> <sup>b</sup> | Temp. (°C) | Time (h) | Yield (%)       | dr ( <i>syn/anti</i> ) <sup>c</sup> | ee <sub>syn</sub> <sup>d</sup> (%) |
|----------------|-----------------|-----------------------|------------|----------|-----------------|-------------------------------------|------------------------------------|
| 1              | 0.5             | 0.2                   | 30         | 5        | 90              | 86 : 14                             | >99                                |
| 2              | 0.1             | 0.2                   | 30         | 23       | 91              | 86 : 14                             | >99                                |
| 3 <sup>e</sup> | 0.5             | 0.2                   | 30         | 24       | 61 <sup>f</sup> | 86 : 14                             | >99                                |
| 4              | 0.5             | 0.2                   | 18         | 22       | 87              | 89 : 11                             | >99                                |
| 5              | 0.5             | 0.2                   | 0          | 47       | 93              | 92 : 8                              | >99                                |
| 6              | 0.2             | 0.2                   | 0          | 94       | 73              | 92 : 8                              | >99                                |
| 7              | 0.5             | 0.4                   | 0          | 34       | 94              | 92 : 8                              | >99                                |
| 8              | 0.5             | 0.5                   | 0          | 28       | 93              | 92 : 8                              | >99                                |

<sup>a</sup> Conditions: 0.8 mmol of **1a**, respective mol% of (*R,R*)-**D**, 134  $\mu$ L of HCO<sub>2</sub>H/Et<sub>3</sub>N (5 : 2) in 1.6–4.0 mL of CH<sub>2</sub>Cl<sub>2</sub>. Complete conversions except where indicated. <sup>b</sup> Initial concentration of  $\alpha$ -amido  $\beta$ -keto ester. <sup>c</sup> Determined by <sup>1</sup>H NMR of the crude product. <sup>d</sup> Determined by SFC analysis. <sup>e</sup> 1 : 1 mixture of HCO<sub>2</sub>H/Et<sub>3</sub>N used. <sup>f</sup> 64% conversion obtained under these conditions.

Table 3 Substrate scope<sup>a</sup>

| Entry | ATH product 2 | Time (h) | Yield (%) | dr (syn/anti) <sup>b</sup> | ee <sub>syn</sub> <sup>c</sup> (%) |
|-------|---------------|----------|-----------|----------------------------|------------------------------------|
| 1     |               | 28       | 93        | 92:8                       | >99                                |
| 2     |               | 48       | 98        | 93:7                       | >99                                |
| 3     |               | 70       | 96        | 93:7                       | >99                                |
| 4     |               | 48       | 96        | 94:6                       | >99                                |
| 5     |               | 64       | 96        | 92:8                       | >99                                |
| 6     |               | 45       | 86        | 91:9                       | >99                                |
| 7     |               | 23       | 98        | 92:8                       | >99                                |
| 8     |               | 23       | 95        | 93:7                       | >99                                |
| 9     |               | 25       | 98        | 94:6                       | >99                                |
| 10    |               | 72       | 70        | 13:87                      | >99 52 <sub>anti</sub>             |
| 11    |               | 22       | 96        | 97:3                       | >99                                |
| 12    |               | 42       | 63        | 87:13                      | 96                                 |

Table 3 (continued)

| Entry           | ATH product 2 | Time (h)       | Yield (%) | dr (syn/anti) <sup>b</sup> | ee <sub>syn</sub> <sup>c</sup> (%) |
|-----------------|---------------|----------------|-----------|----------------------------|------------------------------------|
| 13              |               | 15             | 93        | 98:2                       | >99                                |
| 14              |               | 24             | 96        | >99:1                      | 99                                 |
| 15              |               | 34             | 98        | >99:1                      | >99                                |
| 16              |               | 1 <sup>d</sup> | 96        | >99:1                      | >99                                |
| 17              |               | 46             | 97        | 80:20                      | >99                                |
| 18              |               | 24             | 98        | 75:25                      | >99                                |
| 19              |               | 240            | 72        | 2:98                       | >99                                |
| 20 <sup>d</sup> |               | 92             | 74        | 3:97                       | 99                                 |
| 21              |               | 240            | 86        | >99:1                      | >99                                |
| 22 <sup>d</sup> |               | 24             | 80        | >99:1                      | >99                                |
|                 |               |                |           |                            |                                    |
|                 |               |                |           |                            |                                    |
|                 |               |                |           |                            |                                    |

<sup>a</sup> Conditions: 0.8 mmol of **1**, 0.5 mol% of (*R,R*)-**D**, 134 μL of HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) in 1.6 mL of CH<sub>2</sub>Cl<sub>2</sub> at 0 °C. Complete conversions except for compounds **1j** and **1r** for which 73–82% conv. were obtained. <sup>b</sup> Determined by <sup>1</sup>H NMR of the crude product. <sup>c</sup> Determined by SFC or HPLC analysis. <sup>d</sup> Reaction carried out at 30 °C.

Compounds bearing substituted phenyl groups on the ketone functional group generally gave the corresponding reduced *syn* products in high yields with high diastereoselections and excellent enantioselectivities irrespective of the electron-donating or electron-withdrawing character of the substituents (Table 3, entries 1–9). An exception to this trend was observed for **1j** having a sterically hindered *ortho*-tolyl substituent on the ketone, which delivered in moderate yield the *anti* compound as the

major isomer (*syn/anti* 13 : 87) albeit with a low enantiomeric excess (52% ee), whereas the *syn* isomer was produced in >99% ee (Table 3, entry 10). On the other hand, heteroaryl ketones afforded excellent levels of diastereo- and enantioinductions and the reduced compounds were obtained in very good yields with the exception of compound **1l**, which produced **2l** in 87 : 13 dr and 96% ee (Table 3, entries 11–15). Furthermore, for the amido ester **1o** bearing a thienyl substituent on the ketone, no temperature effect was observed because the reaction could be carried out at 30 °C within only 1 h without any alteration of the dr or ee (Table 3, entries 15 and 16). In addition, the reduction of **1o** was efficiently performed on gram-scale demonstrating the usefulness of this method. The substrate scope was then expanded to  $\alpha$ -amido  $\beta$ -keto esters containing an alkyl ketone. For these compounds, the reduced *syn* products were obtained with lower diastereomeric ratios while the ee remained >99% (Table 3, entries 17 and 18). As for the sterically demanding substrate **1j**, a reversal of diastereoselectivity was observed as well, with the amido ester **1r** having an isopropyl substituent on the ketone. This time the *anti* isomer was formed with a very high level of diastereo- and enantioinductions albeit after a prolonged reaction time of 10 days (Table 3, entry 19), which could be reduced to 92 h by working at 30 °C with no loss of stereoselectivity (Table 3, entry 20). Finally, the Rh-catalyzed ATH of substrate **1s** having an alkyne residue proceeded with near-perfect diastereo- and enantioselectivities in either 10 days at 0 °C (Table 3, entry 21) or in only 24 h at 30 °C (Table 3, entry 22).

In summary, the rhodium-catalyzed asymmetric transfer hydrogenation of  $\alpha$ -amido  $\beta$ -keto esters *via* DKR appears to be an efficient tool for the synthesis of *syn*  $\alpha$ -benzoylamido  $\beta$ -hydroxy esters, which until now were not directly attainable through ATH. The reaction proceeded under mild conditions using a low catalyst loading with tolerance for a diverse set of functional groups, delivering the reduced compounds in good yields, high diastereomeric ratios, and excellent enantioselectivities for a wide range of substrates. Furthermore, the usefulness of this method was demonstrated by the efficient gram-scale reduction of **1o**.

This work was supported by the Ministère de l'Éducation Nationale, de l'Enseignement Supérieur et de la Recherche (MENESR) and the Centre National de la Recherche Scientifique (CNRS). We gratefully acknowledge the China Scholarship Council (CSC) for a grant to L.-S. Z. We would like to thank L.-M. Chamoreau and G. Gontard for the X-ray analysis. This manuscript is dedicated to Prof. Miguel Yus on the occasion of his 70th birthday.

## Conflicts of interest

There are no conflicts to declare.

## Notes and references

- For selected reviews on DKR through AH/ATH, see: (a) R. Noyori, M. Tokunaga and M. Kitamura, *Bull. Chem. Soc. Jpn.*, 1995, **68**, 36; (b) S. Caddick and K. Jenkins, *Chem. Soc. Rev.*, 1996, **25**, 447;

- (c) R. S. Ward, *Tetrahedron: Asymmetry*, 1995, **6**, 1475;
- (d) V. Ratovelomanana-Vidal and J.-P. Genêt, *Can. J. Chem.*, 2000, **78**, 846; (e) F. F. Huerta, A. B. E. Minidis and J.-E. Bäckvall, *Chem. Soc. Rev.*, 2001, **30**, 321; (f) O. Pàmies and J.-E. Bäckvall, *Chem. Rev.*, 2003, **103**, 3247; (g) H. Pellissier, *Tetrahedron*, 2003, **59**, 8291; (h) H. Pellissier, *Tetrahedron*, 2008, **64**, 1563; (i) H. Pellissier, *Tetrahedron*, 2011, **67**, 3769; (j) Y. Hamada, *Chem. Rec.*, 2014, **14**, 235; (k) F. Foubelo, C. Nájera and M. Yus, *Tetrahedron: Asymmetry*, 2015, **26**, 769; (l) P.-G. Echeverria, T. Ayad, P. Phansavath and V. Ratovelomanana-Vidal, *Synthesis*, 2016, 2523.
- M. Perez, P.-G. Echeverria, E. Martínez-Arripe, M. Ez Zoubir, R. Touati, Z. Zhang, J.-P. Genêt, P. Phansavath, T. Ayad and V. Ratovelomanana-Vidal, *Eur. J. Org. Chem.*, 2015, 5949.
- X. Wang, L. Xu, L. Yan, H. Wang, S. Han, Y. Wu and F. Chen, *Tetrahedron*, 2016, **72**, 1787.
- L. H. Bourdon, D. J. Fairfax, G. S. Martin, C. J. Mathison and P. Zhichkin, *Tetrahedron: Asymmetry*, 2004, **15**, 3485.
- (a) B. Seashore-Ludlow, P. Villo, C. Häcker and P. Somfai, *Org. Lett.*, 2010, **12**, 5274; (b) B. Seashore-Ludlow, F. Saint-Dizier and P. Somfai, *Org. Lett.*, 2012, **14**, 6334; (c) B. Seashore-Ludlow, P. Villo and P. Somfai, *Chem. – Eur. J.*, 2012, **18**, 7219.
- Z. Liu, C. S. Shultz, C. A. Sherwood, S. Krska, P. G. Dormer, R. Desmond, C. Lee, E. C. Sherer, J. Shpungin, J. Cuff and F. Xu, *Tetrahedron Lett.*, 2011, **52**, 1685.
- P.-G. Echeverria, J. Cornil, C. Féraud, A. Guérinot, J. Cossy, P. Phansavath and V. Ratovelomanana-Vidal, *RSC Adv.*, 2015, **5**, 56815.
- X. Wang, L. Xu, F. Xiong, Y. Wu and F. Chen, *RSC Adv.*, 2016, **6**, 37701.
- Q. Llopis, C. Féraud, G. Guillaumot, P. Phansavath and V. Ratovelomanana-Vidal, *Synthesis*, 2016, 3357.
- B. Mohar, A. Valleix, J. Desmurs, M. Felemez and C. Mioskowski, *Chem. Commun.*, 2001, 2572.
- G. Sun, Z. Zhou, Z. Luo, H. Wang, L. Chen, Y. Xu, S. Li, W. Jian, J. Zeng, B. Hu, X. Han, Y. Lin and Z. Wang, *Org. Lett.*, 2017, **19**, 4339.
- (a) Z. Wu, T. Ayad and V. Ratovelomanana-Vidal, *Org. Lett.*, 2011, **13**, 3782; (b) F. Berhal, Z. Wu, Z. Zhang, T. Ayad and V. Ratovelomanana-Vidal, *Org. Lett.*, 2012, **14**, 3308; (c) D. Cartigny, F. Berhal, T. Nagano, P. Phansavath, T. Ayad, J.-P. Genêt, T. Ohshima, K. Mashima and V. Ratovelomanana-Vidal, *J. Org. Chem.*, 2012, **77**, 4544; (d) Z. Wu, M. Perez, M. Scalone, T. Ayad and V. Ratovelomanana-Vidal, *Angew. Chem., Int. Ed.*, 2013, **52**, 4925; (e) L. Monnereau, D. Cartigny, M. Scalone, T. Ayad and V. Ratovelomanana-Vidal, *Chem. – Eur. J.*, 2015, **21**, 11799; (f) T. Ayad, P. Phansavath and V. Ratovelomanana-Vidal, *Chem. Rec.*, 2016, **16**, 2750.
- (a) P.-G. Echeverria, C. Féraud, P. Phansavath and V. Ratovelomanana-Vidal, *Catal. Commun.*, 2015, **62**, 95; (b) D. S. Matharu, D. J. Morris, A. M. Kawamoto, G. J. Clarkson and M. Wills, *Org. Lett.*, 2005, **7**, 5489; (c) D. S. Matharu, J. E. D. Martins and M. Wills, *Chem. – Asian J.*, 2008, **3**, 1374; (d) J. Dimroth, U. Schedler, J. Keilitz, R. Haag and R. Schomäcker, *Adv. Synth. Catal.*, 2011, **353**, 1335; (e) J. Dimroth, J. Keilitz, U. Schedler, R. Schomäcker and R. Haag, *Adv. Synth. Catal.*, 2010, **352**, 2497.
- The Rh-catalyzed ATH of the corresponding *N*-dibenzyl compound, using 10 mol% of complex (*R,R*)-**D**, resulted in no conversion, even at 40 °C. This result confirmed what Wang and co-workers observed with Cp\*RhTfDPEN in ref. 11.
- X.-M. Zhang, H.-L. Zhang, W.-Q. Lin, L.-Z. Gong, A.-Q. Mi, X. Cui, Y.-Z. Jiang and K.-B. Yu, *J. Org. Chem.*, 2003, **68**, 4322.
- The absolute configuration of **2a** was further confirmed by comparison with authentic samples of compounds (*2R,3S*)-**2a** and (*2S,3R*)-**2a** (prepared by ruthenium-catalyzed AH of *rac*-**1a** with  $[\{\text{RuCl}(\text{R-SYNPHOS})\}_2(\mu\text{-Cl})_3]^- [\text{Me}_2\text{NH}_2]^+$  and  $[\{\text{RuCl}(\text{S-SYNPHOS})\}_2(\mu\text{-Cl})_3]^- [\text{Me}_2\text{NH}_2]^+$ , respectively) using HPLC analysis. The absolute configurations of **2e** and **2g** were assigned by using the same method.
- L.-S. Zheng, Q. Llopis, P.-G. Echeverria, C. Féraud, G. Guillaumot, P. Phansavath and V. Ratovelomanana-Vidal, *J. Org. Chem.*, 2017, **82**, 5607.

## RESEARCH ARTICLE

View Article Online

View Journal | View Issue



Cite this: *Org. Chem. Front.*, 2018, 5, 1366

Received 21st December 2017

Accepted 27th February 2018

DOI: 10.1039/c7qo01142c

rsc.li/frontiers-organic

# Ruthenium-catalyzed dynamic kinetic asymmetric transfer hydrogenation: stereoselective access to *syn* 2-(1,2,3,4-tetrahydro-1-isoquinolyl)ethanol derivatives†

Long-Sheng Zheng, Phannarath Phansavath\* and Virginie Ratovelomanana-Vidal \*

An efficient, stereoselective route to 2-(1,2,3,4-tetrahydro-1-isoquinolyl)ethanol derivatives through an asymmetric transfer hydrogenation of ring-substituted  $\beta$ -amino ketones via dynamic kinetic resolution has been developed. The reaction proceeded under mild conditions in the presence of RuCl<sub>2</sub>[(*S,S*)-TsDPEN](benzene) and HCO<sub>2</sub>H/Et<sub>3</sub>N (5 : 2) as the hydrogen source, delivering in good yields a variety of *syn* 2-(1,2,3,4-tetrahydro-1-isoquinolyl)ethanol derivatives with excellent enantioselectivities (up to 99% ee) and diastereomeric ratios up to 71 : 29 dr.

Although the asymmetric transfer hydrogenation (ATH) of prochiral ketones<sup>1</sup> appears as an ideal protocol to access biologically relevant enantiopure alcohols, the asymmetric reduction of racemic  $\alpha$ - or  $\beta$ -substituted ketones through a dynamic kinetic resolution (DKR)<sup>2</sup> process stands as an efficient method to set multiple stereocenters in a single step. In this field, a transition metal-catalyzed ATH-DKR of  $\alpha$ -substituted ketones has been extensively reported. On the other hand, examples involving  $\beta$ -substituted ketones are scarce and usually require racemization of the  $\beta$ -stereocenter through elimination-induced epimerization by either an intra- or intermolecular conjugate elimination/conjugate addition pathway (Fig. 1a). Liu and co-workers previously described the ruthenium-mediated ATH-DKR of phthalide derivatives to access 3-(2-hydroxy-2-arylethyl)isobenzofuran-1(3*H*)-ones.<sup>3</sup> Ashley and Sherer then reported the ATH-DKR of  $\beta$ -substituted chromanones to produce valuable chromanols.<sup>4</sup> Finally, Liu and Wang developed the ATH-DKR of racemic  $\alpha$ -aryl- $\gamma$ -keto malononitriles to synthesize enantioenriched 3,4-dihydro-2*H*-pyran-carbonitriles through the spontaneous cyclization of the reduced products.<sup>5</sup> However, to the best of our knowledge, there is no report on the transition-metal-catalyzed ATH-DKR of  $\beta$ -amino ketones to access chiral 1,3-aminoalcohols. Because of their pivotal bioactivities in pharmaceuticals, tetra-

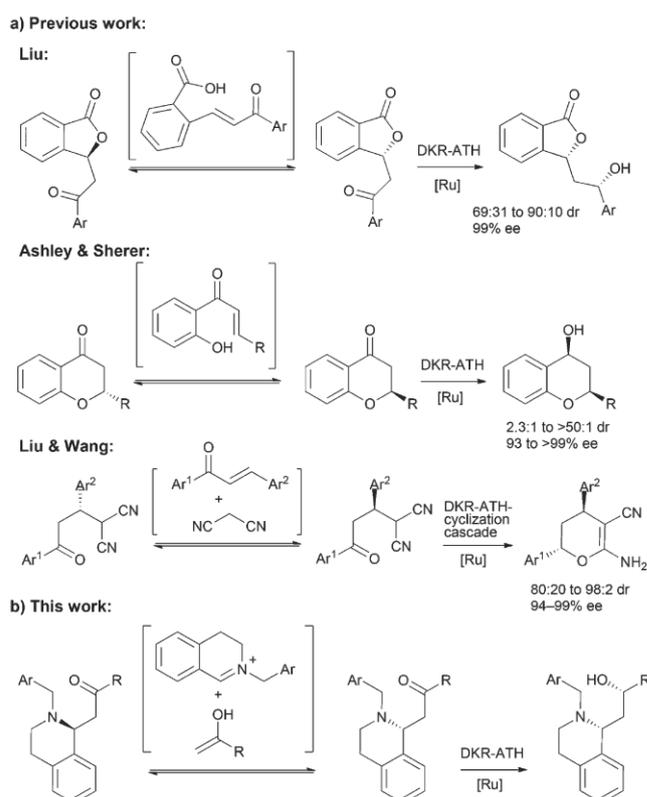


Fig. 1 Transition metal catalyzed DKR-ATH of  $\beta$ -substituted ketones.

PSL Research University, Chimie ParisTech-CNRS, Institut de Recherche de Chimie Paris, 75005 Paris, France. E-mail: phannarath.phansavath@chimie-paristech.fr, virginie.vidal@chimie-paristech.fr

† Electronic supplementary information (ESI) available. CCDC 1812327 and 1812328. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c7qo01142c

hydroisoquinoline (THIQ)-containing derivatives have attracted much attention in recent years.<sup>6,7</sup> As part of an ongoing program aimed at developing efficient methods for the asym-

metric reduction of functionalized ketones,<sup>8</sup> we report herein a ruthenium-catalyzed ATH-DKR process to prepare enantio-enriched 2-(1,2,3,4-tetrahydro-1-isoquinolyl)ethanol derivatives bearing 1,3-stereocenters through the epimerization of the  $\beta$ -stereocenter by an intermolecular elimination (retro-Mannich)/addition pathway (Fig. 1b).

The initial investigation aimed toward identifying an ideal catalyst system for the ATH of a racemic  $\beta$ -amino keto derivative **1a** was carried out at 30 °C in dichloromethane, using 1.2 mol% of chiral Ru(II) complexes **4a–4e** or a Rh(III) precatalyst **4f**<sup>9</sup> in the presence of HCO<sub>2</sub>H/Et<sub>3</sub>N (5 : 2) as the hydrogen source (Table 1). The results showed that the ATH reactions catalyzed by the ruthenium complexes **4a–4c** afforded the corresponding 1,3-aminoalcohols **2a : 3a** with diastereomeric ratios from 67 : 33 to 76 : 24 in favour of the *syn* isomer **2a** and with excellent enantioselectivities (96–99% ee, Table 1, entries 1–4). Of the above-mentioned complexes **4a–4c**, RuCl[(*R,R*)-TsDPEN](*p*-cymene) **4a** provided a slightly higher diastereoselectivity (76 : 24 dr), but with a low conversion of 47% (Table 1, entry 1) although a better 64% conversion could be achieved by increasing the amount of HCO<sub>2</sub>H/Et<sub>3</sub>N (5 : 2) to 11.0 equiv. (Table 1, entry 2). Interestingly, a high conversion (97%) and a good yield (76%) were obtained with RuCl[(*S,S*)-TsDPEN](benzene) **4b** (Table 1, entry 3), whereas the use of RuCl[(*S,S*)-TsDPEN](mesitylene) **4c** was less efficient in terms of conversion (Table 1, entry 4). We next examined the

ruthenium- and rhodium-tethered complexes **4d–4e** and **4f**, respectively. Excellent to full conversions were attained in these cases but unfortunately with virtually no diastereoselectivity (Table 1, entries 5–7). The reaction led in all cases to varying amounts of by-products arising from a competitive reduction of the retro-Mannich adducts, which produced 1-phenylethanol and 2-benzyl-1,2,3,4-tetrahydroisoquinoline. From these results, we chose to carry out the optimization study with complex (*S,S*)-**4b** which showed the best compromise between high conversion and reasonable dr, and which led to excellent enantioselectivities for both reduced products **2a** and **3a**. We then explored the solvent effect on the ATH of compound **1a** by using the previous reaction conditions in the presence of catalyst (*S,S*)-**4b** (Table 2). When THF was used as a solvent instead of dichloromethane, the diastereoselectivity slightly improved (72 : 28 dr) but a lower yield was observed (Table 2, entries 1 and 2). On the other hand, full conversion was attained in a shorter time (3 h instead of 24 h) with CH<sub>3</sub>OH, but a loss of diastereoselectivity (52 : 48 dr) was observed and the aminoalcohols **2a : 3a** were obtained with a lower yield because higher levels of by-products were formed in this case (Table 2, entry 3). Switching from dichloromethane to dichloroethane (DCE) did not change the outcome of the reaction (Table 2, entry 4). An increase of the reaction temperature to 40 °C had no beneficial effect except that it only produced a higher proportion of by-products and hence a lower

**Table 1** Screening of the DKR-ATH of **1a** with various precatalysts<sup>a</sup>

| Entry          | Cat.      | Conv. <sup>b</sup> (%) | Yield <sup>c</sup> (%) | dr ( <b>2a</b> : <b>3a</b> ) <sup>b</sup> | ee <sup>d</sup> (%) |
|----------------|-----------|------------------------|------------------------|---|---------------------|
| 1              | <b>4a</b> | 47                     | —                      | 76 : 24                                   | 96 (-)/98 (-)       |
| 2 <sup>e</sup> | <b>4a</b> | 64                     | —                      | 73 : 27                                   | 99 (-)/99 (-)       |
| 3              | <b>4b</b> | 97                     | 76                     | 68 : 32                                   | 98 (+)/99 (+)       |
| 4              | <b>4c</b> | 88                     | 68                     | 67 : 33                                   | 99 (+)/99 (+)       |
| 5              | <b>4d</b> | 96                     | 68                     | 52 : 48                                   | 97 (-)/96 (-)       |
| 6              | <b>4e</b> | 96                     | —                      | 49 : 51                                   | 99 (+)/99 (+)       |
| 7              | <b>4f</b> | 100                    | —                      | 47 : 53                                   | 96 (-)/98 (-)       |

<sup>a</sup> Reaction conditions: **1a** (0.42 mmol), **4** (1.2 mol%), HCO<sub>2</sub>H/Et<sub>3</sub>N (5 : 2) (2.75 equiv.), CH<sub>2</sub>Cl<sub>2</sub> (1.3 mL), 30 °C, 24 h. <sup>b</sup> Determined by <sup>1</sup>H NMR analysis of the crude product after the ATH reaction. <sup>c</sup> Isolated yield of **2a : 3a**. In the case of unsatisfactory conv. and/or dr, isolation of the reduced products was not attempted. <sup>d</sup> Determined by HPLC analysis using a chiral stationary phase. <sup>e</sup> 11.0 equiv. of HCO<sub>2</sub>H/Et<sub>3</sub>N (5 : 2) were used, reaction time was 40 h.

**Table 2** Optimization of the reaction conditions for the DKR-ATH of **1a** with (*S,S*)-**4b**<sup>a</sup>

| Entry          | Solvent                                      | HCO <sub>2</sub> H/Et <sub>3</sub> N (5 : 2) (equiv.) | Conv. <sup>b</sup> (%) | Yield <sup>c</sup> (%) | dr ( <b>2a</b> : <b>3a</b> ) <sup>b</sup> | ee <sup>d</sup> (%) |
|----------------|--|---|------------------------|------------------------|---|---------------------|
| 1              | CH <sub>2</sub> Cl <sub>2</sub>              | 2.75  | 97                     | 76                     | 68 : 32                                   | 98/99               |
| 2              | THF  | 2.75  | 87                     | 67                     | 72 : 28                                   | 98/99               |
| 3 <sup>e</sup> | CH <sub>3</sub> OH                           | 2.75  | 100                    | 60 <sup>f</sup>        | 52 : 48                                   | 99/99               |
| 4              | DCE  | 2.75  | 97                     | 74                     | 68 : 32                                   | 98/99               |
| 5 <sup>g</sup> | CH <sub>2</sub> Cl <sub>2</sub>              | 2.75  | 98                     | 65                     | 69 : 31                                   | 98/99               |
| 6 <sup>h</sup> | CH <sub>2</sub> Cl <sub>2</sub>              | 2.75  | 91                     | 73                     | 72 : 28                                   | 99/99               |
| 7              | CH <sub>2</sub> Cl <sub>2</sub> <sup>i</sup> | 2.75  | 95                     | 70                     | 66 : 34                                   | 98/99               |
| 8              | CH <sub>2</sub> Cl <sub>2</sub>              | 8.25  | 100                    | 79                     | 63 : 37                                   | 99/99               |
| 9 <sup>j</sup> | CH <sub>2</sub> Cl <sub>2</sub>              | 4.0 (1 : 5)   | 45                     | 23 <sup>f</sup>        | 68 : 32                                   | 89/96               |
| 10             | CH <sub>2</sub> Cl <sub>2</sub> <sup>j</sup> | 2.0 (1 : 1)   | 29                     | 19 <sup>f</sup>        | 74 : 26                                   | 79/92               |
| 11             | CH <sub>2</sub> Cl <sub>2</sub>              | — <sup>k</sup>  | 100                    | 75                     | 69 : 31                                   | 99/99               |

<sup>a</sup> Reaction conditions: **1a** (0.42 mmol), (*S,S*)-**4b** (1.2 mol%), HCO<sub>2</sub>H/Et<sub>3</sub>N (5 : 2) (2.75 equiv.), CH<sub>2</sub>Cl<sub>2</sub> (1.3 mL, 0.32 mol L<sup>-1</sup>), 30 °C, 24 h.

<sup>b</sup> Determined by <sup>1</sup>H NMR analysis of the crude product after the ATH reaction. <sup>c</sup> Isolated yield of **2a : 3a**. <sup>d</sup> Determined by HPLC analysis using a chiral stationary phase. <sup>e</sup> The reaction time was 3 h. <sup>f</sup> Yield determined by <sup>1</sup>H NMR analysis of the crude product after the ATH reaction. <sup>g</sup> The reaction temperature was 40 °C. <sup>h</sup> The reaction was run at 0 °C for 110 h. <sup>i</sup> CH<sub>2</sub>Cl<sub>2</sub> (2.0 mL, 0.21 mol L<sup>-1</sup>). <sup>j</sup> The reaction time was 48 h. <sup>k</sup> 1.0 equiv. of HCO<sub>2</sub>H/DABCO (5 : 3) was used instead of HCO<sub>2</sub>H/Et<sub>3</sub>N (5 : 2).

metric reduction of functionalized ketones,<sup>8</sup> we report herein a ruthenium-catalyzed ATH-DKR process to prepare enantio-enriched 2-(1,2,3,4-tetrahydro-1-isoquinolyl)ethanol derivatives bearing 1,3-stereocenters through the epimerization of the  $\beta$ -stereocenter by an intermolecular elimination (retro-Mannich)/addition pathway (Fig. 1b).

The initial investigation aimed toward identifying an ideal catalyst system for the ATH of a racemic  $\beta$ -amino keto derivative **1a** was carried out at 30 °C in dichloromethane, using 1.2 mol% of chiral Ru(II) complexes **4a–4e** or a Rh(III) precatalyst **4f**<sup>9</sup> in the presence of HCO<sub>2</sub>H/Et<sub>3</sub>N (5 : 2) as the hydrogen source (Table 1). The results showed that the ATH reactions catalyzed by the ruthenium complexes **4a–4c** afforded the corresponding 1,3-aminoalcohols **2a : 3a** with diastereomeric ratios from 67 : 33 to 76 : 24 in favour of the *syn* isomer **2a** and with excellent enantioselectivities (96–99% ee, Table 1, entries 1–4). Of the above-mentioned complexes **4a–4c**, RuCl[(*R,R*)-TsDPEN](*p*-cymene) **4a** provided a slightly higher diastereoselectivity (76 : 24 dr), but with a low conversion of 47% (Table 1, entry 1) although a better 64% conversion could be achieved by increasing the amount of HCO<sub>2</sub>H/Et<sub>3</sub>N (5 : 2) to 11.0 equiv. (Table 1, entry 2). Interestingly, a high conversion (97%) and a good yield (76%) were obtained with RuCl[(*S,S*)-TsDPEN](benzene) **4b** (Table 1, entry 3), whereas the use of RuCl[(*S,S*)-TsDPEN](mesitylene) **4c** was less efficient in terms of conversion (Table 1, entry 4). We next examined the

ruthenium- and rhodium-tethered complexes **4d–4e** and **4f**, respectively. Excellent to full conversions were attained in these cases but unfortunately with virtually no diastereoselectivity (Table 1, entries 5–7). The reaction led in all cases to varying amounts of by-products arising from a competitive reduction of the retro-Mannich adducts, which produced 1-phenylethanol and 2-benzyl-1,2,3,4-tetrahydroisoquinoline. From these results, we chose to carry out the optimization study with complex (*S,S*)-**4b** which showed the best compromise between high conversion and reasonable dr, and which led to excellent enantioselectivities for both reduced products **2a** and **3a**. We then explored the solvent effect on the ATH of compound **1a** by using the previous reaction conditions in the presence of catalyst (*S,S*)-**4b** (Table 2). When THF was used as a solvent instead of dichloromethane, the diastereoselectivity slightly improved (72 : 28 dr) but a lower yield was observed (Table 2, entries 1 and 2). On the other hand, full conversion was attained in a shorter time (3 h instead of 24 h) with CH<sub>3</sub>OH, but a loss of diastereoselectivity (52 : 48 dr) was observed and the aminoalcohols **2a : 3a** were obtained with a lower yield because higher levels of by-products were formed in this case (Table 2, entry 3). Switching from dichloromethane to dichloroethane (DCE) did not change the outcome of the reaction (Table 2, entry 4). An increase of the reaction temperature to 40 °C had no beneficial effect except that it only produced a higher proportion of by-products and hence a lower

**Table 1** Screening of the DKR-ATH of **1a** with various precatalysts<sup>a</sup>

| Entry          | Cat.      | Conv. <sup>b</sup> (%) | Yield <sup>c</sup> (%) | dr ( <b>2a</b> : <b>3a</b> ) <sup>b</sup> | ee <sup>d</sup> (%) |
|----------------|-----------|------------------------|------------------------|---|---------------------|
| 1              | <b>4a</b> | 47                     | —                      | 76 : 24                                   | 96 (–)/98 (–)       |
| 2 <sup>e</sup> | <b>4a</b> | 64                     | —                      | 73 : 27                                   | 99 (–)/99 (–)       |
| 3              | <b>4b</b> | 97                     | 76                     | 68 : 32                                   | 98 (+)/99 (+)       |
| 4              | <b>4c</b> | 88                     | 68                     | 67 : 33                                   | 99 (+)/99 (+)       |
| 5              | <b>4d</b> | 96                     | 68                     | 52 : 48                                   | 97 (–)/96 (–)       |
| 6              | <b>4e</b> | 96                     | —                      | 49 : 51                                   | 99 (+)/99 (+)       |
| 7              | <b>4f</b> | 100                    | —                      | 47 : 53                                   | 96 (–)/98 (–)       |

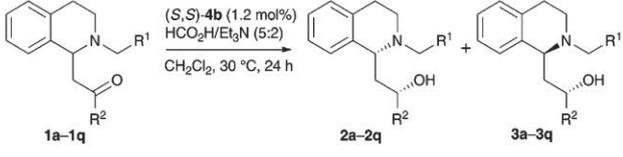
<sup>a</sup> Reaction conditions: **1a** (0.42 mmol), **4** (1.2 mol%), HCO<sub>2</sub>H/Et<sub>3</sub>N (5 : 2) (2.75 equiv.), CH<sub>2</sub>Cl<sub>2</sub> (1.3 mL), 30 °C, 24 h. <sup>b</sup> Determined by <sup>1</sup>H NMR analysis of the crude product after the ATH reaction. <sup>c</sup> Isolated yield of **2a : 3a**. In the case of unsatisfactory conv. and/or dr, isolation of the reduced products was not attempted. <sup>d</sup> Determined by HPLC analysis using a chiral stationary phase. <sup>e</sup> 11.0 equiv. of HCO<sub>2</sub>H/Et<sub>3</sub>N (5 : 2) were used, reaction time was 40 h.

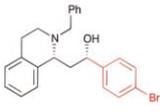
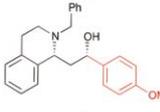
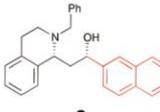
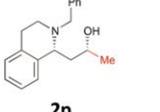
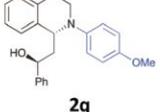
**Table 2** Optimization of the reaction conditions for the DKR-ATH of **1a** with (*S,S*)-**4b**<sup>a</sup>

| Entry          | Solvent                                      | HCO <sub>2</sub> H/Et <sub>3</sub> N (5 : 2) (equiv.) | Conv. <sup>b</sup> (%) | Yield <sup>c</sup> (%) | dr ( <b>2a</b> : <b>3a</b> ) <sup>b</sup> | ee <sup>d</sup> (%) |
|----------------|--|---|------------------------|------------------------|---|---------------------|
| 1              | CH <sub>2</sub> Cl <sub>2</sub>              | 2.75  | 97                     | 76                     | 68 : 32                                   | 98/99               |
| 2              | THF  | 2.75  | 87                     | 67                     | 72 : 28                                   | 98/99               |
| 3 <sup>e</sup> | CH <sub>3</sub> OH                           | 2.75  | 100                    | 60 <sup>f</sup>        | 52 : 48                                   | 99/99               |
| 4              | DCE  | 2.75  | 97                     | 74                     | 68 : 32                                   | 98/99               |
| 5 <sup>g</sup> | CH <sub>2</sub> Cl <sub>2</sub>              | 2.75  | 98                     | 65                     | 69 : 31                                   | 98/99               |
| 6 <sup>h</sup> | CH <sub>2</sub> Cl <sub>2</sub>              | 2.75  | 91                     | 73                     | 72 : 28                                   | 99/99               |
| 7              | CH <sub>2</sub> Cl <sub>2</sub> <sup>i</sup> | 2.75  | 95                     | 70                     | 66 : 34                                   | 98/99               |
| 8              | CH <sub>2</sub> Cl <sub>2</sub>              | 8.25  | 100                    | 79                     | 63 : 37                                   | 99/99               |
| 9 <sup>j</sup> | CH <sub>2</sub> Cl <sub>2</sub>              | 4.0 (1 : 5)   | 45                     | 23 <sup>f</sup>        | 68 : 32                                   | 89/96               |
| 10             | CH <sub>2</sub> Cl <sub>2</sub> <sup>j</sup> | 2.0 (1 : 1)   | 29                     | 19 <sup>f</sup>        | 74 : 26                                   | 79/92               |
| 11             | CH <sub>2</sub> Cl <sub>2</sub>              | — <sup>k</sup>  | 100                    | 75                     | 69 : 31                                   | 99/99               |

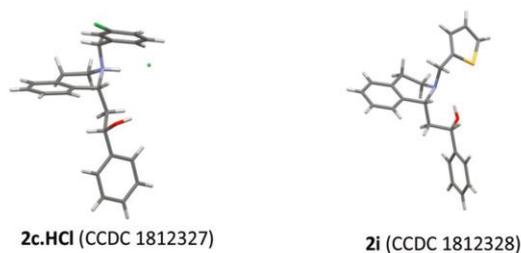
<sup>a</sup> Reaction conditions: **1a** (0.42 mmol), (*S,S*)-**4b** (1.2 mol%), HCO<sub>2</sub>H/Et<sub>3</sub>N (5 : 2) (2.75 equiv.), CH<sub>2</sub>Cl<sub>2</sub> (1.3 mL, 0.32 mol L<sup>-1</sup>), 30 °C, 24 h. <sup>b</sup> Determined by <sup>1</sup>H NMR analysis of the crude product after the ATH reaction. <sup>c</sup> Isolated yield of **2a : 3a**. <sup>d</sup> Determined by HPLC analysis using a chiral stationary phase. <sup>e</sup> The reaction time was 3 h. <sup>f</sup> Yield determined by <sup>1</sup>H NMR analysis of the crude product after the ATH reaction. <sup>g</sup> The reaction temperature was 40 °C. <sup>h</sup> The reaction was run at 0 °C for 110 h. <sup>i</sup> CH<sub>2</sub>Cl<sub>2</sub> (2.0 mL, 0.21 mol L<sup>-1</sup>). <sup>j</sup> The reaction time was 48 h. <sup>k</sup> 1.0 equiv. of HCO<sub>2</sub>H/DABCO (5 : 3) was used instead of HCO<sub>2</sub>H/Et<sub>3</sub>N (5 : 2).

Table 3 (Contd.)



| Entry | ATH product 2  | Yield <sup>b</sup> (%) | dr (2 : 3) <sup>c</sup> | ee for 2/3 <sup>d</sup> (%) |
|-------|--|------------------------|-------------------------|-----------------------------|
| 13    |   | 60                     | 69 : 31                 | 96/98                       |
| 14    |   | 79                     | 61 : 39                 | 98/99                       |
| 15    |   | 75                     | 63 : 37                 | 94/98                       |
| 16    |   | 65                     | 71 : 29                 | 81/99                       |
| 17    |  | — <sup>e</sup>         | —                       | —                           |

<sup>a</sup> Reaction conditions: **1** (0.42 mmol), (*S,S*)-**4b** (1.2 mol%), HCO<sub>2</sub>H/Et<sub>3</sub>N (5 : 2) (2.75 equiv.), CH<sub>2</sub>Cl<sub>2</sub> (1.3 mL), 30 °C, 24 h. <sup>b</sup> Isolated yield of **2** : **3**. <sup>c</sup> Determined by <sup>1</sup>H NMR analysis of the crude product after the ATH reaction. <sup>d</sup> Determined by HPLC analysis using a chiral stationary phase. <sup>e</sup> The ATH reaction only led to unidentified by-products.

Fig. 2 X-ray structures of **2c**·HCl and **2i**.

## Conclusions

In summary, an efficient asymmetric synthesis of 2-(1,2,3,4-tetrahydro-1-isoquinolyl)ethanol derivatives, which act as *N*-methyl-D-aspartate (NMDA) receptor inhibitors, was developed by asymmetric reduction through a dynamic kinetic resolution process. This practical synthesis features the first application of Ru-catalyzed asymmetric transfer hydrogenation to establish enantiomerically enriched 1,3-aminoalcohol derivatives bearing the tetrahydroisoquinoline scaffold. The

reaction proceeded under mild conditions, using a low catalyst loading of (*S,S*)-**4b** and HCO<sub>2</sub>H/Et<sub>3</sub>N (5 : 2) as the hydrogen source, delivering a variety of 2-(1,2,3,4-tetrahydro-1-isoquinolyl)ethanol derivatives with excellent enantioselectivities (up to 99% ee) for the *syn* products. Furthermore, the usefulness of this method was demonstrated by the efficient gram-scale reduction of **1a**.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

This work was supported by the Ministère de l'Éducation Nationale, de l'Enseignement Supérieur et de la Recherche (MENESR) and the Centre National de la Recherche Scientifique (CNRS). We gratefully acknowledge the China Scholarship Council (CSC) for a grant to L.-S. Z. We are grateful to C. Féraud for technical assistance. We thank L.-M. Chamoreau and G. Gontard for the X-ray analysis.

## Notes and references

- For selected reviews and chapters on the ATH of ketones, see: (a) G. Zassinovich, G. Mestroni and S. Gladiali, *Chem. Rev.*, 1992, **92**, 1051; (b) R. Noyori and S. Hashiguchi, *Acc. Chem. Res.*, 1997, **30**, 97; (c) M. J. Palmer and M. Wills, *Tetrahedron: Asymmetry*, 1999, **10**, 2045; (d) K. Everaere, A. Mortreux and J.-F. Carpentier, *Adv. Synth. Catal.*, 2003, **345**, 67; (e) S. Gladiali and E. Alberico, *Chem. Soc. Rev.*, 2006, **35**, 226; (f) S. M. Joseph, J. S. Samec, J.-E. Bäckvall, P. G. Andersson and P. Brandt, *Chem. Soc. Rev.*, 2006, **35**, 237; (g) T. Ikariya and A. J. Blacker, *Acc. Chem. Res.*, 2007, **40**, 1300; (h) A. J. Blacker, in *Handbook of Homogeneous Hydrogenation*, ed. J. G. de Vries and C. J. Elsevier, Wiley-VCH, Weinheim, 2007, p. 1215; (i) C. Wang, X. Wu and J. Xiao, *Chem. – Asian J.*, 2008, **3**, 1750; (j) B. Štefane and F. Požgan, *Catal. Rev.*, 2014, **56**, 82; (k) D. Wang and D. Astruc, *Chem. Rev.*, 2015, **115**, 6621; (l) F. Foubelo, C. Nájera and M. Yus, *Tetrahedron: Asymmetry*, 2015, **26**, 769; (m) T. Ayad, P. Phansavath and V. Ratovelomanana-Vidal, *Chem. Rec.*, 2016, **16**, 2754; (n) H. G. Nedden, A. Zanotti-Gerosa and M. Wills, *Chem. Rec.*, 2016, **16**, 2623.
- For selected recent reviews on DKR, see: (a) K. Nakano and M. Kitamura, *Dynamic kinetic resolution (DKR)*, in *Separation of Enantiomers: Synthetic Methods*, ed. M. H. Todd, Wiley-VCH, Weinheim, Germany, 2014, p. 161; (b) G. A. Applegate and D. B. Berkowitz, *Adv. Synth. Catal.*, 2015, **357**, 1619; (c) J.-H. Xie and Q.-L. Zhou, *Aldrichimica Acta*, 2015, **48**, 33; (d) H. Pellissier, *Tetrahedron*, 2016, **72**, 3133; (e) P.-G. Echeverria, T. Ayad, P. Phansavath and V. Ratovelomanana-Vidal, *Synthesis*, 2016, 2523; (f) V. Bhat,

- E. R. Welin, X. Guo and B. M. Stoltz, *Chem. Rev.*, 2017, **117**, 4528.
- 3 T. Cheng, Q. Ye, Q. Zhao and G. Liu, *Org. Lett.*, 2015, **17**, 4972.
- 4 E. R. Ashley, E. C. Sherer, B. Pio, R. K. Orr and R. T. Ruck, *ACS Catal.*, 2017, **7**, 1446.
- 5 D. Zheng, Q. Zhao, X. Hu, T. Cheng, G. Liu and W. Wang, *Chem. Commun.*, 2017, **53**, 6113.
- 6 (a) W. Liu, S. Liu, R. Jin, H. Guo and J. Zhao, *Org. Chem. Front.*, 2015, **2**, 288; (b) D. Zhao and F. Glorius, *Angew. Chem., Int. Ed.*, 2013, **52**, 9616.
- 7 (a) E. Anakabe, D. Badia, L. Carillo and J. L. Vicario, *Recent Res. Dev. Organomet. Chem*, 2001, **5**, 63; (b) M. Chrzanowska and M. D. Rozwadowska, *Chem. Rev.*, 2004, **104**, 3341; (c) A. L. Zein, G. Valluru and P. E. Georghiou, in *Studies in Natural Products Chemistry*, Elsevier B. V., Oxford, UK, 2012, vol. 38, pp. 53–80.
- 8 (a) Z. Wu, T. Ayad and V. Ratovelomanana-Vidal, *Org. Lett.*, 2011, **13**, 3782; (b) F. Berhal, Z. Wu, Z. Zhang, T. Ayad and V. Ratovelomanana-Vidal, *Org. Lett.*, 2012, **14**, 3308; (c) D. Cartigny, F. Berhal, T. Nagano, P. Phansavath, T. Ayad, J.-P. Genêt, T. Ohshima, K. Mashima and V. Ratovelomanana-Vidal, *J. Org. Chem.*, 2012, **77**, 4544; (d) Z. Wu, M. Perez, M. Scalone, T. Ayad and V. Ratovelomanana-Vidal, *Angew. Chem., Int. Ed.*, 2013, **52**, 4925; (e) L. Monnereau, D. Cartigny, M. Scalone, T. Ayad and V. Ratovelomanana-Vidal, *Chem. – Eur. J.*, 2015, **21**, 11799.
- 9 (a) P.-G. Echeverria, C. Féraud, P. Phansavath and V. Ratovelomanana-Vidal, *Catal. Commun.*, 2015, **62**, 95; (b) D. S. Matharu, D. J. Morris, A. M. Kawamoto, G. J. Clarkson and M. Wills, *Org. Lett.*, 2005, **7**, 5489.
- 10 W. Chen and D. Seidel, *Org. Lett.*, 2014, **16**, 3158.

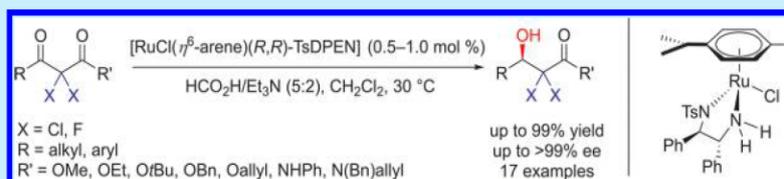


# Synthesis of Enantioenriched $\alpha,\alpha$ -Dichloro- and $\alpha,\alpha$ -Difluoro- $\beta$ -Hydroxy Esters and Amides by Ruthenium-Catalyzed Asymmetric Transfer Hydrogenation

Long-Sheng Zheng, Phannarath Phansavath,\* and Virginie Ratovelomanana-Vidal\*<sup>ID</sup>

PSL Research University, Chimie ParisTech-CNRS, Institut de Recherche de Chimie Paris, 75005 Paris, France

**S** Supporting Information

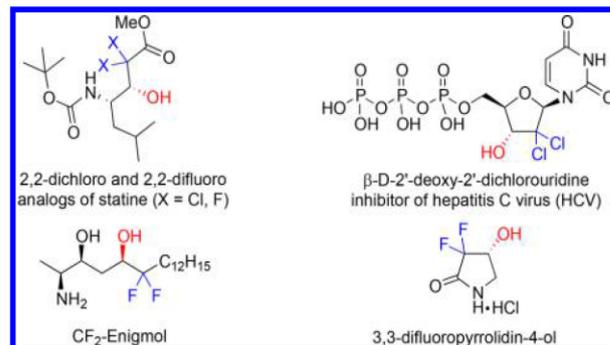


**ABSTRACT:** A mild and convenient approach was developed to prepare a series of  $\alpha,\alpha$ -dihalogeno  $\beta$ -hydroxy esters or amides by using commercially available Noyori's complex  $[\text{RuCl}(p\text{-cymene})(R,R)\text{-TsDPEN}]$  as a catalyst ( $S/C = 100\text{--}200$ ) in the asymmetric transfer hydrogenation of the corresponding ketones. Moderate to high yields (up to 99%) and excellent enantioselectivities (up to >99% ee) were achieved for a series of variously substituted dichloro and difluoro  $\beta$ -hydroxy esters and amides.

Because of the ability of halogen atoms to improve oral absorption, blood-brain barrier permeability, or metabolic and chemical stability, halogenated compounds play a significant role in medicinal chemistry. The majority of the halogenated drugs approved by the FDA are fluorine and chlorine compounds,<sup>1,2</sup> and the introduction of a dichloromethylene or difluoromethylene fragment into bioactive molecules has created a new trend in drug discovery. Enantiomerically pure  $\alpha,\alpha$ -dichlorosubstituted or  $\alpha,\alpha$ -difluoro-substituted secondary alcohols are found in many biologically relevant molecules, such as statine analogues,<sup>3a</sup> a potent inhibitor of hepatitis C virus replication,  $\beta$ -D-2'-deoxy-2'-dichlorouridine prodrug,<sup>3b</sup> and the fluorinated Enigmol analogue  $\text{CF}_2$ -Enigmol, having enhanced antitumor activity.<sup>3c</sup> Alternatively,  $\alpha,\alpha$ -dichlorosubstituted or  $\alpha,\alpha$ -difluoro-substituted secondary alcohols can serve as valuable building blocks in medicinal chemistry as with 3,3-difluoropyrrolidin-4-ol<sup>3d</sup> (Figure 1).

Access to  $\alpha,\alpha$ -dichloro and  $\alpha,\alpha$ -difluoro  $\beta$ -hydroxyester derivatives has been reported through enzymatic<sup>4a</sup> or organo-catalyzed<sup>4b</sup> kinetic resolution, as well as through enantioselective Mukaiyama aldol reactions.<sup>4c–e</sup> As far as asymmetric reduction of  $\alpha,\alpha$ -dihalogeno  $\beta$ -keto esters is concerned, rhodium- or ruthenium-catalyzed asymmetric hydrogenation<sup>4f,g</sup> and bioreduction<sup>4h,i</sup> have been described (Scheme 1).

These approaches mainly focused on difluorinated compounds and suffered from low yields in the case of kinetic resolution and bioreduction. As part of an ongoing program aimed at developing efficient methods for the asymmetric reduction of functionalized ketones,<sup>5</sup> we report herein the ruthenium-catalyzed asymmetric transfer hydrogenation (ATH) of  $\alpha,\alpha$ -dichloro and  $\alpha,\alpha$ -difluoro  $\beta$ -ketoester derivatives to access the corresponding dihalogenated alcohols



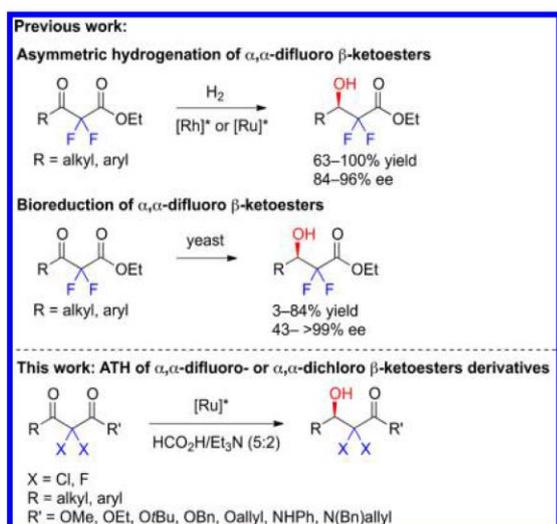
**Figure 1.**  $\alpha,\alpha$ -Dichloro- or  $\alpha,\alpha$ -difluoro-containing bioactive molecules.

efficiently in high yields and excellent enantioselectivities. The ATH of ketones has received significant attention in the past two decades, because it is one of the most powerful and useful methods for the generation of enantiomerically enriched secondary alcohols from the corresponding prochiral ketones, because of its high performance, in terms of activity and selectivity, and its operational simplicity.<sup>6</sup> Although the preparation of enantiomerically enriched  $\text{CF}_3$ ,<sup>7a–f</sup>  $\text{CCl}_3$ ,<sup>7g</sup> or difluoro-substituted<sup>7h–j</sup> alcohols was described through ATH, to our knowledge, the ATH of  $\alpha,\alpha$ -dihalogenated  $\beta$ -ketoester derivatives has not been reported.<sup>7k</sup>

We first investigated the enantioselective reduction of benzyl 2,2-dichloro-3-oxobutanoate **1a** as a model reaction by using the tethered rhodium complex  $(R,R)$ -**3a** (0.5 mol %),  $\text{HCO}_2\text{H}/\text{Et}_3\text{N}$  (5:2) azeotropic mixture as the hydrogen

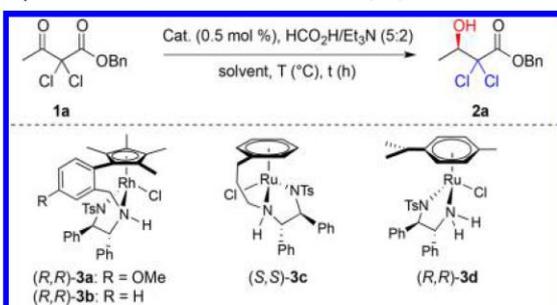
**Received:** June 21, 2018

**Published:** August 9, 2018

Scheme 1. Asymmetric Reduction of  $\alpha,\alpha$ -Dihalogeno  $\beta$ -Keto Esters

source, and  $\text{CH}_2\text{Cl}_2$  as a solvent at 20 °C. Under these conditions, full conversion was achieved within 4 h and the corresponding alcohol (*R*)-**2a** was obtained in 77% yield with a high enantioselectivity (98% enantiomeric excess (ee); see Table 1, entry 1). Wills' tethered rhodium complex (*R,R*)-**3b**<sup>9</sup> afforded the same enantioinduction (98% ee) and a better yield (84% yield; see Table 1, entry 2). The catalyst screening also included tethered ruthenium complexes. Thus, (*S,S*)-**3c**<sup>10</sup> was used in the ATH of **1a** to give (*S*)-**2a** in 91% yield and 99% ee, albeit with a longer reaction time of 20 h (Table 1,

Table 1. Optimization of Reaction Conditions for ATH of Benzyl 2,2-Dichloro-3-oxobutanoate (**1a**)<sup>a</sup>

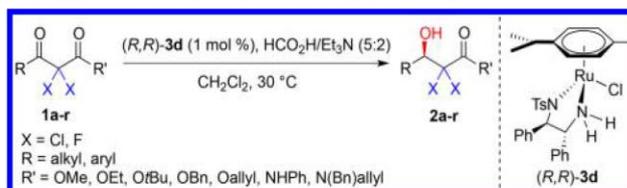


| entry          | catalyst  | solvent                     | temperature (°C) | time (h) | yield <sup>b</sup> (%) | ee <sup>c</sup> (%) |
|----------------|-----------|-----------------------------|------------------|----------|------------------------|---------------------|
| 1              | <b>3a</b> | $\text{CH}_2\text{Cl}_2$    | 20               | 4        | 77                     | 98                  |
| 2              | <b>3b</b> | $\text{CH}_2\text{Cl}_2$    | 20               | 5        | 84                     | 98                  |
| 3              | <b>3c</b> | $\text{CH}_2\text{Cl}_2$    | 20               | 20       | 91                     | −99                 |
| 4              | <b>3d</b> | $\text{CH}_2\text{Cl}_2$    | 20               | 20       | 92                     | >99                 |
| 5              | <b>3d</b> | $\text{CH}_2\text{Cl}_2$    | 40               | 5        | 91                     | >99                 |
| 6 <sup>d</sup> | <b>3d</b> | $\text{CH}_2\text{Cl}_2$    | 40               | 3        | 87                     | >99                 |
| 7 <sup>e</sup> | <b>3d</b> | $\text{CH}_2\text{Cl}_2$    | 40               | 3        | 83                     | >99                 |
| 8              | <b>3d</b> | EtOAc                       | 40               | 17       | 64                     | >99                 |
| 9              | <b>3d</b> | THF                         | 40               | 17       | 67 <sup>f</sup>        | >99                 |
| 10             | <b>3d</b> | <i>i</i> -Pr <sub>2</sub> O | 40               | 3        | 86                     | >99                 |
| 11             | <b>3d</b> | <i>i</i> -PrOH              | 40               | 5        | 81                     | >99                 |
| 12             | <b>3d</b> | $\text{CH}_2\text{Cl}_2$    | 30               | 7        | 96                     | >99                 |

<sup>a</sup>General conditions: **1a** (0.6 mmol), catalyst (0.006 mmol),  $\text{HCO}_2\text{H}/\text{Et}_3\text{N}$  (5:2) (101  $\mu\text{L}$ ),  $\text{CH}_2\text{Cl}_2$  (3.0 mL). <sup>b</sup>Isolated yield, full conversion except where indicated. <sup>c</sup>Determined by SFC. <sup>d</sup>[0.4 M]:  $\text{CH}_2\text{Cl}_2$  (1.5 mL). <sup>e</sup>[0.6 M]:  $\text{CH}_2\text{Cl}_2$  (1.0 mL). <sup>f</sup>92% conversion.

entry 3). We also examined Noyori's catalyst (*R,R*)-**3d**,<sup>11</sup>  $[\text{RuCl}(\textit{p}\text{-cymene})(\textit{R,R})\text{-TsDPEN}]$ , which gave similar results after 20 h (Table 1, entry 4). Interestingly, the reaction time was shortened to 5 h when the ATH was conducted at 40 °C, affording (*R*)-**2a** in 91% yield and >99% ee (Table 1, entry 5). An increase of the reaction concentration from 0.2 mol L<sup>−1</sup> to 0.4 and 0.6 mol L<sup>−1</sup> led to a faster reaction at 40 °C, but with a lower yield (87% or 83%, respectively; see Table 1, entries 6 and 7). We pursued the optimization of the reaction parameters by a solvent screening. Excellent ee values were obtained in EtOAc and THF after 17 h, albeit in lower yields, with only 92% conversion observed in the latter case (Table 1, entries 8 and 9). *i*-Pr<sub>2</sub>O and *i*-PrOH were then investigated, giving full conversions within either 3 or 5 h, with 86% and 81% yields, respectively, and >99% ee (Table 1, entries 10 and 11). Dichloromethane therefore appeared as the more suitable solvent for this reaction and a slightly higher 96% yield could even be attained by running the reduction at 30 °C for 7 h instead of 40 °C (Table 1, entries 5 and 12). Based on the above screening, the optimized conditions were set as follows: (*R,R*)-**3d** (0.5 mol %) as the precatalyst,  $\text{HCO}_2\text{H}/\text{Et}_3\text{N}$  (5:2) (2.0 equiv),  $\text{CH}_2\text{Cl}_2$  (0.2 M) at 30 °C.

With these optimized conditions in hand, we then investigated the scope of the Ru-catalyzed ATH of  $\alpha,\alpha$ -dihalogeno  $\beta$ -ketoester derivatives with a series of variously substituted dichloro and difluoro compounds **1a–1r** (see Table 2). The asymmetric reduction of compounds **1b–1d** bearing a benzyl ester and an alkyl ketone proceeded with longer reaction times (21–24 h), compared to the reaction with **1a**, and afforded alcohols **2b–2d** with excellent enantioselectivities, although a lower yield was obtained in the latter case, probably because of the more sterically demanding isobutyl substituent (Table 2, entries 2–4 vs entry 1). The *tert*-butyl and allyl ester analogues **1e** and **1f** of the standard substrate **1a**, were readily reduced to **2e** and **2f** with high levels of enantioselectivity (Table 2, entries 5 and 6). The ruthenium-mediated reduction of allyl, ethyl, or methyl ester derivatives **1g**, **1h**, and **1i** afforded the corresponding alcohols **2g** and **2h** in 98% and 72% yields, and 99% ee, whereas only traces of **2i** having a more hindered isopropyl substituent were detected (Table 2, entries 7–9). On the other hand,  $\alpha,\alpha$ -dichloro  $\beta$ -ketoester **1j** having a pentynyl substituent on the ketone was converted to **2j** in 76% yield and 98.5% ee (Table 2, entry 10). Although a high enantioselectivity was observed for the ATH of compound **1k** bearing a hexasubstituted benzene ring on the alkyl residue, the reaction proceeded with only 48% yield (Table 2, entry 11). Furthermore, the reduction of aromatic  $\beta$ -ketoesters **1l** and **1m** was also investigated. Both the yields and ee values were moderate for these substrates (Table 2, entries 12 and 13). In addition, fluorinated alkyl compounds were also evaluated and  $\alpha,\alpha$ -difluoro  $\beta$ -ketoesters **1n** and **1o** were efficiently reduced, even at room temperature, in excellent 99% yields and 98% ee (Table 2, entries 14 and 15). A quantitative yield was also obtained in the preparation of the benzyl alcohol derivative **2p**, although the ee was only moderate, as previously observed for the parent dichlorinated compound **2l** (Table 2, entries 16 and 12). Furthermore, the substrate scope was extended to  $\alpha,\alpha$ -dichloro  $\beta$ -keto amides with the ATH of compounds **1q** and **1r**. Thus, enantiomerically enriched *N*-phenyl-2,2-dichloro-3-hydroxybutanamide **2q** and *N*-allyl-*N*-benzyl-2,2-dichloro-3-hydroxybutanamide **2r** were readily prepared with high yields and ee values (Table 2, entries 17 and 18). The absolute

Table 2. ATH of  $\alpha,\alpha$ -Dichloro- and  $\alpha,\alpha$ -Difluoro- $\beta$ -Keto Esters and Amides<sup>a</sup>

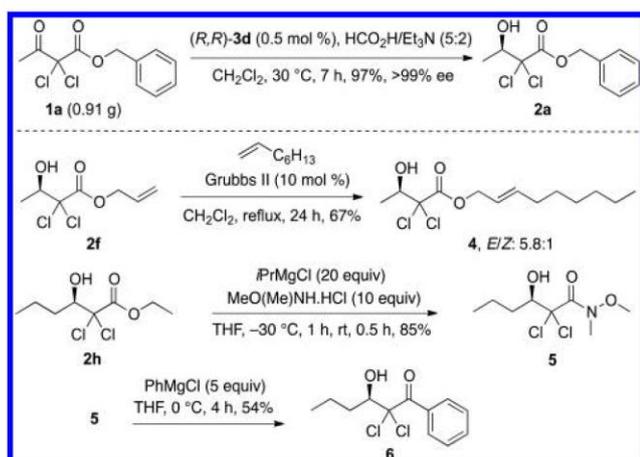
| entry          | product | time (h) | yield (%) <sup>b</sup> | ee (%) <sup>c</sup> | entry           | product | time (h) | yield (%) <sup>b</sup> | ee (%) <sup>c</sup> |
|----------------|---------|----------|------------------------|---------------------|-----------------|---------|----------|------------------------|---------------------|
| 1              |         | 7        | 96                     | >99                 | 11              |         | 24       | 48                     | 98                  |
| 2              |         | 22       | 70                     | >99                 | 12              |         | 24       | 50                     | 70                  |
| 3              |         | 21       | 90                     | 98                  | 13              |         | 24       | 34                     | 71                  |
| 4              |         | 24       | 26 <sup>d</sup>        | >99                 | 14 <sup>g</sup> |         | 5        | 99                     | 98                  |
| 5 <sup>e</sup> |         | 2.5      | 95                     | 99                  | 15 <sup>g</sup> |         | 13       | 99                     | 98                  |
| 6 <sup>e</sup> |         | 2.5      | 88                     | >99                 | 16              |         | 5        | 99                     | 56                  |
| 7              |         | 8        | 98                     | 99                  | 17 <sup>e</sup> |         | 14       | 93                     | 98.5                |
| 8              |         | 22       | 72                     | >99                 | 18              |         | 3        | 99                     | 98                  |
| 9              |         | 22       | —                      | —                   |                 |         |          |                        |                     |
| 10             |         | 9        | 76                     | 98.5                |                 |         |          |                        |                     |

<sup>a</sup>Conditions: **1a–1r** (0.6 mmol), (*R,R*)-**3d** (0.006 mmol), CH<sub>2</sub>Cl<sub>2</sub> (3.0 mL), HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) azeotropic mixture (101  $\mu$ L), 30 °C. The reaction was monitored by TLC and/or <sup>1</sup>H NMR. <sup>b</sup>Isolated yield. <sup>c</sup>Determined by SFC or HPLC analysis. <sup>d</sup>51% conversion. <sup>e</sup>Reaction conducted on 1.0 mmol of **1** with 0.005 mmol of (*R,R*)-**3d**. <sup>f</sup>Traces of product **2i**, ee not measured. <sup>g</sup>Reaction performed at room temperature.

configuration of alcohol **2q** was unambiguously assigned as (*R*) by X-ray crystallographic analysis. In addition, comparison of the optical rotation value of compound **2p** with the reported literature data confirmed its (*R*) absolute configuration ( $[\alpha]_{\text{D}}^{25} = -6.8$  (c 1.0, CHCl<sub>3</sub>), lit.<sup>12</sup>  $[\alpha]_{\text{D}}^{24} = -13.4$  (c 1.29, CHCl<sub>3</sub>, 97% ee). By analogy, we conjecture that the remainder of the ATH products **2** followed the same trend.<sup>13</sup> In addition, a scale-up experiment was performed on compound **1a** (0.91 g, 3.48 mmol), using a lower catalyst loading of 0.5 mol %, and furnished the same yield and ee value as that observed on a 0.6 mmol scale (see Scheme 2). Furthermore, post-functionaliza-

tion of **2f** and **2h** was studied. Thus, a cross metathesis between allyl (*R*)-2,2-dichloro-3-hydroxybutanoate **2f** and 1-octene using Grubbs II catalyst allowed formation of alkene **4** in 67% yield as a 5.8:1 mixture of *E* and *Z* isomers. On the other hand, ethyl (*R*)-2,2-dichloro-3-hydroxyhexanoate **2h** was readily converted into the corresponding  $\beta$ -hydroxy Weinreb amide **5** in the presence of *N,O*-dimethylhydroxylamine hydrochloride and isopropylmagnesium chloride in 85% yield. The amide could then serve as a ketone precursor and was, for instance, transformed to the phenyl ketone **6** via treatment with phenylmagnesium chloride (see Scheme 2).

## Scheme 2. Scale-Up Experiment and Post-functionalization Reactions



In conclusion, highly enantiomerically enriched  $\alpha,\alpha$ -dichloro or  $\alpha,\alpha$ -difluoro  $\beta$ -hydroxy esters and  $\beta$ -hydroxy amides can be prepared through ruthenium-catalyzed asymmetric transfer hydrogenation (ATH) of the corresponding ketones under mild conditions. The use of commercially available precatalyst [RuCl(*p*-cymene)(*R,R*)-TsDPEN] (*S/C* = 100–200) in the presence of formic acid/triethylamine (5:2) as the hydrogen source allowed the efficient reduction of a wide range of nonaromatic  $\alpha,\alpha$ -dihalogeno  $\beta$ -keto esters in good to high yields (up to 99% yield) and with excellent enantioselectivities (up to >99% ee), whereas aromatic derivatives led to fair ee values. The reaction was tolerant of various esters, as well as being applicable to amides. Moreover, the ATH was efficiently performed on gram-scale with compound **1a**, demonstrating the usefulness of this method.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01943.

Experimental procedures, compound characterization data, NMR spectra and HPLC or SCF data for all new compounds (PDF)

## Accession Codes

CCDC 1850872 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif), or by emailing [data\\_request@ccdc.cam.ac.uk](mailto:data_request@ccdc.cam.ac.uk), or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

## ■ AUTHOR INFORMATION

### Corresponding Authors

\*E-mail: [phannarath.phansavath@chimie-paristech.fr](mailto:phannarath.phansavath@chimie-paristech.fr) (P. Phansavath).

\*E-mail: [virginie.vidal@chimie-paristech.fr](mailto:virginie.vidal@chimie-paristech.fr) (V. Ratovelomanana-Vidal).

### ORCID

Virginie Ratovelomanana-Vidal: 0000-0003-1167-1195

## Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

This work was supported by the Ministère de l'Éducation Nationale, de l'Enseignement Supérieur et de la Recherche (MENESR) and the Centre National de la Recherche Scientifique (CNRS). We gratefully acknowledge the China Scholarship Council (CSC) for a grant to L.-S. Z. We thank G. Gontard for the X-ray analysis (Sorbonne Université, Paris).

## ■ REFERENCES

- (1) Hernandez, M. Z.; Cavalcanti, S. M. T.; Moreira, D. R. M.; de Azevedo, W. F., Jr.; Leite, A. C. L. *Curr. Drug Targets* **2010**, *11*, 303.
- (2) Wilcken, R.; Zimmermann, M. O.; Lange, A.; Joerger, A. C.; Boeckler, F. M. *J. Med. Chem.* **2013**, *56*, 1363.
- (3) (a) Yamamoto, T.; Ishibuchi, S.; Ishizuka, T.; Haratake, M.; Kunieda, T. *J. Org. Chem.* **1993**, *58*, 1997. (b) Pinho, P.; Kalayanov, G.; Westerlind, H.; Rosenquist, Å.; Wähling, H.; Sund, C.; Almeida, M.; Ayesa, S.; Tejbrant, J.; Targett-Adams, P.; Eneroth, A.; Lindqvist, A. *Bioorg. Med. Chem. Lett.* **2017**, *27*, 3468. (c) Miller, E. J.; Mays, S. G.; Baillie, M. T.; Howard, R. B.; Culver, D. G.; Saindane, M.; Pruet, S. T.; Holt, J. J.; Menaldino, D. S.; Evers, T. J.; Reddy, G. P.; Arrendale, R. F.; Natchus, M. G.; Petros, J. A.; Liotta, D. C. *ACS Med. Chem. Lett.* **2016**, *7*, 537. (d) Si, C.; Fales, K. R.; Torrado, A.; Frimpong, K.; Kaoudi, T.; Vandever, H. G.; Njoroge, F. G. *J. Org. Chem.* **2016**, *81*, 4359.
- (4) (a) Kaneda, T.; Komura, S.; Kitazume, T. *J. Fluorine Chem.* **2005**, *126*, 17. (b) Zhou, H.; Xu, Q.; Chen, P. *Tetrahedron* **2008**, *64*, 6494. (c) Iseki, K.; Kuroki, Y.; Asada, D.; Takahashi, M.; Kishimoto, S.; Kobayashi, Y. *Tetrahedron* **1997**, *53*, 10271. (d) Iseki, K.; Kuroki, Y.; Asada, D.; Kobayashi, Y. *Tetrahedron Lett.* **1997**, *38*, 1447. (e) Imashiro, R.; Kuroda, T. *J. Org. Chem.* **2003**, *68*, 974. (f) Kuroki, Y.; Asada, D.; Iseki, K. *Tetrahedron Lett.* **2000**, *41*, 9853. (g) Blanc, D.; Ratovelomanana-Vidal, V.; Gillet, J.-P.; Genêt, J.-P. *J. Organomet. Chem.* **2000**, *603*, 128. (h) Mochizuki, N.; Sugai, T.; Ohta, H. *Biosci., Biotechnol., Biochem.* **1994**, *58*, 1666. (i) Ema, T.; Kadoya, T.; Akihara, K.; Sakai, T. *J. Mol. Catal. B: Enzym.* **2010**, *66*, 198.
- (5) (a) Echeverria, P.-G.; Cornil, J.; Féraud, C.; Guérinot, A.; Cossy, J.; Phansavath, P.; Ratovelomanana-Vidal, V. *RSC Adv.* **2015**, *5*, 56815. (b) Monnereau, L.; Cartigny, D.; Scalone, M.; Ayad, T.; Ratovelomanana-Vidal, V. *Chem.—Eur. J.* **2015**, *21*, 11799. (c) Perez, M.; Echeverria, P.-G.; Martinez-Arripe, E.; Ez Zoubir, M.; Touati, R.; Zhang, Z.; Genet, J.-P.; Phansavath, P.; Ayad, T.; Ratovelomanana-Vidal, V. *Eur. J. Org. Chem.* **2015**, *2015*, 5949. (d) Ayad, T.; Phansavath, P.; Ratovelomanana-Vidal, V. *Chem. Rec.* **2016**, *16*, 2754. (e) Zheng, L.-S.; Féraud, C.; Phansavath, P.; Ratovelomanana-Vidal, V. *Chem. Commun.* **2018**, *54*, 283. (f) Zheng, L.-S.; Phansavath, P.; Ratovelomanana-Vidal, V. *Org. Chem. Front.* **2018**, *5*, 1366.
- (6) (a) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97. (b) Palmer, M. J.; Wills, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2045. (c) Everaere, K.; Mortreux, A.; Carpentier, J.-F. *Adv. Synth. Catal.* **2003**, *345*, 67. (d) Gladiali, S.; Alberico, E. *Chem. Soc. Rev.* **2006**, *35*, 226. (e) Samec, J. S. M.; Bäckvall, J.-E.; Andersson, P. G.; Brandt, P. *Chem. Soc. Rev.* **2006**, *35*, 237. (f) Ikariya, T.; Blacker, A. J. *Acc. Chem. Res.* **2007**, *40*, 1300. (g) Blacker, A. J. In *Handbook of Homogeneous Hydrogenation*; de Vries, J. G., Elsevier, C. J., Eds.; Wiley-VCH: Weinheim, 2007, 1215. (h) Foubelo, F.; Nájera, C.; Yus, M. *Tetrahedron: Asymmetry* **2015**, *26*, 769. (i) Wang, D.; Astruc, D. *Chem. Rev.* **2015**, *115*, 6621. (j) Echeverria, P.-G.; Ayad, T.; Phansavath, P.; Ratovelomanana-Vidal, V. *Synthesis* **2016**, *48*, 2523.
- (7) (a) Soleimannejad, J.; Sisson, A.; White, C. *Inorg. Chim. Acta* **2003**, *352*, 121. (b) Sterk, D.; Stephan, M. S.; Mohar, B. *Tetrahedron Lett.* **2004**, *45*, 535. (c) Sterk, D.; Stephan, M.; Mohar, B. *Org. Lett.* **2006**, *8*, 5935. (d) Mejía, E.; Aardoom, R.; Togni, A. *Eur. J. Inorg. Chem.* **2012**, *2012*, 5021. (e) Cotman, A. E.; Cahard, D.; Mohar, B. *Angew. Chem., Int. Ed.* **2016**, *55*, 5294. (f) Mohar, B.; Stephan, M.





## Résumé

Ce manuscrit présente le développement de méthodes efficaces pour accéder à des alcools fonctionnalisés énantioenrichis tels que des  $\alpha,\alpha$ -dihalogéno  $\beta$ -hydroxy esters et amides, ainsi qu'à des aminoalcools 1,2 et 1,3 et des diols 1,2 énantioenrichis, en utilisant des réactions de transfert d'hydrogène asymétrique (THA) catalysées par des complexes de Ru ou Rh, associées à un processus de dédoublement cinétique dynamique (DCD). Les réactions s'effectuent dans des conditions douces avec un faible taux catalytique, et conduisent aux produits réduits avec de très bonnes diastéréo- et énantiosélectivités. Des dérivés *syn* et *anti*-aminoalcools 1,2 ont été préparés par réactions de THA, catalysées par des complexes de Ru ou Rh, des  $\alpha$ -amido  $\beta$ -cétoesters correspondants. Une série de nouveaux complexes Rh(III)/Cp\* contenant des ligands *N*-(*p*-tolylsulfonyl)-1,2-diphényléthylène-1,2-diamine ou pentafluorobenzènesulfonyl-DPEN été préparés, caractérisés et évalués dans le THA d'une large gamme de (hétéro) arylcétones ou d' $\alpha$ -alcoxy  $\beta$ -céto esters. Enfin, une approche stéréosélective efficace vers des dérivés de 2-(1,2,3,4-tétrahydro-1-isoquinolyl) éthanol par THA de  $\beta$ -amino-cétones cycliques via un processus de DCD a également été développée.

## Mots Clés

catalyse asymétrique, hydrogénation, hétérocycles, réduction, transfert d'hydrogène, métaux de transition

## Abstract

This manuscript presents the development of efficient methods to access enantioenriched functionalized alcohols such as  $\alpha,\alpha$ -dihalogeno  $\beta$ -hydroxy esters and amides, as well as 1,2- and 1,3 aminoalcohol and 1,2-diol derivatives, using Ru- or Rh-catalyzed asymmetric transfer hydrogenation (ATH) reactions combined with a dynamic kinetic resolution process (DKR). The reactions usually proceeded with a low catalyst loading, under mild conditions and afforded the desired reduced products with very high levels of diastereo- and enantioselectivities. Both *syn* and *anti* 1,2-aminoalcohol derivatives were prepared through Ru- or Rh-catalyzed ATH of the corresponding  $\alpha$ -amido  $\beta$ -ketoesters. A series of new tethered Rh(III)/Cp\* complexes containing *N*-(*p*-tolylsulfonyl)-1,2-diphenylethylene-1,2-diamine or pentafluorobenzenesulfonyl-DPEN ligands have been prepared, characterized, and evaluated in the asymmetric transfer hydrogenation of a wide range of (hetero)aryl ketones or  $\alpha$ -alkoxy  $\beta$ -keto esters. Finally, an efficient, stereoselective route to 2-(1,2,3,4-tetrahydro-1-isoquinolyl)ethanol derivatives through an asymmetric transfer hydrogenation of ring-substituted  $\beta$ -amino ketones via DKR has also been developed.

## Keywords

asymmetric catalysis, hydrogenation, hétérocycles, reduction, transfer hydrogenation, transition metal



