



**palladium-catalyzed asymmetric allylic alkylation :
control of all-carbon quaternary centers in
nitrogen-containing heterocycles**

Tao Song

► **To cite this version:**

Tao Song. palladium-catalyzed asymmetric allylic alkylation : control of all-carbon quaternary centers in nitrogen-containing heterocycles. Organic chemistry. Université Paris sciences et lettres, 2018. English. NNT : 2018PSLET012 . tel-02496962

HAL Id: tel-02496962

<https://pastel.hal.science/tel-02496962>

Submitted on 3 Mar 2020

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 au Laboratoire de Chimie Organique,
ESPCI Paris

Palladium-Catalyzed Asymmetric Allylic Alkylation : Control Of All-Carbon Quaternary Centers In Nitrogen-Containing Heterocycles

Ecole doctorale n°406

Chimie moléculaire Paris Centre

Spécialité Chimie Moléculaire

Soutenue par **Tao SONG**

le 24 Octobre **2018**

Dirigée par **Pr. Janine COSSY**
et **Dr. Stellios ARSENIYADIS**

COMPOSITION DU JURY :

M. BELMONT Philippe
Univ. Paris-Descartes Rapporteur

M. NAY Bastien
Ecole Polytechnique Rapporteur

Mme. VIDAL Virginie (President)
Chimie-ParisTech Examineur

M. LEBOEUF David
Univ. Paris-Sud Examineur

Mme. COSSY Janine
ESPCI-PSL Directeur de thèse

M. ARSENIYADIS Stellios
QMUL-UK Co-Directeur de thèse

Acknowledgments

There are so many people which should be appreciated in this acknowledgment, without them, it would have been impossible to finish my thesis. The first one that I would like to thank is Pr. Janine Cossy for giving me this precious opportunity to study in her group to pursue my PhD. The great support and wise guidance from her helped me to have a great improvement of my professional and personal abilities during these three years studying in the LCO. Her concern and encouragement through the past three years are also appreciated. Besides the profound knowledge, her passion for organic chemistry has deeply impacted our young researchers, and gave us an outstanding role model for our future career!

Another important people which I would like to thank is Dr. Stelios Arseniyadis. Without his great help, it would have been impossible for me to go abroad and pursue a PhD in Paris. Thanks for all of the efforts he has done for me since the first time I contacted him for applying a PhD position. It is my honor to be part of SA group and have a supervisor like him. Even though we didn't work in the same place, he was always available to discuss and solve the problems which I met in my research and life in the past three years. Here, I would like to thank him again for his great help!

I also want to thank all of my jury members: Pr. Philippe Belmont, Dr. Bastien Nay, Dr. Virgile Vidal and Dr. David Leboeuf. I appreciate them for the time and effort they spend and do for reviewing my works.

Pr. Yongmin Zhang and Dr. Gilles Lemière are also appreciated for their kindly discussions and guidance for my thesis.

The China Scholarship Council is also gratefully acknowledged for the generous financial support.

Then, I would like to thank all of the group members in the LCO. I was really fortunate to work with all these amazing chemists for three years. Firstly, I would like to thank the timeless members: Pr. Véronique Bellosta, Dr. Amandine Guérinot, Dr. Andrei Corbu and Dr. Domingo Gomez Pardo, especially Dr. Christophe Meyer who shared a lot of knowledge on organic chemistry to all of the students and always took care of me before he left the lab every day. Then, I would like to thank all of the students who worked with me together in the LCO. For the SA members: Morgan who gave me great help for my experiments and life, and also taught me so much

knowledge on the French culture and a lot of interesting words which helped me find a way to adapt to the new environment; Marllon who shared so many experiences of experiment to me and discussed the problems which I met during my research. I also want to thank the students of my generation: Etienne and Zeina for all of the great help from them, both of them always treat me like a brother and help me as possible as they can from the first day I joined the group. I am very lucky to work with you! I would like to say sorry for “TBM”-Zeina for asking her to the hydrogenation with me together so many times. I also want to thank the former members: Thomas, Sarah, Alexandra, Florence, Guillaume M, Guillaume B, Laurine, Baptiste for all of the great help from them. For the younger generation: Guillaume, Alexandre, Aziz, Tomas, Khalil, Claire, Ondine, Nicolas, Gauthier, thanks for their great help and all of pleasures from them, especially for different kind of beers which I tasted. In addition, I also want to thank the great help from all of the post-doctors: Johan, Thibault, Morgan, Pierre-Antoine, Aurélie, Mohamed, Simon, Geoffrey, Andrea, and, especially, Parth who helped me as possible as he can and shared so much knowledge to me. I also would like thank Marion for her kindly invitation to play interesting games with them together. Maria, who I also want to thank her for the great encouragement and kind concern.

For the other important people in the LCO who I would like to thank are Isabelle, Hélène, Arthur and Thomas. Thanks so much for their outstanding works and services for all of the LCO members.

At the same time, I would also like to thank Pr. Li-wen Xu and all of the members from his group in Hangzhou Normal University. The studying in Pr. Xu’s group was one of my precious experience which completely changed my life and led me to pursue a further study in organic chemistry. Pr. Xu helped me find a direction which I could spend my life to do something meaningful.

I also want to thank my friends, Fei, Longsheng, Xingfeng, Hu Wang, Wenhui, Yunlong, Weisheng, Muyi, Jianxing, Deshan, and Peiyuan.... Thanks for all of the knowledge, experiment skills and concern from them during these years. In particularly, Fei, who was the first student to pursue a PhD abroad from Pr. Xu’s group, deeply encouraged the other younger students from the same group (including me) to pursue a further study in organic chemistry abroad; Longsheng, who taught me

everything patiently when I was a master student; Deshan who we met three years before at Shanghai, thanks my brother for all of the concern and support from you.

Last but not least, thanks for the great support from my family, especially my wife Qing and my parents who always support me without any condition and encourage me to overcome all of the problems in my life, I can't find a word to express how deep I do love you. The great support from Qing's parents are also appreciated! Thanks so much for what they have done for Qing and me!

Table of Contents

Abbreviation list.....	13
Résumé en Français.....	17
Abstract.....	53
 Chapter I: Enantioselective Synthesis of Optically Active Succinimide Derivatives through Palladium-Catalyzed Asymmetric Allylic Alkylation.....	 55
 1. Succinimide unit in natural products and/or bioactive compounds.....	 57
1.1. Natural occurrence and biological activity.....	57
1.1.1. Hirsutellones A-E.....	58
1.1.2. Haterumaimides A-I.....	58
1.1.3. Ethosuximide.....	59
1.1.4. Ranirestat.....	60
 2. Enantioselective synthesis of succinimide derivatives.....	 60
2.1. Enantioselective synthesis of succinimide derivatives bearing a tertiary stereogenic center.....	60
2.1.1. Asymmetric organocatalytic conjugate addition of nucleophiles to maleimides	60
2.1.2. Organocatalytic ring expansion of β -lactams.....	64
2.1.3. Transition metal-catalyzed enantioselective hydrogenation.....	67
2.1.4. Rhodium-catalyzed 1,4-addition of arylboronic acids to maleimide....	68
2.2. Enantioselective synthesis of succinimide derivatives bearing a quaternary stereogenic center.....	70
2.2.1. Rhodium-catalyzed 1,4-addition of arylboronic acids to monosubstituted maleimides.....	67
2.2.2. Enantioselective copper-catalyzed click cycloaddition for the desymmetrization of maleimide-based bis(alkynes).....	71
2.2.3. NHC-catalyzed asymmetric [3+2]-cycloaddition.....	72

2.2.4. Cyclization of amine and chiral carboxylic acid derivatives.....	74
3. Results and discussion.....	76
3.1. Context and objective.....	76
3.2. Synthesis of succinimide derivatives and allylic reagents.....	81
3.2.1. Synthesis of monosubstituted succinimide derivatives.....	81
3.2.2. Synthesis of allylic reagents.....	84
3.3. Optimization of Pd-AAA conditions of succinimide derivatives.....	87
3.3.1. Influence of different bases.....	87
3.3.2. Influence of the solvent.....	88
3.3.3. Influence of the ligand.....	89
3.3.4. Influence of the temperature.....	90
3.3.5. Influence of the leaving groups on the allylic reagent.....	91
3.4. Scope of the reaction.....	92
3.4.1. α -Substituted succinimides.....	92
3.4.1.1. Influence of the <i>N</i> -protecting group.....	92
3.4.1.2. Influence of the substituted group at the C3-position.....	93
3.4.2. Allyl acetates.....	94
3.4.2.1. 2-substituted allyl acetates.....	94
3.4.2.2. 3-substituted allyl acetates.....	95
3.4.3. Pd-AAA of six-membered ring substrates.....	97
3.4.4. Pd-AAA vs Pd-ADAA of α -aromatic substituted succinimides.....	98
3.5. Influence of the catalyst loading.....	99
3.6. Origin of the enantioselectivity.....	100
3.7. Post-functionalization of allylated succinimide derivatives.....	101
3.7.1. Hydrogenation of allylated succinimide derivatives.....	102
3.7.2. Ozonolysis of allylated succinimide derivatives.....	103
3.7.3. Cross-metathesis of allylated succinimide derivatives.....	103
3.7.4. Synthesis of spirocyclic compounds.....	104
3.7.5. Synthesis of optically active pyrrolidine derivatives.....	105
4. Conclusion.....	106
Experimental Section- Chapter I.....	107

Chapter II: Direct Palladium-Catalyzed Asymmetric Allylation of Cyclic Silyl Dienol Ethers: A Straightforward Entry Into α -Quaternary γ -Lactams.....197

1. γ-Lactams in natural products and/or bioactive compounds.....	199
1.1. Natural occurrence and biological activity.....	199
1.1.1. (–)-Pramanicin.....	199
1.1.2. (+)-Lactacystin.....	200
1.1.3. (–)-Salinosporamide A.....	202
1.1.4. (–)-Clausenamide.....	203
2. Enantioselective synthesis of γ-lactam derivatives.....	204
2.1. Enantioselective synthesis of γ -lactam derivatives bearing a tertiary stereogenic centre.....	204
2.1.1. Asymmetric electrophilic substitutions of α,β -unsaturated γ -lactams and 2-siloxypyrroles.....	204
2.1.1.1. Vinylogous Michael addition.....	205
2.1.1.2. Vinylogous Mannich-type addition.....	207
2.1.1.3. Vinylogous Mukaiyama aldol reaction.....	208
2.1.2. Brønsted-acid catalyzed asymmetric tandem reactions.....	210
2.1.3. Lewis-acid catalyzed domino-ring-opening/cyclization from optical pure aziridines with enolates.....	211
2.1.4. Transition metal-catalyzed reactions.....	213
2.1.4.1. Rhodium-catalyzed intramolecular reductive cyclization.....	214
2.1.4.2. Ruthenium-catalyzed asymmetric auto-tandem allylic amidation..	214
2.2. Enantioselective synthesis of γ -lactam derivatives bearing a quaternary stereogenic center.....	216
2.2.1. Organocatalytic enantioselective sulfenylation of deconjugated butyrolactams.	216
2.2.2. NHC-catalyzed enantioselective addition of enals to isatin-derived ketimines.....	217
2.2.3. Asymmetric vinylogous Michael addition.....	218

2.2.4. Auxiliary based stereoselective allylation active bicyclic lactam.....	219
2.2.5. Transition metal-catalyzed asymmetric reactions.....	220
2.2.5.1. Ni-catalyzed enantioselective C-acylation.....	220
2.2.5.2. Ru-catalyzed dehydrative intramolecular <i>N</i> -allylation.....	222
2.2.5.3. Pd-catalyzed asymmetric decarboxylative allylic alkylation.....	223
3. Results and discussion.....	223
3.1. Context and objective.....	223
3.2. Synthesis of α,γ -disubstituted 2-silyloxypyrrole substrates.....	224
3.2.1. Synthesis of α,β -unsaturated ketones (Aldol condensation).....	225
3.2.2. Synthesis of γ -ketoacids (Conjugate addition and nef-type oxidation).....	226
3.2.3. Synthesis of α,γ -disubstituted- α,β -unsaturated lactams (Cyclization).....	227
3.2.4. Synthesis of α,γ -disubstituted 2-silyloxypyrroles (Silylation).....	229
3.3. Synthesis allylic reagents.....	231
3.4. Optimization of the Pd-AAA conditions.....	233
3.4.1. Influence of the leaving group of allylic reagent.....	233
3.4.2. Influence of the chiral phosphine ligand.....	235
3.4.3. Influence of the solvent.....	236
3.4.4. Influence of the temperature.....	237
3.4.5. Influence of catalysts loading.....	238
3.5. Substrate scope and limitation.....	239
3.5.1. Substrate scope of N-protected 2-silyloxypyrroles	239
3.5.2. Substrate scope of 2-silyloxypyrroles substituted at the α - and γ -position	240
3.5.3. Substrate scope of different β -substituted allyl benzoates.....	242
3.5.4. Substrate scope with allyl benzoate and other 2-silyloxypyrroles.....	244
3.5.5. Scale-up of the reaction.....	245
3.6. Origin of the enantioselectivity.....	246
3.7. Post-functionalization.....	247
3.7.1. Synthesis of optically active pyrrolidinones.....	247
3.7.2. Synthesis of optically active pyrrolidines.....	247
3.7.3. Cope rearrangement vs 1,3-migration of allylated products.....	249

4. Conclusion	251
Experimental Section –Chapter II.....	253
General conclusion.....	349
Perspective.....	353
Reference.....	357

Abbreviation List

[α] _D	specific rotation at wavelength of sodium D line
AAA	asymmetric allylic alkylation
AIBN	Azobisisobutyronitrile
App	apparent
Ar	Aryl
ARI	aldose reductase inhibitor
Bn	benzyl
Boc	<i>tert</i> -butyloxycarbonyl
br	broad signal
BSA	<i>N,O</i> -bis(trimethylsilyl)acetamide
Bu	butyl
Bz	benzoyl
<i>c</i>	concentration
CAN	Ceric ammonium nitrate
Cbz	carboxybenzyl
Cp	Cyclopentadienyl
CuAAC	Copper-catalyzed azide-alkyne cycloaddition
d	doublet
dba	dibenzylideneacetone
DBU	1,8-diazobicyclo[5.4.0]undec-7-ene
DIBAL-H	Diisobutylaluminium hydride
DIPEA	<i>N,N</i> -diisopropylethylamine
DMAP	4-(<i>N,N</i> -dimethylamino)pyridine
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
DSP	diabetic sensorimotor polyneuropathy
ee	enantiomeric excess
eq	equation
equiv	equivalent
Et	ethyl

EtOAc	ethyl acetate
GC-MS	gas chromatography-mass spectrometry
h	hour
HATU	2-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
HRMS	high resolution mass spectrometry
<i>i</i> Pr	isopropyl
IR	Infrared
<i>J</i>	coupling constant
LA	Lewis acid
LDA	lithium diisopropylamide
LG	Leaving group
LiHMDS	lithium bis(trimethylsilyl)amide
<i>m</i>	<i>meta</i>
m	multiplet
Me	methyl
MIC	minimum inhibitory concentration
min	minute
Mp	meting point
MS	mass spectrometry
MTBE	methyl <i>tert</i> -butyl ether
NaHMDS	sodium bis(trimethylsilyl)amide
ND	non-determined
NHC	N-heterocyclic carbene
NMR	nuclear magnetic resonance
Nu	Nucleophile
<i>o</i>	<i>ortho</i>
OFBA	<i>o</i> -fluorobenzoic acid
OTf	triflate
<i>p</i>	<i>para</i>
PE	petroleum ether
PG	protecting group

Ph	phenyl
PHOX	phosphinoxazoline
PTZ	Pentylene TetraZol
Py	Pyridine
rac	racemic
red-Al	Sodium bis(2-methoxyethoxy)aluminumhydride
rt	room temperature
s	singlet
SFC	supercritical fluid chromatography
T	temperature
<i>t</i>	<i>tert or triplet</i>
TBACN	tetrabutylammonium cyanide
TBS	<i>tert</i> -butyldimethylsilyl
<i>t</i> -Bu	<i>tert</i> -butyl
TES	triethylsilyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	<i>N,N,N',N'</i> -tetramethylethylenediamine
TMS	trimethylsilyl or TetraMethyl Succinimide
<i>t_R</i>	retention time
Ts	tosyl

Résumé en Français

Introduction générale

L'obtention d'hétérocycles azotés à 5 chaînons portant un centre stéréogène quaternaire est un défi important en chimie organique. Lors de cette thèse, nous avons développé, avec succès, deux méthodes synthétiques permettant d'accéder à des motifs succinimides et γ -lactames possédant un centre quaternaire. Pour ce faire, nous avons utilisé une réaction d'**Alkylation Allylique Asymétrique** pallado-catalysée (**Pd-AAA**).

Ce manuscrit est constitué de deux chapitres, le premier s'intitule : « Synthèse énantiosélective de succinimides optiquement actifs par réaction de type Pd-AAA », le second chapitre s'intitule : « Alkylation allylique asymétrique d'éthers de diénols silylés cycliques : une méthode efficace d'accès à des γ -lactames portant un centre stéréogène quaternaire en position α ». Pour chaque chapitre, un résumé de l'état de l'art est également inclu.

Chapitre I

Synthèse énantiosélective de dérivés succinimide optiquement actifs par l'intermédiaire d'alkylation allylique asymétrique catalysée au palladium

Introduction : Le fragment succinimide au sein de produits naturels et/ou de composés bioactifs

De nombreux produits naturels biologiquement actifs ainsi que des produits pharmaceutiques contiennent un motif succinimide optiquement pur (Figure 1), telle que l'hirsutellone A, isolée à partir du pathogène *Hirsutella nivea* BCC 2594 en 2005. Ce composé a démontré une inhibition notable de la croissance de la bactérie *Mycobacterium tuberculosis* H₃₇Ra. Il convient également de citer l'Haterumaimide A qui est un produit naturel important dont il a été démontré une potentielle utilisation en tant qu'inhibiteur de la synthèse de protéines ainsi qu'une activité anticancéreuse. (+)-Ethosuximide, qui est un dérivé succinimide comprenant un centre stéréogène quaternaire relié à quatre atomes de carbones, est un médicament clé connu comme anticonvulsivant. Pour finir, ranirestat est un inhibiteur d'aldose réductase.

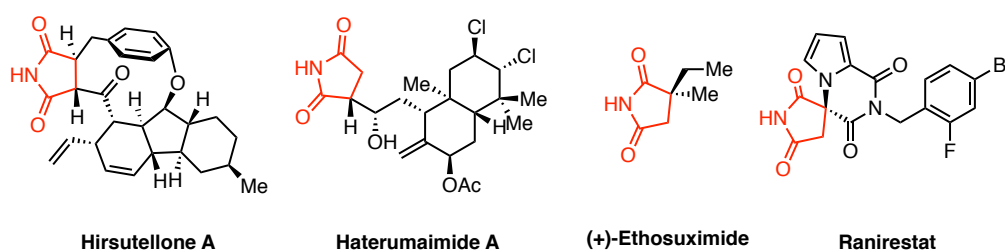


Figure 1. Exemples sélectionnés de produits naturels et pharmaceutiques contenant un fragment succinimide.

1. Méthodes principales pour la construction asymétrique de succinimides optiquement actifs

Au cours de la dernière décennie, de nombreux efforts ont été entrepris par les chimistes afin de développer diverses stratégies pour la synthèse de succinimides optiquement actifs du fait de la présence de ces derniers au sein de produits naturels

et pharmaceutiques. Ce chapitre décrit les différentes approches décrites dans la littérature pour la construction de succinimides optiquement actifs contenant un centre stéréogène tertiaire ou quaternaire en position α .

1.1. Synthèse énantiosélective de succinimides optiquement actifs comportant un centre stéréogène tertiaire

Ces dernières années ont vu le développement de nombreuses stratégies efficaces pour la synthèse de succinimides comportant un centre stéréogène tertiaire. L'une des méthodes les plus conventionnelles et directes est l'addition conjuguée asymétrique organo-catalysée sur des dérivés maléimides, qui sont utilisés en tant qu'excellents accepteurs de Michael. En 2009, Melchiorre *et al.*⁹ ont rapporté le premier exemple de ce type impliquant des composés 1,3-dicarbonylés et des maléimides, utilisant des dérivés de la quinine comme catalyseur. Une large gamme de composés dicarbonylés tri-substitués ont été employés en tant que nucléophiles pro-chiraux afin de générer les adduits de Michael correspondant comportant des centres stéréogènes tertiaires et quaternaires avec de bons rendements, d'excellentes stéréosélectivités (jusqu'à >98:2 rd et 98% ee) (Schéma 1).¹¹

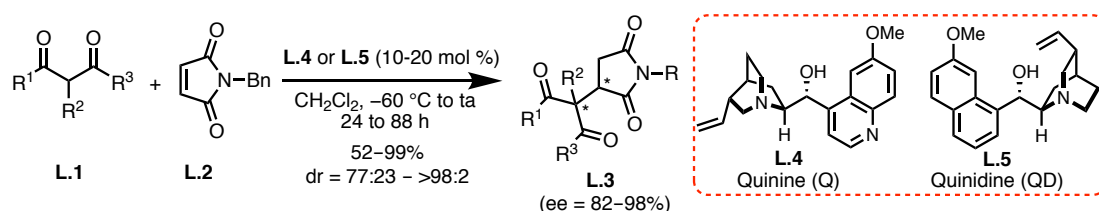


Schéma 1. Addition conjuguée asymétrique de composés 1,3-dicarbonylés sur des maléimides catalysée par des dérivés de la quinine.

L'expansion de cycle énantiopure de β -lactames est également une stratégie utile pour la synthèse de succinimides optiquement actifs. A ce sujet, Alcaide *et al.* ont développé deux types de conditions réactionnelles pour la préparation de ces fragments. Premièrement, une expansion de cycle de dérivés 4-(arylimino)méthylazetidines-2-ones **L.7** promue par du cyanure de tétrabutylammonium (TBACN) suivie par l'hydrolyse sélective d'imines (Schéma 2).^{12a}

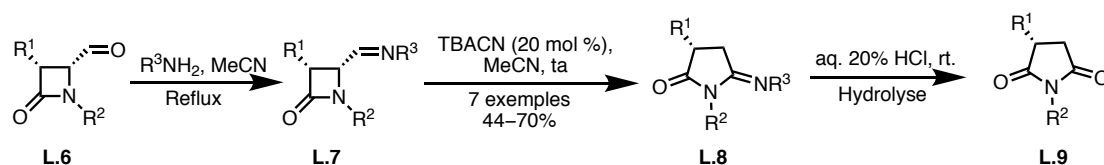


Schéma 2. Expansion de cycle de β -lactames énantiopures promue par TBACN pour la préparation de succinimides optiquement actifs.

En second lieu, Alcaide *et al.* ont rapporté une stratégie élégante pour l'obtention en une étape de succinimides de type **L.12** par expansion de cycle de 4-oxoazétidin-2-carbaldéhyde **L.10** (Schéma 3). Cette approche implique l'inversion de la polarité de l'aldéhyde (Umpolung) grâce à **L.11**.^{12b}

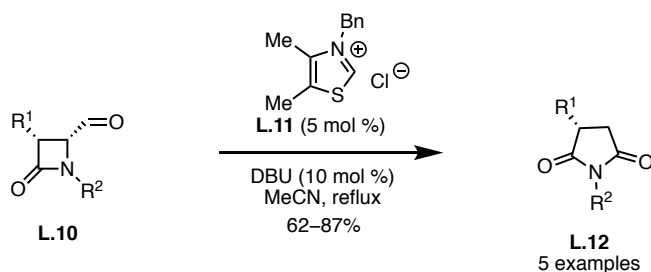


Schéma 3. Expansion de cycle de β -lactames promue par un carbène *N*-hétérocyclique pour la préparation de succinimides.

1.2 Synthèse énantiosélective de succinimides optiquement actifs comprenant un centre stéréogène quaternaire

Malgré un nombre important de méthodes développées au cours de cette dernière décennie, la construction énantiosélective de composés cycliques et acycliques comprenant un centre stéréogène quaternaire reste un défi en synthèse asymétrique. A notre connaissance, seules quelques stratégies efficaces ont été rapportées à ce jour.

Par exemple, Hayashi *et al.*²⁶ ont développé une addition 1,4 asymétrique d'acides boroniques sur des maléimides mono-substitués **L.13** catalysée au rhodium. De cette façon, il a été possible d'isoler les dérivés succinimides 3,3'-disubstitués **L.16** et **L.17** correspondants avec d'excellent rendements (82-98%) ainsi que d'excellentes stéréosélectivités (jusqu'à >98:2 rd et 98% ee) (Schéma 4).

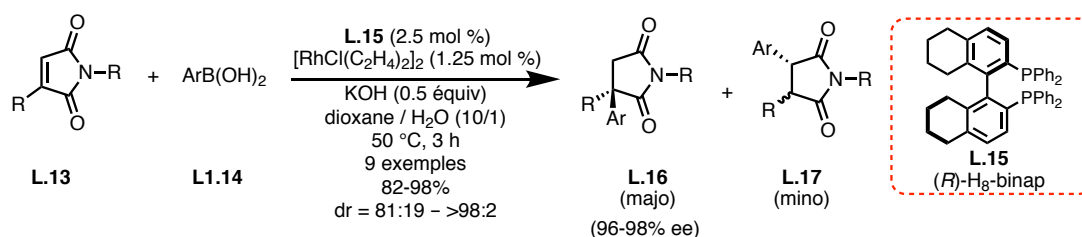


Schéma 4. Addition 1,4 asymétrique d'acides boroniques sur des maléimides mono-substitués catalysée au rhodium.

Récemment, Xu *et al.*²⁷ ont réalisé la désymétrisation de succinimides pro-chiraux en utilisant une cycloaddition [3+2] asymétrique d'azide-alcyne catalysée par du cuivre et impliquant des bis(alcyne) maléimides **L.18**. Pour cela, un nouveau ligand phosphinique chirale **L.20** a été développé et utilisé afin d'obtenir **L.21** avec de bons rendements (60-80%) et des excès énantiomériques allant jusqu'à 99% (Schéma 5).

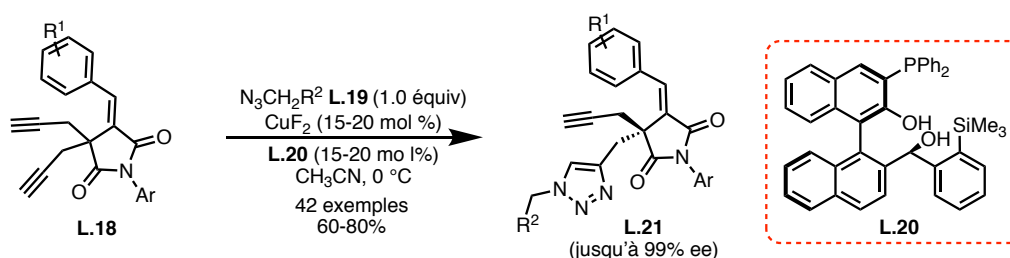


Schéma 5. Désymétrisation de succinimides prochiraux catalysée au cuivre.

Une autre approche pour l'obtention de succinimides optiquement actifs a été développée par Ender *et al.*²⁸ Ces derniers ont mis au point un système catalytique impliquant un carbène *N*-hétérocyclique chiral pour la cycloaddition [3+2] asymétrique entre des énales **L.22** et des α -cétoamides **L.23**. Les succinimides correspondants **L.25** ont été obtenus avec de très bons rendements ainsi que de très bonnes régiosélectivités et énantiosélectivités (Schéma 6).

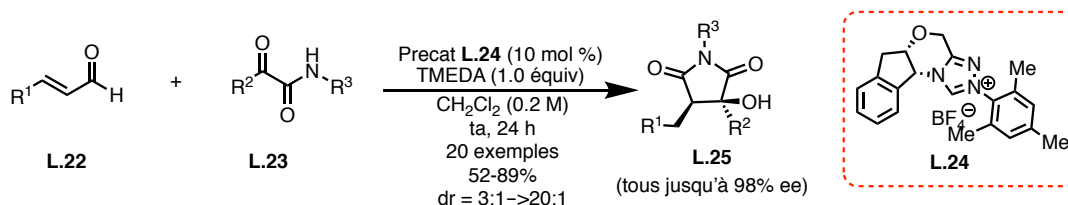


Schéma 6. Catalyse employant un carbène *N*-hétérocyclique chiral pour la cycloaddition [3+2] asymétrique entre des énales et des α -cétoamides.

2. Contexte et objectifs

Malgré le fait que plusieurs méthodes ont été précédemment développées pour la synthèse de succinimides optiquement actifs comprenant un centre stéréogénique quaternaire, il y a toujours la nécessité de mettre au point des stratégies à la fois plus efficaces et plus directes. L'Alkylation Allylique Asymétrique pallado-catalysée (Pd-AAA), aussi connue sous le nom de "réaction de Tsuji-Trost", est particulièrement importante en synthèse asymétrique. En effet, cette méthode est l'une des plus efficaces et des plus directes pour la construction de centres stéréogènes *via* la formation d'une nouvelle liaison carbone-carbone ou carbone-hétéroatome (O, S, N, P). Cette réaction implique soit une attaque nucléophile sur l'intermédiaire Pd- π -allyle, soit une substitution allylique de type S_N2' .

Inspirés par les travaux précédents réalisés au laboratoire sur la Pd-AAA, nous avons envisagé d'appliquer cette réaction aux succinimides mono-substitués afin d'accéder aux succinimides allylés correspondants comprenant un centre stéréogène quaternaire en position α (Schéma 7). Cette méthode permettrait en effet un accès plus direct et surtout sélectif à de tels substrats.

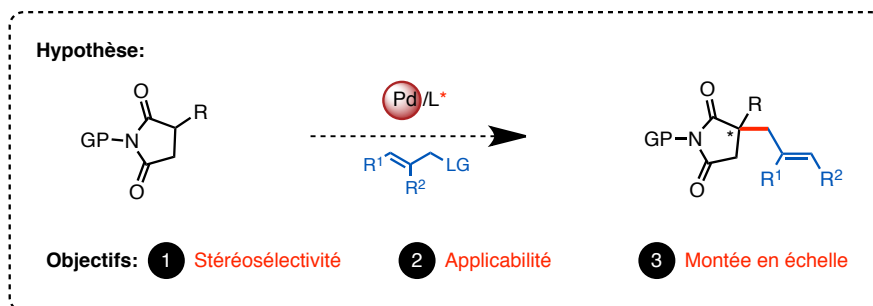


Schéma 7. Postulat de départ pour la construction de succinimides optiquement actifs comprenant un centre stéréogène quaternaire par l'intermédiaire de la Pd-AAA.

2.1. Résultats et discussions

2.1.1. Synthèse des substrats succinimides et des réactifs allyliques

Une large gamme de substrats pro-chiraux avec différents groupements protecteurs a été substituée suivant deux méthodes de synthèse. La première consiste à traiter les succinimides **L.27** par une base, suivi par la neutralisation de l'énolate

résultant par un chlorure d'acyle. En utilisant cette méthode, les substrats **L.30** ont été obtenus avec des rendements allant de 30% à 80% (Schéma 8). La seconde stratégie permettant d'accéder au composé **L.34** font intervenir le diacide **L.31**. L'intermédiaire **L.32** a été obtenu par traitement de **L.31** avec la benzylamine, et le succinimide correspondant a été ensuite transformé en ester allylique **L.34** (Schéma 9).

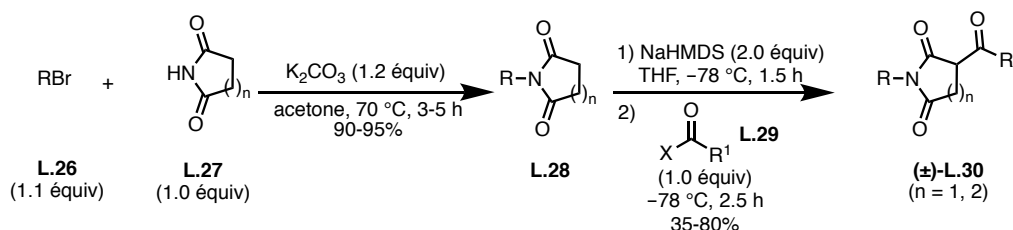


Schéma 8. Synthèse des substrats succinimides **L.30**.

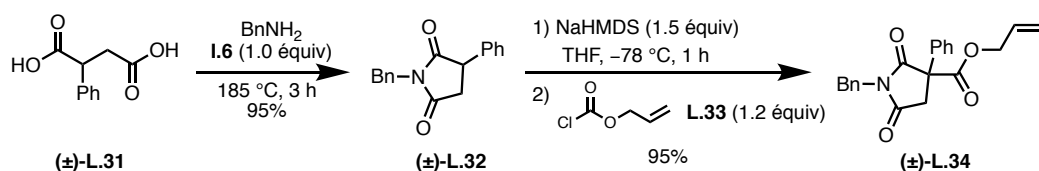


Schéma 9. Synthèse des substrats succinimides **L.32** et **L.34**.

Afin d'étudier la Pd-AAA, différents acétates allyliques β -substitués ont également été préparés. Ces derniers ont été synthétisés en trois étapes à partir d'aldéhydes aromatiques et d'ylures de triphénylphosphine par l'intermédiaire d'une réaction de Wittig, d'une réduction assistée par du DIBAL-H et d'une acylation. D'une manière générale, tous les acétates allyliques β -substitués **L.38** ont été isolés avec de bons rendements (Schéma 10).

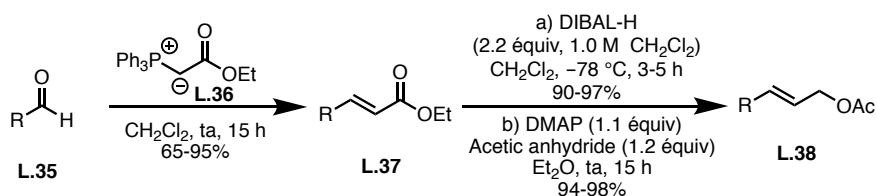


Schéma 10. Synthèse d'acétates allyliques β -substitués.

2.1.2. Optimisation des conditions réactionnelles

Afin de vérifier notre hypothèse, le substrat succinimide **L.30a** a été utilisé comme substrat modèle pour explorer les conditions réactionnelles en utilisant l'acétate d'allyle **I.19a** comme donneur d'allyle.

La réaction a tout d'abord été réalisée en utilisant le ligand de Trost (*R,R*)-DACH-Phényl **11** (10 mol %) en présence de Pd₂(dba)₃ (5 mol %) comme catalyseur. L'influence de la base a été évaluée et résumée dans le Tableau 1. Pour toutes ces bases, le produit d'allylation **L.39a** a été obtenu avec des rendements compris entre 37% et 97% et des excès énantiomériques compris entre 30% et 79%. Signalons que lorsque une base lithiée, telle que le LDA ou LiHMDS, est utilisée, une inversion de la sélectivité a été observée (Tableau 1, entrées 11 et 12). Nous avons également pu observer que la réaction pouvait avoir lieu en l'absence de base ; le produit allylé étant obtenu avec un rendement quasi quantitatif (94%) et une bonne énantiosélectivité (76% ee) (Tableau 1, entrée 13).

Tableau 1. Influence de différentes bases sur la Pd-AAA

Entrée	Base	Additif (x équiv)	Rdt de L.39a (%) ^b	ee de L.39a (%) ^c
1	K ₂ CO ₃	-	91	78
2	Li ₂ CO ₃	-	81	76
3	Na ₂ CO ₃	-	96	77
4 ^d	Na ₂ CO ₃	-	95	79
5	DBU	-	92	54
6	BSA	-	97	63
7	Et ₃ N	-	96	78
8	Et ₃ N	Zn(OAc) ₂ (1.2)	97	77
9	Et ₃ N	ZnCl ₂ (1.2)	30	63
10	NaH	-	86	20
11	LDA	-	37	-20
12	LiHMDS	-	45	-33
13	-	-	94	76

^a Toutes les réactions ont été réalisées sur une échelle de 0.2 mmol. ^b Rendement isolé.

^c Déterminé par analyse SFC. ^d 1.0 équiv de Na₂CO₃ a été utilisé.

L'influence du solvant a également été évaluée en présence de Na₂CO₃ (1.0 équiv). Les résultats sont résumés dans le Tableau 2. De manière générale, le produit allylé **L.39a** a été obtenu avec d'excellents rendements, cependant une légère diminution de l'énantiosélectivité a été observée lorsque les réactions ont été menées dans le dichlorométhane (58% ee), le toluène (64% ee) ou encore le 1,4-dioxane (49% ee) (Tableau 1, entrées 1, 2 et 4). Par ailleurs, quand la réaction a été réalisée dans des solvants polaires, comme le DMF (10%, 31% ee) et l'acétonitrile (60%, 49% ee) le produit d'allylation **L.39a** a été obtenu avec des rendements et des énantiosélectivités plus faibles que dans les autres solvants (Tableau 2, entrées 3 et 4). Enfin, le THF a fourni les meilleurs résultats aussi bien en terme d'efficacité que de sélectivité (Tableau 2, entrée 9).

Tableau 2. Influence de différents solvants sur la Pd-AAA

$\text{L.30a} + \text{L.34a (1.0 \text{ \textit{equiv}})} \xrightarrow[\text{solvant, 0 } ^\circ\text{C, 24 h}]{\text{(R,R)-L1 (10 mol \%), Pd}_2\text{(dba)}_3 \text{ (5 mol \%), Na}_2\text{CO}_3 \text{ (1.0 \textit{equiv})}}$
 L.39a

$(R,R)\text{-L1}$

Entrée	Solvant	Rdt de L.39a (%) ^b	ee de L.39a (%) ^c
1	CH ₂ Cl ₂	95	58
2	Toluene	96	64
3	DMF	10	31
4	CH ₃ CN	60	49
5	1,4-dioxane	92	49
6	Et ₂ O	95	76
7	MTBE	96	72
8	2-Me-THF	95	77
9	THF	95	79
10 ^d	THF	94	76

^a Toutes les réactions ont été réalisées sur une échelle de 0.2 mmol. ^b Rendement isolé.

^c Déterminé par analyse SFC. ^d Sans Na₂CO₃.

Encouragés par ces premiers résultats, nous avons poursuivi l'optimisation des conditions réactionnelles en étudiant l'influence des différents ligands ainsi que de la température. Les résultats sont résumés dans le Tableau 3. De manière générale, toutes les réactions ont fourni de bons résultats. Les ligands bis-phosphine de symétrie C₂, **L1** (76% ee), **L2** (37% ee) et **L3** (–48% ee), ont fourni de meilleurs énantiosélectivités par rapport aux autres ligands biphosphines chiraux de type BINAP (**L4**, –6% ee) et SEGPHOS (**L5**, 26% ee), et les ligands oxazolines de type N/P (**L6**, –21% ee) (Tableau 3, entrées 2 à 7). Enfin, le ligand de Trost (*R,R*)-DACH-Phényl **L1** a fourni les meilleurs résultats en terme de réactivité et d'énantiosélectivité (Tableau 3, entrée 2).

Afin d'améliorer l'énantiosélectivité, l'influence de la température a été évaluée. Nous avons constaté que l'énantiosélectivité pouvait être augmentée à 86% en réalisant la réaction à –20 °C en l'absence de base. A l'inverse, en présence de Na₂CO₃ (1.0 équiv), l'énantiosélectivité était de 83% (Tableau 3, entrées 8 et 9).

Malheureusement, aucune amélioration n'a pu être observée lorsque la réaction a été réalisée à $-40\text{ }^{\circ}\text{C}$ (Tableau 3, entrées 10 et 11). A la vue de ces résultats, nous avons choisi de fixer la température à $-20\text{ }^{\circ}\text{C}$.

Tableau 3. Influence des ligands chiraux et de la température sur la Pd-AAA

CCOC(=O)C1CC(=O)N(C1)Cc2ccccc2 + CCOC=C
 $\xrightarrow[\text{solvant, } T\text{ }^{\circ}\text{C, 24 h}]{\text{Pd}_2(\text{dba})_3\text{ (5 mol \%), Na}_2\text{CO}_3\text{ (x equiv)}}$
CCOC(=O)[C@H](C=C)C1CC(=O)N(C1)Cc2ccccc2

L.30a **L.34a** (1.0 équiv) **L.39a**

Entrée	L	x	T ($^{\circ}\text{C}$)	Rdt de L.39a (%) ^b	ee de L.39a (%) ^c
1	L1	1.0	0	95	79
2	L1	-	0	94	76
3	L2	-	0	86	37
4	L3	-	0	84	-48
5	L4	-	0	91	-6
6	L5	-	0	95	-26
7	L6	-	0	96	-21
8	L1	1.0	-20	95	83
9	L1	-	-20	88	86
10	L1	1.0	-40	93	83
11	L1	-	-40	56	87

L1
(*R,R*)-DACH-Phenyl Trost Ligand

L2
(*R,R*)-DACH-Naphthyl Trost Ligand

L3
(*R,R*)-ANDEN-Phenyl Trost Ligand

L4
(*R*)-BINAP

L5
(*R*)-SEGPPOS

L6
(*S*)-(*t*-Bu)-PHOX

^a Toutes les réactions ont été réalisées sur une échelle de 0.2 mmol. ^b Rendement isolé.

^c Déterminé par analyse SFC.

2.1.3. Champ d'application de la réaction

Avec les meilleures conditions en main, nous avons par la suite examiné la nature des différents substrats succinimides α -substitués. L'ensemble des produits d'allylation ont pu être obtenus avec de bons rendements (75-96%) et des énantiosélectivités allant de modeste à excellente (11-87%) (Schéma 11). Les résultats expérimentaux nous ont également indiqué que le groupement protecteur sur l'atome d'azote n'avait pas une grande influence sur la sélectivité.

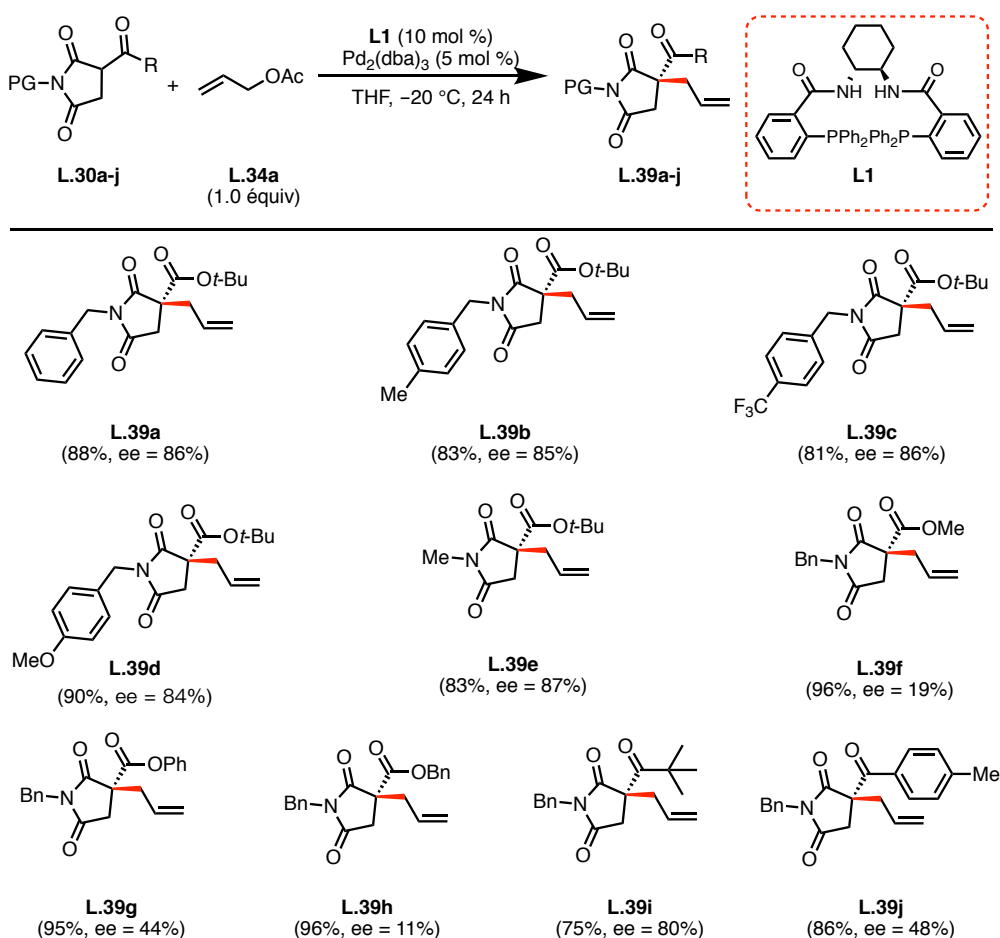


Schéma 11. Etude de la réaction sur des substrats succinimides possédant différents groupements protecteurs sur l'atome d'azote et différents substituants en position C3

D'autre part, différents acétates allyliques α -substitués ont également été testés dans les conditions optimisées. La réactivité de ces acétates allyliques α -substitués s'est révélée beaucoup moins importante ce qui nous a poussés à réaliser les réactions à ta. Dans ces conditions, les produits allylés correspondants ont été

obtenus avec de rendements souvent bons compris entre 30% et 85%, et des excès énantiomériques modestes à relativement élevés (47-89% ee) (Schéma 12).

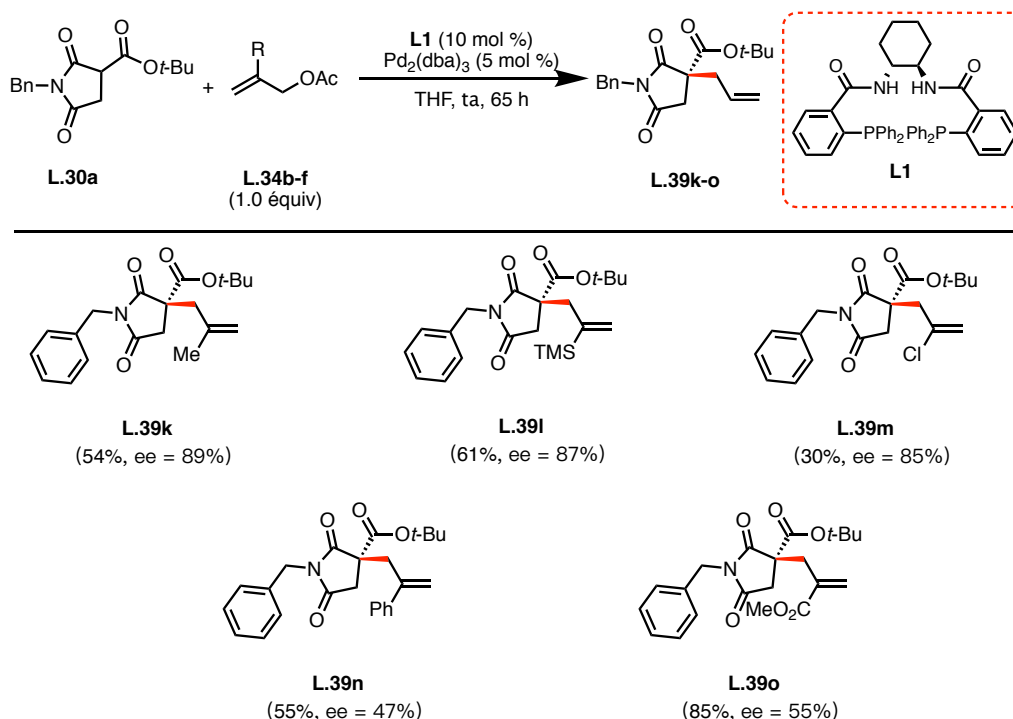


Schéma 12. Variation des acétates d'allyle α -substitués utilisés comme partenaire

Une variété d'acétates d'allyliques α -substitués a également été examinée. Ces derniers ont fourni les produits désirés avec en général d'excellents rendements et de très bons excès énantiomériques (72-96% ee) (Schéma 13), particulièrement les dérivés de l'acétate cinnamique. Les acétates d'allyliques portant un substituant hétérocyclique, tel qu'un thiophène ou encore un furane, en position β sont également tolérés dans cette réaction de Pd-AAA et ont fourni les produits d'allylation correspondants **L.39za** (94%, 95% ee) et **L.39zb** (76%, 96% ee) avec d'excellents excès énantiomériques (Schéma 13). De la même manière, les acétates allyliques substitués par un groupement alkyl en position β se sont également avérés efficaces ; fournissant les produits d'allylation **L.39zd** (45%, 90% ee) et **L.39ze** (26%, 79% ee) avec de très bonnes sélectivités (Schéma 13).

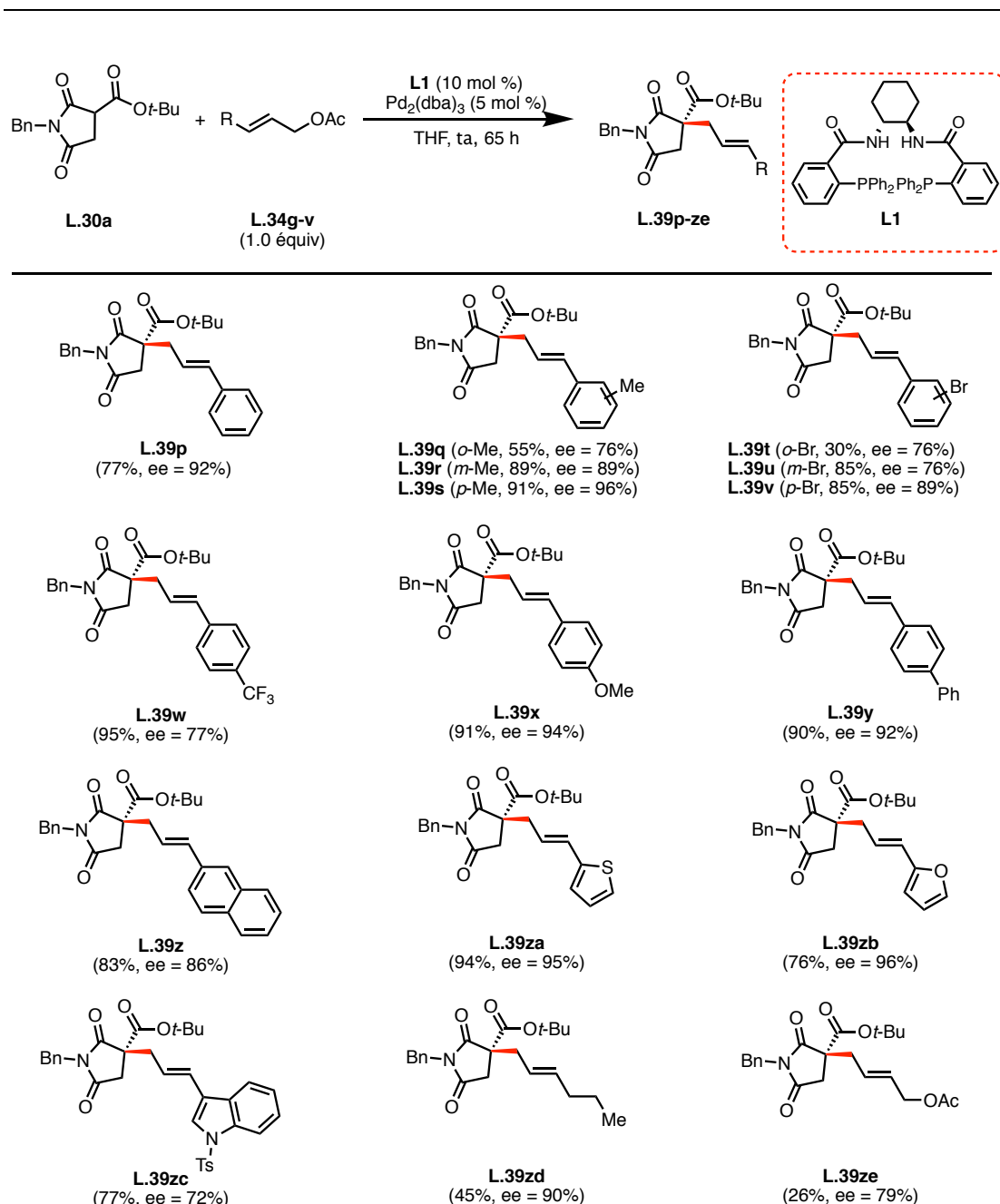


Schéma 13. Variation des acétates d'allyle β -substitués

Un substrat possédant un cycle à six chaînons a également été engagé dans la réaction en utilisant les conditions optimisées. Ainsi, lorsque le substrat **L.30k** a été mis en réaction avec l'acétate d'allyle dans les conditions standards [**L1** (10 mol %), $\text{Pd}_2(\text{dba})_3$ (5 mol %), THF, -20°C], seules des traces du produit désiré **L.39zf** ont été observées. Afin d'améliorer la formation du produit désiré, le substrat **L.30k** a été engagé une nouvelle fois mais cette fois ci à ta. Dans ces conditions, le produit d'allylation **L.39zf** a été obtenu avec un rendement de 48% et un excès énantiomériques de 73%. Paradoxalement, lorsque le substrat **L.30k** a été mis en

réaction avec l'acétate cinnamique à ta, le produit d'allylation désiré **L.39zg** a été obtenu avec un faible rendement de 10% et seulement 44% d'excès énantiomérique (Schéma 14).

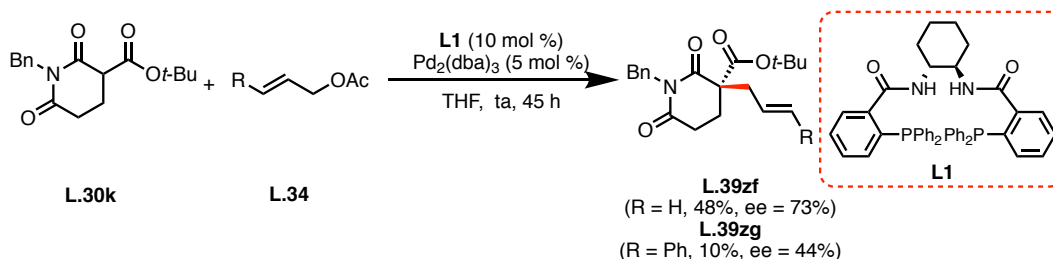


Schéma 14. Etude de la réactivité d'un substrat cyclique dans les conditions optimisées

Afin d'élargir le champ d'application de la réaction, la réactivité du substrat succinimide **L.32** possédant un groupement phényle en position C3 a été étudiée. Malheureusement, le produit d'allylation **L.39zh** a été obtenu avec un faible rendement (36%) et sans aucune sélectivité (6% ee) (Schéma 15, éq. 1). Afin de contrôler si une stratégie se basant sur une décarboxylation améliorerait l'énantiosélectivité, une Pd-AAA et une Pd-DAAA (alkylation allylique asymétrique décarboxylative catalysée au Pd) ont été menées en parallèle. Le succinimide **L.34** a ainsi été engagé dans les mêmes conditions réactionnelles [$\text{Pd}_2(\text{dba})_3$ (5 mol %), **L1** (10 mol %), THF, ta]. Si la version intramoléculaire de l'allylation a permis d'obtenir le produit d'allylation **L.39zh** avec un excellent rendement (96%), aucune énantiosélectivité n'a pu être observée (Schéma 15, éq. 2).

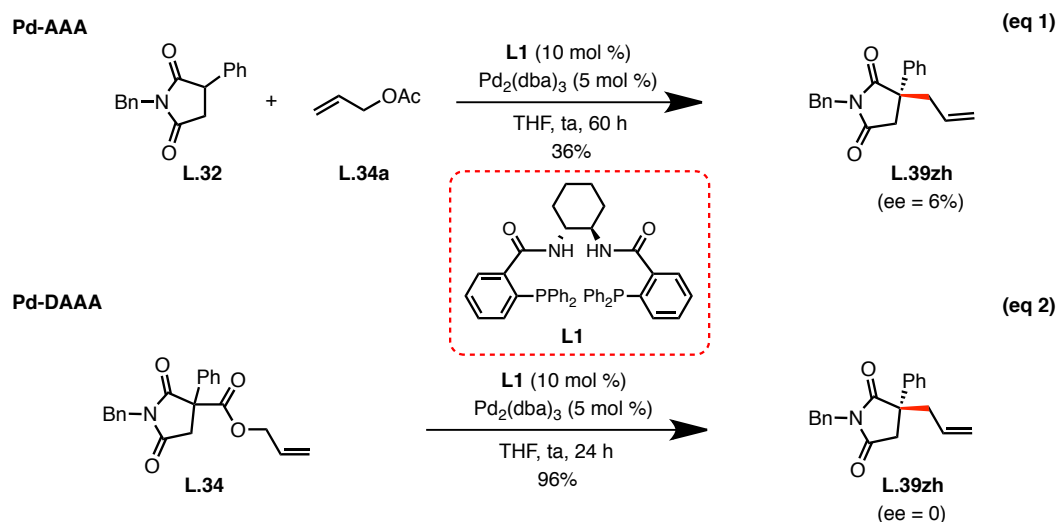


Schéma 15. Pd-AAA vs Pd-DAAA

2.1.4. Post-fonctionnalisation

Afin de démontrer l'utilité synthétique de notre méthode, les produits allylés **L.39a** et **L.39q** ont été post-fonctionnalisés (Schéma 16). Nous avons ainsi pu convertir le composé **L.39a** en dérivé spirocyclique correspondant (**L.39a** et **L.39a**) sans observer d'érosion de l'énantiosélectivité. De la même manière, nous avons également pu engager le composé **L.39a** dans une réaction d'ozonolyse, d'hydrogénation ou encore de métathèse croisée pour accéder aux composés **L.41**, **L.41** et **L.43** de manière efficace. Enfin, le dérivé **L.39q** a pu être converti en la pyrrolidine correspondante par réduction au Red-Al. Encore une fois, aucune érosion de la sélectivité n'a pu être détectée.

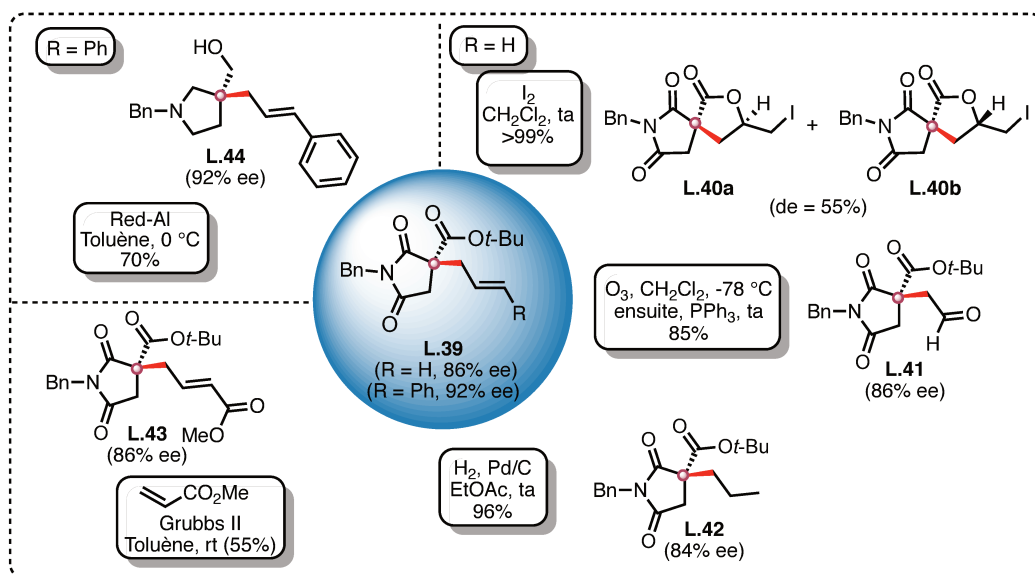


Schéma 16. Post-fonctionnalisation des dérivés de succinimides allylés

3. Résumé

Nous avons pu développer une réaction d'alkylation allylique asymétrique pallad-catalysée (Pd-AAA) à la fois efficace et hautement énantiosélective. Cette réaction à l'avantage de ne pas nécessiter l'utilisation d'une base et permet d'accéder aux dérivés succinimides optiquement actifs correspondants avec d'excellents excès énantiomériques. Le ligand de Trost (*R,R*)-DACH-Phényl **L1** s'est avéré être le ligand de choix. Quant aux acétates allyliques, ceux substitués en position C2 ou C3 ont fourni les produits allylés correspondants avec de bons rendements et d'excellentes sélectivités, en particulier pour les dérivés de l'acétate cinnamique. L'utilité synthétique de la méthode a également pu être validée en transformant ces dérivés allylés en différentes briques moléculaires optiquement actives (Schéma 16 and 17).

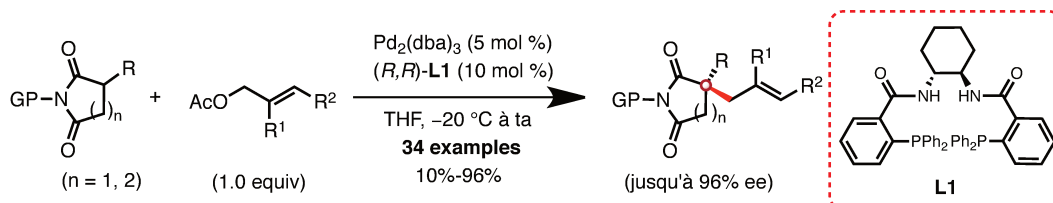


Schéma 17. Pd-AAA pour accéder à des succinimides optiquement actifs possédant un centre stéréogène quaternaire en position α .

Chapitre II

Allylation asymétrique d'ethers dienol silylés cyclique : Un accès direct aux γ -lactames α -quaternaire

Introduction: les γ -lactames dans les produits naturels et/ou composés bioactifs

Le motif γ -lactame, aussi appelé pyrrolidine-2-one et γ -butyrolactame, est l'un des hétérocycles azotés les plus importants, étant présent dans de nombreux produits naturels et pharmaceutiques. Nous pouvons citer comme exemple la (–)-pramanicine, qui possède une bonne activité antimicrobienne contre *Cryptococcus neoformans* et *Candida parapsilosis* ainsi qu'une bonne activité antibactérienne contre *Bacillus subtilis*. La (+)-lactacystine qui a été le premier inhibiteur de protéasome découvert, et la (–)-clausenamide qui a montré des propriétés d'amélioration de la mémoire et de l'apprentissage chez des animaux amnésiques modèles. (Figure 2).⁸⁴

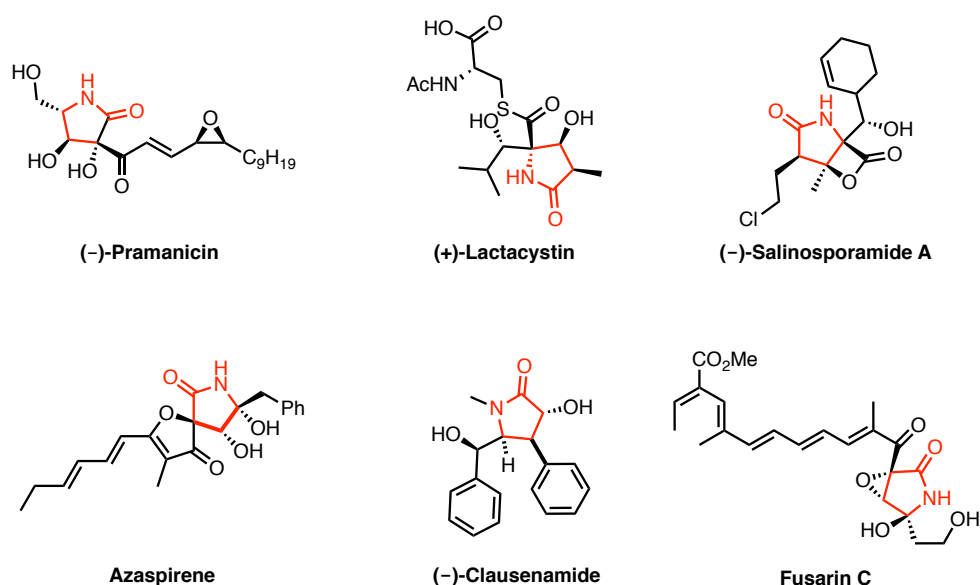


Figure 2. Exemples de produits naturels et pharmaceutiques contenant des γ -lactames

1. Principales méthodes pour la construction de γ -lactames asymétriques optiquement actifs

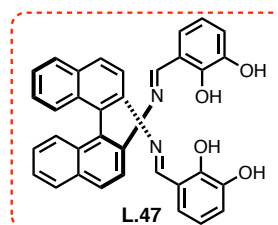
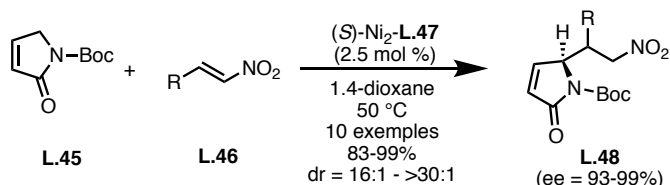
Durant cette dernière décennie, de nombreux groupes de recherche ont contribué au développement de méthodes efficaces permettant d'accéder aux γ -

lactames énantiorenrichis. Dans ce chapitre, nous présenterons ces différentes stratégies.

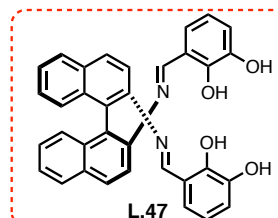
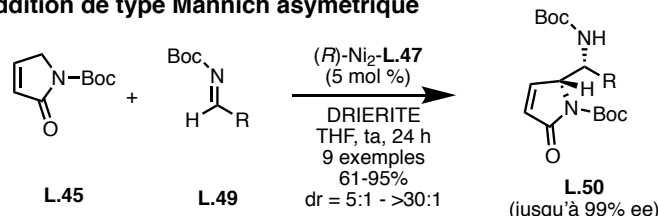
1.1. Synthèse énantiosélective de γ -lactames portant un centre stéréogène tertiaire.

Récemment, des méthodes efficaces ont été développées pour synthétiser des γ -lactames optiquement actifs portant un centre stéréogène tertiaire. Une des approches les plus populaires est la substitution électrophile asymétrique de γ -lactames α,β -insaturés **L.45** et 2-silyloxypyrroles **L.51**⁹⁵ à travers des réactions d'addition de Michael,⁹⁷⁻⁹⁹ ou de Mannich^{97a} ainsi que dans des réactions d'aldolisation¹⁰¹⁻¹⁰² (Schéma 18).

a). Addition de Michael asymétrique



b). Addition de type Mannich asymétrique



c). Addition de type aldol asymétrique

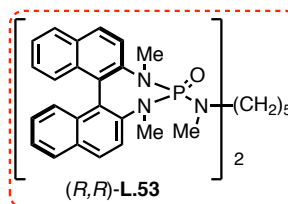
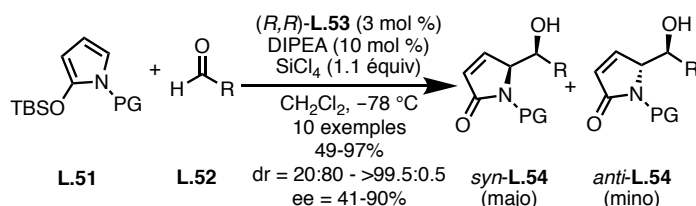
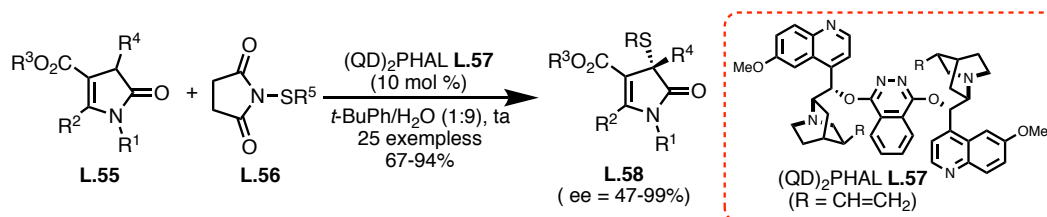


Schéma 18. Synthèse de γ -lactames optiquement actifs par substitution électrophile asymétrique de γ -lactames α,β -insaturé ou 2-silyloxypyrroles

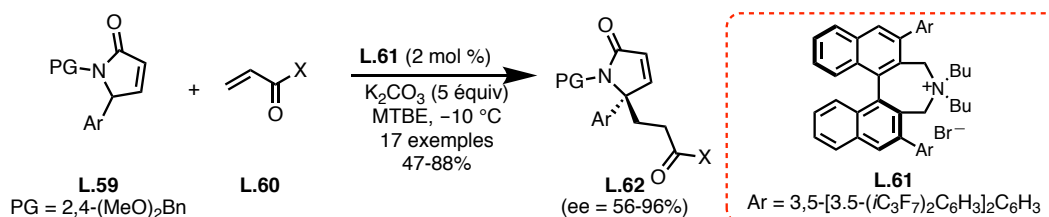
1.2. Synthèse énantiosélective de γ -lactames optiquement actifs portant un centre stéréogène quaternaire

La synthèse asymétrique de composés cycliques ou acycliques possédant un centre quaternaire reste un défi majeur en chimie organique. A notre connaissance, il n'existe que très peu de méthodes efficaces permettant d'accéder à des γ -lactames optiquement pur possédant un centre quaternaire. La plupart de ces méthodes impliquent soit des γ -lactames pro-chiraux impliqués dans des réactions de sulfénylation énantiosélective organocatalysées,¹⁰⁹ des additions de Michael¹¹¹ ou encore des réactions d'acylations énantiosélectives (Schéma 19).¹¹⁴

a). Sulfénylation énantiosélective organocatalysée



b). Addition de Michael asymétrique catalysée par transfert de phase



c). C-acylation énantiosélective catalysée par le Ni

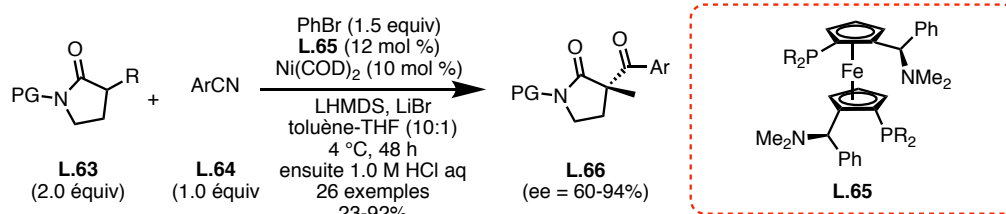


Schéma 19. Exemples de synthèse asymétrique de γ -lactames possédant un centre stéréogène quaternaire

2. Contexte et objectifs

Bien qu'un certain nombre d'outils ont été mis au point, il est toujours intéressant de développer de nouvelles méthodes à la fois plus simples, plus efficaces et surtout applicable à une plus grande variété de substrats. Considérant notre précédent travail sur la synthèse asymétrique de succinimides possédant un centre quaternaire à travers une réaction d'alkylation allylique asymétrique pallado-catalysée (Pd-AAA), nous avons envisagé d'appliquer cette réaction clé aux 2-silyloxypyrroles α,γ -

disubstitués afin d'accéder aux γ -lactames optiquement actifs correspondants (Schéma 20).

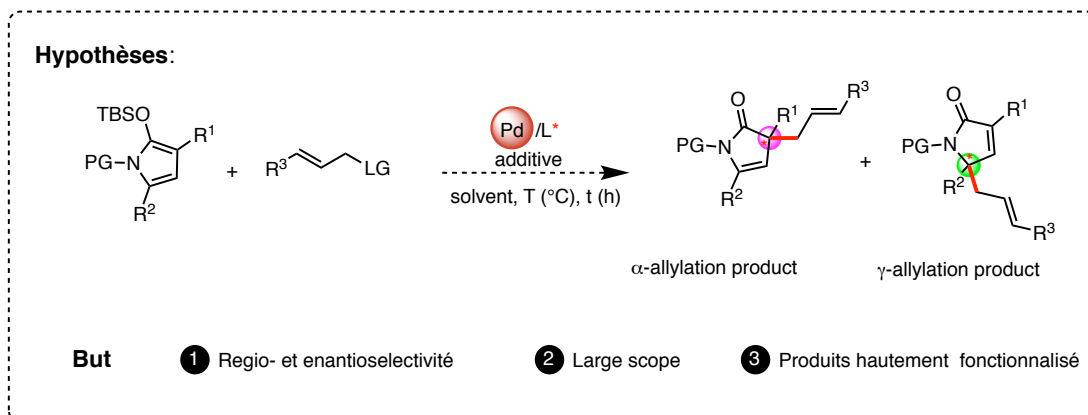


Schéma 20. Pd-AAA des 2-silyloxypyrroles α,γ -disubstitués

2.1. Résultats et discussions

2.1.1. Synthèse des 2-silyloxypyrroles et du partenaire allyle.

Afin de vérifier la faisabilité de notre hypothèse, divers 2-silyloxypyrroles **L.72** ont été synthétisés en cinq étapes avec de bons rendements en partant d'aldéhydes aromatiques ou de l'acétophénone via une condensation, suivie d'une addition conjuguée, puis une oxydation de type Nef et enfin une silylation (Schéma 21).

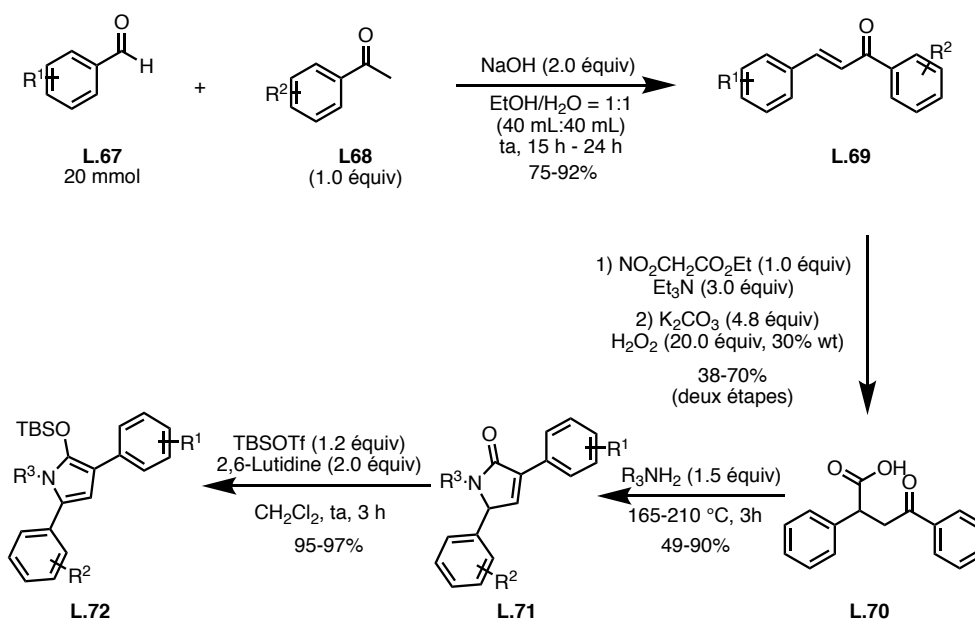


Schéma 21. Synthèse des α,γ -disubstitués 2-silyloxypyrroles

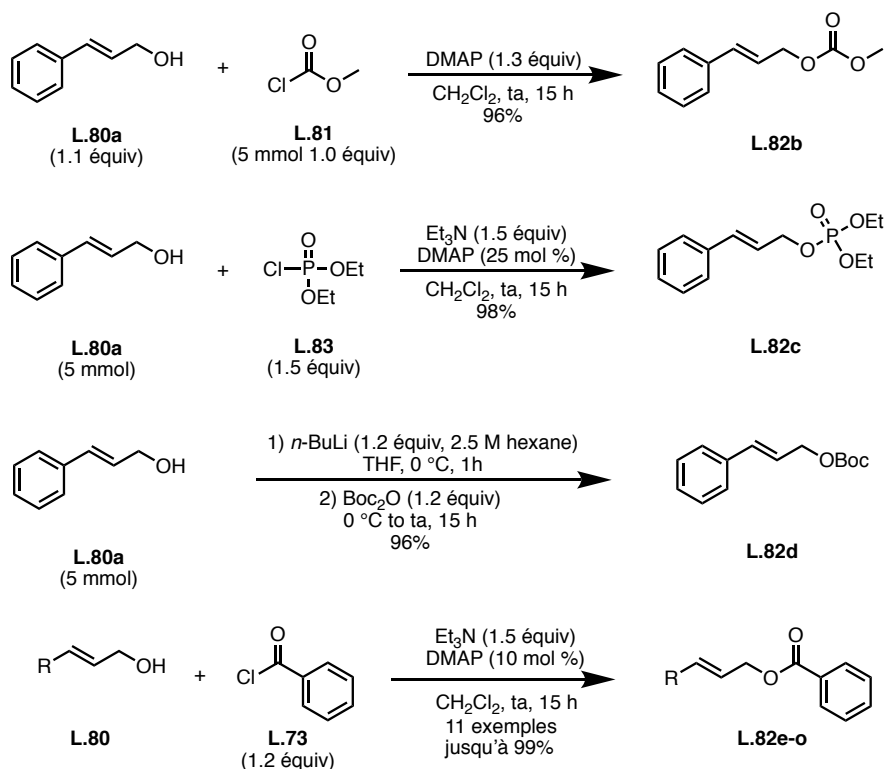


Schéma 23. Synthèse des partenaires allyliques

2.1.2. Optimisation des conditions de la réaction

Afin d'optimiser les conditions de la réaction de Pd-AAA nous avons choisi d'utiliser le α,γ -diphenyl 2-silyloxypyrrole **L.72a** comme substrat modèle. Nous avons ainsi évalué la réactivité, ainsi que la régiosélectivité et l'énantiosélectivité des différents partenaires allyliques. Nous avons ainsi pu évaluer différents réactifs d'allylation, comme **L.82a** (LG = OAc), **L.82b** (LG = OCO₂Me), **L.82c** [LG = OP(O)OEt₂], **L.82d** (LG = OBoc) et **L.82e** (LG = OBz). Les résultats sont présentés Tableau 4. Nous avons ainsi été ravis de constater que le benzoate de cinnamyl **L.82e** nous a fournis les meilleurs résultats en terme de rendement et d'énantiosélectivité (>99%, 58% ee) (Table 4, entrées 7 et 8).

Tableau 4. Influence des différents groupes partants (GP), additifs et températures

L.72a
(0.1 mmol)

L.82a-e (1.5 equiv)

L1 (10 mol %)

$\text{Pd}_2(\text{dba})_3$ (5 mol %)

THF, T °C, t (h)

L.83a

+

L.84a

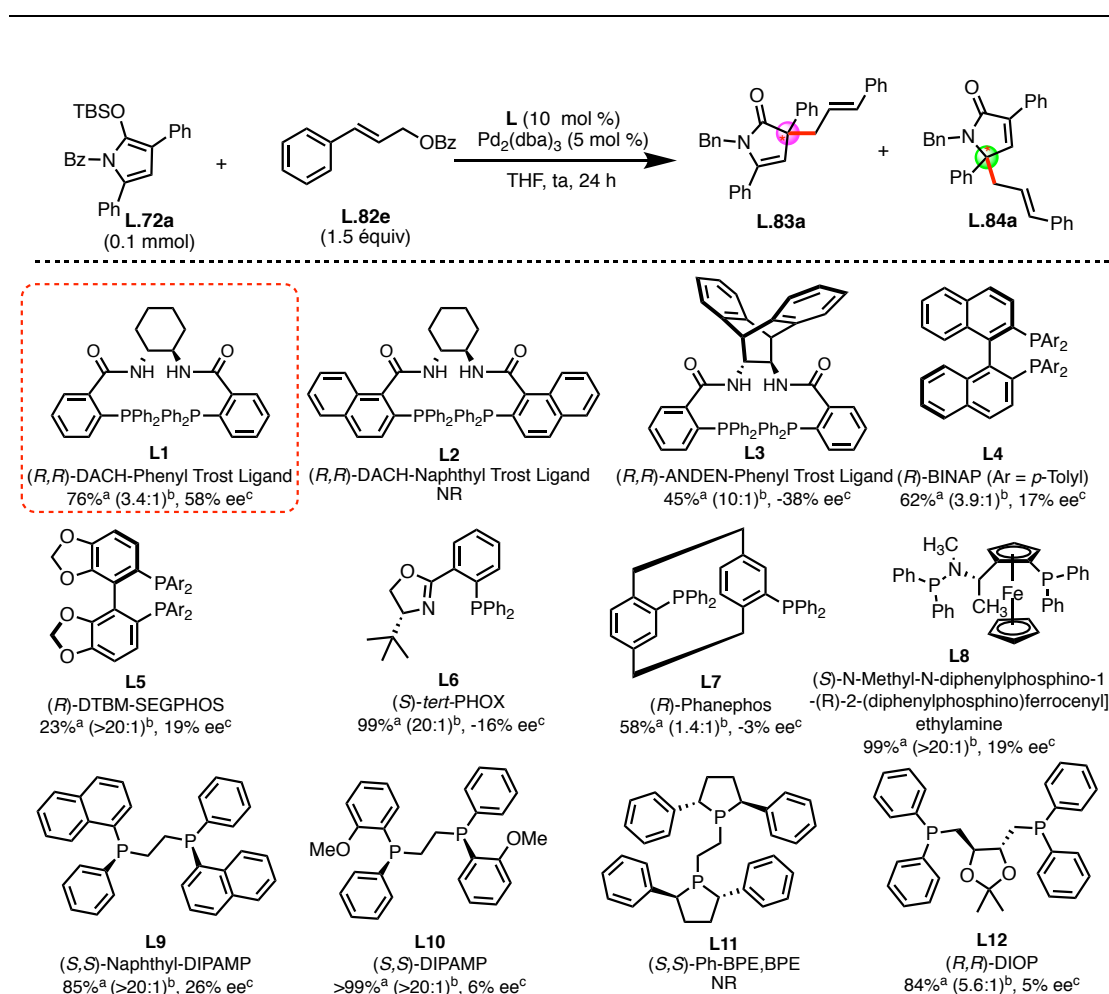
L1

Entrée	II.83, LG	T (°C)	t (h)	Taux de conversion		Rdt de II.3a	ee ^b de II.3a
				(II.3a+II.4a)	(II.3a/4a) ^a		

1	II.82a, OAc	ta	36	trace	-	-
2	II.82a, OAc	60	24	19% (13:1)	17%	33%
3 ^c	II.82a, OAc	60	22	>99% (3.8:1)	78%	20%
4	II.82b, OCO ₂ Me	60	24	57% (2.6:1)	40%	25%
5	II.82c, OP(O)OEt ₂	60	24	36% (2:1)	24%	20%
6	II.82d, OBoc	60	24	71% (5.5:1)	58%	-3%
7	II.82e, OBz	60	24	>99% (3.5:1)	76%	58%
8	II.82e, OBz	ta	22	>99% (3.4:1)	75%	58%

^a Déterminé par analyse RMN ¹H du brut réactionnel; ^b Déterminé par SFC. ^c 1.0 équiv de AcONa a été utilisé comme additif.

Encouragé par ces premiers résultats, nous avons décidé d'optimiser les conditions réactionnelles en utilisant le benzoate de cinnamyl comme donneur d'allyle. Afin d'améliorer la régiosélectivité ainsi que l'énantiosélectivité de la réaction, une variété de ligands chiraux de type phosphine a été étudiée. Les résultats sont rapportés dans le Schéma 24 ci-après. Nous constatons que les meilleurs excès énantiomériques sont toujours obtenus en utilisant le ligand (*R,R*)-DACH-Phenyl Trost (**L1**). Soulignons que des ligands chiraux de type N/P oxazoline (PHOX, **L6** ; 99%, **L.83a/L.84a** > 20:1), ferrocène phosphine (**L8** ; 99%, **L.83a/L.84a** > 20:1) et naphthyl-DIPAMP (**L9** ; 85%, **L.83a/L.84a** > 20:1) ont également permis d'obtenir le produit désiré avec de bons rendements et une excellente régiosélectivité, mais des excès énanriomériques relativement faibles. C'est pourquoi le ligand **L1** a été choisi pour la suite.



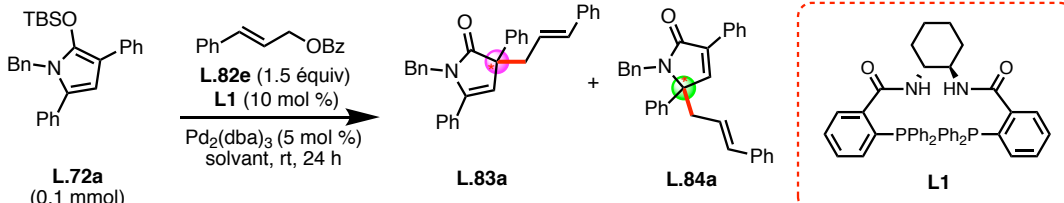
^a Rendement isolé; ^b Déterminé par analyse RMN ^1H sur le brut réactionnel; ^c Déterminé par SFC.

Schéma 24. Différents ligands chiraux utilisés dans la réaction Pd-AAA

L'influence du solvant a également été étudiée ; les résultats sont rapportés dans le Tableau 5. Ainsi, les solvants tels que l'éther diéthylique (Tableau 5, entrée 3 ; 65%, **L.83a/L.84a** = 3.3:1, 59% ee sur **L.83a**), l'acétonitrile (Tableau 5, entrée 6 ; 68%, **L.83a/L.84a** = 3.3:1, 54% ee sur **L.83a**) ou le DMF (Tableau 5, entrée 7 ; 62%, **L.83a/L.84a** = 2.3:1, 35% ee sur **L.83a**) induisent des résultats similaires. Lorsque le CH_2Cl_2 (Tableau 5, entrée 4 ; 27%, **L.83a/L.84a** = 2.6:1, 47% ee sur **L.83a**) et le toluène (Tableau 5, entrée 5 ; 18%, **L.83a/L.84a** = 3.8:1, 43% ee sur **L.83a**) ont été utilisés, le produit souhaité a été obtenu avec un faible rendement et une faible régiosélectivité et qui plus est une légère diminution de l'énantiosélectivité. De manière intéressante, lorsque le 2-méthyl-THF (Tableau 5, entrée 2) a été utilisé, un très bon rendement de 78% et une très bonne régiosélectivité (**L.83a/L.84a** = 11.6:1) sur le produit désiré ont

été obtenus. Cependant, le produit majoritaire **L.83a** a été obtenu avec un excès énantiomérique modéré (51% ee).

Tableau 5. Influence de différents solvants

				
Entrée	Solvant	Taux de conversion (II.3a+II.4a) (II.3a/II.4a) ^a	Rdt de II.3a	ee ^b de II.3a
1	THF	>99% (3.4:1)	76%	58%
2	2-Me-THF	85% (11.6:1)	78%	51%
3	Et ₂ O	81% (4.3:1)	65%	59%
4	CH ₂ Cl ₂	38% (2.6:1)	27%	47%
5	toluène	23% (3.8:1)	18%	43%
6	CH ₃ CN	89% (3.3:1)	68%	54%
7	DMF	89% (2.3:1)	62%	35%

^a Déterminé par analyse RMN ¹H du brut réactionnel; ^b Déterminé par SFC.

En considérant la réactivité du benzoate de cinnamyl, la réaction de Pd-AAA a été réalisée à plus basse température. Comme le 2-Me-THF et le THF ont permis d'obtenir le produit désiré avec une très bonne régiosélectivité, la réaction a été réalisée en parallèle dans le 2-Me-THF et le THF. A notre grande surprise, les produits allylés désirés **L.83a** et **L.84a** ont été obtenus avec de bons rendements et une bonne régiosélectivité (11:1) en faveur du produit **L.83a**. L'excès énantiomérique du produit majoritaire **L.83a** a été amélioré, passant ainsi de 58% à 82% pour une température de -20 °C dans le THF (Tableau 6, entrée 5). A titre de comparaison, dans le 2-Me-THF l'excès énantiomérique a été de seulement 70% (Tableau 6, entrée 6). Lorsque la température du milieu réactionnel a été abaissée à -30 °C, le produit allylé désiré a été obtenu après 45 h de réaction avec un bon rendement et une bonne régiosélectivité (12:1) en faveur du produit **L.83a**. Il est important de noter que dans ces conditions, l'excès énantiomérique du produit α-allylé **L.83a** atteint 84% (Tableau 6, entrée 7). Malheureusement, aucune amélioration des précédents résultats n'a été

observée lorsque la température a été abaissée à $-40\text{ }^{\circ}\text{C}$. En effet, en dépit d'une plus grande régiosélectivité ($> 20:1$), la réactivité ainsi que l'énantiosélectivité ont quant à elles diminuées (Tableau 6, entrée 9). Des additifs tels que le benzoate de *n*-tétrabutylammonium (*n*-Bu₄NOBz) ou le benzoate de sodium ont été ajoutés à la réaction dans le but d'améliorer la régiosélectivité ainsi que l'énantiosélectivité de la réaction. Malheureusement, aucune amélioration n'a pu être observée (Tableau 6, entrées 8 et 10).

Tableau 6. Influence de différentes températures

L.72a
(0.1 mmol)

$\xrightarrow[\text{Pd}_2(\text{dba})_3 \text{ (5 mol \%)}]{\text{Ph-CH=CH-OBz (L.82e, 1.5 \text{ \textit{equiv}})} \text{ L1 (10 mol \%)} \text{ solvant, T (}^{\circ}\text{C), t (h)}}$

L.83a + **L.84a**

L1

Entrée	Solvant	T ($^{\circ}\text{C}$)	t (h)	Taux de conversion (II.3a+II.4a) (II.3a/4a) ^a	Rdt de II.3a	ee ^b de II.3a
1	THF	rt	24	>99% (3.4:1)	76%	58%
2	2-Me-THF	rt	24	85% (11.6:1)	78%	51%
3	THF	0	24	83% (4.5:1)	68%	74%
4	2-Me-THF	0	24	74% (14:1)	69%	68%
5	THF	-20	24	79% (12:1)	73%	82%
6	2-Me-THF	-20	24	54% ($>20:1$)	54%	70%
7	THF	-30	45	96% (12:1)	89%	84%
8 ^c	THF	-30	45	31% ($>20:1$)	31%	76%
9 ^d	THF	-40	65	52% ($>20:1$)	52%	78%
10 ^e	THF	-40	40	62% (6.6:1)	54%	67%

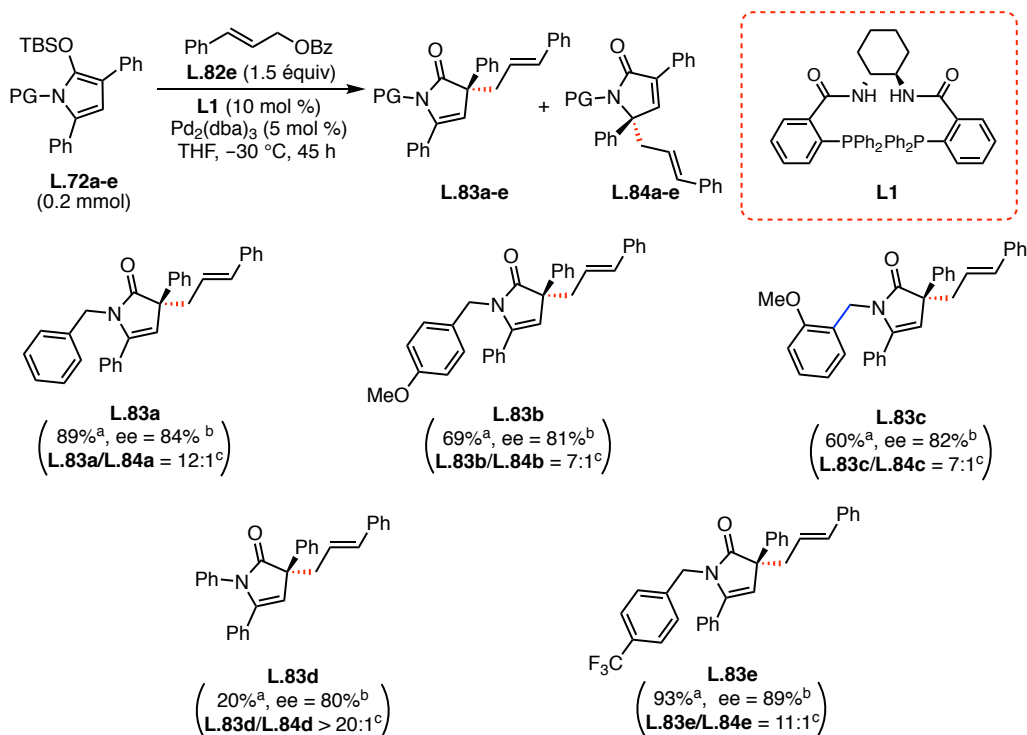
^a Déterminé par analyse RMN ^1H du brut réactionnel; ^b Déterminé par SFC; ^c Additif: *n*-BuNOBz (10 mol %);

^d Additif : tamis moléculaire (20 mg); ^e Additif : NaOBz (20 mol %).

2.1.3. Champ d'application de la réaction

Avec les conditions réactionnelles optimisées en main [THF, $-30\text{ }^{\circ}\text{C}$, 10 mol % du ligand (*R,R*)-DACH-Phenyl Trost **L₁** et 5 mol % de $\text{Pd}_2(\text{dba})_3$], le champ d'application de la réaction de Pd-AAA a pu être étudié en utilisant divers 2-silyloxypyrroles α,γ -disubstitués et divers dérivés d'allyle benzoates.

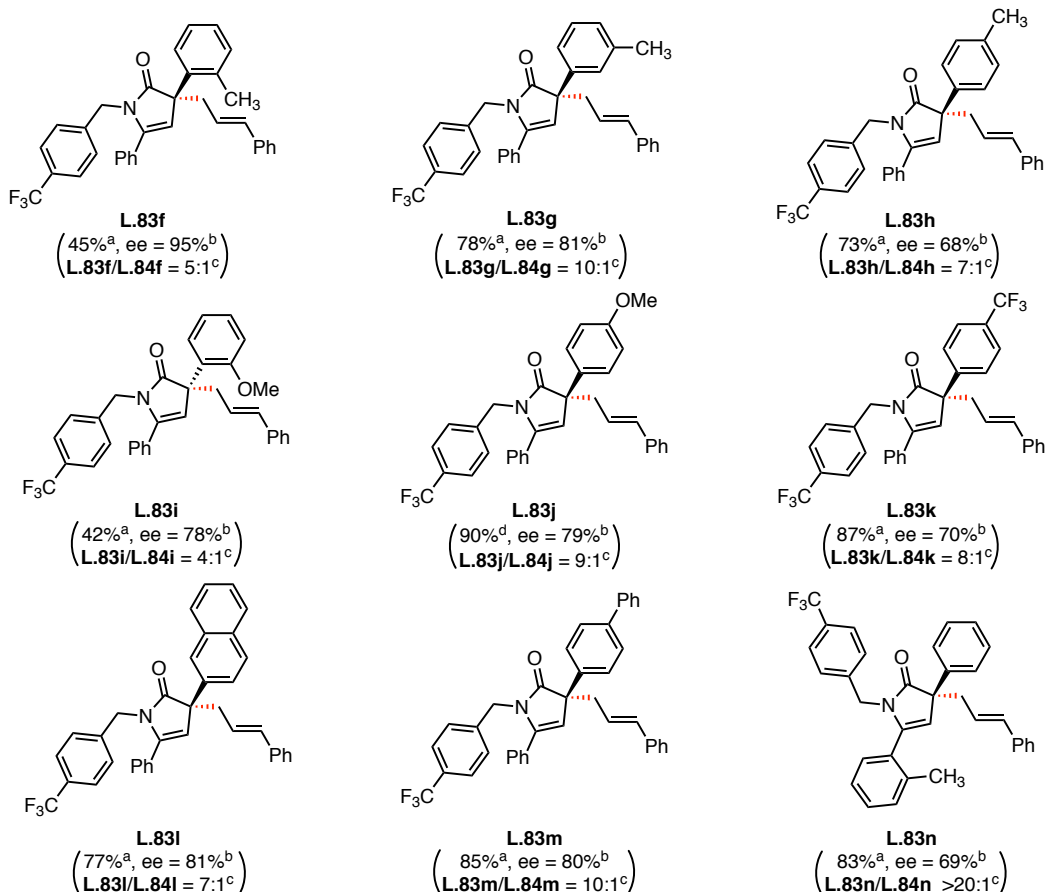
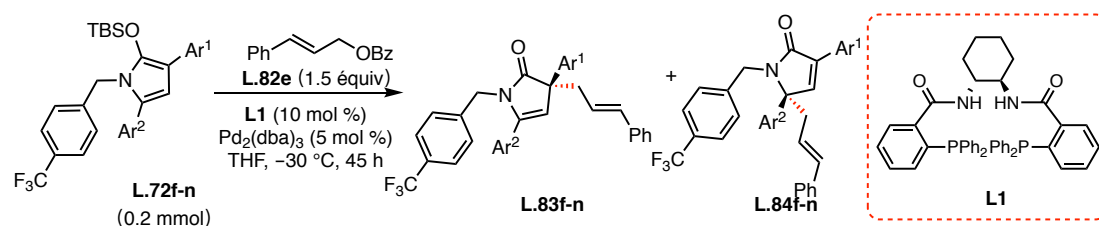
Dans un premier temps, une variété de 2-silyloxypyrroles α,γ -disubstitués portant différents groupes protecteurs sur l'atome d'azote ont été étudiés (**L.72a-e**). Les résultats expérimentaux ont montré une excellente régiosélectivité ainsi qu'une très bonne énantiosélectivité pour le substrat **L.72e** possédant un groupement protecteur de type *para*-trifluorométhyl benzyl sur l'atome d'azote (Schéma 25, **L.72e**). Pour les substrats **L.72b** et **L.72c** possédant un groupe protecteur de type *para*/*mé*ta-méthoxy benzyl, les produits d'allylation **L.83b** et **L.83c** ont été obtenus avec de bons rendements (respectivement 60% et 69%) et de bons excès énantiomériques (respectivement 81% et 82%). A noter qu'une régiosélectivité de 7:1 a été observée pour ces deux produits d'allylation (Schéma 25, **L.83b** et **L.83c**). Dans un second temps, lorsque le groupe protecteur *N*-benzyl a été remplacé par un groupe *N*-phényl, le produit désiré **L.83d** a été obtenu avec une bonne énantiosélectivité (80% ee) et une excellent régiosélectivité (> 20:1). Toutefois, le rendement en produit **L.83d** a été très faible (20%).



^a Rendement isolé; ^b Déterminé par SFC; ^c Déterminé par analyse RMN ^1H du brut réactionnel.

Schéma 25. Champ d'application des 2-silyloxypyrroles avec différents groupes protecteurs sur l'azote

Comme nous venons de l'étudier, le groupe protecteur sur l'azote de type *para*-trifluorométhyl benzyle s'est montré le plus efficace pour notre réaction. Ainsi, différents 2-silyloxypyrroles protégés par un groupe *para*-trifluorométhyl benzyl sur l'azote et substitués en position α et/ou γ par des groupes aromatiques ont été synthétisés dans le but d'être évalués dans notre réaction de Pd-AAA. Les résultats sont rapportés ci-après (Schéma 26). Dans les conditions optimisées, tout les substrats étudiés ont pu être allylés avec des rendements modérés à excellents (42%-90%), des régiosélectivités allant de 4:1 à > 20:1 et des excès énantiomériques allant de 68% à 95%. Il est important de noter que la présence d'un substituant aryl en position α ou γ des 2-silyloxypyrroles entraîne une augmentation de la réactivité, de la régiosélectivité ainsi que de l'énantiosélectivité (Schéma 26).



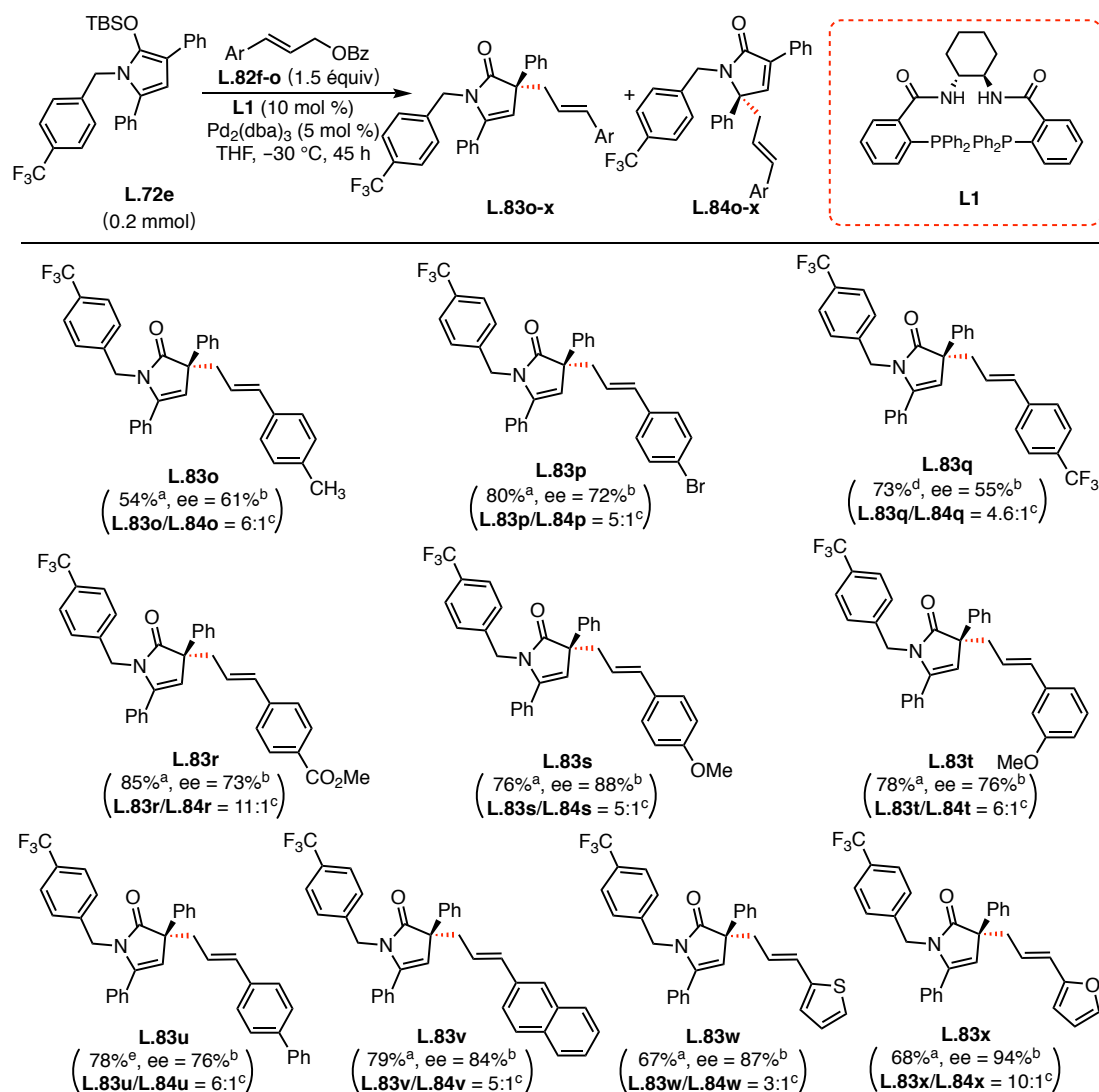
^a Rendement isolé; ^b Déterminé par SFC; ^c Déterminé par analyse RMN ^1H du brut réactionnel. ^d

Rendement global sur **L.83j** et **L.84j** (**L.83j**/**L.84j** = 5.5:1)

Schéma 26. Champ d'application des 2-silyloxypyrroles avec différents substituants en position α et/ou γ

Hormis ces 2-silyloxypyrroles α,γ -disubstitués, différents benzoate d'allyle β -substitués ont été évalués et ce, en utilisant le 2-silyloxypyrrole **L.72e** comme substrat modèle. Les résultats sont rapportés dans le Schéma 27. Dans un premier temps, la réactivité de dérivés de benzoate de cinnamyle portant différents substituants en position *para* sur le cycle aromatique (Me, Br, MeO, CO_2R ...) a été étudiée. Ces benzoates de cinnamyle se sont montrés particulièrement efficaces dans notre

réaction de Pd-AAA et les produits d'allylation désirés ont été obtenus avec une grande régiosélectivité (5:1 à 11:1) et énantiosélectivité (55% à 88% ee) (Schéma 27). Dans un second temps, des substituants aromatiques tels qu'un groupe biphenyle ou naphtyl ont également été évalués. Pour ces substituants, les produits d'allylation **L.83u** (78%, 76% ee, **L.83u/L.84u** = 6:1) et **L.83v** (79%, 84% ee, **L.83v/L.84v** = 5:1) ont été obtenus avec de très bons rendements, une régiosélectivité et une énantiosélectivité également très bonnes (Schéma 27). Notons au passage que les produits d'allylation **L.83u** et **L.84u** obtenus avec un ratio 4:1 n'ont pas pu être séparés. Enfin, les benzoates d'allyle portant un hétérocycle de type thiophène ou encore furane ont permis d'obtenir les produits souhaités **L.83w** (67%, 87% ee, **L.83w/L.84w** = 3:1) et **L.83x** (68%, 94%, **L.83x/L.84x** = 10:1) avec des rendements modérés mais de très bonnes régiosélectivités et énantiosélectivités (Schéma 27).



^a Rendement isolé; ^b Déterminé par SFC; ^c Déterminé par analyse RMN ¹H du brut réactionnel. ^d Rendement global sur **L.83q** et **L.84q** (**L.83q/L.84q** = 4.3:1) ; ^e Rendement global sur **L.83u** et **L.84u** (**L.83u/L.84u** = 4:1).

Schéma 27. Champ d'application de divers allyle benzoates β-substitué

Le substrat **L.72a** a également été testé dans nos conditions optimisées de Pd-AAA et en utilisant le benzoate d'allyle **L.82p** comme source d'allyle. Le produit d'allylation **L.83y** a ainsi été obtenu avec un excellent rendement (> 99%), une excellente régiosélectivité (**L.83y/L.84y** > 20:1) mais un excès énantiomérique sur **L.83y** relativement moyen (64% ee) (Schéma 28, éq 1). Le 2-silyloxypyrrole **L.79** a pour finir été étudié dans des conditions similaires et en utilisant le benzoate d'allyle **L.82e**. Le produit d'allylation **L.83z** a été obtenu avec un rendement de 62%, une excellente régiosélectivité (**L.83z/L.84z** > 20:1) et un excès énantiomérique moyen (66% ee) (Schéma 28, éq 2)

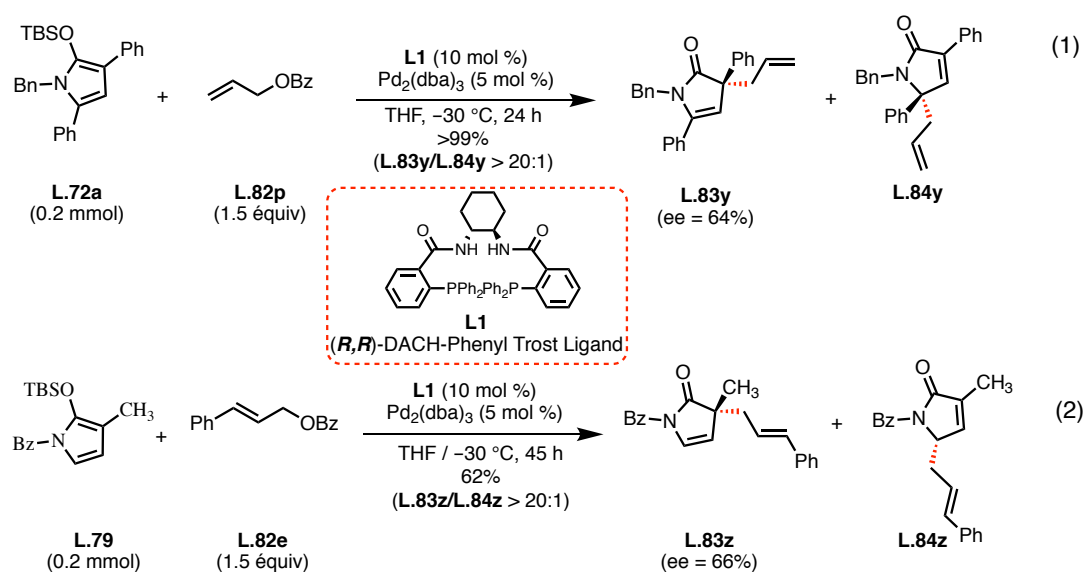


Schéma 28. Autres résultats concernant le champ d'application

2.1.4. Post-fonctionnalisation

Afin de démontrer l'intérêt synthétique de cette méthode, les produits d'allylation **L.83a** et **L.83c** ont été converti en une seule étape en dérivés de type pyrrolidine et pyrrolidinone (Schéma 29).

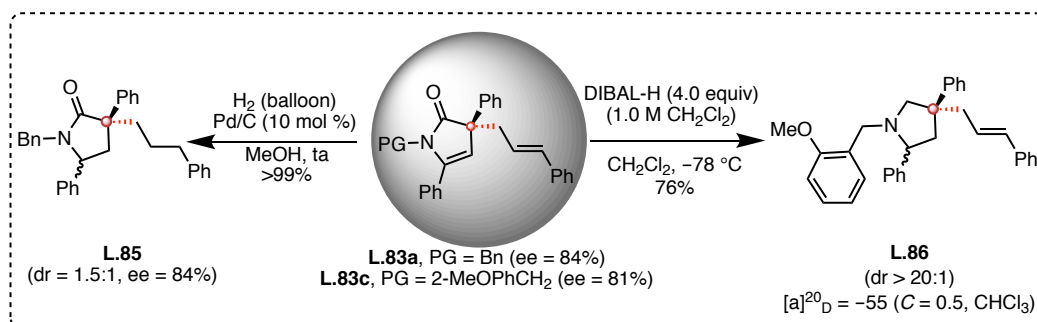


Schéma 29. Post-fonctionnalisation des γ -lactames optiquement actifs

3. Résumé

En conclusion, nous avons développé une réaction palladocatalysée asymétrique d'alkylation allylique de 2-silyloxypyrroles α,γ -disubstitué. Cette méthode, efficace, hautement énantiosélective et sans additifs permet l'obtention de γ -lactames optiquement actifs possédant un centre quaternaire. Le ligand chiral de Trost (*R,R*)-DACH-phényle (**L₁**) s'est montré particulièrement efficace pour effectuer cette transformation. Ainsi, une librairie de 2-silyloxypyrroles α,γ -disubstitués a été synthétisée et évaluée dans les conditions réactionnelles optimisées. Les produits γ -allylés ont été obtenus avec des rendements particulièrement bons, des régiosélectivités élevées (3:1 à > 20:1) et des excès énantiomériques atteignant 95%. De plus, les produits allylés obtenus peuvent être facilement convertis pour donner accès aux pyrrolidinones ou pyrrolidine correspondantes (Schéma 30).

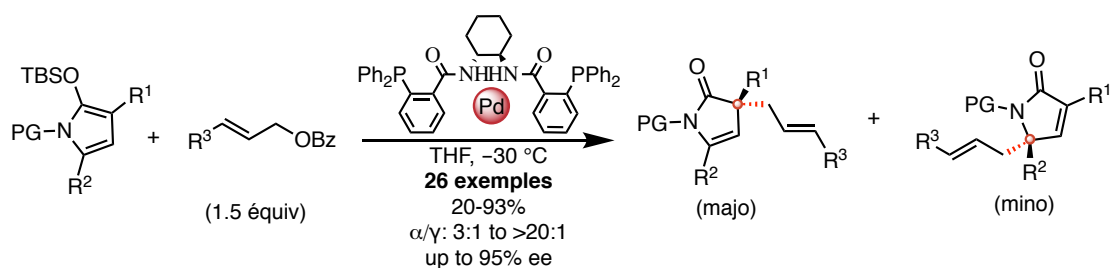
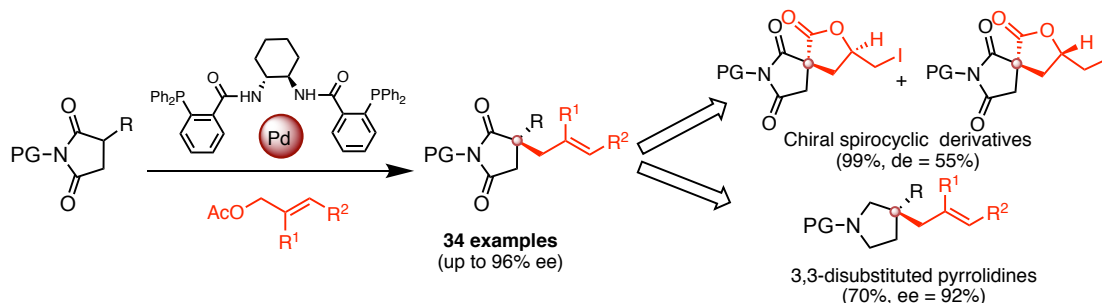


Schéma 30. Synthèse de γ -lactames optiquement actifs par réaction de type Pd-AAA

Abstract

Asymmetric construction *N*-containing five membered ring heterocycles bearing an all-carbon α -quaternary stereogenic center is a challenge in organic synthesis. In this thesis, we have successfully developed two mild synthetic methods to access the functionalized *N*-containing heterocycles, succinimides and γ -lactam derivatives, bearing an all-carbon α -quaternary center in high enantioselectivities through palladium-catalyzed **Asymmetric Allylic Alkylation (Pd-AAA)**.

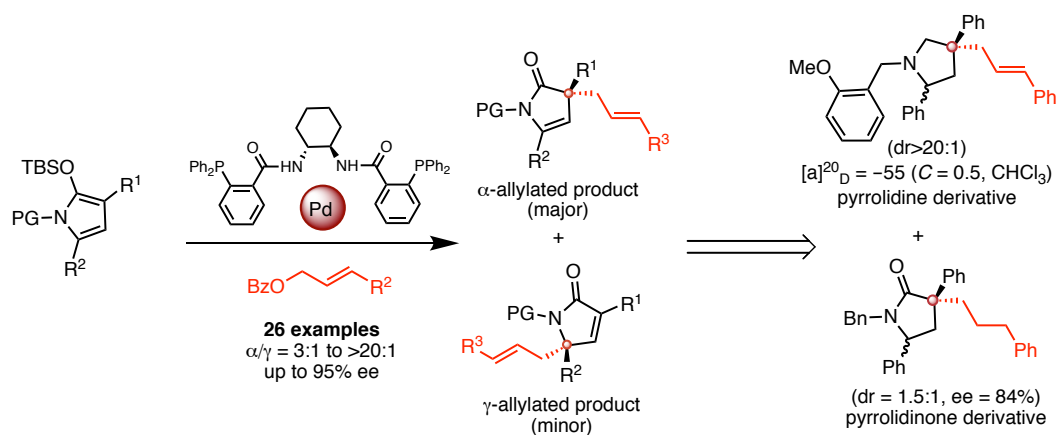
In the first chapter, the synthesis of diversely optically active substituted five-membered ring succinimide derivatives was successfully developed by a base-free, palladium-catalyzed **Asymmetric Allylic Alkylation (Pd-AAA)**. The method allows a straightforward entry into succinimide derivatives bearing an all-carbon α -quaternary stereogenic center in high yields and good to excellent enantioselectivities. To further demonstrate the synthetic utility of the method, the allylated products were further converted to various optically active building blocks, including the optically active pyrrolidine derivatives and spirocyclic derivatives, using simple transformations.



Scheme I. Synthesis of optically active succinimides bearing an all-carbon α -quaternary stereogenic center via Pd-AAA

In the second chapter, another method to access optically active pyrrolidine derivatives from α,γ -disubstituted 2-silyloxypyrroles was also developed. When α,γ -disubstituted 2-silyloxypyrroles and allylic benzoates were treated by chiral palladium catalyst without any additive, palladium-catalyzed **Asymmetric Allylic Alkylation (Pd-AAA)** took place and a variety of highly functionalized β,γ -unsaturated γ -lactams bearing a quaternary center were obtained in good yields, good to high regio- and

enantioselectivities. The obtained enantioenriched γ -lactams were easily converted to optically active pyrrolidine derivatives by using simple transformations.



Scheme II. Synthesis of optically active γ -lactams bearing an all-carbon quaternary stereogenic center via Pd-AAA

Keywords: asymmetric catalysis, allylic alkylation, palladium, succinimides, lactams, all-carbon quaternary stereogenic centers

Chapter I

Enantioselective Synthesis of Optically Active Succinimide Derivatives through Palladium-Catalyzed Asymmetric Allylic Alkylation

1. Succinimide unit in natural products and/or bioactive compounds

1.1 Natural occurrence and biological activity

Since the isolation by Komura and co-workers^{1a} of andrimid, which was shown to exhibit interesting antibiotic activities, the chiral succinimide moiety has been found in a number of biologically active natural products and pharmaceuticals, such as hirsutellone A, haterumaimide A, (+)-ethosuximide and ranirestat (Figure 1).¹ In view of the number of compounds bearing this intriguing motif, we decided to focus on the most representative ones.

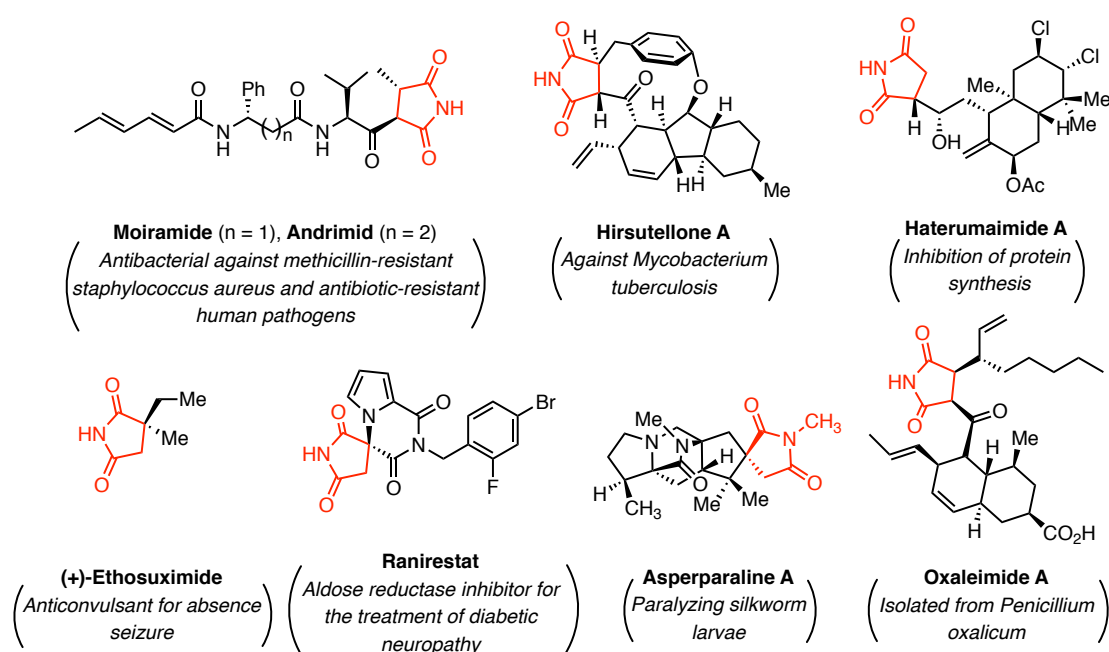


Figure 1. Typical examples of succinimide-containing natural products and pharmaceuticals.

¹ (a) Fredenhagen, A.; Tamura S. Y.; Kenny, P. T. M.; Komura, H.; Naya, Y.; Nakanishi, K. *J. Am. Chem. Soc.* **1987**, *109*, 4409-4411; (b) Coulter, D. A.; Huguenard, J. R.; Prince, D. A. *Br. J. Pharmacol.* **1990**, *100*, 800-806; (c) Malochet-Grivois, C.; Roussakis, C.; Robillard, N.; Biard, J. F.; D. Riou, D.; Debitus, C.; Verbist, J. F. *Anti-Cancer Drug Des.* **1992**, *7*, 493-502; (d) Hayashi, H.; Nishimoto, Y.; Nozaki, H. *Tetrahedron Lett.* **1997**, *38*, 5655-5658; (e) Todorovic, S. M.; Lingle, C. J. *J. Neurophysiol.* **1998**, *79*, 240-252; (f) Uddin, M. J.; Kokubo, K.; Ueda, K.; Suenaga, K.; Uemura, D. *J. Nat. Prod.* **2001**, *64*, 1169-1173; (g) Gomora, J. C.; Daud, A. N.; Weiergräber, M.; Perez-Reyes, E. *Mol. Pharmacol.* **2001**, *60*, 1121-1132. (h) Ando, Y.; Fuse, E.; Figg, W. D. *Clin. Cancer Res.* **2002**, *8*, 1964-1973; (i) Freiberg, C.; Brunner, N. A.; Schiffer, G.; Lampe, T.; Pohlmann, M.; Habich, D.; Ziegelbauer, K. *J. Biol. Chem.* **2004**, *279*, 26066-26073; (j) Isaka, M.; Rugserree, N.; Maithip, P.; Kongsaree, P.; Prabpai, S.; Thebtaranonth, Y. *Tetrahedron* **2005**, *61*, 5577-5583; (k) Bril, V.; Hirose, T.; Tomioka, S.; Buchanan, R. *Diabetes Care* **2009**, *32*, 1256-1260; (l) Sato, M.; Dander, J. E.; Sato, C.; Hung, Y.-S.; Gao, S.-S.; Tang, M.-C.; Hang, L.; Winter, J. M.; Garg, N. K.; Watanabe, K.; Tang, Y. *J. Am. Chem. Soc.* **2017**, *139*, 5317-5320.

1.1.1 Hirsutellones A-E

Tuberculosis is one of the most serious endemic disease, causing over two million deaths and eight million new cases each year.² With the emergence of multi-drug resistant strains, there is an urgent need to develop new antitubercular drugs.³ Based on this observation, Isaka *et al.*^{1j} reported the isolation and structure elucidation of a new class of antitubercular alkaloids, hirsutellones A-E, which were isolated from the insect pathogenic fungus, *Hirsutella nivea* BCC 2594.

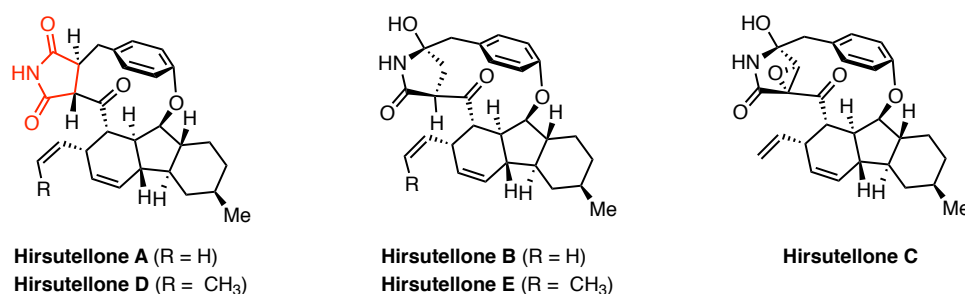


Figure 2. Structure of hirsutellones A-E.

This new alkaloids have some unique structural features: they bear a highly strained 12- or 13-membered ring containing a succinimide or a γ -lactam, a tricyclic polyketide moiety and a *p*-substituted phenyl ether. These compounds exhibit significant growth inhibitory activity against *Mycobacterium tuberculosis* H₃₇Ra, especially hirsutellone A, which contains a succinimide moiety.

1.1.2 Haterumaimides A-I

Besides hirsutellones A-E, another important class of compounds called haterumaimides A-I were isolated from marine organisms, namely the ascidian *Lissoclinum* sp., collected from the coast of Hateruma Island in Japan by Uddin and co-workers.^{1f, 4} Interestingly, all of these chlorinated labdane alkaloids possess a

² (a) World health Organization. WHO Fact Sheet No104. (b) Smith, C. V.; Shama, V.; Sacchettini, J. C. *Tuberculosis* **2004**, *84*, 45-55.

³ (a) Cantrell, C. R.; Franzblau, S. G.; Fischer, N. H. *Planta Med.* **2001**, *67*, 685-694; (b) Duncan, K. *Tuberculosis* **2003**, *83*, 201-207. (c) Duncan, K., III; Barry, C. E. *Curr. Opin. Microbiol.* **2004**, *7*, 460-465.

⁴ Uddin, M. J.; Kokubo, S.; Suenaga, K.; Ueda, K.; Uemura, D. *Heterocycles* **2001**, *54*, 1039-1047.

succinimide moiety and exhibit cytotoxicity against mouse lymphocytic leukemia cells (P388) and inhibit the first cleavage of fertilized sea urchin eggs. These biological activities indicate that the heterumaimides A-E can potentially be used as protein synthesis inhibitors,⁵ antitumor drugs as well as physiological tools.^{1c}

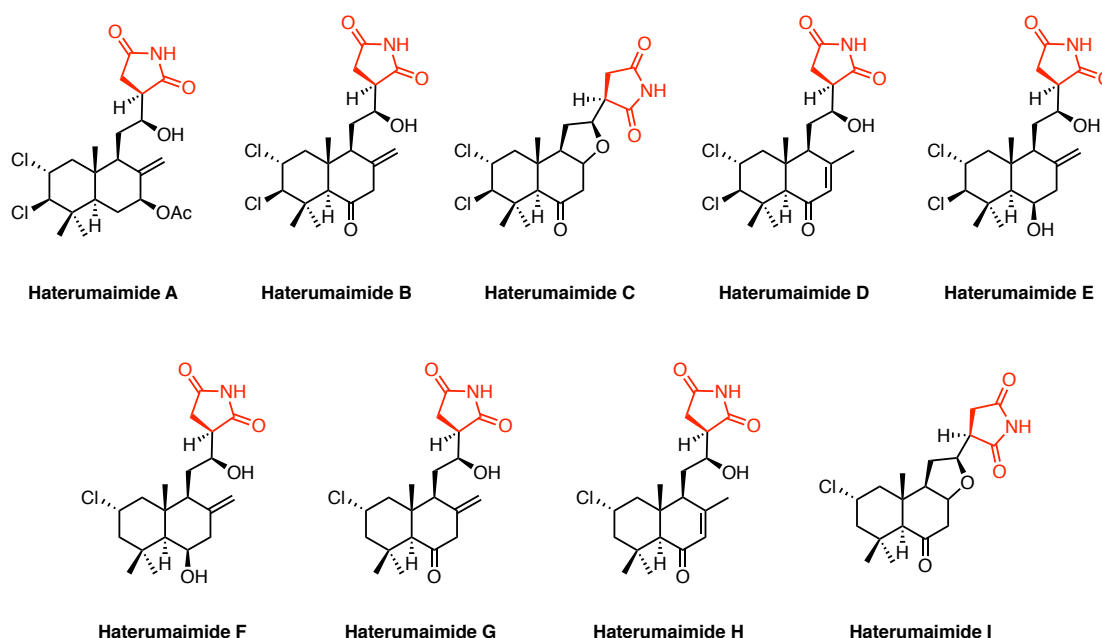


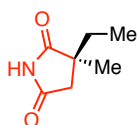
Figure 3. Structure of heterumaimides A-I.

1.1.3. (+)-Ethosuximide

The succinimide motif is also present in a number of pharmaceuticals. For instance, ethosuximide is clinically used as an anticonvulsant agent. Coulter *et al.*^{1b} showed that ethosuximide significantly occluded the γ -aminobutyric acid-blocking action of TetraMethyl Succinimide (TMS), picrotoxin and PentyleneTetraZol (PTZ), suggesting this occluding action could be responsible for the anticonvulsant activity of (+)-ethosuximide in some chemically-induced seizures. (+)-Ethosuximide was also shown to reduce low-threshold calcium current in the thalamic neurons.^{1e,6}

⁵ Robert, F.; Gao, H. Q.; Donia, M.; Merrick, W. C.; Hamann, M. T.; Pettetier, J. *RNA* **2006**, *12*, 717-725.

⁶ Gomora, J. C.; Daud, A. N.; Weiergräber, M.; Perez-Reyes, E. *Mol. Pharmacol.* **2001**, *60*, 1121-1132.

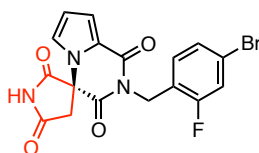


(+)-Ethosuximide

Figure 4. Structure of (+)-ethosuximide.

1.1.4. Ranirestat

Another representative pharmaceutical is ranirestat, previously known as AS-3201. This aldose reductase inhibitor (ARI) developed by Dainippon Pharmaceuticals (Osaka, Japan), was shown to penetrate the sural nerve and inhibit sorbitol accumulation in patients with diabetic sensorimotor polyneuropathy (DSP).^{1h,7}



Ranirestat

Figure 5. Structure of ranirestat.

2. Enantioselective synthesis of succinimide derivatives

Due to the potential applications of chiral succinimide-containing natural products and pharmaceuticals, chemists have devoted a lot of efforts to develop new strategies to build the chiral succinimide motif.

2.1. Enantioselective synthesis of succinimide derivatives bearing a tertiary stereogenic center

2.1.1. Asymmetric organocatalytic conjugate addition of nucleophiles to maleimides

⁷ Bril, V.; Buchanan R. A. *The AS-3201 Study Group Diabetes Care* **2004**, 27, 2369-2375.

In the past decades, a number of methods have been developed to synthesize optically active succinimides bearing a tertiary stereogenic center. One of the most conventional and straightforward method is the asymmetric organocatalytic conjugate addition of nucleophiles to maleimides. Indeed, maleimides are excellent Michael acceptors for asymmetric conjugate addition of various nucleophiles, and dipolarophiles/dienophiles in asymmetric cycloadditions (Figure 6).⁸

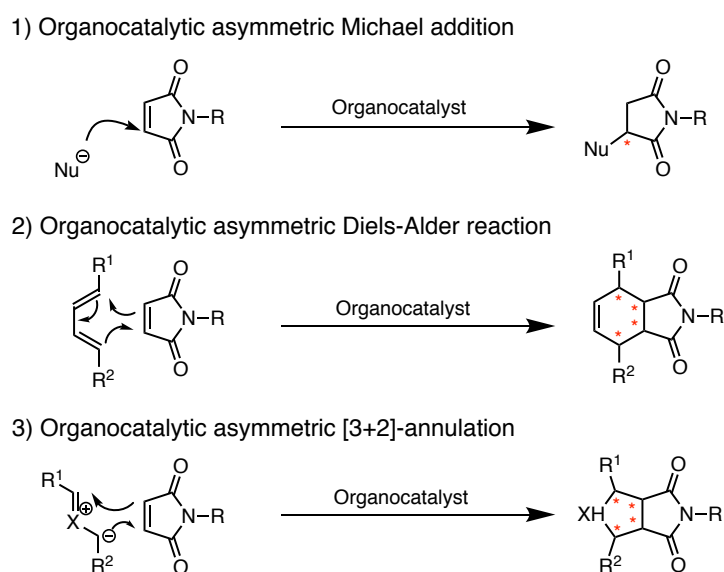


Figure 6. Maleimides used as Michael acceptors, dienophiles/dipolarophiles in organocatalytic asymmetric addition and cycloaddition

The first example of an asymmetric organocatalytic conjugate addition on a maleimide was reported by Melchiorre *et al.*⁹ in 2006. These authors successfully obtained high reactivities and enantioselectivities using natural cinchona alkaloids, quinine and quinidine, as catalysts. A variety of trisubstituted dicarbonyl compounds, such as diketones and β -ketoesters, were successfully used as prochiral nucleophiles to generate the corresponding Michael adducts with vicinal quaternary and tertiary stereogenic centers, simultaneously (Table 1). After intensive screening of the reaction conditions, the Michael adducts were obtained with good to high yields (52%-99%), moderate to excellent regioselectivities (77:23 to >98:2) and up to 98% ee when quinidine used (Table 1, entry 4).

⁸ Chauhan, P.; Kaur, J.; Chimni, S. S. *Chem. Asian. J.* **2013**, *8*, 328-346.

⁹ Bartoli, G.; Bosco, M.; Carlone, A.; Cavalli, A.; Locatelli, M.; Mazzanti, A.; Ricci, P.; Sambri, L.; Melchiorre, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 4966-4970.

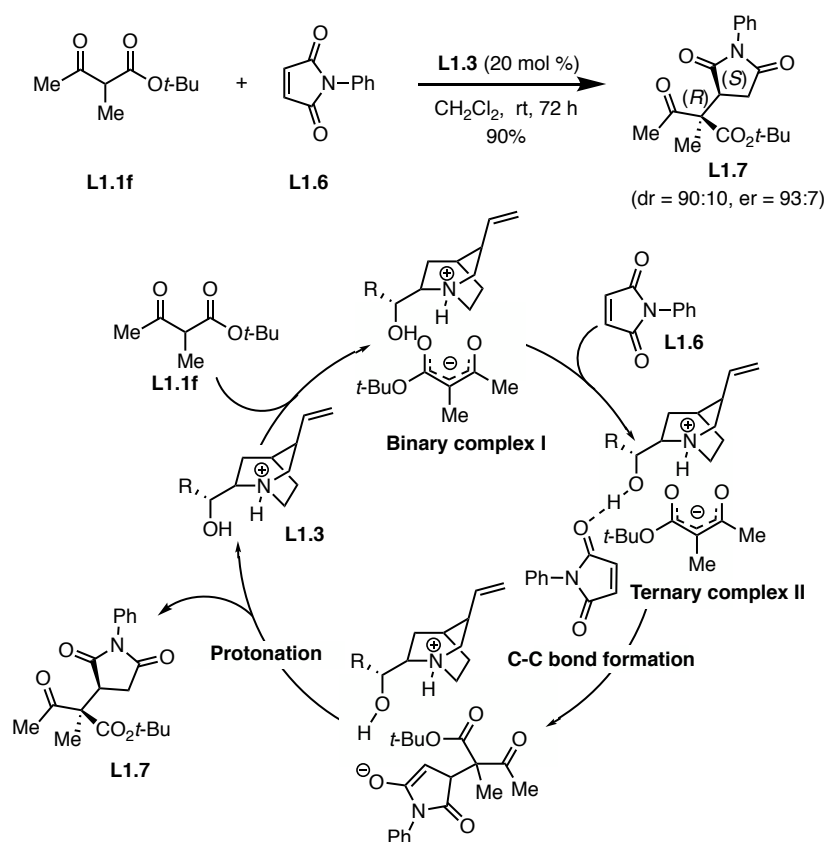
Table 1. Cinchona alkaloid catalyzed asymmetric conjugate addition on maleimides.

Entry	L1.1	Cat. (x mol %)	T (°C)	Yield of L1.5 (%)	dr	ee (%)
1	L1.1a	L1.3 (10)	-20	>95	94:6	92
2	L1.1a	L1.3 (10)	-20	>95	94:6	87
3	L1.1b	L1.3 (10)	-30	99	84:16	94
4	L1.1b	L1.4 (10)	-60	99	87:13	98
5	L1.1c	L1.3 (10)	-60	98	91:9	94
6	L1.1c	L1.4 (10)	-60	99	90:10	95
7	L1.1d	L1.4 (20)	-15	52	93:7	85
8	L1.1e	L1.4 (20)	-15	63	77:23	85
9	L1.1f	L1.4 (20)	rt	75	92:8	92
10	L1.1g	L1.3 (15)	-30	72	92:8	82
11	L1.1g	L1.4 (15)	-60	99	92:8	91
12	L1.1h	L1.3 (15)	-60	99	>98:2	89
13	L1.1h	L1.4 (15)	-60	91	>98:2	93
14	L1.1i	L1.3 (20)	-60	55	95:5	82
15	L1.1i	L1.4 (20)	-15	72	95:5	84

Later, Cucinotta *et al.*¹⁰ have realized mechanistic studies to rationalize the formation of succinimides **L1.7**. They showed that the cinchona alkaloids worked as bifunctional catalysts, exhibiting a dual mode of activation for both the 1,3-dicarbonyl

¹⁰ Cucinotta, C. S.; Kosa, M.; Melchiorre, P.; Cavalli, A.; Gervasio, F. L. *Chem. Eur. J.* **2009**, *15*, 7913-7921.

substrate and the maleimide. They showed that the reaction started with the formation of the non-covalent binary complex **I** between the tertiary amine of the catalyst and **L1.1f**. The binary complex **I** would further react with the maleimide **L1.6** to form a ternary complex **II** through a hydrogen bonding between the substrate **L1.6** and the secondary hydroxyl group of the catalyst **L1.3**. The Michael adduct is then obtained from this ternary complex **II** through a C-C bond formation and a protonation, while the cinchona alkaloid catalyst is regenerated for the next catalytic cycle (Scheme 1).

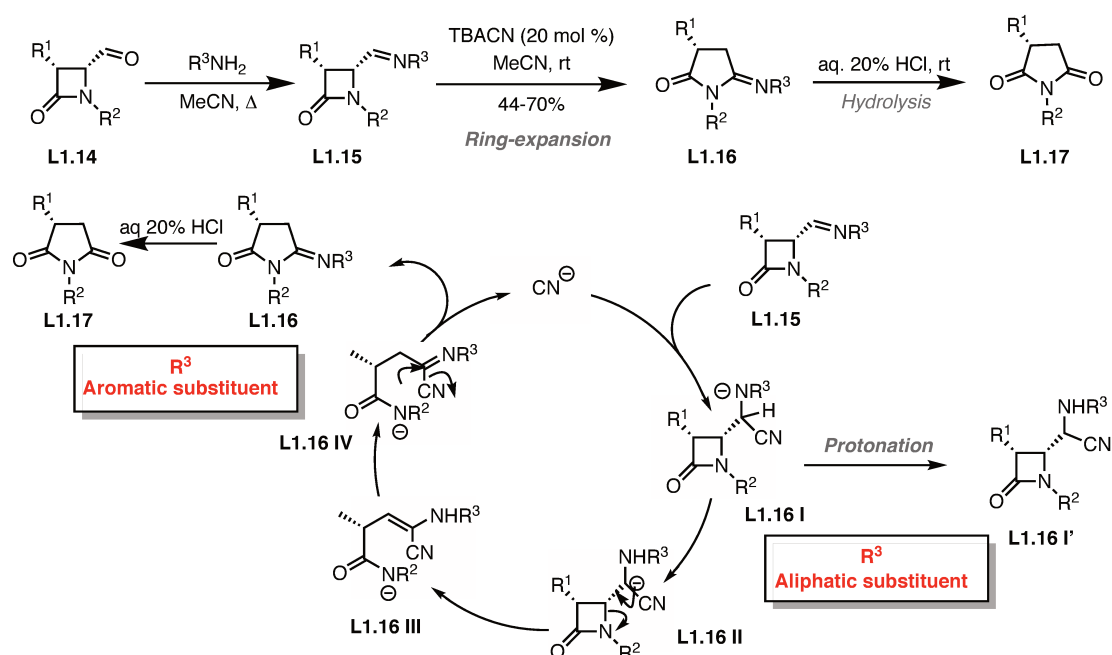


Scheme 1. Quinine-catalyzed Michael addition of β -ketoesters with *N*-phenylmaleimide and proposed mechanism.

Besides the natural cinchona alkaloids, other optically active organic catalysts were also evaluated by other researchers which are summarized in Figure 7.¹¹

¹¹ a) Ye, W.; Jiang, Z.; Zhao, Y.; Li, S.; Goh, M.; Leow, D.; Soh, Y.-T.; Tan, C.-H. *Adv. Synth. Catal.* **2007**, *349*, 2454-2458; b) Jiang, Z.; Ye, W.; Yang, Y.; Tan, C.-H. *Adv. Synth. Catal.* **2008**, *350*, 2345-2351; c) Jiang, Z.; Pan, Y.; Zhao, Y.; Ma, T.; Lee, R.; Yang, Y.; Huang, K.-W.; Wong, M. W.; Tan, C.-H. *Angew. Chem. Int. Ed.* **2009**, *48*, 3627-3631; d) Qin, Y.; Yang, G.; Yang, L.; Li, J.; Cui, Y. *Catal. Lett.* **2011**, *141*, 48-488; e) Shirakawa, S.; Terao, S. J.; He, R.; Maruoka, K. *Chem. Commun.* **2011**, *47*, 10557-10559; f) Gómez-Torres, E.; Alonso, D. A.; Gómez-Bengo, E.; Nájera, C. *Org. Lett.*

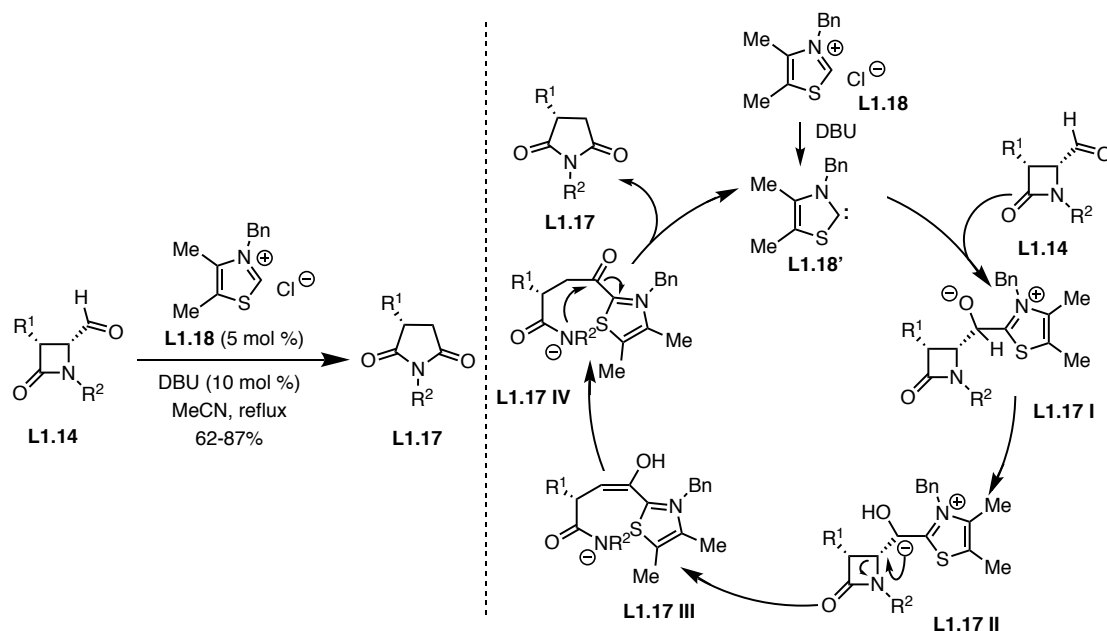
to afford the desired product **L1.16**, while an aliphatic substituent R^3 was detrimental to the cleavage of the N1-C4 bond (Scheme 2).



Scheme 2. TBACN-promoted ring-expansion of enantio-enriched β -lactams to access optically active succinimides and the proposed catalytic cycle

With the formation of **L1.17**, the possible mechanism can be explained by the nucleophilic attack of the cyanide to the imine that leads to the intermediate **L1.16 I**, which is then converted to the corresponding α -cyano carbanion **L1.16 II**. The N1-C4 bond is then cleaved to form the intermediate **L1.16 III**, which is further converted to the imino nitrile amide intermediate **L1.16 IV**. This latter undergoes an intramolecular nucleophilic substitution to generate the corresponding ring-expansion product **L1.16**, while the cyanide ion is regenerated for the next catalytic cycle (Scheme 2).

An elegant strategy was later developed by the same group. The method involved the use of a thiazolium chloride and DBU to promote the ring expansion of 4-oxoazetidin-2-carbaldehyde **L1.14** using an umpolung strategy by reversing the polarity of the aldehyde.^{12b} The corresponding succinimides, bearing a tertiary stereogenic center, were obtained in moderate to high yields (62-87%) (Scheme 3).



Scheme 3. *N*-heterocyclic carbene-promoted ring-expansion of β -lactams to access succinimides and the proposed catalytic cycle.

The *N*-heterocyclic carbene **L1.18'**, which is generated *in situ* from the exposure of the thiazolium chloride to DBU, adds onto the aldehyde to form **L1.17 I**, which then undergoes a 1,2-hydrogen shift to form intermediate **L1.17 II**. The strain of the β -lactam favors the N1-C4 bond cleavage to afford the enol-amide intermediate **L1.17 III**, which then isomerizes to produce the succinimide **L1.17** thereby releasing the *N*-heterocyclic carbene for the next catalytic cycle (Scheme 3).^{13,14}

2.1.3. Transition metal-catalyzed enantioselective hydrogenation

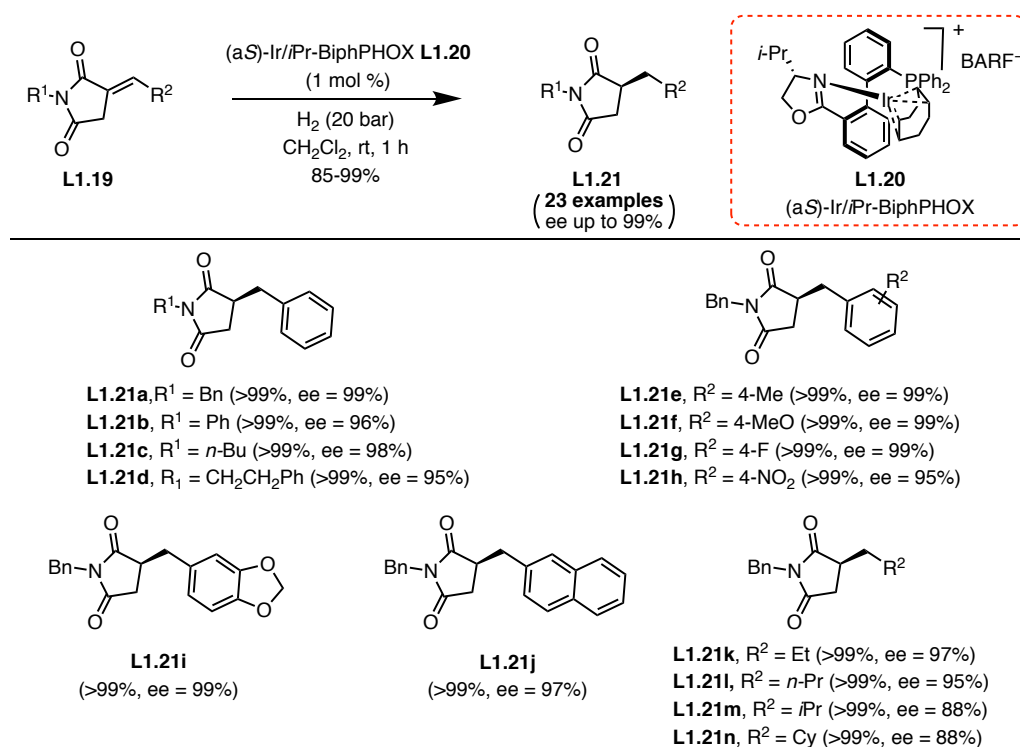
Optically active succinimides can also be accessed through a transition metal-catalyzed asymmetric hydrogenation of α -alkylidene succinimides or a 3-substituted maleimides. Recently, Zhang *et al.*¹⁵ reported an efficient asymmetric hydrogenation of α -alkylidene succinimides using an Ir/*i*PrBiphPHOX complex affording a variety of

¹³ Domingo, L. R.; Aurell, M. J.; Arnó, M. *Tetrahedron* **2009**, 65, 3432-3440.

¹⁴ A similar strategy was reported simultaneously, see: Li, G.-Q.; Li, Y.; Dai, L.-X.; You, S.-L. *Org. Lett.* **2007**, 9, 3519-3521.

¹⁵ a) Liu, Y.-Y.; Zhang, W.-B. *Angew. Chem. Int. Ed.* **2013**, 52, 2203-2206; b) Liu, Y.-Y.; Gridnev, I. D.; Zhang, W.-B. *Angew. Chem. Int. Ed.* **2014**, 53, 1901-1905.

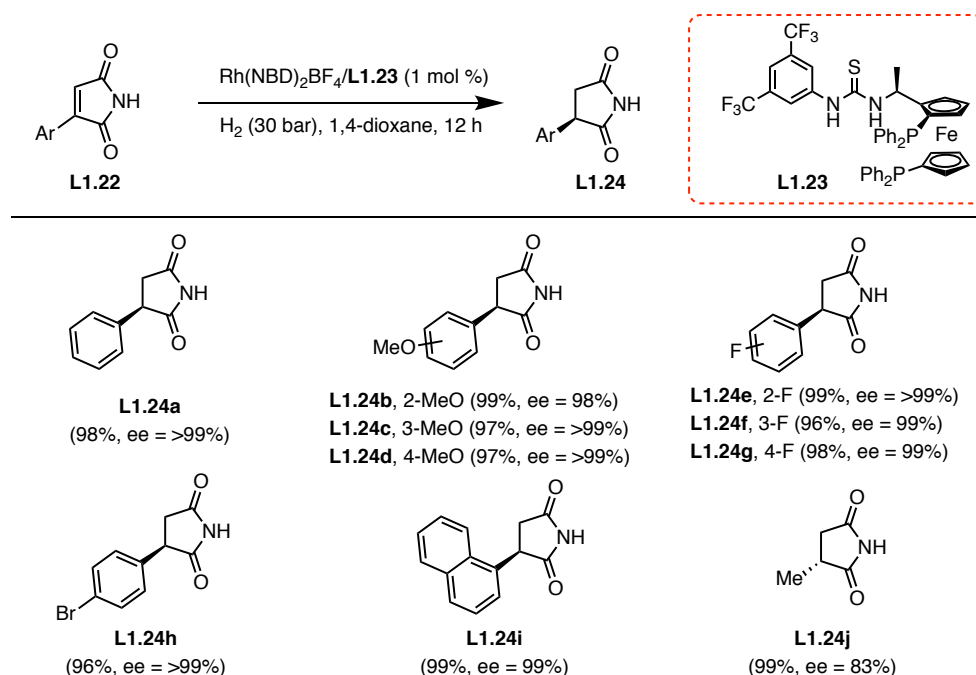
the corresponding α -substituted succinimides in high yields (85-99%) and excellent enantioselectivities (ee up to 99%) (Scheme 4).



Scheme 4. Ir-catalyzed asymmetric hydrogenation of α -alkylidene succinimides.

A highly enantioselective Rh-catalyzed asymmetric hydrogenation of 3-substituted maleimides in the presence of a bisphosphine-thiourea ligand was also reported by Zhang and co-workers.¹⁶ A variety of mono-substituted maleimides were thus prepared and subjected to the asymmetric hydrogenation conditions. The corresponding mono-substituted succinimides were generally obtained in high yields and excellent enantioselectivities (Scheme 5).

¹⁶ Han, Z.; Li, P.; Zhang, Z.; Chen, C.; Wang, Q.; Dong, X.-Q.; Zhang, X. *ACS Catal.* **2016**, *6*, 6214-6218.



Scheme 5. Rh-catalyzed asymmetric hydrogenation of 3-substituted maleimides.

2.1.4. Rhodium-catalyzed 1,4-addition of arylboronic acids to maleimide.

Another efficient and common strategy to access optically active succinimides involves the use of a Rh-catalyzed conjugate addition of arylboronic acids to maleimides. The first example of Rh-catalyzed asymmetric 1,4-addition of aryl boronic acids to α,β -unsaturated ketones was reported by Miyaura *et al.* in 1998.¹⁷ Since then, the enantioselective Rh-catalyzed conjugate addition became one of the most powerful reaction to form C-C bonds. Thanks to the work of Hayashi *et al.*,¹⁸ Michelet *et al.*,¹⁹ Knochel *et al.*,²⁰ Ratovelomanana-Vidal *et al.*²¹ and Shimada *et al.*,²² this reaction was also successfully applied to the asymmetric synthesis of optically active succinimides bearing a tertiary stereogenic center. For example, Hayashi *et al.* used

¹⁷ Tajara, Y.; Ogasawara, M.; Hayashi, T.; Sakai, M.; Miyaura, N. *J. Am. Chem. Soc.* **1998**, *120*, 5579-5580.

¹⁸ a) Shintani, R.; Ueyama, K.; Yamada, I.; Hayashi, T. *Org. Lett.* **2004**, *6*, 3425-3427; b) Shintani, R.; Duan, W.-L.; Nagano, T.; Okada, A.; Hayashi, T. *Angew. Chem. Int. Ed.* **2005**, *44*, 4611-4614; c) Duan, W.-L.; Iwamura, H.; Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2007**, *129*, 2130-2138.

¹⁹ Le Boucher d'Herouville, F.; Millet, A.; Scalone, M.; Michelet, V. *J. Org. Chem.* **2011**, *76*, 6925-6930.

²⁰ Thaler, T.; Guo, L.-N.; Steib, A. K.; Raducan, M.; Karaghiosoff, K.; Mayer, P.; Knochel, P. *Org. Lett.* **2011**, *13*, 3182-3185.

²¹ Berhal, F.; Wu, Z.; Genet, J.-P.; Ayad, T.; Ratovelomanana-Vidal, V. *J. Org. Chem.* **2011**, *76*, 6320-6326.

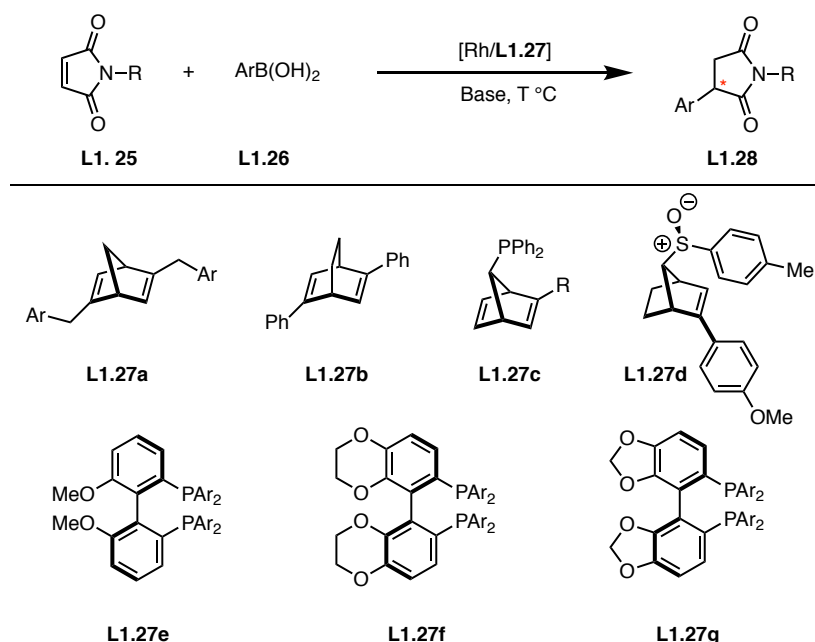
²² Korenaga, T.; Ko, A.; Shimada, K. *J. Org. Chem.* **2013**, *78*, 9975-9980.

an optically active norbornadiene ligand for the Rh-catalyzed asymmetric 1,4-addition of arylboronic acids to maleimides affording the corresponding optically active succinimides in good to excellent enantioselectivities (ee up to 92%) (Table 2).

Table 2. Rh-catalyzed asymmetric 1,4-addition of arylboronic acids to maleimides.

entry	R	Ar	yield in L1.28 (%)	ee (%)
1	Me	Ph	88	85
2	Cy	Ph	85	87
3	Bn	Ph	88	69
4	Cy	4-MeOC ₆ H ₄	77	84
5	Cy	4-F-C ₆ H ₄	88	85
6	Cy	3-Cl-C ₆ H ₄	92	82
7	Cy	2-Me-C ₆ H ₄	95	92

A variety of optically active diene ligands, phosphine-olefin bidentate ligands and electron-poor diphosphine ligands have also been used for this 1,4-conjugate addition of arylboronic acids to succinimides (Scheme 6).²²



Scheme 6. Different chiral ligands using for Rh-catalyzed asymmetric conjugate addition of arylboronic acids to maleimides.

2.2 Enantioselective synthesis of succinimide derivatives bearing a quaternary stereogenic center.

Despite the number of methods reported in the literature over the past decades, the enantioselective construction of cyclic²³ and acyclic²⁴ compounds bearing a quaternary stereogenic center remains a challenge.²⁵ This is particularly the case for succinimides bearing a quaternary stereogenic center.

2.2.1 Rhodium-catalyzed 1,4-addition of arylboronic acids to mono-substituted maleimides.

One of the methods that allows a straightforward and highly enantioselective access to optically active succinimides bearing a quaternary stereogenic center is the Rh-catalyzed asymmetric 1,4-addition of arylboronic acids to monosubstituted maleimides. This strategy, first reported by Hayashi *et al.*, allows a highly enantioselective access to the corresponding chiral succinimides bearing a quaternary stereogenic center.²⁶

Various optically active diene ligands and diphosphine ligands were evaluated. The regioselectivity appeared to be dramatically improved (**L1.31**/**L1.32** = 87:13) when using (*R*)-H₈-BINAP as the chiral ligand, the 3,3'-disubstituted succinimide **L1.31** being obtained in up to 97% ee. A variety of arylboronic acids and various 3-substituted maleimides were investigated under the optimal conditions and the chiral 3,3'-

²³ a) Liu, Y.; Han, S.-J.; Liu, W.-B.; Stoltz, B. M. *Acc. Chem. Res.* **2015**, *48*, 740-751; b) Quasdorf, K. W.; Overman, L. E. *Nature* **2014**, *516*, 181-191; c) Marek, I.; Minko, Y.; Pasco, M.; Mejuch, T.; Gilboa, N.; Chechik, H.; Das, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 2682-2694; d) Hong, A. Y.; Stoltz, B. M. *Eur. J. Org. Chem.* **2013**, 2745-2759; e) Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369-396; f) Christoffers, J.; Baro, A. *Adv. Synth. Catal.* **2005**, *347*, 1473-1482; g) Peterson, E. A.; Overman, L. E. *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 11943-11948; h) Christoffers, J.; Mann, A. *Angew. Chem. Int. Ed.* **2001**, *40*, 4591-4597; i) Corey, E. J.; Guzman-Perez, A. *Angew. Chem. Int. Ed.* **1998**, *37*, 388-401; j) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037-2066.

²⁴ a) Feng, J.; Holmes, M.; Krische, M. J. *Chem. Rev.* **2017**, *117*, 12564-12580; b) Singh, S.; Bruffaerts, J.; Vasseur, A.; Marek, I. *Nat. Commun.* **2017**, *8*, 14200-14209; c) Pupo, G.; Properzi, R.; List, B. *Angew. Chem. Int. Ed.* **2016**, *55*, 6099-6102; d) Roy, S. R.; Didier, D.; Kleiner, A.; Marek, I. *Chem. Sci.* **2016**, *7*, 5989-5994; e) Zhang, F.-G.; Eppe, G.; Marek, I. *Angew. Chem. Int. Ed.* **2016**, *55*, 714-718; f) Trost, B. M.; Donckele, E. J.; Thaisrivongs, D. A.; Osipov, M.; Masters, J. T. *J. Am. Chem. Soc.* **2015**, *137*, 2776-2784; g) Eppe, G.; Didier, D.; Marek, I. *Chem. Rev.* **2015**, *115*, 9175-9206; h) Delaye, P.-O.; Didier, D.; Marek, I. *Angew. Chem. Int. Ed.* **2013**, *52*, 5333-5337.

²⁵ Peng, X.-P.; Cao, Z.-Y.; Wang, Y.-H.; Zhou, F.; Zhou, J. *Chem. Rev.* **2016**, *116*, 7330-7396.

²⁶ Shintani, R.; Duan, W.-L.; Hayashi, T. *J. Am. Chem. Soc.* **2006**, *128*, 5628-5629.

disubstituted succinimides could be isolated in generally high yields, good to high regioselectivities and excellent enantioselectivities (Table 3).

Table 3. Rh-catalyzed asymmetric construction of enantioenriched succinimides bearing a quaternary stereogenic center

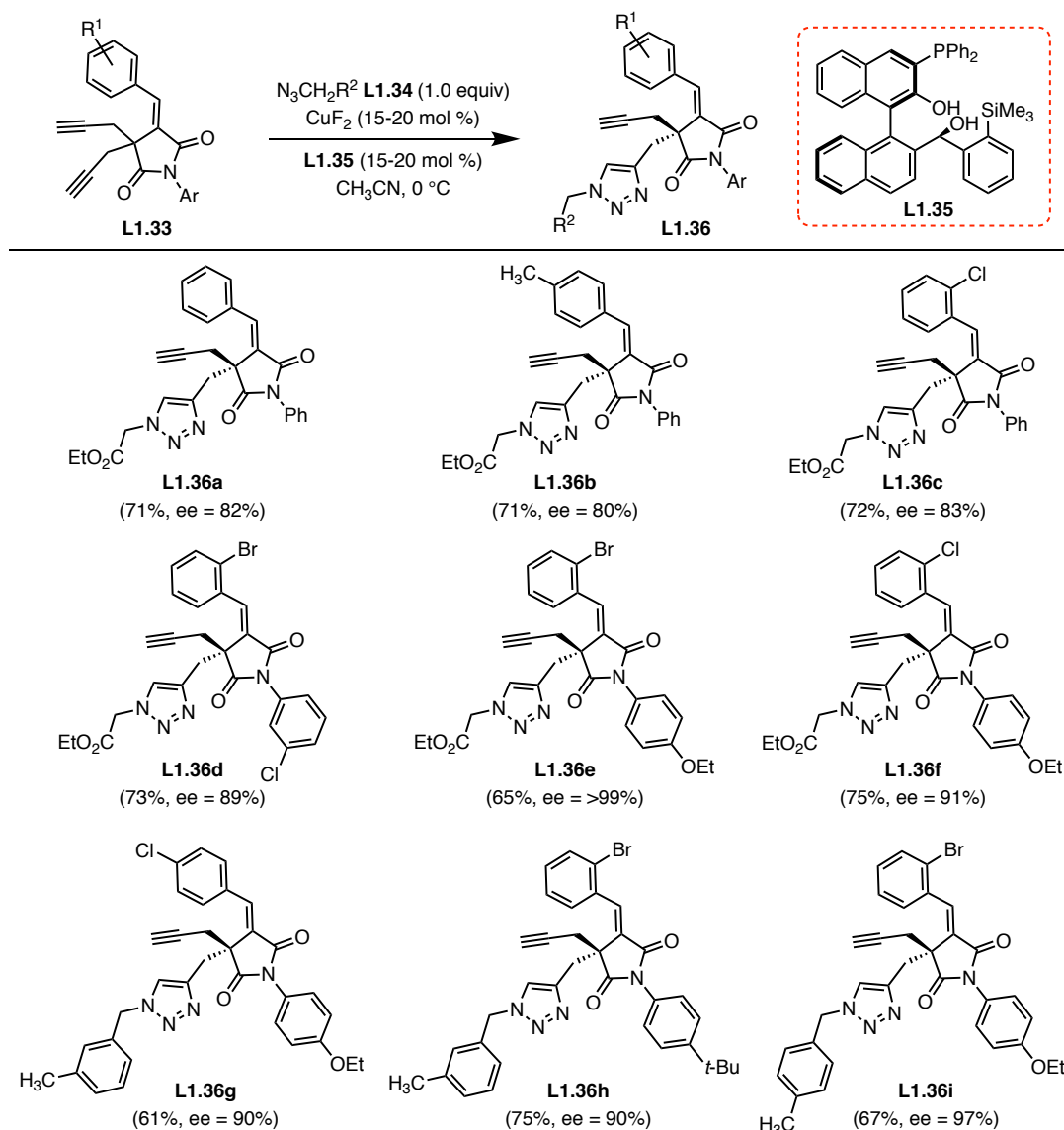
Entry	R	Ar	Yield (%) ^a	L1.31/L1.32	ee of L1.31 (%)
1	Et	Ph	98	87:13	97
2	Et	3-Cl-C ₆ H ₄	95	92:8	97
3	Et	2-naphthyl	90	86:14	96
4	Et	2-MeC ₆ H ₄	82	>98:2	90
5	Me	Ph	98	81:19	96
6	Me	4-MeO-C ₆ H ₄	95	84:16	90
7	Me	4-F-C ₆ H ₄	95	86:14	96
8	<i>i</i> Pr	Ph	90	97:3	98
9	<i>i</i> Pr	4-Me-C ₆ H ₄	85	97:3	98

^a Yield of **L1.31** and **L1.32** combined.

2.2.2. Enantioselective copper-catalyzed click reaction and desymmetrization of succinimide-base bis(alkynes)

Another interesting strategy to access optically active succinimides bearing a quaternary stereogenic center is through an enantioselective desymmetrization. Recently, Xu *et al.*²⁷ developed a chiral multifunctional phosphine ligand **L1.35** and successfully applied it to the enantioselective Cu-catalyzed azide-alkyne cycloaddition (CuAAC) on a maleimide-based bis(alkyne) **L1.33**, which afforded the corresponding optically active succinimide **L1.36** bearing a quaternary stereogenic center in very good yields and good to high enantioselectivities (ee up to 99%) (Scheme 7). This new type of multifunctional chiral phosphine ligand, **L1.35**, was found to play a crucial role in obtaining high enantioselectivities.

²⁷ a) Song, T.; Li, L.; Zhou, W.; Zheng, Z. J.; Deng, Y.; Xu, Z.; Xu, L. W. *Chem. Eur. J.* **2015**, *21*, 554-558; b) Chen, M. Y.; Song, T.; Zheng, Z. J.; Xu, Z.; Cui, Y. M.; Xu, L. W. *RSC Adv.* **2016**, *6*, 58698-58708.



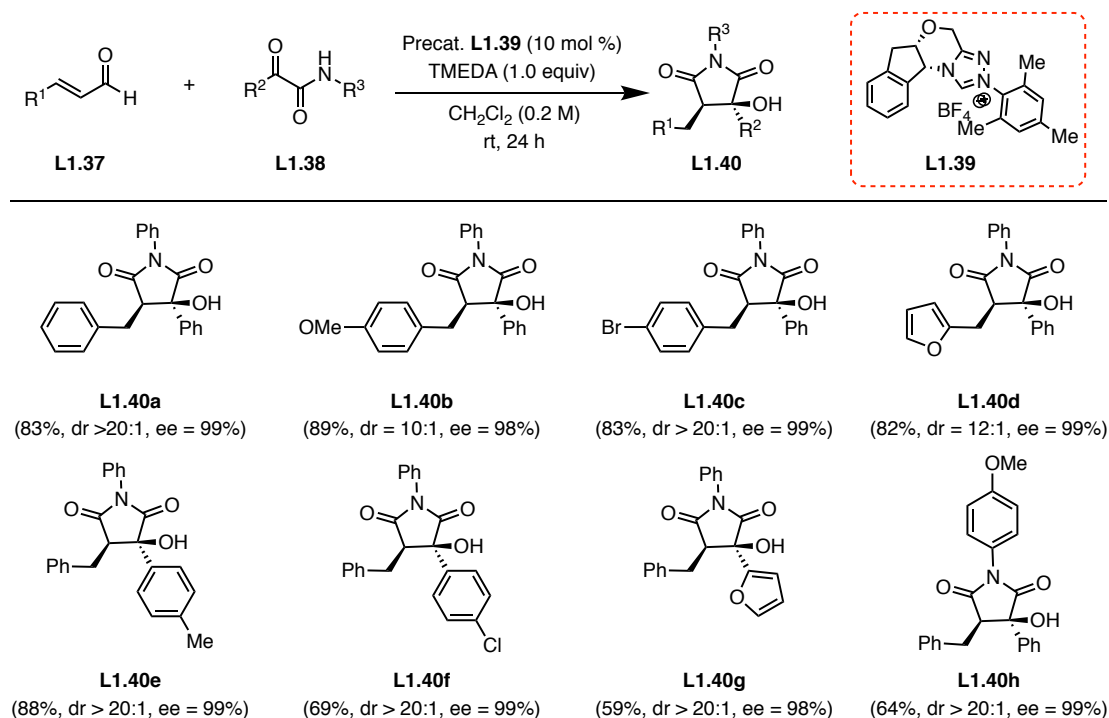
Scheme 7. Copper-catalyzed desymmetrization of succinimide-based bis(alkynes)

2.2.3. N-heterocyclic carbene-catalyzed asymmetric [3+2]-cycloaddition

Recently, Enders and co-worker developed a method to synthesize optically active succinimides from α -ketoamides and α,β -unsaturated aldehydes *via* a [3+2]-cycloaddition catalyzed by a chiral N-heterocyclic carbene (NHC) precatalyst.²⁸ Various enals, **L1.37**, and α -ketoamides, **L1.38**, were prepared and successfully subjected to this cycloaddition. The corresponding succinimides **L1.40** were obtained

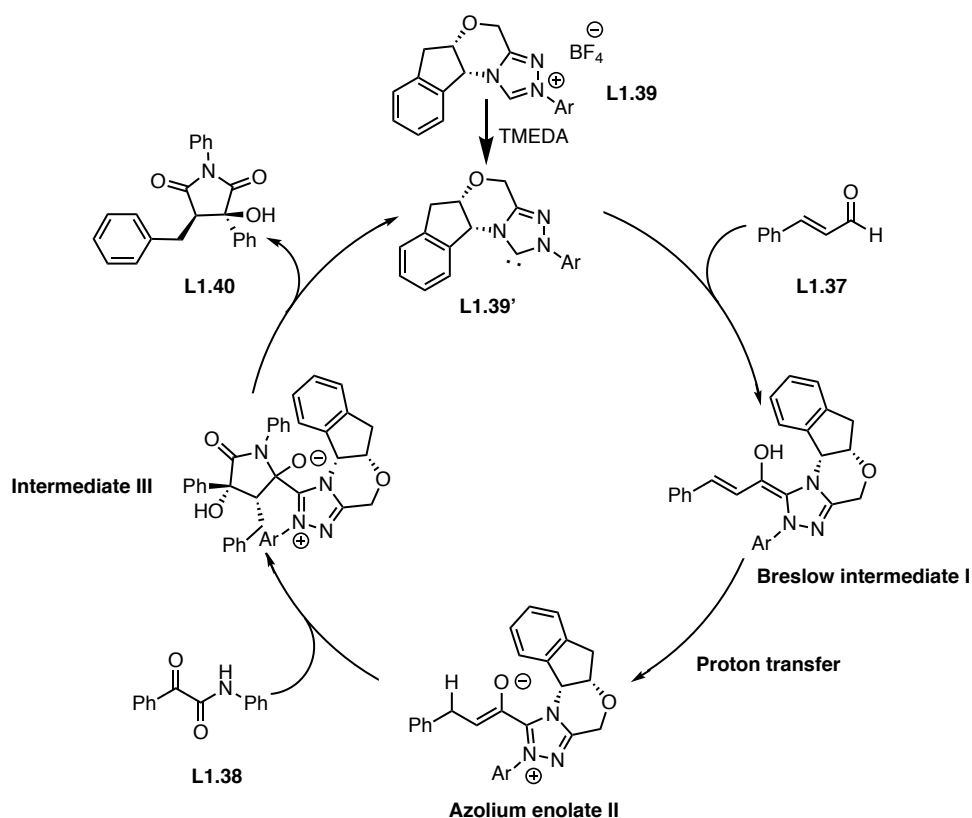
²⁸ Wang, L.; Ni, Q.-J.; Blümel, M.; Shu, T.; Raabe, G.; Enders, D. *Chem. Eur. J.* **2015**, *21*, 8033-8037.

in good yields, high regioselectivities and excellent enantioselectivities (ee up to 99%) (Scheme 8).



Scheme 8. NHC-catalyzed asymmetric [3+2]-cycloaddition of enals and α -ketoamides

Mechanistically, heterocyclic carbene **L1.39'**, which is generated *in situ* from the triazolium salt **L1.39** by deprotonation, reacts with aldehyde **L1.37** to form the Breslow intermediate **I**. After proton transfer followed by a [3+2]-cycloaddition with α -ketoamide **L1.38**, intermediate **III** is formed which then releases cycloadduct **L1.40**, while the heterocyclic carbene is regenerated for next catalytic cycle (Scheme 9).



Scheme 9. Plausible catalytic cycles of NHC-catalyzed [3+2]-cycloaddition.

2.2.4. Cyclization of amines and chiral carboxylic acid derivatives

Optically active succinimides can also be accessed by cyclization of an amino acid derivative. Several groups contributed to this field in the past decade. For example, in 2008, Fillion *et al.*²⁹ developed a Cu-catalyzed asymmetric 1,4-addition of dialkylzinc to Meldrum's acid derivatives. The corresponding addition products **L1.43**, bearing an all-carbon α -quaternary center were obtained generally in high yields and good to excellent enantioselectivities. Most importantly, the treatment of **L1.43** by benzylamine led to the optically active succinimides **L1.44** (Scheme 10).

²⁹ Wilsily, A.; Fillion, E. *Org. Lett.* **2008**, *10*, 2801-2804.

Carboxylic acid **L1.49** was synthesized from the Michael adduct **L1.48** by a Pinnick oxidation (NaClO_2 , NaH_2PO_4 , 2-methyl-2-butene, *t*-BuOH/ H_2O). The carboxylic acid **L1.49** was then reacted with *p*-methoxybenzylamine in the presence of HATU and *i*-Pr₂EtN to produce amide **L1.50**, while succinimide **L1.51** was ultimately obtained after sequential base-mediated cyclization/radical denitration. Finally, deprotection of the PMB-group with ceric ammonium nitrate (CAN) afforded (+)-(*S*)-ethosuximides.

3. Results and discussion

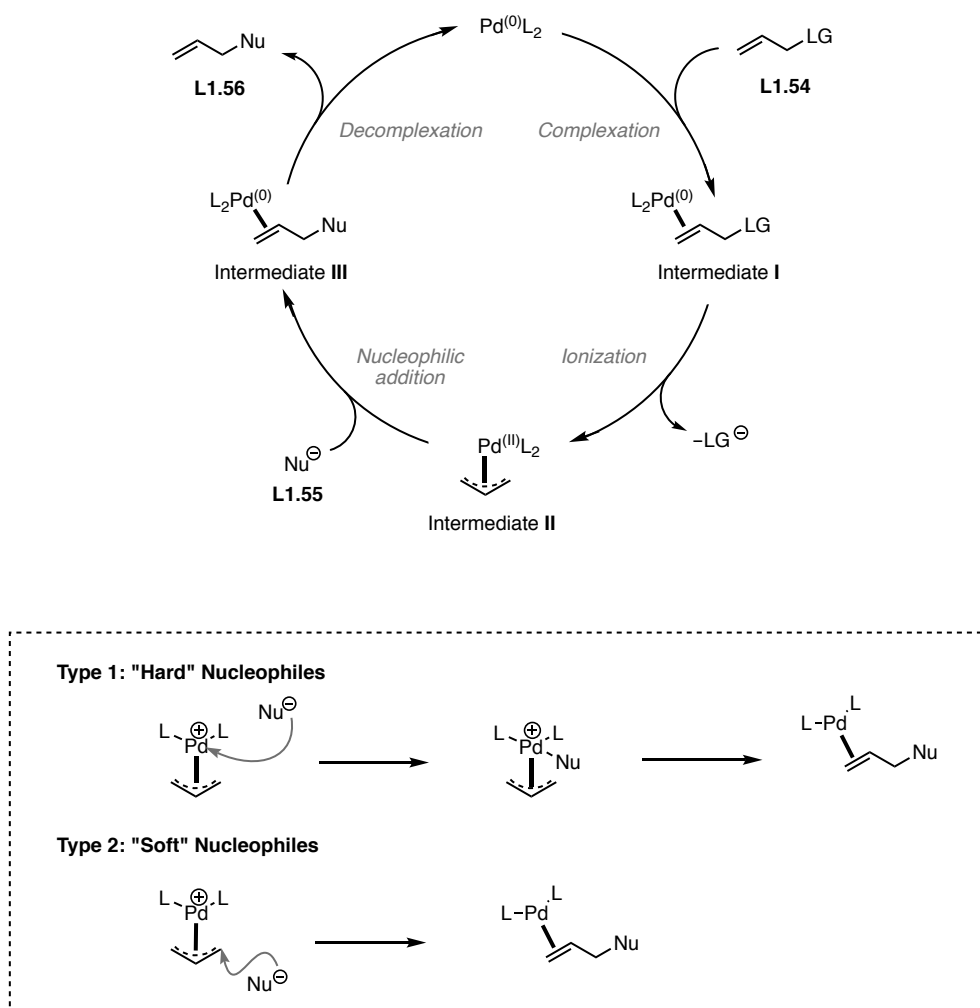
3.1 Context and objective

As shown previously, the synthesis of chiral succinimides bearing an all carbon quaternary stereogenic center remains a challenge. In this context, we hypothesized that the Palladium-catalyzed Asymmetric Allylic Alkylation (Pd-AAA), also referred to as the Tsuji-Trost reaction, could be an alternative. Indeed, thanks to the pioneering work of Tsuji *et al.*³¹ and Trost *et al.*,³² the Pd-AAA has become one of the most powerful reaction to form C-C and C-X (X = O, S, N, P) bonds.³³ This reaction involves a nucleophilic attack on a Pd- π -allylic complex or an S_N2'-type allylic substitution. The general catalytic cycle of the Pd-AAA involves five steps. The initial step is the coordination of the allylic electrophilic substrate to the low-valent Pd(0) center to form intermediate **I**, which undergoes ionization and oxidative addition to generate the cationic Pd(II)- π -allylic complex **II**. The subsequent nucleophilic addition then depends on the nature of the nucleophile. Hence, when "hard" nucleophiles are used, these nucleophiles first attack the metal center before a reductive elimination occurs to form the corresponding allylated product and regenerate the catalyst (Type 1) (Scheme 20). In contrast, the "soft" type nucleophiles attack the allylic terminal carbon on the opposite face of the Pd complex, while decomplexation releases the allylated product and regenerates the catalyst (Type 2) (Scheme 12).

³¹ Tsuji, J.; Takahashi, H.; Morikawa, Masanobu. *Tetrahedron Lett.* **1965**, 49, 4387-4388.

³² Trost, B. M.; Fullerton, T. J. *J. Am. Chem. Soc.* **1973**, 95, 292-294.

³³ Selected reviews, see: a) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.*, **1996**, 96, 395-422; b) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, 103, 2921-2944; c) Lu, Z.; Ma, S. *Angew. Chem., Int. Ed.*, **2008**, 47, 258-297; d) Trost, B. M.; Zhang, T.; Sieber, J. D. *Chem. Sci.*, **2010**, 1, 427-440; e) Trost, B. M. *Org. Process Res. Dev.* **2012**, 16, 185-194.



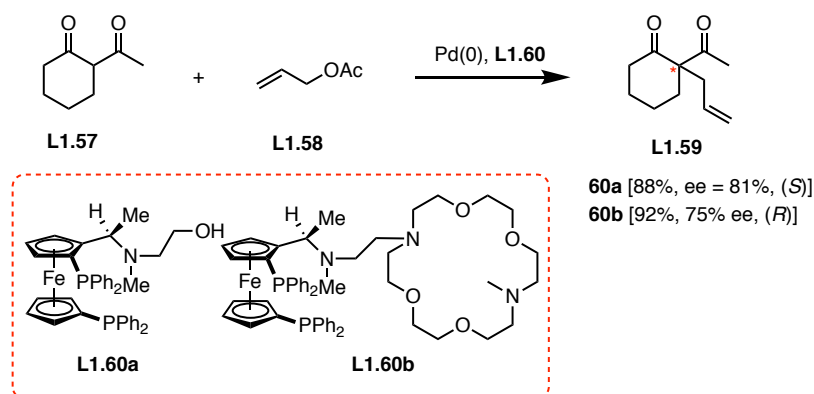
Scheme 12. Catalytic cycle of Pd-AAA.

Over the years, the Pd-AAA proved to be a straightforward and highly enantioselective approach to construct all carbon quaternary stereocenters.^{23,24} Hayashi *et al.*³⁴ and Ito *et al.*³⁵ both investigated this Pd-AAA and came up with the optically active ferrocenylphosphine ligands **L1.60a** and **L1.60b**, which were successfully used in the allylation of 1,3-diketones (Scheme 13). Interestingly, these two ligands led to the opposite enantiomers. Subsequently, Trost *et al.*³⁶ reported the first asymmetric allylation of β -ketoesters with enantioselectivities reaching up to 95% ee using the C_2 -symmetric bis-phosphine ligand (*R,R*)-**L1.62** (Scheme 14).

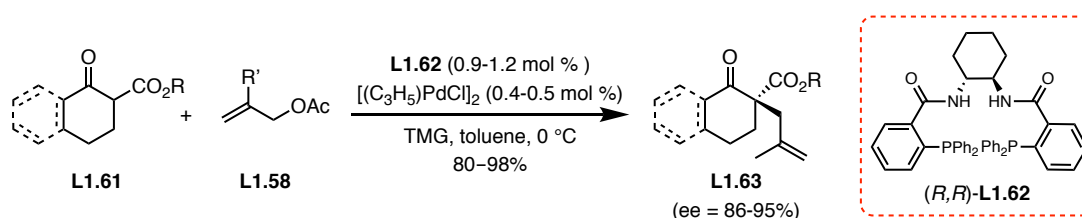
³⁴ Hayashi, T.; Kanehira, K.; Hagihara, T.; Kumada, M. *J. Org. Chem.* **1988**, *53*, 113-120.

³⁵ Sawamura, M.; Nagata, H.; Sakamoto, H.; Ito, Y. *J. Am. Chem. Soc.* **1992**, *114*, 2586-2592.

³⁶ Trost, B. M.; Radinov, R.; Grenzer, E. M. *J. Am. Chem. Soc.* **1997**, *119*, 7879-7880.



Scheme 13. Pd-AAA of 1,3-diketones.



Scheme 14. Pd-AAA of β -ketoesters.

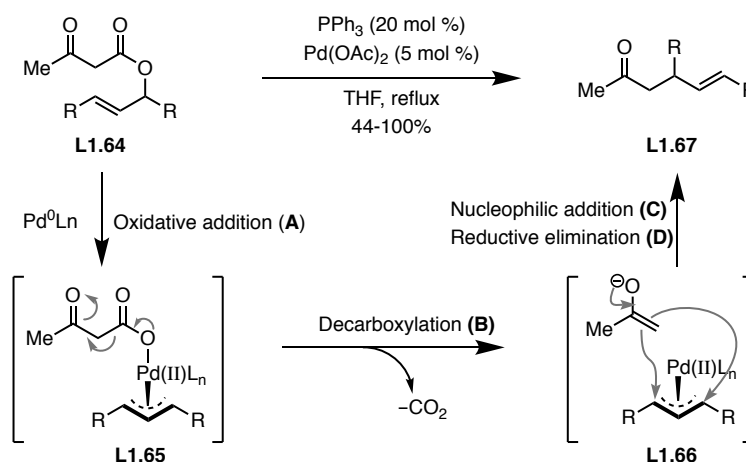
Inspired by these pioneering works, many other groups have contributed to extend the substrate scope of this reaction. Hence, a series of 1,3-dicarbonyl compounds were shown to be suitable substrates for the asymmetric allylation.³³ Various chiral biphosphines and P,N-chelating ligands were shown to induce high levels of enantioselectivity on a broad range of substrates.³⁷

Due to the continuous evolution of this method, another type of palladium-catalyzed asymmetric allylation was developed, namely the **Palladium catalyzed Decarboxylative Asymmetric Allylic Alkylation** (Pd-DAAA). The first racemic decarboxylative allylation was reported by Tsuji *et al.* in 1983 (Scheme 15).³⁸ They used a low valence palladium-catalyst to promote an intramolecular allylation of an acetoacetic acid-derived allylic ester to afford the decarboxylated allylated products in up to quantitative yield. Mechanistically, the first step involves an oxidative addition

³⁷ Rios, I. G.; Rosas-Hernandez, A.; Martin, E. *Molecules* **2011**, *16*, 970–1010.

³⁸ a) Tsuji, J.; Minami, I.; Shimizu, I. *Tetrahedron Lett.* **1983**, *24*, 1793–1796; b) Tsuji, J.; Shimizu, I.; Minami, I.; Ohashi, Y.; Sugiura, T.; Takahashi, K. *J. Org. Chem.* **1985**, *50*, 1523–1529; c) Tsuji, J.; Minami, I. *ACC. Chem. Res.* **1987**, *20*, 140–145.

of the Pd(0) onto the substrate **L1.64** to form the intermediate **L1.65**, which subsequently undergoes a decarboxylation to generate intermediate **L1.66**. After a regioselective nucleophilic addition and reductive elimination, the allylated product **L1.67** is produced.



Scheme 15. Pd-catalyzed decarboxylative allylic alkylation.

The first asymmetric palladium-catalyzed decarboxylative allylic alkylations were reported by Stoltz *et al.*³⁹ (Scheme 16, eq 1), Trost *et al.*⁴⁰ and Tunge *et al.*,⁴¹ independently. The chiral (*S*)-(*t*-Bu)-PHOX ligand **L1.69** and (*R,R*)-**L1.62** were found to be particularly effective, affording the corresponding allylated products in high yields and good to excellent enantioselectivities. Soon after, the Pd-DAAA was applied to β -ketoesters **L1.71** (Scheme 16, eq 2),⁴² *N*-containing heterocycles **L1.73** (Scheme 16, eq 3)⁴³ and other suitable prochiral allyl enol carbonates.⁴⁴

³⁹ Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044-15045.

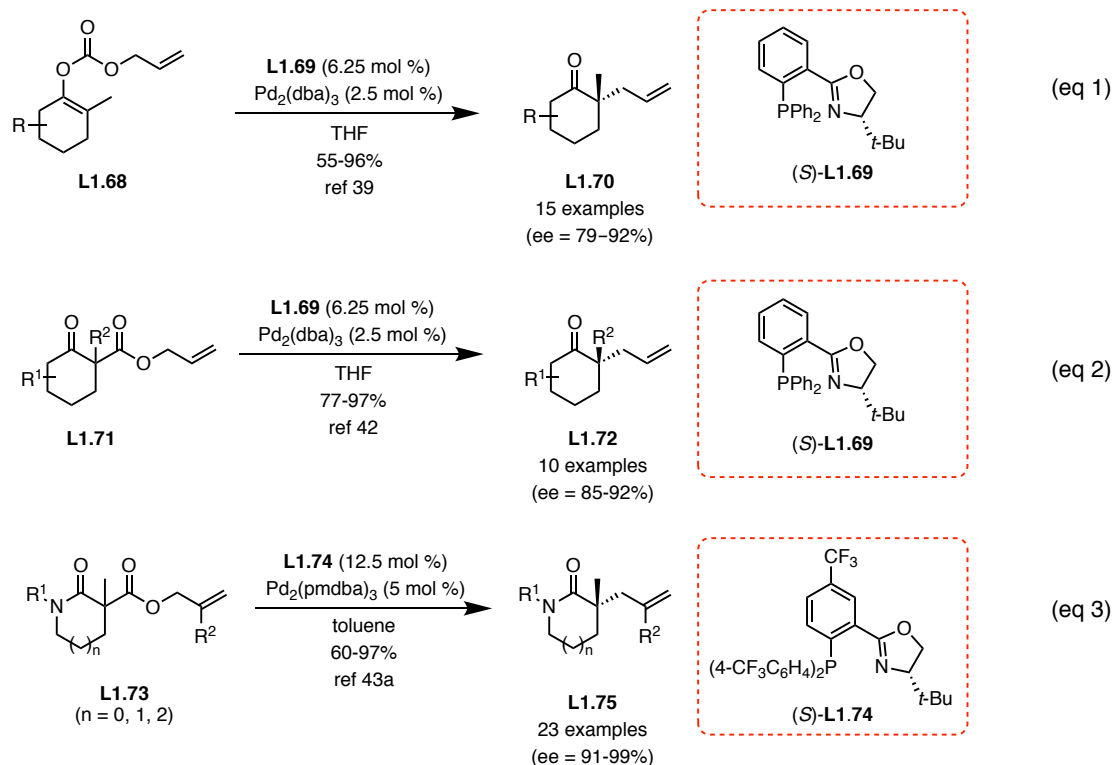
⁴⁰ a) Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 2846-2847 b) Trost, B. M.; Xu, J.; Schmidt, T. *J. Am. Chem. Soc.* **2009**, *131*, 18343-18357.

⁴¹ Stereocenter generated at the allyl fragment as a tertiary center, see: Burger, E. C.; Tunge, J. A. *Org. Lett.* **2004**, *6*, 4113-4115.

⁴² Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2005**, *117*, 7084-7087.

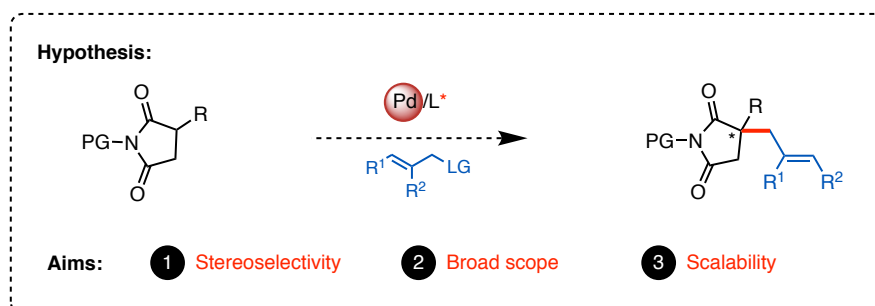
⁴³ a) Behenna, D. C.; Liu, Y.; Yurino, T.; Kim, J.; White, D. E.; Virgil, S. C.; Stoltz, B. M. *Nat. Chem.* **2012**, *4*, 130-133; b) Korch, K. M.; Eidamshaus, C.; Behenna, D. C.; Nam, S.; Horne, D.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2015**, *54*, 179-183.

⁴⁴ For selected examples, see: a) Alexy, E. J.; Virgil, S. C.; Bartberger, M. D.; Stoltz, B. M. *Org. Lett.* **2017**, *19*, 5007-5009; b) Starkov, P.; Moore, J. T.; Duquette, D. C.; Stoltz, B. M.; Marek, I. *J. Am. Chem. Soc.* **2017**, *139*, 9615-9620; c) De Oliveira, M. N.; Fournier, J.; Arseniyadis, S.; Cossy, J. *Org. Lett.* **2017**, *19*, 14-17; d) Craig, R. A., II; Loskot, S. A.; Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M. *Org. Lett.* **2015**, *17*, 5160-5163; e) Fournier, J.; Lozano, O.; Menozzi, C.; Arseniyadis, S.; Cossy, J. *Angew. Chem. Int. Ed.* **2013**, *52*, 1257-1261; f) Weaver, J. D.; Ka, B. J.; Morris, D. K.; Thompson, W.; Tunge, J. A. *J. Am. Chem. Soc.* **2010**, *132*, 12179-12181; g) Trost, B. M.; Xu, J.; Schmidt, T. J.



Scheme 16. Pd-DAAA of different substrates.

Based on these reports, we envisioned to apply the Pd-AAA to monosubstituted succinimides with the aim of accessing the corresponding allylated products bearing an all-carbon α -quaternary stereogenic center (Scheme 17). This would allow a particularly straightforward and potentially enantioselective route to such compounds.

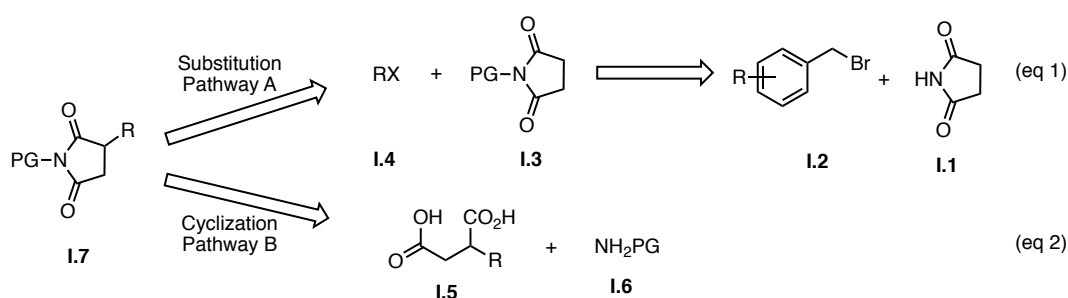


Scheme 17. Hypothesis to construct optically active succinimides bearing a quaternary stereogenic center by using a Pd-AAA

3.2. Synthesis of succinimide derivatives and allylic reagents

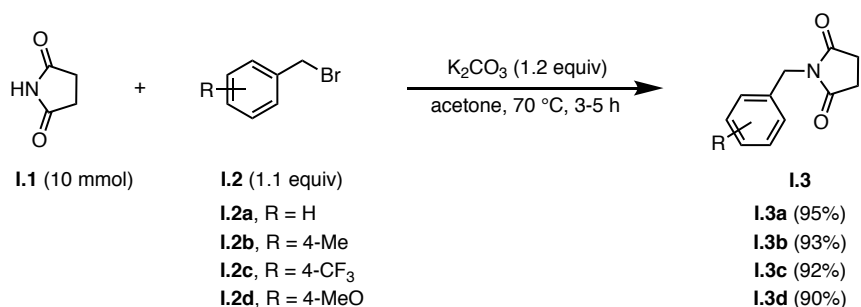
3.2.1. Synthesis of monosubstituted succinimide derivatives

We initiated our study by the synthesis of monosubstituted succinimides **I.7**, which could be prepared according to two different strategies: either through the functionalization of a succinimide derivative (pathway A) (Scheme 18, eq 1) or through the formation of the succinimide moiety starting from a pre-functionalized precursor (pathway B) (Scheme 18, eq 2).



Scheme 18. Strategies for the synthesis of monosubstituted succinimides.

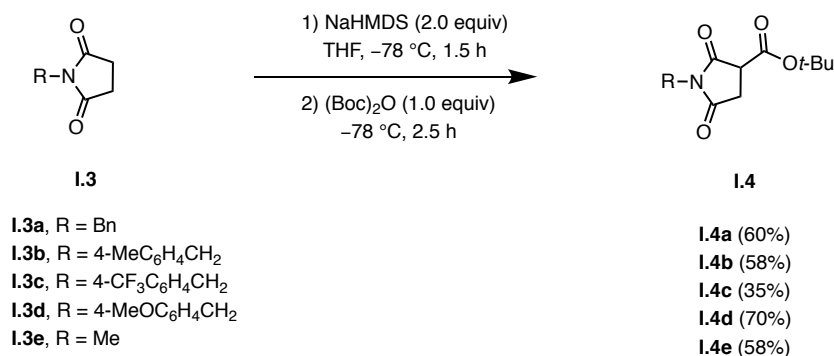
For pathway A, various *N*-protected succinimides **I.3** were synthesized starting from the corresponding unprotected succinimide **I.1** [K_2CO_3 , acetone, 70 °C]. As a general trend, compounds **I.3a-d** were obtained in high yields ranging from 90% to 95% (Scheme 19).⁴⁵



Scheme 19. Synthesis of the *N*-protected succinimides **I.3**.

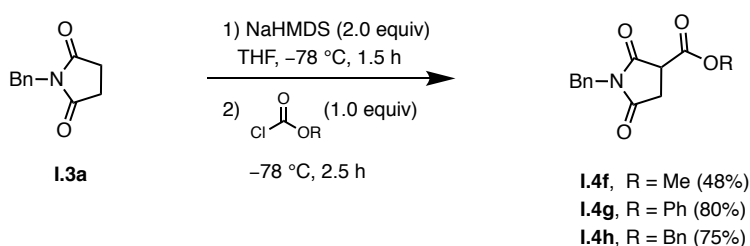
⁴⁵ a) Khan A.; Marson, C. M.; Porter, R. A. *Synth. Commun.* **2001**, 31, 1753-1764; b) Smith, A. M.; Rzepa, H. S.; White, A. J.; Billen, D.; Hii, K. K. *J. Org. Chem.* **2010**, 75, 3085-3096.

Following the results reported in the literature pertaining to the Pd-AAA of 1,3-dicarbonyl compounds, we decided to prepare a series of substrates bearing an electron-withdrawing group at the C3-position. Substrates **I.4a-e** were prepared in a two-step one-pot procedure involving a deprotonation [NaHMDS, THF, $-78\text{ }^{\circ}\text{C}$] followed by an acylation [Boc_2O , THF, $-78\text{ }^{\circ}\text{C}$] (Scheme 20). Compound **I.4a-e** were isolated in moderate to good yields (35-70%).



Scheme 20. Synthesis of the succinimide derivatives **I.4a-e**.

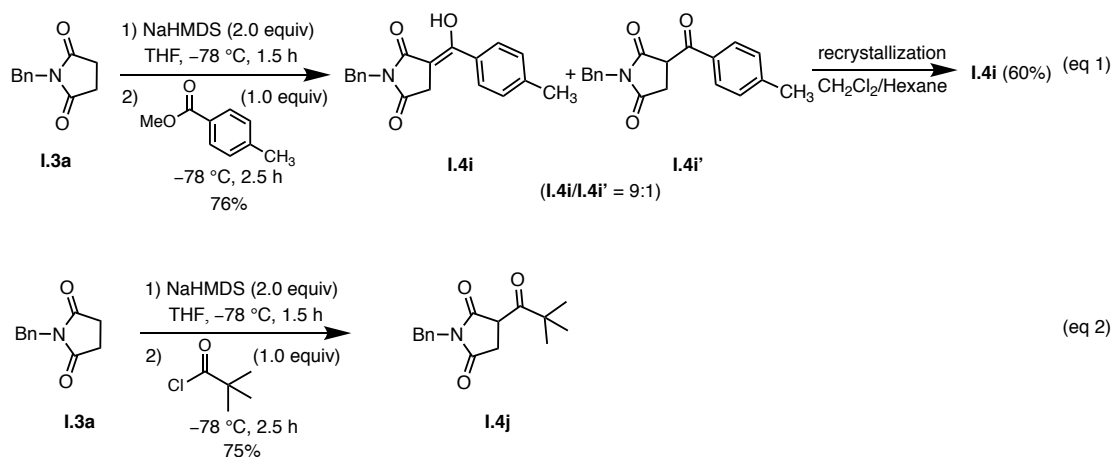
To increase the structural diversity for the ester substituent, the succinimide derivatives **I.4f-h** were also prepared in moderate to good yields after treatment by a base (NaHMDS, $-78\text{ }^{\circ}\text{C}$) and subsequent addition of various alkyl or aryl chloroformates (Scheme 21).



Scheme 21. Synthesis of succinimide derivatives **I.4f-h**.

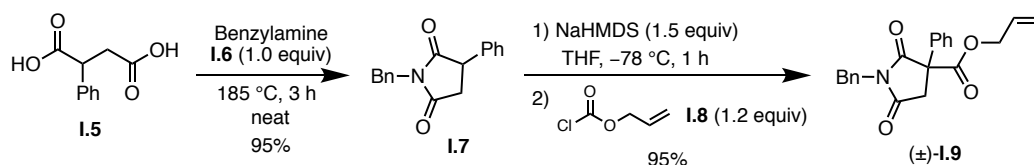
Substrates **I.4i** and **I.4i'**, both substituted by a ketone at the C3-position, were prepared by treatment of **I.3a** under basic condition (NaHMDS, $-78\text{ }^{\circ}\text{C}$) and quenching the enolate by methyl 4-methylbenzoate. It is worth noting that **I.4i** and **I.4i'** were obtained as a 9:1 mixture in 75% overall yield (Scheme 22). After recrystallization in

hexane and CH_2Cl_2 , **I.4i** was obtained as a pure compound in 60% yield and subsequently used as substrate for the Pd-AAA reaction (Scheme 22, eq 1). In addition, when substrate **I.3a** was treated with the same base (NaHMDS, $-78\text{ }^\circ\text{C}$) and the resulting enolate was quenched with pivaloyl chloride, succinimide **I.4j** was obtained as a pure compound in a good 75% yield (Scheme 22, eq 2).



Scheme 22. Synthesis of the succinimide derivatives **I.4i-j**.

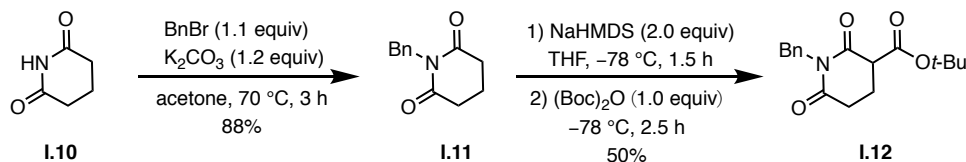
In addition to these substrates, we also prepared compound **I.7**, which bears a phenyl group at the C3-position. The latter was synthesized through pathway B (Scheme 18). Hence, the treatment of diacid **I.5** with benzylamine **I.6** [$185\text{ }^\circ\text{C}$, neat] led to the corresponding succinimide **I.7** (95%). The allylic β -keto ester **I.9** was eventually prepared through the standard C-acylation conditions. Thus, treatment of **I.7** with NaHMDS in THF at $-78\text{ }^\circ\text{C}$, followed by the addition of the allyl chloroformate **I.8** produced compound **I.9** in 95% yield (Scheme 23).



Scheme 23. Synthesis of the succinimide derivatives **I.7** and **I.9**.

The six-membered ring substrate **I.12** was also prepared from glutarimide, **I.10**. After protection of the nitrogen by a benzyl group [K_2CO_3 , BnBr, acetone], the

corresponding succinimide **I.11** was isolated in 88% yield, and then converted to compound **I.12** using di-*tert*-butyl dicarbonate under basic conditions. The succinimide **I.12** was isolated in 50% yield (Scheme 24).



Scheme 24. Synthesis of the six-membered substrate **I.12**.

All of the compounds were eventually engaged in a Pd-AAA process, the results are reported in the next section.

3.2.2. Synthesis of the allylic reagents

In parallel to the synthesis of the succinimide precursors, a variety of substituted allyl acetates were also prepared.⁴⁶ The β -substituted allyl acetates were synthesized in three steps from aldehydes **I.13** and commercially available triphenyl phosphorus ylide **I.14** using a Wittig olefination, a DIBAL-mediated reduction and an acylation.

Firstly, the Wittig olefination was realized in CH_2Cl_2 (rt, 15 h) and the resulting α,β -unsaturated esters were obtained as a mixture of (*E*)- and (*Z*)-isomers in good yields (65-95%). It is worth noting that the *E/Z* ratio was in general higher than 15:1, except for the 2-bromo benzylaldehyde for which the *E/Z* ratio was limited to 6:1. In addition, the *E*- and *Z*-stereoisomers **I.17** were separated successfully, except for the **I.17d** and **I.17d'** which were obtained as a mixture in a 7:1 ratio in favor of the (*E*)-isomer (Table 4, entry 4).

⁴⁶ Dr. Marllon Nascimento de Oliveira synthesized and generously share some substituted allyl acetates he had prepared, see: De Oliveira, M. N.; Arseniyadis, S.; Cossy, J. *Chem. Eur. J.* **2018**, *24*, 4810-4814.

Table 4. Synthesis the α,β -unsaturated esters **I.17**.

$\text{R-CHO} + \text{Ph}_3\text{P}^+\text{CH}_2\text{COOEt} \xrightarrow{\text{CH}_2\text{Cl}_2, \text{rt}, 15 \text{ h}} \text{R-CH=CH-COOEt} + \text{R-CH=CH-COOEt}$

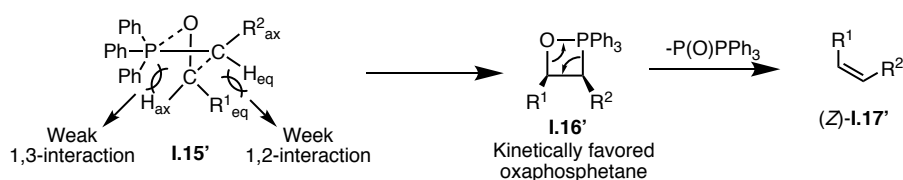
I.13 **I.14** **(E)-I.17a-m** **(Z)-I.17'a-m**

Wittig olefination

Entry	I.13 , R	Yield of I.17 (%) ^a	I.17 / I.17' ^b
1	I.12a , 2-Me-Ph	I.17a (80)	I.17a / I.17a' (12:1)
2	I.12b , 3-Me-Ph	I.17b (87)	I.17b / I.17b' (>15:1)
3	I.12c , 4-Me-Ph	I.17c (93)	I.17c / I.17c' (13:1)
4	I.12d , 2-Br-Ph	I.17d ^c (95)	I.17d / I.17d' (6:1)
5	I.12e , 3-Br-Ph	I.17e (93)	I.17e / I.17e' (>15:1)
6	I.12f , 4-Br-Ph	I.17f (95)	I.17f / I.17f' (>15:1)
7	I.12g , 4-CF ₃ -Ph	I.17g (92)	I.17g / I.17g' (>15:1)
8	I.12h , 4-MeO-Ph	I.17h (93)	I.17h / I.17h' (>15:1)
9	I.12i , biphenyl	I.17i (65)	I.17i / I.17i' (>15:1)
10	I.12j , 2-naphthyl	I.17j (70)	I.17j / I.17j' (>15:1)
11	I.12k , thiophene	I.17k (90)	I.17k / I.17k' (>15:1)
12	I.12l , furan	I.17l (87)	I.17l / I.17l' (>15:1)
13	I.12m , 1-tosyl-1 <i>H</i> -indole	I.17m (95)	I.17m / I.17m' (>15:1)

^a Isolated yield of **I.17**. ^b Determine ¹H NMR on the crude reaction mixture. ^c The totally yield of **I.17d** and **I.17d'** in a ratio of 7:1.

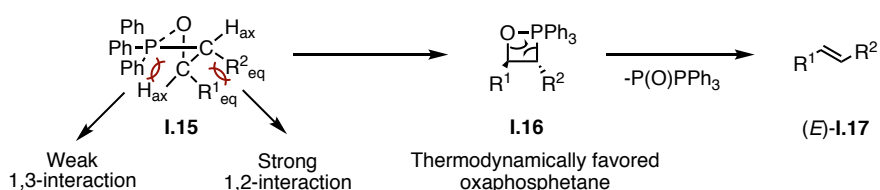
The mechanism of a Wittig reaction is a [2+2]-cycloaddition between an ylide and a carbonyl. This cycloaddition is suprafacial-antarafacial and involves an orbital overlap between the π orbital of the ylide and the π^* orbital of the carbonyl.⁴⁷ According to this [2+2]-cycloaddition, there are two possible transition states. The first transition state is kinetically favored as there are less steric interactions. This transition state leads to the *cis*-oxaphosphetane which after decomposition produces the (Z)-olefin product **I.17'** (Scheme 25).

**Scheme 25.** Kinetically favored intermediate of Wittig reaction

⁴⁷ See a review for the mechanism of Wittig reaction: Byrne, P. A.; Gilheany, D. G. *Chem. Soc. Rev.*, **2013**, 42, 6670-6696.

The second transition state, which should lead to the formation of the (*E*)-olefin product **I.17**, and involves a *trans*-oxaphosphetane. In this transition state, a strong 1,2-interaction is observed which explains that this transition state is not favored (Scheme 26).

In our case, when a stabilized ylide ($R^2 = \text{CO}_2\text{Et}$) is used, the reaction is slow, thus the thermodynamic intermediate, *trans*-oxaphosphetane, is formed and the (*E*)-**I.17** is obtained as the major product.



Scheme 26. Thermodynamically favored intermediate

The α,β -unsaturated esters **I.17a-l** were subsequently converted to the corresponding allylic alcohols **I.18a-l** using DIBAL-H (2.2 equiv) as the reductive agent (CH_2Cl_2 , -78°C). These alcohols (**I.18a-l**) were then converted to the corresponding allylic acetates **I.19** in quantitative yield using acetic anhydride (1.2 equiv) in the presence of DMAP (1.1 equiv) in diethyl ether at rt for 15 h.

Table 5. Synthesis of allylic reagents **I.19**.

Entry	I.17 , R	Yield of I.18a-m (%) ^a	Yield of I.19a-m (%) ^b
1	I.17a , 2-Me-Ph	I.18a (93)	I.19a (94)
2	I.17b , 3-Me-Ph	I.18b (94)	I.19b (95)
3	I.17c , 4-Me-Ph	I.18c (96)	I.19c (98)
4	I.17d , 2-Br-Ph	I.18d (95)	I.19d (97)
5	I.17e , 3-Br-Ph	I.18e (94)	I.19e (95)
6	I.17f , 4-Br-Ph	I.18f (94)	I.19f (95)
7	I.17g , 4-CF ₃ -Ph	I.18g (93)	I.19g (96)
8	I.17h , 4-MeO-Ph	I.18h (93)	I.19h (95)
9	I.17i , biphenyl	I.18i (90)	I.19i (94)
10	I.17j , 2-naphthyl	I.18j (91)	I.19j (94)
11	I.17k , thiophene	I.18k (94)	I.19k (95)
12	I.17l , furan	I.18l (93)	I.19l (96)

^a Isolated yield of **I.18a-l**. ^b Isolated yield of **I.19a-l**.

3.3. Optimization of Pd-AAA conditions of succinimide derivatives

3.3.1. Influence of different bases

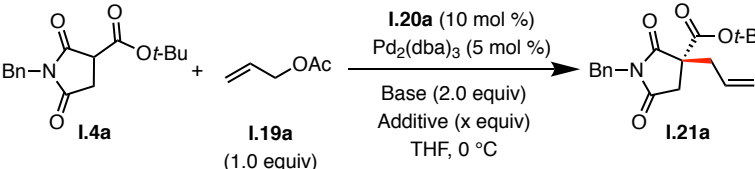
With various monosubstituted succinimides in hand, we started to explore the reaction conditions for the Pd-AAA. We chose succinimide **I.4a** as a model substrate and explored the various reaction parameters. We initiated our study by evaluating the nature of the base using allyl acetate **I.19a** as the allyl donor along with Pd₂(dba)₃ and (*R,R*)-DACH-Phenyl Trost ligand **I.20a**. Interestingly, the desired allylated product **I.21a** was obtained in high yields and high enantioselectivities independently of the base used. Inorganic bases, such as K₂CO₃, Li₂CO₃ and Na₂CO₃, led to excellent yields (81-96%) and high levels of enantioselectivity (76-79% ee) (Table 6, entries 1-4). When organic bases, such as *N,O*-bis(trimethylsilyl)acetamide (BSA), DBU, and Et₃N were used, the allylated product **I.21a** was obtained in good yields (92-97%) and moderate to good enantioselectivities (54-78% ee) (Table 6, entries 5-7). In addition, we also evaluated the use of additives, such as Zn(OAc)₂ and ZnCl₂. Hence, when 1.2 equiv of Zn(OAc)₂, in conjunction with Et₃N were used, the desired allylated product **I.21a** was obtained in a quantitative yield (97%) and a similar level of enantioselectivity (77% ee). In contrast, when the reaction was realized with 1.2 equiv of ZnCl₂, **I.21a** was obtained in only 30% yield and with a slight decrease of the enantioselectivity (63% ee) (Table 6, entries 8-9). Stronger bases such as NaH were also used but the allylated product **I.21a** was obtained with a dramatic decrease in enantioselectivity (20% ee) (Table 6, entry 10). Interestingly, when a lithiated base, such as LDA and LiHMDS, was used, an inversion of the selectivity was observed (Table 6, entries 11-12). This result contrasted with the selectivity obtained when using NaHMDS (Table 6, entry 13). This inversion of selectivity is most probably the result of a coordination of the lithium to the two carbonyl groups (ester and amide) as previously mentioned by Trost *et al.*⁴⁸

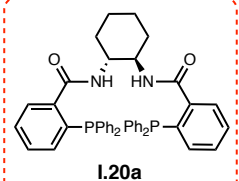
Considering the acidity of the proton at the α -position, we were curious whether the reaction could also proceed without the use of any base. Indeed, the acetate anion which is released during the process should be able to abstract the α -proton to generate the reactive enolate. To demonstrate our hypothesis, a reaction was run in

⁴⁸ Trost, B. M.; Xu, J.; Schmidt, T. *J. Am. Chem. Soc.* **2009**, *131*, 18343-18357.

the absence of a base under otherwise identical conditions (Table 6, entry 14). To our delight, the allylated product **I.21a** was obtained with an excellent yield (94%) and a similar enantioselectivity (76% ee) compared to the one obtained when the reaction was realized in the presence of a base (Table 6, entry 14).

Table 6. Effect of different bases and additives in Pd-AAA^a





I.20a

Entry	Base	Additive (x equiv)	Yield of I.21a (%) ^b	ee of I.21a (%) ^c
1	K ₂ CO ₃	-	91	78
2	Li ₂ CO ₃	-	81	76
3	Na ₂ CO ₃	-	96	77
4 ^d	Na ₂ CO ₃	-	95	79
5	DBU	-	92	54
6	BSA	-	97	63
7	Et ₃ N	-	96	78
8	Et ₃ N	Zn(OAc) ₂ (1.2)	97	77
9	Et ₃ N	ZnCl ₂ (1.2)	30	63
10	NaH	-	86	20
11	LDA	-	37	-20
12	LiHMDS	-	45	-33
13	NaHMDS	-	20	9
14	-	-	94	76

^a All reactions were run on a 0.2 mmol scale. ^b Isolated yield. ^c Determined by SFC analysis. ^d 1.0 equiv Na₂CO₃ was used.

3.3.2. Influence of the solvent

The influence of the solvent was then studied. As shown in Table 7, solvents such as CH₂Cl₂, toluene, DMF, CH₃CN and dioxane led to slightly lower selectivities (Table 7, entries 1-5) than solvents such as Et₂O, MTBE, 2-Me-THF and THF (Table 7, entries 6-9). The use of polar solvents such as DMF or CH₃CN had a detrimental effect on the reactivity leading to a low isolated yield of **I.21a**. Ultimately, running the reaction in THF led to the best results both in terms of reactivity and selectivity as showcased by the yield and the ee obtained (95% yield, 75% ee) (Table 7, entry 9). Once again, the

reaction could also be run in the absence of a base with any noticeable loss in either the reactivity or selectivity (Table 7, entry 10).

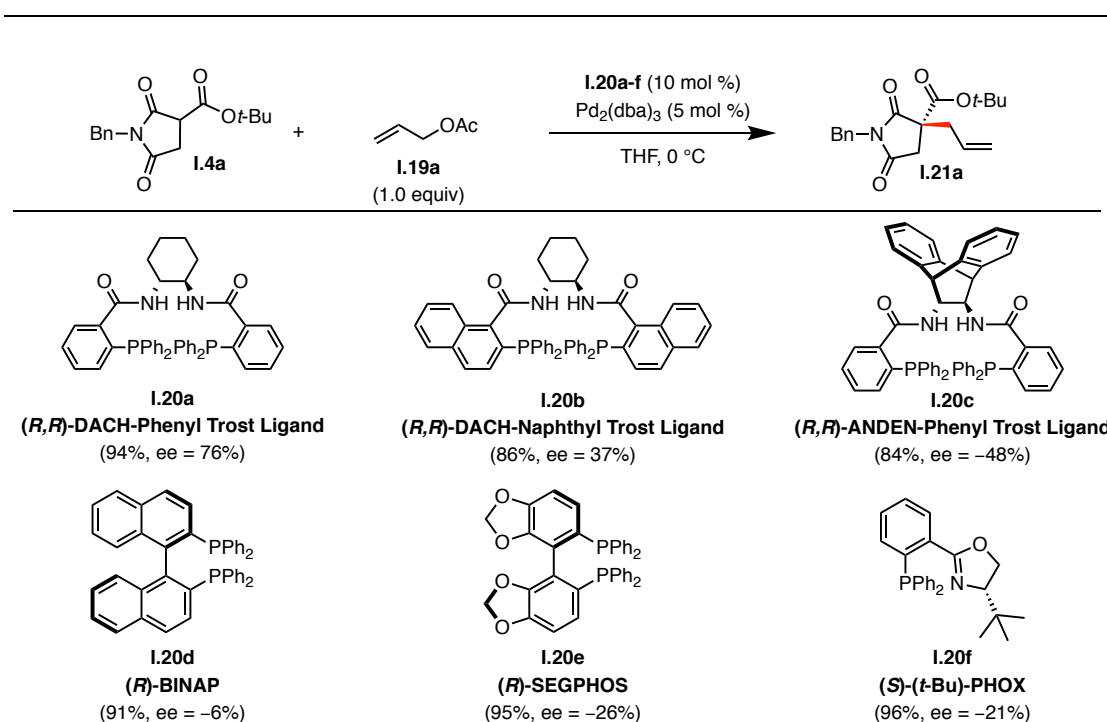
Table 7. The influence of different solvent in Pd-AAA^a

Entry	Solvent	Yield of I.21a (%) ^b	ee of I.21a (%) ^c
1	CH ₂ Cl ₂	95	58
2	Toluene	96	64
3	DMF	10	31
4	CH ₃ CN	60	49
5	1,4-dioxane	92	49
6	Et ₂ O	95	76
7	MTBE	96	72
8	2-Me-THF	95	77
9	THF	95	79
10 ^d	THF	94	76

^a All reactions were run on a 0.2 mmol scale. ^b Isolated yield. ^c Determined by SFC analysis. ^d without Na₂CO₃.

3.3.3. Influence of the ligand

Encouraged by these preliminary results, we decided to further optimize the conditions by screening various ligands. In order to improve the value of the ee, six optically active chiral phosphines were thus screened under our optimized base-free conditions. As a general trend, all reactions went to completion independently of the ligand used, however the C₂-symmetric bis-phosphine ligands **I.20a**, **I.20b** and **I.20c** induced higher levels of enantioselectivity than BINAP (**I.20d**, –6% ee), SEGPHOS (**I.20e**, 26% ee), and the N/P-type oxazoline (PHOX) ligand (**I.20f**, –21% ee) (Scheme 27). Ultimately, (*R,R*)-DACH-Phenyl Trost ligand **I.20a** led to the best results both in terms of reactivity and enantioselectivity.



Scheme 27. Different chiral ligands in Pd-AAA.

3.3.4. Influence of the temperature

To further improve the enantioselectivity, we also checked the effect of the temperature. Hence, a series of reactions were run in THF at low temperatures (0 °C, -20 °C and -40 °C) using **I.20a** (10 mol %) and $\text{Pd}_2(\text{dba})_3$ (5 mol %) in the presence or the absence of a base. To our delight, we were able to improve the enantioselectivity of the Pd-AAA process without noticeably altering the reactivity by running the reaction at -20 °C (Table 8, entry 4). Unfortunately, this result could not be further improved by lowering the temperature to -40 °C (Table 8, entries 5-6).

Table 8. The influence of the reaction temperature^a

Entry	x	T (°C)	Yield of I.21a (%) ^b	ee of I.21a (%) ^c
1	1.0	0	95	79
2	-	0	94	76
3	1.0	-20	95	83
4	-	-20	88	86
5	1.0	-40	93	83
6	-	-40	56	87

^a All reactions were run on a 0.2 mmol scale. ^b Isoalted yield. ^c Determined by SFC analysis.

3.3.5. Influence of the leaving groups on the allylic reagent

With our optimized conditions in hand [I.20a (10 mol %), Pd₂(dba)₃ (5 mol %), THF, -20 °C], we next evaluated the nature of the leaving group. The reactions were thus run in the presence of various allylic donors including allyl methyl carbonate I.19b and allyl benzoate I.19c (Table 9). As a general trend, allyl acetate and allyl benzoate were found to provide the best results in terms of enantioselectivity (ee = 86%) compared to allyl methyl carbonate (ee = 63%), but overall allyl acetate remained the reagent of choice.

Table 9. Influence of the allyl donor.^a

Entry	I.19, LG	Yield of I.21a (%) ^b	ee of I.21a (%) ^c
1	I.19a, -OAc	88	86
2	I.19b, -OCO ₂ Me	96	63
3	I.19c, -OBz	58	86

^a All reactions were run on a 0.2 mmol scale. ^b Isoalted yield. ^c Determined by SFC analysis.

After completing the optimization of the reaction conditions, we next evaluated the substrate scope. All reactions were run in THF at $-20\text{ }^{\circ}\text{C}$ using (*R,R*)-DACH-Phenyl Trost ligand **I.20a** (10 mol %) and $\text{Pd}_2(\text{dba})_3$ (5 mol %) in the absence of any added base and using various allyl acetates.

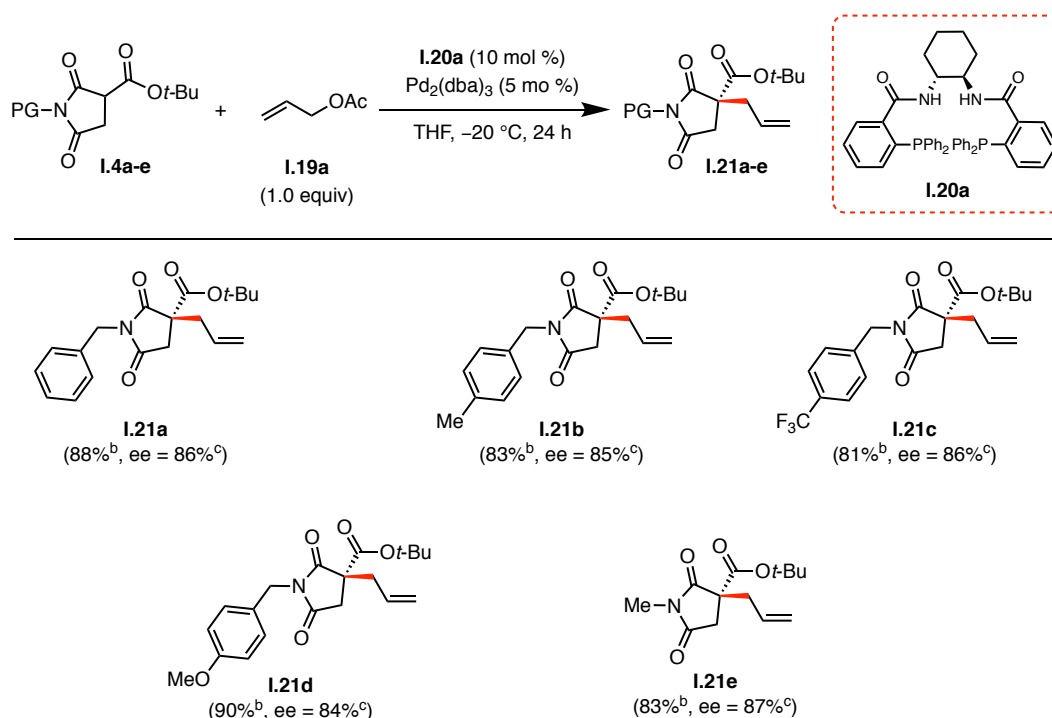
3.4. Scope of the reaction

As mentioned above, we pursued our investigation by evaluating the scope and limitation of the reaction by applying our optimized conditions to various α -substituted succinimides and using various substituted allyl donors.

3.4.1. α -Substituted succinimides

3.4.1.1. Influence of the *N*-protecting group.

The first structural element that was evaluated was the nature of the protecting group on the nitrogen atom. We thus tested substrates **I.4a-e**, which all have a *tert*-butyl ester substituent at the α -position. The results showed that the introduction of electron-donating or electron-withdrawing substituents on the benzyl protecting group had no effect on the enantioselectivity outcome of the reaction as the resulting allylated products were obtained with very similar ees (**I.21a-d**, ee = 84%-87%) (Scheme 28). Interestingly, when replacing the *N*-benzyl protecting group by a *N*-methyl group, the outcome of the reaction remained unchanged as the allylated product **I.21e** was also obtained with a similar ee (87%).

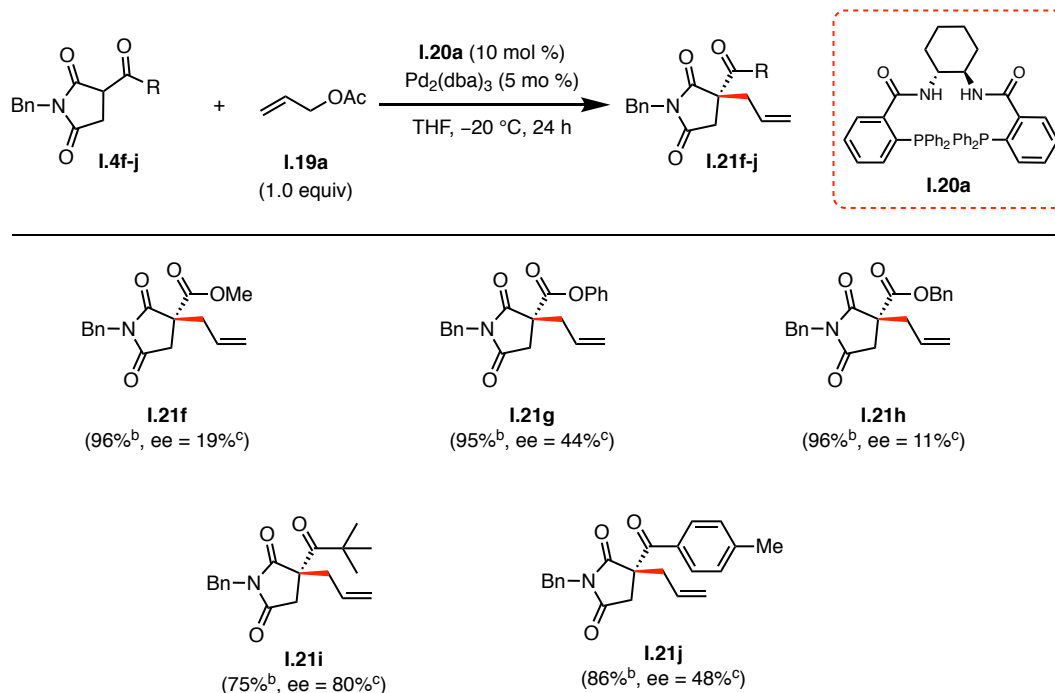


^a All reactions were run on a 0.2 mmol scale. ^b Isoalted yield. ^c Determined by SFC analysis.

Scheme 28. Substrate scope of succinimides in different *N*-protecting groups.^a

3.4.1.2. Influence of the substituent group at the C3-position

The nature of the acyl group at the C3-position was also evaluated. Hence, replacing the *tert*-butyl ester by a methyl ester (I.21f, 19% ee), a phenyl ester (I.21g, 44% ee) or a benzyl ester (I.21h, 11% ee) had a detrimental effect on the enantioselectivity, however the reactivity remained roughly unchanged. Replacing the ester moiety by a *tert*-butyl ketone (I.21i, ee = 80%) or a *para*-methyl phenyl ketone (I.21j, 48% ee) confirmed the importance of the steric hindrance imposed by the substituent at the C3-position (Scheme 29).



^a All reactions were run on a 0.2 mmol scale. ^b Isoalted yield. ^c Determined by SFC analysis.

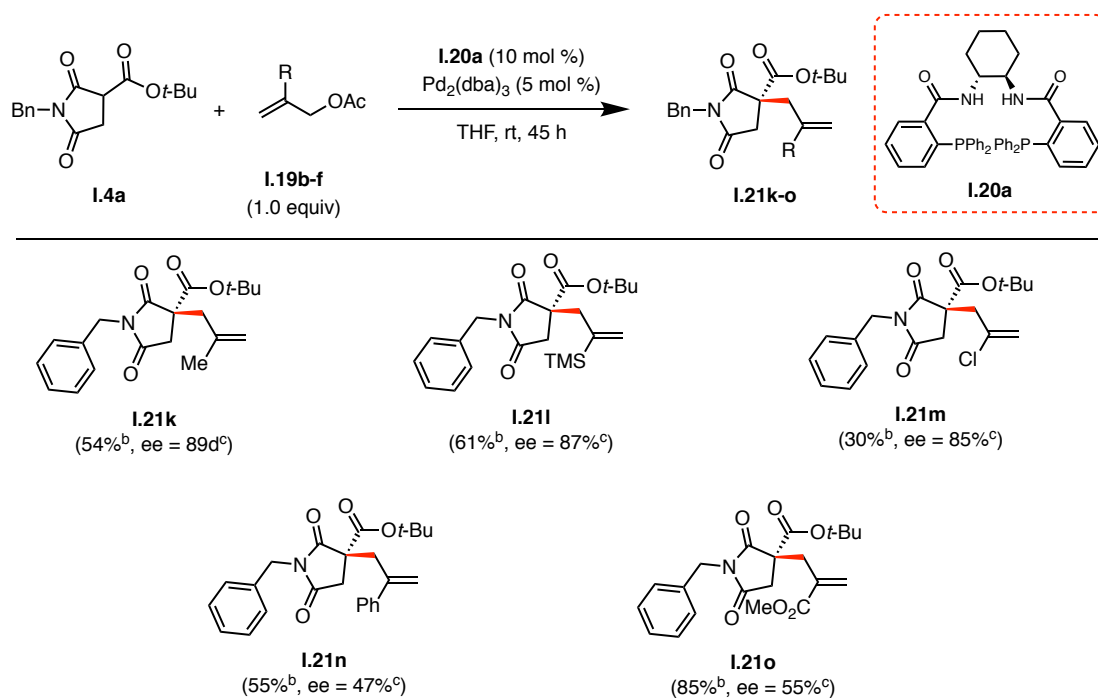
Scheme 29. Substrate scope of succinimides bearing different substituents at the C3-position.^a

3.4.2. Allyl acetates

3.4.2.1. 2-Substituted allyl acetates.

Based on these preliminary results, we next turn our attention on the evaluation of the allyl acetate. We started our study with compound **I.4a** bearing a *tert*-butyl ester substituent at the C3-position and a *N*-benzyl protecting group. Compound **I.4a** was thus subjected to our optimized conditions [**I.20a** (10 mol %), $\text{Pd}_2(\text{dba})_3$ (5 mol %), THF, $-20\text{ }^\circ\text{C}$] using 2-methylallyl acetate. However, only traces of the desired product **I.21k** were observed after 24 h. To circumvent this low reactivity, the reaction was performed at rt and the allylated product **I.21k** was obtained in 54% yield and 89% ee after 45 h. As a higher reactivity had been observed with 2-methyl allyl acetate at rt, the allylation of **I.4a** with the other 2-substituted allyl acetates **I.19b-f** was achieved at rt (Scheme 30). The allyl reagents **I.19b-d**, bearing a 2-methyl, a 2-trimethylsilyl and a 2-chlorine substituent afforded the corresponding allylated products **I.21k-m** with

ees up to 89% albeit in slightly lower yields (30%-61%). Unfortunately, when allyl acetate was substituted by a phenyl or a methyl ester substituent, the corresponding allylated products **I.21n** (ee = 47%) and **I.21o** (ee = 55%) were obtained with much lower ees than **I.21k-m** (ee = 85%-89%) (Scheme 30).



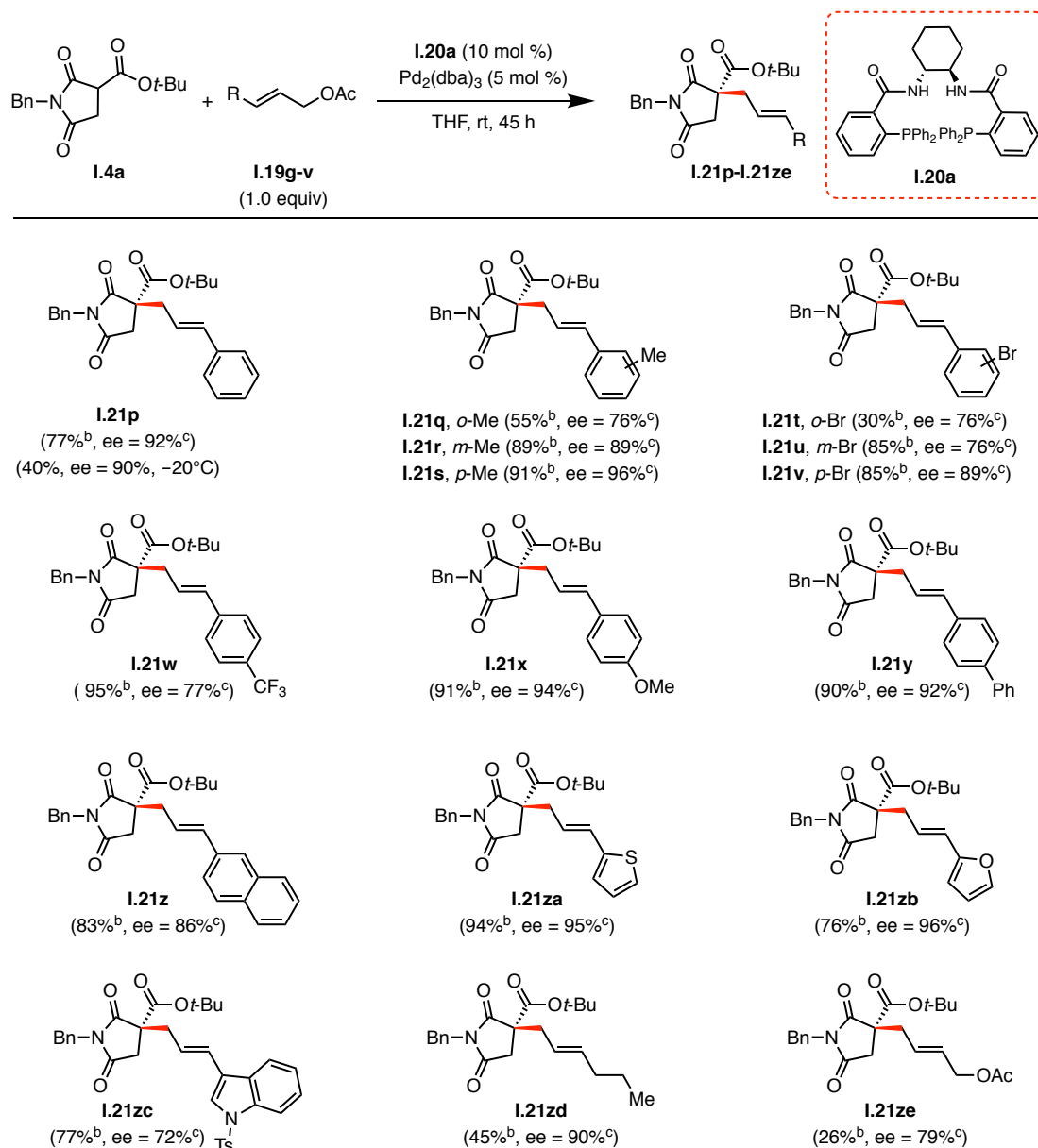
^a All reactions were run on a 0.2 mmol scale. ^b Isoalted yield. ^c Determined by SFC analysis.

Scheme 30. Influence of 2-substituted allyl acetates.

3.4.2.2. 3-Substituted allyl acetates.

A variety of 3-substituted allyl acetates were also examined. When **I.4a** was reacted with **I.19g** at rt under our optimized conditions, the corresponding allylated succinimide was obtained in 77% yield and 92% ee. It is worth noting that when the reaction was performed at $-20\text{ }^\circ\text{C}$, the selectivity wasn't improved (ee = 90%) and the yield didn't exceed 40%. Following these results, all the allylations involving 3-substituted allyl acetates were performed at rt. Interestingly, the corresponding allylated products **I.21r-I.21zf** were all obtained in good to excellent ees ranging from 76% to 96%. The steric and electronic properties of the substituents on the aromatic ring of the cinnamyl acetates were both examined. Overall, the *ortho*-methyl substituted cinnamyl acetate gave the allylated product **I.21q** in a much lower yield

than the *meta*- and *para*-substituted cinnamyl acetates with the latter giving the best results both in terms of yield (91%) and enantioselectivity (96% ee) (Scheme 31). The bromo-substituted cinnamyl acetates were also evaluated and the *para*-bromo substituted cinnamyl acetate was shown to give a better yield (85%) and a higher enantioselectivity (ee = 89%) (**I.21v**) than the analogous *ortho*- and *meta*-bromo substituted cinnamyl acetates **I.21t** and **I.21u**. With these results in hand, we next examined the reactivity of various cinnamyl acetates bearing different substituents at the *para*-position, such as a trifluoromethyl (**I.21w**), a methoxy (**I.21x**) and a phenyl substituent (**I.21y**). The corresponding allylated products (**I.21w-y**) were obtained in high yields (90%-95%) and good to excellent enantioselectivities (ee = 77%-94%). As a general trend, the cinnamyl acetates bearing an aryl group substituted by an electron-donating substituent gave the allylated products in much higher enantioselectivities (**I.21x**, *para*-methoxy, ee = 94%) than the substrates possessing an aromatic ring substituted by an electron-withdrawing group (**I.21w**, *para*-trifluoromethyl, ee = 77%). The reactivity of the 2-naphthyl substituted cinnamyl acetate was also studied and used in the Pd-AAA, which resulted in the formation of the corresponding allylated product **I.21z** in 83% yield and 86% ee. More importantly, 3-substituted allyl acetates bearing a heterocyclic substituent, such as a furan or a thiophene, were also found to be suitable, as the corresponding allylated products **I.21za** and **I.21zb** were obtained in good yields and high levels of enantioselectivity, 95% and 96% ee, respectively. 3-Indole-substituted allyl acetate **I.19t** was also examined and afforded the corresponding allylated product **I.21zc** in a good yield (77%) albeit with a moderate enantioselectivity (72% ee). Two commercially available alkyl-substituted allyl acetates were also engaged in the reaction. Interestingly, while the resulting allylated products **I.21zd** and **I.21ze** were obtained with good ees (90% and 79%, respectively), the yields were unfortunately only moderate (45% and 26%, respectively) (Scheme 31).



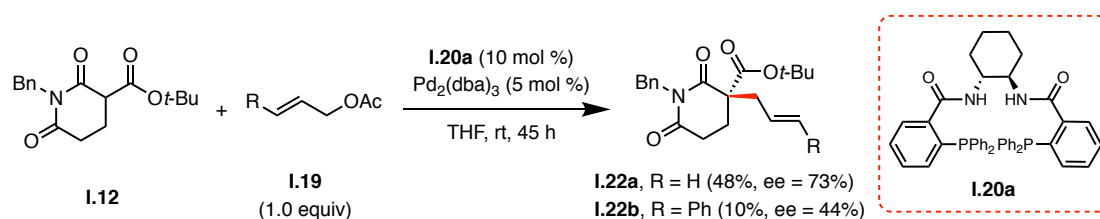
^a All reactions were run on a 0.2 mmol scale. ^b Isoalted yield. ^c Determined by SFC analysis.

Scheme 31. Influence of 3-substituted allyl acetates.^a

3.4.3. Pd-AAA of six-membered ring substrates

Six-membered ring succinimide **1.12** was also evaluated using allyl acetate and cinnamyl acetate as the allyl donors. However, when **1.12** reacted with allyl acetate **1.19a** under our optimized conditions [**1.20a** (10 mol %), $\text{Pd}_2(\text{dba})_3$ (5 mol %), THF, -20 °C], only traces of the desired allylated product **1.22a** were observed. This result indicates that the six-membered ring substrate **1.12** shows a much lower

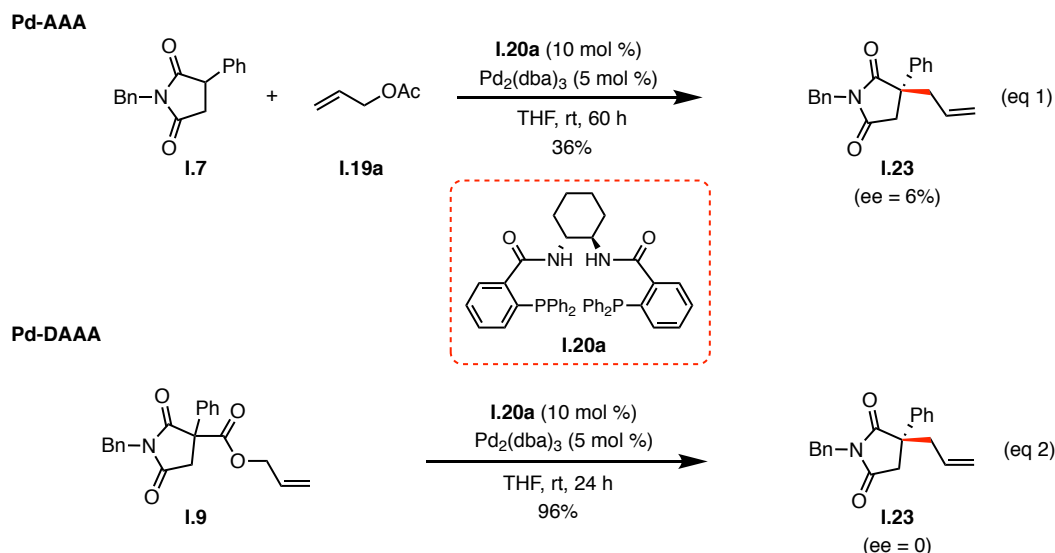
reactivity than the five-membered ring substrate **I.4a**. To overcome the low reactivity observed with **I.12**, the reaction was run at rt for 45 h. The corresponding allylated product **I.22a** was isolated with a moderate yield (48%) but with a good enantioselectivity (ee = 73%) (Scheme 32). Unfortunately, at $-20\text{ }^{\circ}\text{C}$ the allylated product **I.22b** was not obtained. We therefore examined the reactivity of **I.12** in the presence of cinnamyl acetate at rt, but the corresponding allylated product **I.22b** was obtained in only 10% yield and 44% ee (Scheme 32).



Scheme 32. Pd-AAA of six-membered ring substrates.

3.4.4. Pd-AAA vs Pd-ADAA of α -aromatic substituted succinimides

To further enlarge the substrate scope, the reaction was run with the succinimide derivative **I.7** bearing an aryl substituent at the C3-position. Unfortunately, the corresponding allylated product **I.23** was obtained in a low yield (36%) and with barely any enantioselectivity (ee = 6%) (Scheme 33, eq 1). To check whether a decarboxylative strategy would improve the enantioselectivity, a Pd-AAA and a Pd-DAAA were run in parallel. Succinimide **I.9** was thus prepared and subjected to the same reaction conditions [$\text{Pd}_2(\text{dba})_3$ (5 mol %), **I.20a** (10 mol %), THF, rt]. Unfortunately, the intramolecular version of the allylation led to the formation of the corresponding allylated product **I.23** (96% yield), albeit with no enantioselectivity (Scheme 33, eq 2).



Scheme 33. Pd-AAA vs Pd-ADAA.

3.5. Influence of the catalyst loading

After completing the substrate scope, the influence of the catalyst loading was also evaluated on **1.4a** using **1.19a** as the allyl donor (Table 10). Hence, when decreasing the amount of $\text{Pd}_2(\text{dba})_3$ from 10 mol % to 2 mol %, no impact on the enantioselectivity was observed, however the reaction became sluggish and the yield of **1.21p** dropped from 77% to 41% even after a prolonged reaction time (up to 65 h).

Table 10. Influence of the catalyst loading.^a

Entry	x	y	t (h)	Yield of 1.21p (%) ^b	ee of 1.21p (%) ^c
1	10	5	40	77	92
2	6	2.5	65	65	94
3	3	1	65	41	93

^a All reactions were run on a 0.2 mmol scale. ^b Isoalted yield. ^c Determined by SFC analysis.

3.6. Origin of the enantioselectivity

In the past decade, many groups have contributed to determine the mechanism by which the palladium-catalyzed asymmetric allylic alkylation occurs and the selectivity is induced. Recently, Trost and co-workers developed a model to predict the stereoselective outcome of the allylation (Figure 8).⁴⁹

As we discussed in the beginning of this section, the stereodetermining step in the Pd-AAA of a prochiral nucleophile is the nucleophilic addition. The model proposed by Trost predicts the enantioselectivity using a cartoon model designed around the Pd/Trost ligand (*R,R*)-**1.20a** complex (Figure 8). Hence, the enolate intermediate approaches the π -allyl palladium-(*R,R*)-**1.20a** complex by its *Re*-face to avoid any unfavored steric interactions between the amide moiety of the substrate and the "wall" of the ligand, resulting in the formation of the (*S*)-allylated product as the major enantiomer.

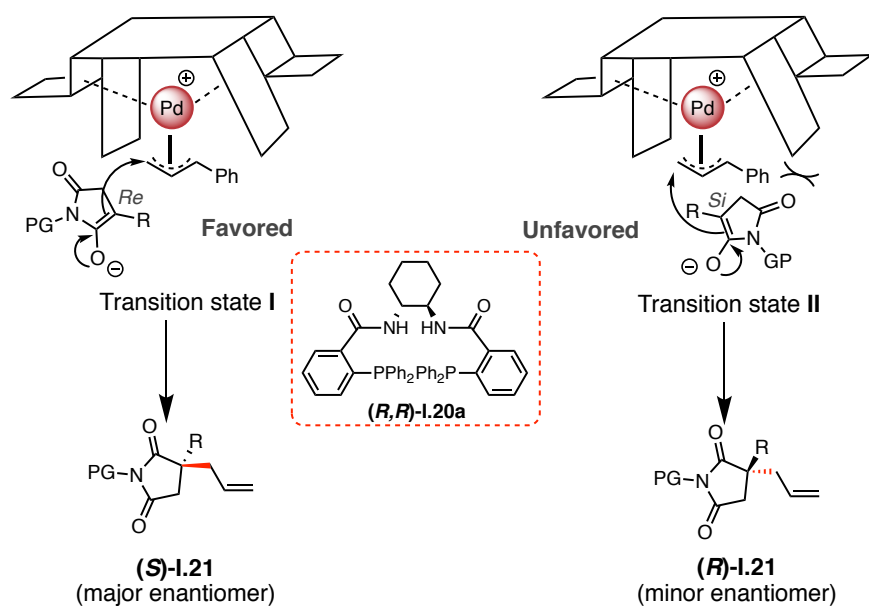


Figure 8. Proposed stereochemical pathway

A single crystal X-Ray diffraction analysis of our allylated product **1.21w** also confirmed this predicted result, and the configuration of the quaternary center is (*S*) (Figure 9).

⁴⁹ Trost, B. M., *Org. Prog. Res. Dev.* **2012**, 16, 185-194.

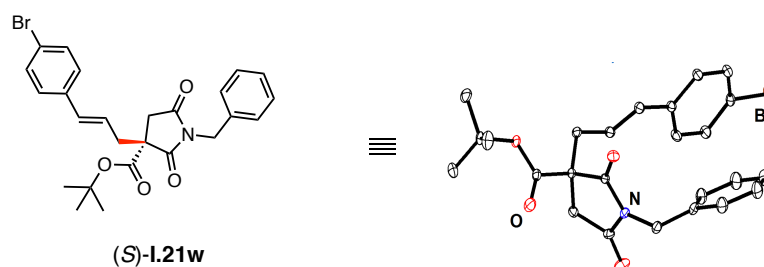


Figure 9. The X-ray structure of allylated product (S)-I.21w

The model also can be used to explain when the succinimide substrate was substituted by a phenyl substituent at the C3-position (**I.7**), a very low ee (6%) was obtained for the allylated product **I.23** (Scheme 23). For this substituted nucleophilic succinimide can equally attack the Pd- π -allylic species on both faces as the steric hindrance induced by the phenyl substituent is equivalent in transition states **I** and **II** (Figure 10). Therefore, there is no favored transition state and the two enantiomers of the allylated product were obtained almost in a 1:1 ratio.

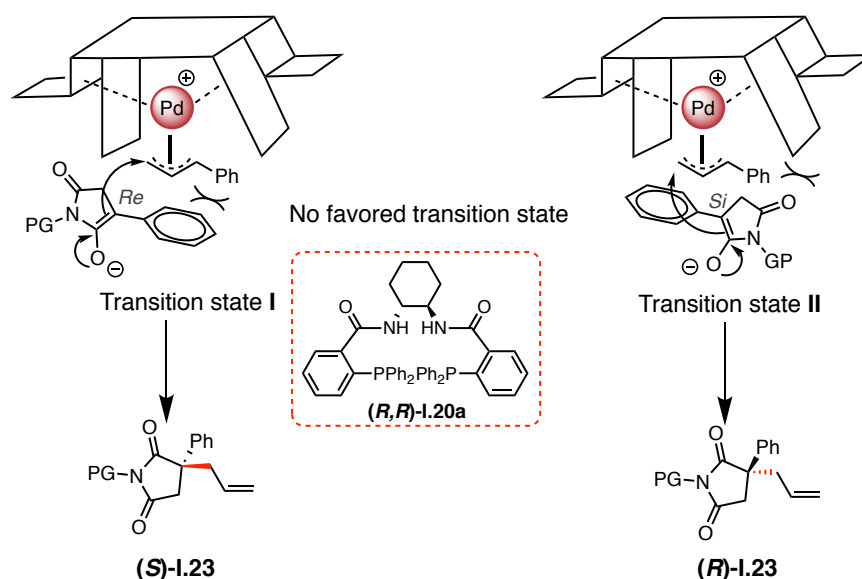


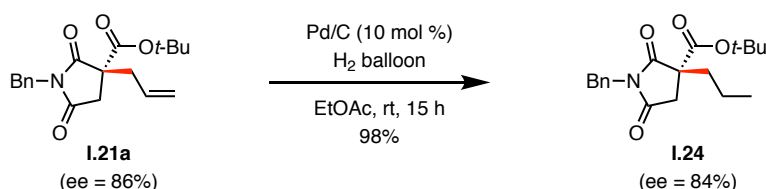
Figure 10. Proposed stereochemical pathway for substrate **I.7**

3.7. Post-functionalization of allylated succinimide derivatives

To further demonstrate the synthetic utility of our method, the allylated products **I.21a** and **I.21q** were further converted to various useful building blocks through simple synthetic transformations.

3.7.1. Hydrogenation of allylated succinimide derivatives

Compound **I.21a** was subjected to a palladium-catalyzed hydrogenation [Pd/C (10 mol %), H₂]. The corresponding reduced product **I.24** was obtained in quantitative yield (>99%) and without any erosion of the ee (Scheme 34). When **I.21q** was hydrogenated in the presence of Pd/C, compound **I.25** was also isolated in quantitative yield (98%) and with a slightly erosion of the ee (ee = 84% compared to the ee of **L.21a**, 86%) (Table 11, entry 1).



Scheme 34. Hydrogenation of the allylated product **I.21a**

We eventually evaluated the conditions for the debenzilation of **I.21q** through a Pd-catalyzed hydrogenation. The results are summarized in Table 11. Unfortunately, we did not succeed in removing the benzyl protecting group. Whether we performed the reaction with Pd(OH)₂ (10-20 mol %) at rt or 60 °C, we only observed the reduction of the double bond.

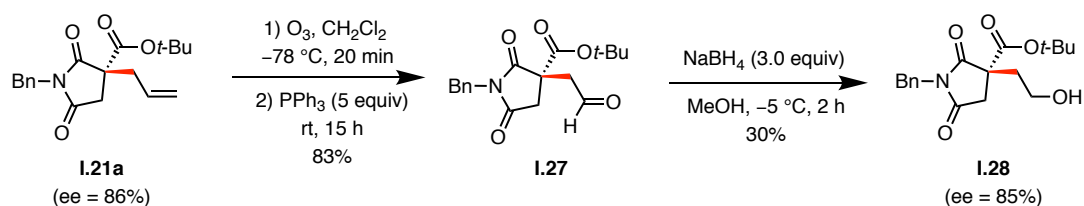
Table 11. Hydrogenation of the allylated product **I.21q**.

entry	H ₂ (x atm)	Pd (y mol %)	T (°C)	yield of I.25 (%) ^a	ee of I.25 (%) ^b
1	1	Pd/C (10)	rt	>99%	94
2	1	Pd(OH) ₂ (10)	rt	>99%	94
3	1	Pd(OH) ₂ (20)	60	>99%	94
4 ^c	6	Pd(OH) ₂ (20)	rt	>99%	94

^a Isolated yield of **I.25**. ^b Determined by SFC. ^c 2.0 equiv AcOH was used as additive.

3.7.2. Ozonolysis of allylated succinimide derivatives

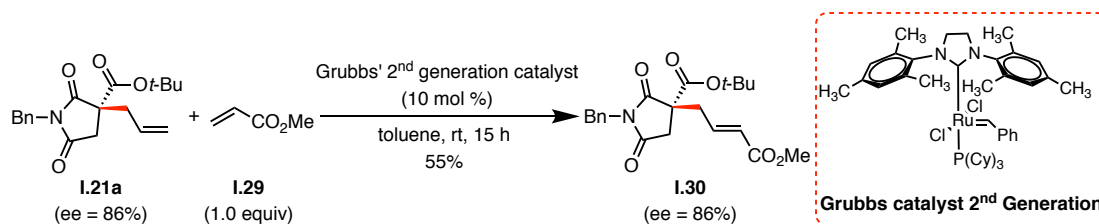
As aldehydes are very useful functional groups in organic synthesis, we subjected compound **I.21a** to the oxidative cleavage of the double bond using ozone [O₃, CH₂Cl₂, –78 °C then PPh₃, rt]. This ozonolysis resulted in the formation of aldehyde **I.27** in 83% yield. To determine the ee of compound **I.27**, the latter was further reduced to the corresponding primary alcohol **I.28** using NaBH₄. HPLC analysis confirmed the fact that no erosion of the ee had occurred in the two-step sequence (Scheme 35).

**Scheme 35.** Synthesis of succinimide derivatives **I.25** and **I.26**

3.7.3. Cross-metathesis of allylated succinimide derivatives

To functionalize the allylated succinimide product **I.21a** with other useful functional groups, a cross-metathesis reaction, between compound **I.21a** and methyl acrylate **I.29**, was evaluated. Interestingly, in the presence of Grubbs' second

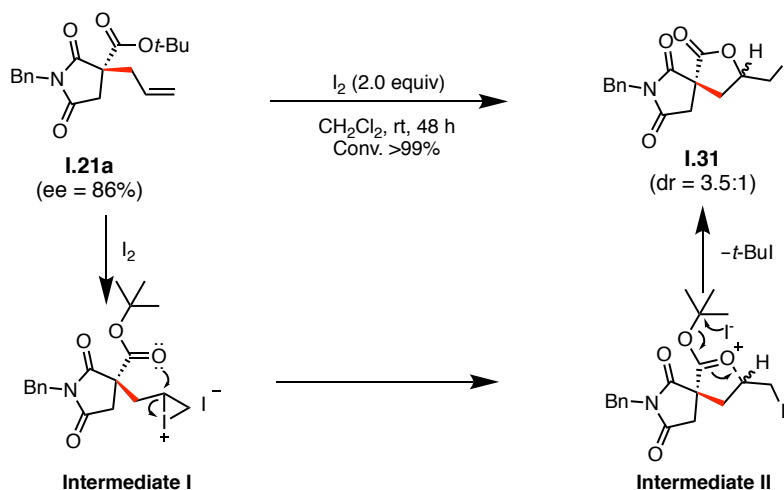
generation catalyst, we were able to isolate the corresponding disubstituted olefin **I.30** in a good yield (55%) and no erosion of the enantioselectivity (Scheme 36).



Scheme 36. Cross-metathesis of the allylated succinimide derivative **I.21a**.

3.7.4. Synthesis of spirocyclic compounds

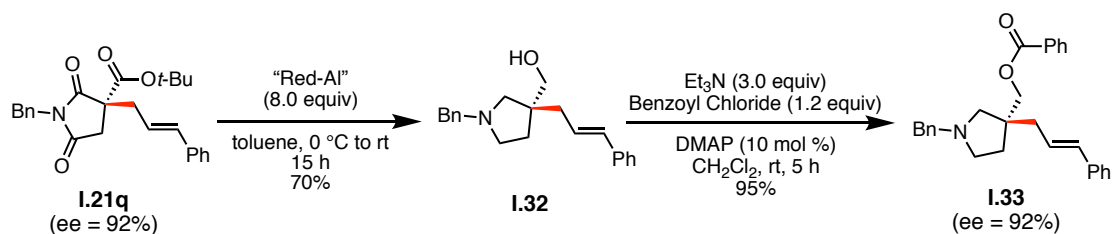
As spirocyclic frameworks can be found in many natural products, we also tried to find suitable conditions allowing the conversion of our allylated products to the corresponding spirocyclic compounds. To our delight, when using 2.0 equiv of iodine, the spirocyclic compound **I.31** was obtained as a mixture of two diastereomers in a 3.5:1 ratio (Scheme 37). The major diastereomer, isolated in 50% yield, kept the same level of enantiomeric excess (86% ee) compared to the starting material **I.21a** (see experimental part for more details). It is worth noting that this spirocyclic compound was formed *via* the iodonium intermediate **I** which subsequently reacted with the carbonyl group to produce intermediate **II**. Then, an iodide ion attacked the *t*-butyl ester moiety and released the spirocyclic compound **I.31** (Scheme 37). It is worth noting that the absolute configuration of the newly formed stereogenic center of the major spirocyclic compound could not be determined unambiguously.



Scheme 37. Synthesis of spriocyclic compound **I.29** via an Iodine induced cyclization.

3.7.5. Synthesis of optically active pyrrolidine derivatives

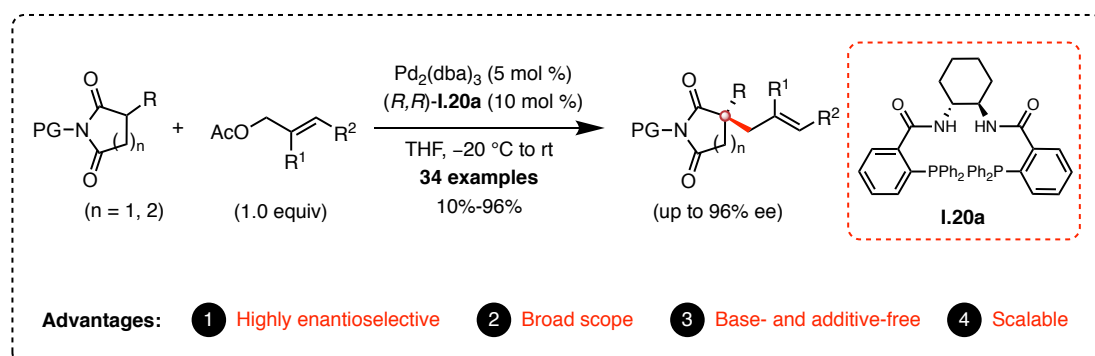
Pyrrolidines could be also obtained from the allylated product **I.21q** by reduction of the two carbonyl moieties using excess of "Red-Al". Pyrrolidine derivative **I.32** was isolated in 70% yield and was further converted to compound **I.33** by protecting the alcohol moiety under standard acylation conditions [Et_3N (3 equiv), benzoyl chloride (1.2 equiv), DMAP (0.1 equiv), CH_2Cl_2 , rt, 95%]. The enantiomeric excess of **I.33** was later determined by SFC, confirming that no erosion of the ee occurred during this multi-step sequence (Scheme 38).



Scheme 38. Synthesis of pyrrolidine derivatives **I.32** and **I.33**.

4. Conclusion

In summary, an efficient base-free and highly enantioselective Pd-catalyzed asymmetric allylic alkylation process was successfully developed to access optically active succinimide derivatives bearing an all-carbon α -quaternary stereogenic center. (*R,R*)-DACH-Phenyl Trost ligand **1.20a** was found to be the most effective ligand to access the allylated succinimides in both high yields and excellent ees (up to 96%). Multifunctional 2- or 3-substituted allyl acetates were tested and gave the corresponding allylated products with high levels of enantioselectivity, especially the cinnamyl acetate derivatives. The absolute configuration of the allylated product was determined by single crystal X-ray diffraction analysis and proved to be (*S*). Most importantly, various useful chiral building blocks could be easily accessed from the allylated succinimides through simple synthetic post-functionalizations (Scheme 39).⁵⁰



⁵⁰ Song, T.; Arseniyadis, S.; Cossy, J. *Chem. Eur. J.* **2018**, *24*, 8076-8080.

Experimental section-Chapter I

Table of Contents

1. General experimental methods.....	111
2. Synthesis of succinimide derivatives.....	113
3. Synthesis of β -substituted allylic reagents.....	128
4. Substrate scope and limitation.....	156
5. Post-functionalization of allylated succinimides.....	187

1. General experimental methods

All reactions were run under an argon atmosphere in oven-dried glassware unless otherwise specified. All commercially available compounds were purchased from Aldrich Chemical Co. and used as received. Anhydrous solvents, such as tetrahydrofuran (THF) and diethyl ether (Et₂O) were distilled from sodium/benzophenone. Dichloromethane (CH₂Cl₂) was distilled from calcium hydride. The other anhydrous solvents, CH₃CN, 1,4-dioxane, MTBE, DMF and 2-Me-THF, were purchased from Sigma Aldrich and used as received.

Analytical thin layer chromatography (TLC) was performed over silica gel plates (Merck 60F254) visualized either with a UV lamp (254 nm) or by using solutions of p-anisaldehyde/sulfuric acid/acetic acid in ethanol or KMnO₄/K₂CO₃ in H₂O followed by heating. Flash chromatography was performed over silica gel (230-400 mesh).

Infrared spectra (IR) were recorded on a Bruker TENSOR™ 27 (IR-FT) with attenuated total reflectance (ATR) and wavenumbers are indicated in cm⁻¹.

¹H NMR spectra were recorded on a Bruker AVANCE 400 at 400 MHz in CDCl₃ (unless otherwise specified) and the observed signals are reported as follows: chemical shift in parts per million from tetramethylsilane with the solvent as an internal indicator (CDCl₃ δ 7.26 ppm, DMSO δ 2.50 ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quintet = quint, m = multiplet or overlap of non-equivalent resonances), integration. ¹³C NMR spectra were recorded at 100 MHz in CDCl₃ (unless otherwise specified) and the observed signals were reported as follows: chemical shift in parts per million from tetramethylsilane with the solvent as an internal indicator (CDCl₃ δ 77.16 ppm, DMSO δ 39.52 ppm), multiplicity on respect to proton. Coupling constants (*J*) are reported in Hertz (Hz). All NMR spectra were obtained at rt unless otherwise specified.

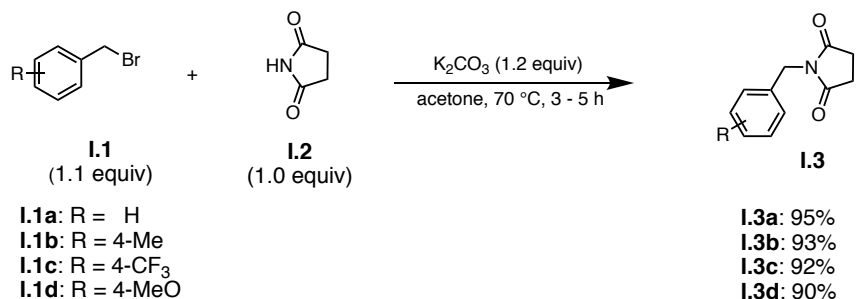
Mass spectra with electronic impact (EI-MS) were recorded with a Shimadzu GCM-QP 2010S gas chromatography-mass spectrometer. High-resolution mass spectra (HRMS) were performed by "Groupe de Spectrometrie de masse de l'Universit. Pierre et Marie Curie (Paris)".

Optical rotations were determined using a Perkin Elmer 343 polarimeter. The enantiomeric excesses were determined by supercritical fluid chromatography (SFC)

analysis on a chiral stationary phase using a Minigram Berger SFC-Mettler Toledo apparatus

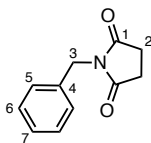
2. Synthesis of succinimide derivatives

Typical preparation of succinimide derivatives **I.3a-d**:



Succinimide **I.2** (1.98 g, 20 mmol) and anhydrous potassium carbonate (3.32 g, 24 mmol, 1.2 equiv) were added to a flame dried 100 mL round bottom flask. Anhydrous acetone (40 mL) was added followed by the addition of benzyl bromide **I.1a** (2.6 mL, 22 mmol, 1.1 equiv). The reaction mixture was then refluxed for 3 h, time after which a fine white precipitate of potassium bromide was formed. After cooling to rt, the mixture was filtered and the solvent was evaporated to give a pale orange solid which was recrystallized from CH₂Cl₂/hexane to give *N*-benzylsuccinimide **I.3a** as white crystals (3.6 g, 95%). The *N*-benzylsuccinimide **I.3a** was used in the next step without further purification.

1-benzylpyrrolidine-2,5-dione (**I.3a**)⁵¹



MW: 189.0790 g.mol⁻¹

Molecular Formula: C₁₁H₁₁NO₂

IR (neat): 3061, 2942, 1697, 1429, 1398, 1343, 1313, 1296, 1252, 1165, 1083 cm⁻¹.

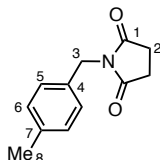
¹H NMR (400 MHz, CDCl₃) δ 7.40 – 7.37 (m, 2H, H_{Ar}), 7.33 – 7.25 (m, 3H, H_{Ar}), 4.65 (s, 2H, H₃), 2.69 (s, 4H, H₂)

¹³C NMR (100 MHz, CDCl₃) δ 177.0 (s, 2C, C₁), 135.9 (s, C₄), 129.0 (s, 2C, C₆ or C₅), 128.7 (s, 2C, C₆ or C₅), 128.1 (s, C₇), 42.5 (s, C₃), 28.3 (s, 2C, C₂)

⁵¹ Ding, G. N.; Lu, B.; Li, Y.-Y.; Wan, J.; Zhang, Z. G.; Xie, X. M, *Adv. Synth. Catal.* **2015**, 357, 1013-1021

MS m/z (relative intensity): 189 (M^+ , 100), 160 (42), 146, (6), 132 (39), 119 (22), 115 (2), 104 (53), 91 (30), 77 (14), 76 (2), 65 (17), 55 (14), 51 (11).

1-(4-methylbenzyl)pyrrolidine-2,5-dione (I.3b)⁵²



MW: 203.0946 g.mol⁻¹

Molecular Formula: C₁₂H₁₃NO₂

Prepared according to the procedure described for **I.3a** from Succinimide **I.2** (0.99 g, 10 mmol, 1.0 equiv), anhydrous potassium carbonate (1.66 g, 12 mmol, 1.2 equiv) and 4-methylbenzyl bromide **I.1b** (1.53 mL, 11 mmol, 1.1 equiv). Compound **I.3b** was obtained as a white solid (1.889 g, 93%)

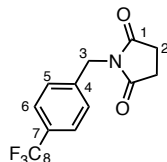
IR (neat): 2942, 1698, 1516, 1430, 1398, 1342, 1310, 1289, 1251, 1165, 1117 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.28 (d, J = 7.9 Hz, 2H, H_{Ar}), 7.11 (d, J = 7.9 Hz, 2H, H_{Ar}), 4.61 (s, 2H, H₃), 2.67 (s, 4H, H₂), 2.31 (s, 3H, H₈)

¹³C NMR (100 MHz, CDCl₃) δ 177.0 (s, 2C, C₁), 137.8 (s, C₄ or C₇), 133.0 (s, C₄ or C₇), 129.4 (s, 2C, C₅ or C₆), 129.0 (s, 2C, C₅ or C₆), 42.2 (s, C₃), 28.3 (s, 2C, C₂), 21.2 (s, C₈).

MS m/z (relative intensity): 203 (M^+ , 100), 188 (4), 174 (24), 160 (71), 146 (22), 132 (16), 118 (53), 105 (19), 91 (17), 77 (21), 65 (9), 55 (15), 51 (6).

1-(4-(trifluoromethyl)benzyl)pyrrolidine-2,5-dione (I.3c)⁵⁰



MW: 257.0664 g.mol⁻¹

Molecular Formula: C₁₂H₁₀F₃NO₂

⁵² Espinosa-Jalapa, N. A.; Kumar, A.; Leitus, G.; Diskin-Posner, Y.; Milstein, D. *J. Am. Chem. Soc.*, **2017**, *139*, 11722-11725.

Prepared according to the procedure described for **I.3a** from Succinimide **I.2** (0.99 g, 10 mmol, 1.0 equiv), anhydrous potassium carbonate (1.66 g, 12 mmol, 1.2 equiv) and 4-(trifluoromethyl)benzyl bromide **I.1c** (1.70 mL, 11 mmol, 1.1 equiv). Compound **I.3c** was obtained as a white solid (2.365 g, 92%).

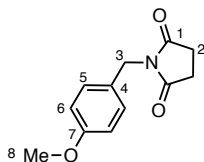
IR (neat): 2950, 1774, 1700, 1641, 1440, 1429, 1403, 1366, 1328, 1295, 1255, 1175, 1160, 1119, 1066, 1056, 1018, 1005 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.56 (d, *J* = 7.9 Hz, 2H, H_{Ar}), 7.50 (d, *J* = 7.8 Hz, 2H, H_{Ar}), 4.69 (s, 2H, H₃), 2.73 (s, 4H, H₂)

¹³C NMR (100 MHz, CDCl₃) δ 176.8 (s, 2C, C₁), 139.6 (s, C₄), 130.4 (q, *J* = 32.9 Hz, C₈), 129.4 (s, 2C, C₅), 125.8 (q, *J* = 3.9 Hz, 2C, C₆), 124.1 (q, *J* = 271.8 Hz, C₇), 42 (s, C₃), 28.3 (s, 2C, C₂)

MS *m/z* (relative intensity): 257 (M⁺, 100), 238 (10), 228 (22), 214 (2), 200 (27), 187 (9), 172 (47), 160 (28), 145 (9), 132 (15), 117 (6), 109 (12), 89 (4), 83 (6), 77 (5), 55 (21).

1-(4-methoxybenzyl)pyrrolidine-2,5-dione (**I.3d**)⁵⁰



MW: 219.0895 g.mol⁻¹

Molecular Formula: C₁₂H₁₃NO₃

Prepared according to the procedure described for **I.3a** from Succinimide **I.2** (0.99 g, 10 mmol, 1.0 equiv), anhydrous potassium carbonate (1.66 g, 12 mmol, 1.2 equiv) and 4-methoxybenzyl bromide **I.1d** (1.60 mL, 11 mmol, 1.1 equiv). Compound **I.3d** was obtained as a white solid (1.972 g, 90%).

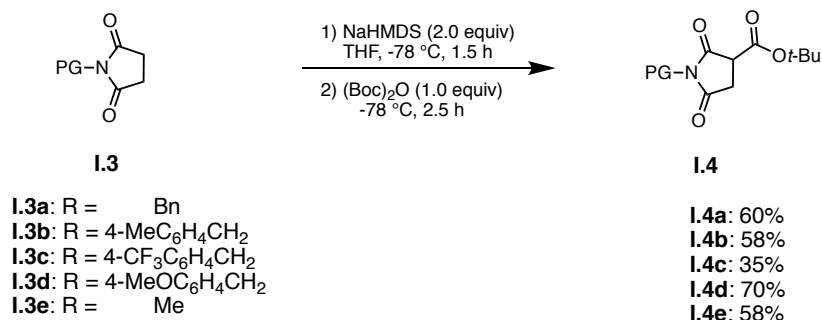
IR (neat): 2940, 2837, 1772, 1695, 1611, 1585, 1513, 1430, 1398, 1342, 1296, 1246, 1164, 1110, 1030, 1003, 967 cm⁻¹.

¹H NMR (400Hz, CDCl₃) δ 7.34 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 6.83 (d, *J* = 8.6 Hz, 2H, H_{Ar}), 4.59 (s, 2H, H₅), 3.78 (s, 3H, H₁₀), 2.68 (s, 4H, H₂ and H₃).

¹³C NMR (101 Hz, CDCl₃) δ 177.1 (s, 2C, C₁ and C₄), 159.4 (s, C₉) 130.6 (s, 2C, C_{Ar}), 128.2 (s, C₆), 114.7 (s, 2C, C_{Ar}), 55.4 (s, C₁₀), 42.0 (s, C₅), 28.3 (s, 2C, C₂ and C₃)

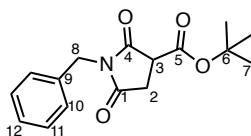
Mz m/z (relative intensity): 219 (M^+ , 100), 190 (35), 160 (31), 148 (14), 134 (37), 121 (23), 104 (1), 91 (9), 77 (13), 65 (6), 55 (13), 51 (6).

Typical preparation of succinimide derivatives I.4a-e:



N-Benzylsuccinimide **I.3a** (2.89 g, 10 mmol, 1.0 equiv) was added to a flamed dried 100 mL round bottom flask. The flask was purged by three consecutive evacuation/backfill cycles. Anhydrous THF (20 mL) was added and the reaction mixture was cooled to -78 °C. NaHMDS (20 mL, 20 mmol, 2.0 equiv, 1.0 M in THF) was then added drop-wise over 10 min. After stirring for 90 min at -78 °C, di-*tert*-butyl dicarbonate (2.18 g, 10.0 mmol, 1.0 equiv) in THF (5 mL) was added and the reaction mixture was stirred at -78 °C for an additional 2 h. The reaction was quenched with a saturated aqueous NH₄Cl solution (5 mL), warmed to rt and extracted with EtOAc (3 × 50 mL). The organic layers were combined, washed with brine (50 mL), dried over anhydrous MgSO₄ and concentrated under reduced pressure to afford a crude residue which was purified by flash column chromatography over silica gel (EtOAc/petroleum ether = 1:10 to 1:5) to afford **I.4a** as a white solid (1.73 g, 60 %).

tert-Butyl-*N*-benzyl-1,4-dioxopyrrolidine-3-carboxylate (**I.4a**)⁵³



MW: 289.1314 g.mol⁻¹

Molecular Formula: C₁₆H₁₉NO₄

⁵³ Smith, A. M.R.; Rzepa, H. S.; White, A. J. P.; Billen, D; Hii, K. K.; *J. Org. Chem.* **2010**, 75, 3085–3096.

Mp: 100–101 °C.

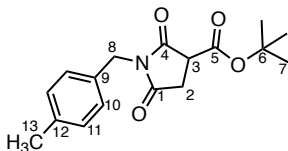
IR (neat): 2940, 1695, 1435, 1364, 1325, 1231, 1147, 1078, 991, 931 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.36 – 7.33 (m, 2H, H_{Ar}), 7.31 – 7.23 (m, 3H, H_{Ar}), 4.69 (d, *J*_{AB} = 14.4 Hz, 1H, H₈), 4.64 (d, *J*_{AB} = 14.0 Hz, 1H, H₈), 3.64 (dd, *J* = 9.3, 4.5 Hz, 1H, H₃), 3.00 (dd, *J* = 18.2, 4.5 Hz, 1H, H₂), 2.84 (dd, *J* = 18.2, 9.3 Hz, 1H, H₂), 1.44 (s, 9H, H₇).

¹³C NMR (100 MHz, CDCl₃) δ 175.1 (s, C₁), 172.5 (s, C₄), 166.5 (s, C₅), 135.4 (s, C₉), 128.7 (s, 2C, C_{Ar}), 128.6 (s, 2C, C_{Ar}), 128.0 (s, C₁₂), 83.4 (s, C₆), 47.7 (s, C₃), 42.8 (s, C₈), 32.4 (s, C₂), 27.8 (s, 3C, C₇).

MS *m/z* (relative intensity): 289 (M⁺, 0.5), 233 (100), 216 (30), 205 (5), 187 (32), 177 (5), 160 (20), 145 (4), 132 (13), 117 (2), 106 (26), 91 (52), 73 (9), 57 (93), 55 (48).

***tert*-Butyl-*N*-(4-methylbenzyl)-2,5-dioxopyrrolidine-3-carboxylate (**I.4b**)**



MW: 303.1471 g.mol⁻¹

Molecular Formula: C₁₇H₂₁NO₄

Prepared according to the procedure described for **I.4a** from *N*-(4-methylbenzyl) pyrrolidine-2,5-dione (1.02 g, 5.0 mmol, 1.0 equiv), NaHMDS (10 mL, 10 mmol, 2.0 equiv, 1.0 M in THF), di-*tert*-butyl dicarbonate (1.09 g, 5.0 mmol, 1.0 equiv) in THF (3 mL). The reaction mixture was stirred at –78 °C for 2 h. Purification by flash column chromatography over silica gel (EtOAc/petroleum ether = 1:10 to 1:5) afforded **I.4b** as a white solid (0.88 g, 58%).

Mp: 95–96 °C.

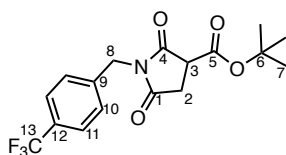
IR (neat): 1703, 1517, 1430, 1394, 1369, 1339, 1309, 1235, 1148, 1048, 991, 912 cm⁻¹

¹H NMR (400 MHz, CDCl₃) δ 7.27 (d, *J* = 8.5 Hz, 2H, H_{Ar}), 7.12 (d, *J* = 7.8 Hz, 2H, H_{Ar}), 4.66 (d, *J*_{AB} = 14.1 Hz, H₈), 4.61 (d, *J*_{AB} = 14.4 Hz, 1H, H₈), 3.64 (dd, *J* = 9.3, 4.5 Hz, 1H, H₃), 3.02 (dd, *J* = 18.2, 4.4 Hz, 1H, H₂), 2.85 (dd, *J* = 18.2, 9.3 Hz, 1H, H₂), 2.32 (s, 3H, H₁₃), 1.46 (s, 9H, H₇).

¹³C NMR (100 MHz, CDCl₃) δ 175.2 (s, C₁), 172.5 (s, C₄), 166.6 (s, C₅), 137.9 (s, C₁₂), 132.5 (s, C₉), 129.4 (s, 2C, C_{Ar}), 128.8 (s, 2C, C_{Ar}), 83.5 (s, C₆), 47.7 (s, C₃), 42.7 (s, C₈), 32.4 (s, C₂), 27.9 (s, 3C, C₇), 21.2 (s, C₁₂).

HRMS (ESI) *m/z*: calcd for C₁₇H₂₁NO₄Na [M+Na]⁺: 326.1363, found: 326.1362.

***Tert*-Butyl-2,5-dioxo-*N*-(4-(trifluoromethyl)benzyl)pyrrolidine-3-carboxylate (**1.4c**)**



MW: 357.1188 g.mol⁻¹

Molecular Formula: C₁₇H₁₈F₃NO₄

Prepared according to the procedure described for **1a** from *N*-[4-(trifluoromethyl)benzyl] pyrrolidine-2,5-dione (1.29 g, 5.0 mmol, 1.0 equiv), NaHMDS (10 mL, 10 mmol, 2.0 equiv, 1.0 M in THF), di-*tert*-butyl dicarbonate (1.09 g, 5.0 mmol, 1.0 equiv) in THF (3 mL). The reaction mixture was stirred at -78 °C for 2 h. Purification by flash column chromatography over silica gel (EtOAc/petroleum ether = 1:10 to 1:5) afforded **1c** as a white solid (0.63 g, 35%).

Mp: 93–94 °C.

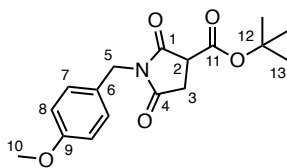
IR (neat): 2942, 1734, 1698, 1433, 1398, 1371, 1326, 1235, 1164, 1147, 1122, 1068, 1019, 993, 919 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.56 (d, *J* = 8.1 Hz, 2H, H_{Ar}), 7.47 (d, *J* = 8.0 Hz, 2H, H_{Ar}), 4.71 (d, *J*_{AB} = 14.0 Hz, 1H, H₈), 4.69 (d, *J*_{AB} = 14.0 Hz, 1H, H₈), 3.67 (dd, *J* = 9.3, 4.4 Hz, 1H, H₃), 3.04 (dd, *J* = 18.3, 4.4 Hz, 1H, H₂), 2.88 (dd, *J* = 18.3, 9.3 Hz, 1H, H_{Ar}), 1.44 (s, 9H, H₇).

¹³C NMR (100 MHz, CDCl₃) δ 175.0 (s, C₁), 172.4 (s, C₄), 166.5 (s, C₅), 139.2 (s, C₉), 130.5 (q, *J* = 32.5 Hz, C₁₂), 129.1 (s, 2C, C₁₀), 125.8 (q, *J* = 3.7 Hz, 2C, C₁₁), 124.1 (q, *J* = 272.0 Hz, C₁₃), 83.8 (s, C₆), 47.8 (s, C₃), 42.4 (s, C₈), 32.5 (s, C₂), 27.9 (s, 3C, C₇).

HRMS (ESI) *m/z*: calcd for C₁₇H₁₈F₃NO₄Na [M+Na]⁺: 380.1080, found: 380.1079.

***tert*-butyl 1-(4-methoxybenzyl)-2,5-dioxopyrrolidine-3-carboxylate (**1.4d**)**⁵¹



MW: 319.1420 g.mol⁻¹

Molecular Formula: C₁₇H₂₁NO₅

Prepared according to the procedure described for **1a** from *N*-(4-methoxybenzyl) pyrrolidine-2,5-dione **1.3d** (1.095 g, 5.0 mmol, 1.0 equiv), NaHMDS (10 mL, 10 mmol, 2.0 equiv, 1.0 M in THF), di-*tert*-butyl dicarbonate (1.09 g, 5.0 mmol, 1.0 equiv) in THF (3 mL). The reaction mixture was stirred at –78 °C for 2 h. Purification by flash column chromatography over silica gel (EtOAc/petroleum ether = 1:10 to 1:5) afforded **1.4d** as a white solid (1.12 g, 70 %).

Mp: 91–92 °C

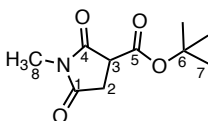
IR (neat): 1701, 1612, 1514, 1433, 1395, 1369, 1339, 1299, 1246, 1147, 1112, 1032, 992, 911 cm⁻¹.

¹H NMR (400Hz, CDCl₃) δ 7.33 – 7.29 (m, 2H, H_{Ar}), 6.84 – 6.80 (m, 2H, H_{Ar}), 4.63 (d, *J*_{AB} = 14 Hz, 1H, H₅), 4.57 (d, *J*_{AB} = 14 Hz, 1H, H₅), 3.77 (s, 3H, H₁₀), 3.63 (dd, *J* = 9.3, 4.5 Hz, 1H, H₂), 3.01 (dd, *J* = 18.2, 4.6 Hz, 1H, H₃), 2.83 (dd, *J* = 18.2, 9.3 Hz, 1H, H₃), 1.45 (s, 9H, H₁₃).

¹³C NMR (101 Hz, CDCl₃) δ 175.2 (s, C₄), 172.6 (s, C₁), 166.6 (s, C₁₁), 169.5 (s, C₉), 130.4 (s, 2C, C₇), 127.8 (s, C₆), 114.1 (s, 2C, C₈), 83.5 (s, C₁₂), 55.4 (s, C₁₀), 47.7 (s, C₂), 42.5 (s, C₅), 32.5 (s, C₃), 28.0 (s, 3C, C₁₃)

Mz *m/z* (relative intensity): 319 (M⁺, 10), 263 (64), 246 (12), 218 (6), 206 (2), 190 (23), 176 (2), 162 (15), 146 (3), 136 (15), 121 (100), 107 (2), 91 (5), 77 (7), 57 (34), 51 (2).

***tert*-Butyl-*N*-methyl-2,5-dioxopyrrolidine-3-carboxylate (**1.4e**)**⁵⁴



⁵⁴ Shi, S. C.; Szostak, M. *Org. Lett.* **2015**, *17*, 5144-5147.

MW: 213.1001 g.mol⁻¹

Molecular Formula: C₁₀H₁₅NO₄

Prepared according to the procedure described for **I.4a** from *N*-(4-methylbenzyl)pyrrolidine-2,5-dione (1.29 g, 5.0 mmol, 1.0 equiv), NaHMDS (10 mL, 10 mmol, 2.0 equiv, 1.0 M in THF), di-*tert*-butyl dicarbonate (1.09 g, 5.0 mmol, 1.0 equiv) and THF (3 mL). The reaction mixture was stirred at -78 °C for 2 h. Purification by flash column chromatography over silica gel (EtOAc/petroleum ether = 1:10 to 1:5) afforded **I.4e** as a white solid (0.51 g, 58%).

Mp: 71–72 °C.

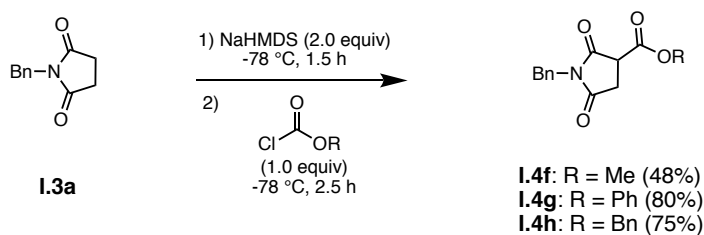
IR (neat): 1782, 1699, 1435, 1384, 1369, 1334, 1280, 1236, 1150, 1060, 994 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 3.57 (dd, *J* = 9.3, 4.8 Hz, 1H, H₃), 2.90 (m, 1H, H₂), 2.87 (s, 3H, H₈), 2.76 (dd, *J* = 18.1, 9.3 Hz, 1H, H₂), 1.37 (s, 9H, H₇).

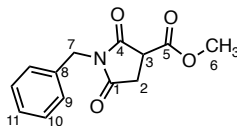
¹³C NMR (100 MHz, CDCl₃) δ 175.4 (s, C₁), 172.6 (s, C₄), 166.6 (s, C₅), 83.1 (s, C₆), 47.4 (s, C₃), 32.2 (s, C₂), 27.7 (s, 3C, C₇), 25.1 (s, C₈).

MS *m/z* (relative intensity): 214 (M⁺, 0.4), 198 (2), 158 (36), 140 (58), 113 (14), 57 (100), 55 (46).

Typical synthesis of succinimide derivatives **I.4f-h**:



Methyl-*N*-benzyl-2,5-dioxopyrrolidine-3-carboxylate (**I.4f**)⁵⁵



MW: 247.0845 g.mol⁻¹

Molecular Formula: C₁₃H₁₃NO₄

⁵⁵ Allous, I.; Comesse, S.; Daïch, A. *Lett. Org. Chem.*, **2008**, 5, 73-78.

Prepared according to the procedure described for **I.4a** from *N*-benzylpyrrolidine-2,5-dione **I.3a** (0.95 g, 5.0 mmol, 1.0 equiv), NaHMDS (10 mL, 10 mmol, 2.0 equiv., 1.0 M in THF), methyl chloroformate (0.39 mL, 5.0 mmol, 1.0 equiv). The reaction mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 2 h. Purification by flash column chromatography over silica gel (EtOAc/petroleum ether = 1:10 to 1:5) afforded **I.4f** as a colorless oil (0.59 g, 48%).

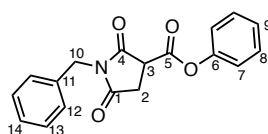
IR (neat): 2954, 1739, 1699, 1431, 1395, 1336, 1228, 1161, 1082, 992, 962, 928 cm^{-1} .

^1H NMR (400 MHz, CDCl_3) δ 7.38 – 7.34 (m, 2H, H_{Ar}), 7.33 – 7.26 (m, 3H, H_{Ar}), 4.98 (d, $J_{\text{AB}} = 12.0\text{ Hz}$, 1H, H_7), 4.92 (d, $J_{\text{AB}} = 12.0\text{ Hz}$, 1H, H_7), 3.81 (s, 3H, H_6), 3.80 (dd, $J = 15.2, 15.2, 1\text{H}$, H_3), 3.10 (dd, $J = 18.3, 4.7\text{ Hz}$, 1H, H_2), 2.89 (dd, $J = 18.3, 9.4\text{ Hz}$, 1H, H_2).

^{13}C NMR (100 MHz, CDCl_3) δ 174.8 (s, C_1), 171.9 (s, C_4), 168.0 (s, C_5), 135.3 (s, C_8), 128.8 (s, C_4 , C_9 and C_{10}), 128.2 (s, C_{11}), 53.5 (s, C_6), 46.4 (s, C_3), 43.1 (s, C_7), 32.3 (s, C_2).

MS m/z (relative intensity): 247 (M^+ , 100), 216 (7), 191 (13), 176 (10), 159 (32), 146 (6), 132 (37), 114 (11), 106 (92), 87 (66), 77 (14), 65 (21), 55 (100).

Phenyl-*N*-benzyl-2,5-dioxopyrrolidine-3-carboxylate (**I.4g**)



MW: 309.1001 $\text{g}\cdot\text{mol}^{-1}$

Molecular Formula: $\text{C}_{18}\text{H}_{15}\text{NO}_4$

Prepared according to the procedure described for **I.4a** from *N*-benzylpyrrolidine-2,5-dione **I.3a** (0.95 g, 5.0 mmol, 1.0 equiv), NaHMDS (10 mL, 10 mmol, 2.0 equiv, 1.0 M in THF), phenyl chloroformate (0.63 mL, 5.0 mmol, 1.0 equiv). The reaction mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 2 h. Purification by flash column chromatography over silica gel (EtOAc/petroleum ether = 1:10 to 1:5) afforded **I.4g** as a yellow solid (1.24 g, 80%).

Mp: 59–60 $^{\circ}\text{C}$.

IR (neat): 1754, 1701, 1501, 1492, 1431, 1395, 1338, 1218, 1189, 1161, 1082, 992, 968, 922 cm^{-1} .

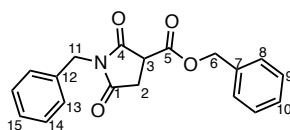
^1H NMR (400 MHz, CDCl_3) δ 7.42 – 7.39 (m, 4H, H_{Ar}), 7.35 – 7.28 (m, 4H, H_{Ar}), 7.12 (d, $J = 7.7\text{ Hz}$, 2H, H_{Ar}), 4.75 (d, $J_{\text{AB}} = 14.4\text{ Hz}$, 1H, H_{10}), 4.70 (d, $J_{\text{AB}} = 14.0\text{ Hz}$, 1H, H_{10}),

4.01 (dd, $J = 9.4, 4.8$ Hz, 1H, H_3), 3.23 (dd, $J = 18.3, 4.8$ Hz, 1H, H_2), 3.01 (dd, $J = 18.3, 9.4$ Hz, 1H, H_2).

^{13}C NMR (100 MHz, CDCl_3) δ 174.6 (s, C_1), 171.6 (s, C_4), 166.3 (s, C_5), 150.3 (s, C_6), 135.2 (s, C_{11}), 129.7 (s, C_{Ar}), 129.3 (s, 2C, C_{Ar}), 128.8 (s, 2C, C_{Ar}), 128.3 (s, C_{Ar}), 126.6 (s, C_{Ar}), 121.2 (s, 3C, C_7), 46.6 (s, C_3), 43.2 (s, C_{10}), 32.3 (s, C_2).

HRMS (ESI) m/z : calcd for $\text{C}_{18}\text{H}_{15}\text{NO}_4\text{Na}$ $[\text{M}+\text{Na}]^+$: 332.0893, found: 332.0894.

Benzyl-*N*-benzyl-2,5-dioxopyrrolidine-3-carboxylate (**1g**)



MW: 323.1158 $\text{g}\cdot\text{mol}^{-1}$

Molecular Formula: $\text{C}_{19}\text{H}_{17}\text{NO}_4$

Prepared according to the procedure described for **1.4a** from *N*-benzylpyrrolidine-2,5-dione **1.3a** (0.95 g, 5.0 mmol, 1.0 equiv), NaHMDS (10 mL, 10 mmol, 2.0 equiv, 1.0 M in THF), benzyl chloroformate (0.7 mL, 5.0 mmol, 1.0 equiv). The reaction mixture was stirred at -78 °C for 2 h. Purification by flash column chromatography over silica gel (EtOAc/petroleum ether = 1:10 to 1:5) afforded **1.4h** as a white solid (1.21 g, 75%).

Mp: 86–87 °C.

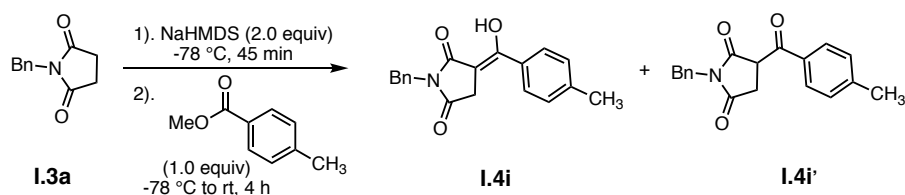
IR (neat): 2961, 1736, 1703, 1497, 1455, 1427, 1406, 1375, 1349, 1258, 1167, 1062, 1008, 931, 903 cm^{-1} .

^1H NMR (400 MHz, CDCl_3) δ 7.40 – 7.31 (m, 7H, H_{Ar}), 7.30 – 7.26 (m, 3H, H_{Ar}), 5.22 (s, 2H, H_6), 4.63 (d, $J_{AB} = 14.4.0$ Hz, 1H, H_{11}), 4.65 (d, $J_{AB} = 14.4.0$ Hz, 1H, H_{11}), 3.81 (dd, $J = 9.4, 4.7$ Hz, 1H, H_3), 3.10 (dd, $J = 18.3, 4.7$ Hz, 1H, H_2), 2.89 (dd, $J = 18.3, 9.6$ Hz, 1H, H_2).

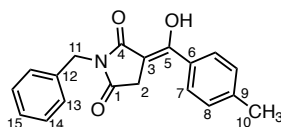
^{13}C NMR (100 MHz, CDCl_3) δ 174.8 (s, C_1), 171.9 (s, C_4), 167.4 (s, C_5), 135.3 (s, C_{Ar}), 134.9 (s, C_{Ar}), 128.8 (s, 4C, C_{Ar}), 128.8 (s, 2C, C_{Ar}), 128.7 (s, C_{Ar}), 128.4 (s, 2C, C_{Ar}), 128.2 (s, C_{Ar}), 68.2 (s, C_6), 46.6 (s, C_3), 43.1 (s, C_{11}), 32.3 (s, C_2).

HRMS (ESI) m/z : calcd for $\text{C}_{19}\text{H}_{17}\text{NO}_4\text{Na}$ $[\text{M}+\text{Na}]^+$: 346.1050, found: 346.1050.

Synthesis of succinimide derivative **1.4i**



***N*-Benzyl-3-(4-methylbenzoyl)pyrrolidine-2,5-dione (I.4i)⁵⁶**



MW: 307.1208 g.mol⁻¹

Molecular Formula: C₁₉H₁₇NO₃

A solution of NaHMDS in THF (10 mL, 10 mmol, 2.0 equiv, 1.0 M in THF) was added by syringe to a solution of *N*-benzylpyrrolidine-2,5-dione **I.3a** (0.95 g, 5.0 mmol, 1.0 equiv) in anhydrous THF (2.5 mL/mmol) at –78 °C. The reaction mixture was stirred at the same temperature for 45 min before a solution of methyl 4-methylbenzoate (0.79 g, 5.25 mmol, 1.05 equiv) in THF (5 mL) was added. The ice bath was eventually removed and the mixture was stirred at rt. After 4 h, H₂O was added and the aqueous layer was extracted with EtOAc (3 x 5 mL). The organic layers were combined, washed with H₂O and brine, dried over anhydrous Na₂SO₄ and filtered. The solvent was removed under reduced pressure to afford a mixture of tautomers **I.4i** and **I.4i'** in a ratio of 9:1. After recrystallization from CH₂Cl₂/hexane, compound **14i** was isolated as a white solid (0.92 g, 60%).

Mp: 92–94 °C.

IR (neat): 3033, 1749, 1706, 1658, 1629, 1607, 1511, 1496, 1432, 1409, 1396, 1348, 1330, 1249, 1209, 1186, 1166, 1126, 1080, 1058, 1002, 947, 925 cm⁻¹

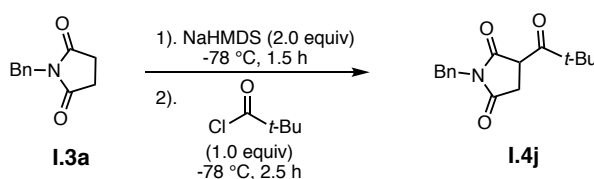
¹H NMR (400 MHz, CDCl₃) δ 12.21 (s_{br}, 1H, OH), 7.62 (d, *J* = 8.3 Hz, 2H, H_{Ar}), 7.46 (d, *J* = 7.3 Hz, 2H, H_{Ar}), 7.39 – 7.26 (m, 5H, H_{Ar}), 4.77 (s, 2H, H₁₁), 3.54 (s, 2H, H₂), 2.43 (s, 3H, H₁₀).

⁵⁶ Agejas, J.; Ortega, L. *J. Org. Chem.* **2015**, *80*, 6509-6514.

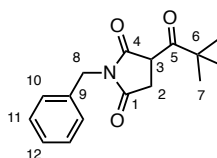
^{13}C NMR (100 MHz, CDCl_3) δ 176.0 (s, C_1), 174.0 (s, C_4), 164.2 (s, C_5), 142.0 (s, C_9), 136.0 (s, C_{12}), 130.4 (s, C_{Ar}), 129.5 (s, C_{Ar}), 129.4 (s, 2C, C_{Ar}), 128.9 (s, C_{Ar}), 128.8 (s, 2C, C_{Ar}), 128.1 (s, C_{Ar}), 127.7 (s, 2C, C_{Ar}), 94.7 (s, C_3), 42.2 (s, C_{11}), 33.9 (s, C_2), 21.6 (s, C_{10}).

HRMS (ESI) m/z : calcd for $\text{C}_{19}\text{H}_{17}\text{NO}_3\text{Na}$ $[\text{M}+\text{Na}]^+$: 330.1101, found: 330.1100.

Synthesis of succinimide derivative **I.4j**:



N-benzyl-3-pivaloylpyrrolidine-2,5-dione (**I.4j**)



MW: 273.1365 $\text{g}\cdot\text{mol}^{-1}$

Molecular Formula: $\text{C}_{16}\text{H}_{19}\text{NO}_3$

Prepared according to the procedure described for **I.3a** from *N*-benzylpyrrolidine-2,5-dione (0.95 g, 5.0 mmol, 1.0 equiv), NaHMDS (10 mL, 10 mmol, 2.0 equiv, 1.0 M in THF), pivaloyl chloride (0.62 mL, 5.0 mmol, 1.0 equiv). The reaction mixture was stirred at $-78\text{ }^\circ\text{C}$ for 2 h. Purification by flash column chromatography over silica gel (EtOAc/petroleum ether = 1:10 to 1:5) afforded **I.4j** as a white solid (1.02 g, 75%).

Mp: 72–73 $^\circ\text{C}$.

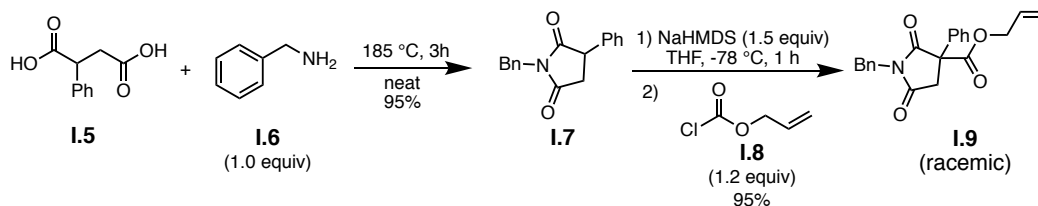
IR (neat): 2971, 2362, 1713, 1687, 1396, 1345, 1162, 1082, 700, 687 cm^{-1}

^1H NMR (400 MHz, CDCl_3) δ 7.25 – 7.14 (m, 5H, H_{Ar}), 4.55 (q, J = 14.3 Hz, 2H, H_8), 4.24 (dd, J = 8.0, 5.2 Hz, 1H, H_3), 2.69 (dd, J = 6.6, 3.5 Hz, 2H, H_2), 1.13 (s, 9H, H_7).

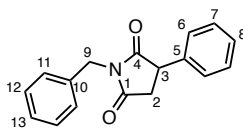
^{13}C NMR (100 MHz, CDCl_3) δ 210.3 (s, C_5), 175.5 (s, C_1), 173.7 (s, C_4), 135.4 (s, C_9), 128.8 (s, 2C, C_{Ar}), 128.6 (s, 2C, C_{Ar}), 128.1 (s, C_{12}), 46.9 (s, C_3), 45.3 (s, C_6), 43.0 (s, C_8), 40.0 (s, C_2), 25.8 (s, 3C, C_7).

HRMS (ESI) m/z : calcd for $\text{C}_{16}\text{H}_{19}\text{N}_1\text{O}_3\text{Na}$ $[\text{M}+\text{Na}]^+$: 296.1257, found: 296.1978.

Synthesis of succinimide derivative **I.7** and **I.9**



1-benzyl-3-phenylpyrrolidine-2,5-dione (**I.7**)⁵⁷:



MW/g (mol): 265.1103 g.mol⁻¹

Molecular Formula: C₁₇H₁₅NO₂

A mixture of 2-phenylsuccinic acid **I.5** (0.97 g, 5 mmol, 1.0 equiv) and benzylamine **I.6** (0.546 mL, 5 mmol, 1.0 equiv) were added into 100 mL over-dried round bottom flask with a magic stir bar. The mixture was heated neat at 185°C for 2 hours. Then, the mixture was cooled and the product was dissolved in CH₂Cl₂. The CH₂Cl₂ phase was washed with brine and dried over anhydrous sodium sulfate. Evaporation of the solvent gave a yellow solid, which was purified by column chromatography on silica gel (PE/EtOAc = 9:1) to afford the title product **I.7** as yellow solid (1.259 g, 95%).

Mp: 58–59 °C.

IR (neat): 1702, 1396, 1344, 1166, 1082, 699 cm⁻¹.

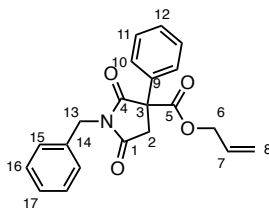
¹H NMR (400 MHz, CDCl₃) δ 7.42 – 7.39 (m, 2H, H_{Ar}), 7.37 – 7.27 (m, 6H, H_{Ar}), 7.19 – 7.14 (m, 2H, H_{Ar}), 4.73 (q, *J* = 14.0 Hz, 2H, H₉), 4.01 (dd, *J* = 9.6, 4.8 Hz, 1H, H₃), 3.20 (dd, *J* = 18.5, 9.6 Hz, 1H, H₂), 2.82 (dd, *J* = 18.5, 4.8 Hz, 1H, H₂).

¹³C NMR (100 MHz, CDCl₃) δ 177.5 (s, C₁), 175.9 (s, C₄), 137.3 (s, C_{Ar}), 135.9 (s, C_{Ar}), 129.3 (s, 2C, C_{Ar}), 128.9 (s, 2C, C_{Ar}), 128.8 (s, 2C, C_{Ar}), 128.1 (s, C_{Ar}), 128.05 (s, C_{Ar}), 127.5 (s, 2C, C_{Ar}), 46.0 (s, C₃), 42.8 (s, C₉), 37.3 (s, C₂).

MS *m/z* (relative intensity): 265 (M⁺, 54), 240 (2), 180 (1), 132 (14), 118 (3), 104 (100), 91 (25), 78 (13), 65 (8), 51 (5).

⁵⁷ Korenaga, T.; Ko, A.; Shimada, K. *J. Org. Chem.* **2013**, *78*, 9975-9980.

Allyl 1-benzyl-2,5-dioxo-3-phenylpyrrolidine-3-carboxylate (I.9):



MW/g (mol): 349.1314 g.mol⁻¹

Molecular Formula: C₂₁H₁₉NO₄

To the solution of 1-benzyl-3-phenylpyrrolidine-2,5-dione **I.7** (1.018 g, 3.84 mmol) in THF (10 mL) at -78 °C was added NaHMDS (5.76 mL, 1.0 M in THF, 5.76 mmol, 1.5 equiv) dropwise. After being kept stirring at -78 °C for 1 hour, allyl chloroformate (0.489 mL, 4.608 mmol, 1.2 equiv) was added. Followed 2 hours later by a saturated aqueous solution of NH₄Cl (5 mL). The aqueous phase was extracted with ethyl acetate (3 × 10 mL) and combined the organic phases dried over Na₂SO₄, filtered and concentrated under reduce pressure to afford the crude residue, which was purified by the fresh column chromatography on silica gel (PE/EtOAc = 90/10 to 80/20) to afford the title product **I.9** as white solid (1.274 g, 95%).

Mp: 78–79 °C.

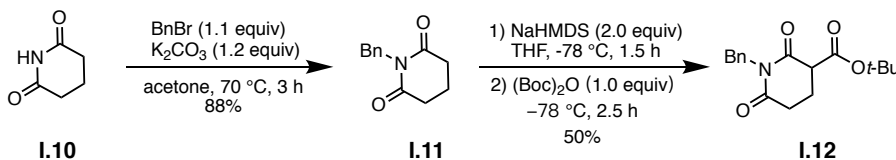
IR (neat): 2360, 1708, 1394, 1345, 1175, 939, 701 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.41 – 7.26 (m, 9H, H_{Ar}), 5.81 – 5.71 (m, 1H, H_{Ar}), 5.20 (dt, *J* = 8.0, 1.4 Hz, 1H, H₇), 5.18 – 5.15 (m, 2H, H₈), 4.81 – 4.70 (m, 2H, H₁₃), 4.63 (dt, *J* = 5.6, 1.4 Hz, 2H, H₆), 3.72 (d, *J* = 18.1 Hz, 1H, H₂), 3.15 (d, *J* = 18.1 Hz, 1H, H₂).

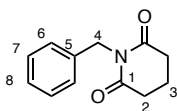
¹³C NMR (400 MHz, CDCl₃) δ 173.9 (s, C₄), 173.3 (s, C₁), 168.7 (s, C₅), 136.3 (s, C₁₄), 135.3 (s, C₉), 130.8 (s, C₇), 129.1 (s, 2C, C_{Ar}), 128.8 (s, 2C, C_{Ar}), 128.7 (s, 2C, C_{Ar}), 128.5 (s, C_{Ar}), 128.2 (s, C_{Ar}), 127.0 (s, 2C, C_{Ar}), 119.3 (s, C₈), 67.3 (s, C₆), 59.7 (s, C₃), 43.2 (s, C₁₃), 41.6 (s, C₂).

HRMS (ESI) *m/z*: calcd for C₂₁H₁₉NO₄Na [M+Na]⁺: 372.1206, found: 372.1206.

Synthesis of succinimide derivative I.11 and I.12



1-benzylpiperidine-2,6-dione (**I.11**)



MW/g(mol): 203.0946 g.mol⁻¹

Molecular Formula: C₁₇H₁₅NO₂

Prepared according to the procedure described for **I.3a** from piperidine-2,6-dione **I.10** (1.13 g, 10 mmol, 1.0 equiv), anhydrous potassium carbonate (1.66 g, 12 mmol, 1.2 equiv) and benzyl bromide **I.1a** (1.30 mL, 11 mmol, 1.1 equiv). Compound **I.3c** was obtained as a colourless oil (1.787 g, 88%).

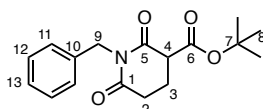
IR (neat): 1724, 1671, 1426, 1379, 1355, 1295, 1230, 1169, 1135, 1087, 1066, 1016 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.36 – 7.33 (m, 2H, H_{Ar}), 7.30 – 7.21 (m, 3H, H_{Ar}), 4.94 (s, 2H, H₄), 2.67 – 2.64 (m, 4H, H₂), 1.95 – 1.88 (m, 2H, H₃).

¹³C NMR (100 MHz, CDCl₃) δ 172.5 (s, 2C, C₁), 137.4 (s, C₅), 128.8 (s, 2C, C_{Ar}), 128.4 (s, 2C, C_{Ar}), 127.4 (s, C₈), 42.7 (s, C₄), 32.9 (s, 2C, C₂), 17.1 (s, C₃).

MS m/z (relative intensity): 203 (M⁺, 100), 175 (25), 160 (1), 146 (56), 132 (7), 118 (28), 104 (55), 91 (41), 84 (49), 77 (15), 65 (19), 55 (13).

tert-Butyl 1-benzyl-2,6-dioxopiperidine-3-carboxylate (**I.12**):



MW: 303.1471 g.mol⁻¹

Molecular Formula: C₁₇H₂₁NO₄

Prepared according to the procedure described for **I.4a** from *N*-benzylpiperidine-2,6-dione **I.11** (1.015 g, 5 mmol, 1.0 equiv), NaHMDS (10 mL, 10 mmol, 2.0 equiv, 1.0 M in THF), di-*tert*-butyl dicarbonate (1.09 g, 5 mmol, 1.0 equiv) in THF (3 mL) was added and the reaction was stirred at –78 °C for 2 h. Purification by flash column chromatography on silica gel (EtOAc/petroleum ether = 1:10 to 1:5) afforded **I.12** as a white solid (0.757 g, 50%).

Mp: 75–77 °C.

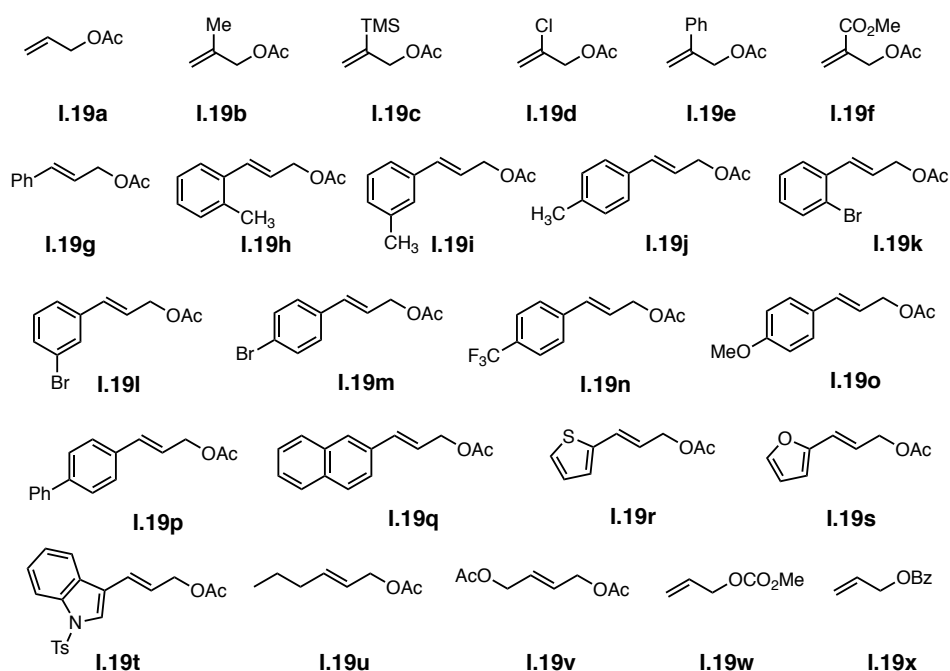
IR (neat): 2972, 1724, 1678, 1456, 1424, 1367, 1338, 1257, 1074, 1019, 985 cm^{-1} .

^1H NMR (400 MHz, CDCl_3) δ 7.37 – 7.34 (m, 2H, H_{Ar}), 7.29 – 7.20 (m, 3H, H_{Ar}), 5.00 (d, $J_{\text{AB}} = 12.0$ Hz, 1H, H_9), 4.92 (d, $J_{\text{AB}} = 12.0$ Hz, 1H, H_9), 3.56 (t, $J = 5.9$ Hz, 1H, H_4), 2.78 – 2.61 (m, 2H, H_2), 2.30 – 2.22 (m, 1H, H_3), 2.16 – 2.08 (m, 1H, H_3), 1.42 (s, 9H, H_8).

^{13}C NMR (100 MHz, CDCl_3) δ 171.6 (s, C_1), 169.0 (s, C_5), 167.7 (s, C_6), 137.0 (s, C_{10}), 128.9 (s, 2C_{Ar}), 128.5 (s, 2C_{Ar}), 127.5 (s, C_{Ar}), 83.2 (s, C_7), 50.2 (s, C_4), 43.1 (s, C_9), 30.4 (s, C_2), 27.9 (s, 3C_8), 20.8 (s, C_3).

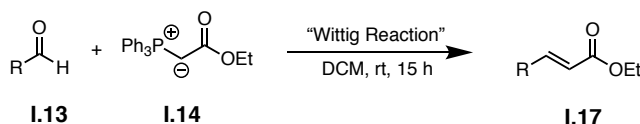
HRMS (ESI) m/z : calcd for $\text{C}_{17}\text{H}_{21}\text{NO}_4\text{Na}$ $[\text{M}+\text{Na}]^+$: 326.1363, found: 326.1376.

3. Synthesis of β -substituted allylic reagents



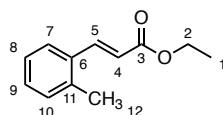
The allyl donor reagents **I.19a**, **I.19g**, **I.19u-x** were commercially available and used directly as received. The α -substituted allyl acetates **I.19b-f** were synthesized by Dr. Marllon Nascimento de Oliveira⁴⁶ and used directly in Pd-AAA. The β -substituted allyl acetates reagents **I.19h-t** were synthesized followed the previous reports.

The general procedure for preparation of α,β -unsaturated ester I.17:



To a stirred solution of aldehyde **I.13** (8 mmol, 1.0 equiv) in CH_2Cl_2 (20 mL) was added ethyl 2-(triphenylphosphoranyliden)acetate **I.14** (1.8 g, 5.25 mmol, 1.05 equiv). The reaction was stirred for 15 h at rt. The mixture solution was then concentrated under reduced pressure, the residue triturated with petroleum ether/ Et_2O (9:1), and the solid removed by filtration. The solvent was removed under reduced pressure and the crude residue was purified by flash column chromatography over silica gel to give the pure α,β -unsaturated esters (*E*)-**I.17**.

ethyl (*E*)-3-(*o*-tolyl)acrylate (**I.17a**)⁵⁸



MW: 190.0994 $\text{g}\cdot\text{mol}^{-1}$

Molecular Formula: $\text{C}_{12}\text{H}_{14}\text{O}_2$

Prepared according to the general procedure from *o*-methyl benzaldehyde **I.13a** (0.925 mL, 8 mmol, 1.0 equiv) and **I.14** (2.88 g, 8.4 mmol, 1.05 equiv) at rt for 15 h. After purification by flash column chromatography on silica gel (EtOAc /petroleum ether = 1:20 to 1:15), the title compound **I.17a** was obtained (1.217 g, 80%).

IR (neat): 2980, 1711, 1633, 1601, 1485, 1462, 1446, 1366, 1312, 1274, 1250, 1220, 1175, 1036, 980 cm^{-1} .

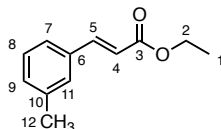
^1H NMR (400 MHz, CDCl_3) δ 8.00 (d, $J = 15.9$ Hz, 1H, H_5), 7.59 – 7.56 (m, 1H, H_{Ar}), 7.32 – 7.21 (m, 3H, H_{Ar}), 6.39 (d, $J = 15.9$ Hz, 1H, H_4), 4.30 (q, $J = 7.2$ Hz, 2H, H_2), 2.46 (s, 3H, H_{12}), 1.37 (t, $J = 7.1$ Hz, 3H, H_1).

^{13}C NMR (101 MHz, CDCl_3) δ 167.2 (s, C_3), 142.4 (s, C_5), 137.7 (s, C_{Ar}), 133.6 (s, C_{Ar}), 130.9 (s, C_{Ar}), 130.1 (s, C_{Ar}), 126.5 (s, C_{Ar}), 126.4 (s, C_{Ar}), 119.4 (s, C_4), 60.6 (s, C_2), 19.9 (s, C_{12}), 14.4 (s, C_1).

⁵⁸ Dakarapu, U. S.; Bokka, A.; Asgari, P.; Trog, G.; Hua, Y.; Nguyen, H. H.; Rahman, N.; Jeon, J. *Org Lett*, **2015**, *17*, 5792-5795.

MS *m/z* (relative intensity): 190 (M^+ , 29), 175 (9), 161 (3), 145 (100), 133 (6), 117 (51), 115 (69), 103 (4), 91 (24), 89 (7), 72 (3), 65 (11), 58 (16), 51 (5).

ethyl (*E*)-3-(*m*-tolyl)acrylate (I.17b)⁵⁵



MW: 190.0994 g.mol⁻¹

Molecular Formula: C₁₂H₁₄O₂

Prepared according to the general procedure from *m*-Tolualdehyde **I.13b** (0.943 mL, 8 mmol, 1.0 equiv) and **I.14** (2.88 g, 8.4 mmol, 1.05 equiv) at rt for 15 h. After purification by flash column chromatography on silica gel (EtOAc/petroleum ether = 1:20 to 1:15), the title compound **I.17b** was obtained (1.328 g, 87%).

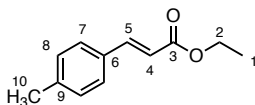
IR (neat): 2980, 1707, 1637, 1483, 1446, 1366, 1309, 1264, 1235, 1174, 1158, 1114, 1094, 1036, 981, 938 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.68 (d, *J* = 16.0 Hz, 1H, H₅), 7.34 – 7.18 (m, 4H, H_{Ar}), 6.43 (d, *J* = 16.0 Hz, 1H, H₄), 4.29 (q, *J* = 7.1 Hz, 2H, H₂), 2.39 (s, 3H, H₁₂), 1.36 (t, *J* = 7.1 Hz, 3H, H₁).

¹³C NMR (101 MHz, CDCl₃) δ 167.2 (s, C₃), 144.9 (s, C₅), 138.7 (s, C_{Ar}), 134.5 (s, C_{Ar}), 131.2 (s, C_{Ar}), 128.9 (s, C_{Ar}), 128.8 (s, C_{Ar}), 125.4 (s, C_{Ar}), 118.2 (s, C₄), 60.6 (s, C₂), 21.5 (s, C₁₂), 14.5 (s, C₁).

MS *m/z* (relative intensity): 190 (M^+ , 41), 175 (5), 161 (10), 145 (100), 131 (10), 117 (33), 115 (44), 102 (4), 91 (20), 65 (11), 51 (4).

ethyl (*E*)-3-(*p*-tolyl)acrylate (I.17c)⁵⁵



MW: 190.0994 g.mol⁻¹

Molecular Formula: C₁₂H₁₄O₂

Prepared according to the general procedure from *p*-Tolualdehyde **I.13c** (0.925 mL, 8 mmol, 1.0 equiv) and **I.14** (2.88 g, 8.4 mmol, 1.05 equiv) at rt for 15 h. After purification by flash column chromatography on silica gel (EtOAc/petroleum ether = 1:20 to 1:15), the title compound **I.17c** was obtained (1.413 g, 93%).

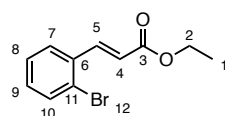
IR (neat): 1709, 1633, 1389, 1311, 1219, 1035, 980, 763 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.66 (d, *J* = 16.0 Hz, 1H, H₅), 7.42 (d, *J* = 8.1 Hz, 2H, H₇), 7.18 (d, *J* = 8.0 Hz, 2H, H₈), 6.39 (d, *J* = 16.0 Hz, 1H, H₄), 4.26 (q, *J* = 7.1 Hz, 2H, H₂), 2.37 (s, 3H, H₁₀), 1.33 (t, *J* = 7.1 Hz, 3H, H₁).

¹³C NMR (101 MHz, CDCl₃) δ 167.3 (s, C₃), 144.7 (s, C₅), 140.7 (s, C₉), 131.8 (s, C₆), 129.7 (s, 2C, C₈), 128.1 (s, 2C, C₇), 117.3 (s, C₂), 60.5 (s, C₂), 21.6 (s, C₁₀), 14.4 (s, C₁).

MS *m/z* (relative intensity): 190 (M⁺, 15), 175 (6), 145 (100), 133 (7), 115 (86), 103 (4.5), 91 (28), 77 (4), 65 (14), 51 (7).

ethyl (*E*)-3-(2-bromophenyl)acrylate (*E*)-**I.17d**⁵⁹



MW: 253.9942 g.mol⁻¹

Molecular Formula: C₁₁H₁₁BrO₂

Prepared according to the general procedure from *o*-bromobenzaldehyde **I.13d** (0.996 mL, 8 mmol, 1.0 equiv) and **I.14** (2.88 g, 8.4 mmol, 1.05 equiv) at rt for 15 h. After purification by flash column chromatography on silica gel (EtOAc/petroleum ether = 1:20 to 1:15), the mixture compound (*E*)-**I.17d** and (*Z*)-**I.17d'** were obtained (1.930 g, 95%).

IR (neat): 2981, 1711, 1636, 1466, 1439, 1366, 1314, 1283, 1267, 1244, 1202, 1177, 1027, 977 cm⁻¹.

¹H NMR of the major product I.17d (400 MHz, CDCl₃) δ 8.05 (d, *J* = 15.9 Hz, 1H, H₅), 7.60 (ddd, *J* = 7.8, 3.6, 1.5 Hz, 2H, H_{Ar}), 7.32 (t, *J* = 7.6 Hz, 1H, H_{Ar}), 7.22 (td, *J* = 7.7, 1.7

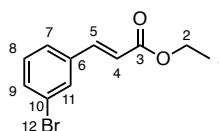
⁵⁹ Zhang, H.; Huang, X. *Adv. Synth. Catal.* **2016**, 358, 3736-3742.

Hz, 1H, H_{Ar}), 6.39 (d, *J* = 15.9 Hz, 1H, H₄), 4.28 (q, *J* = 7.1 Hz, 2H, H₂), 1.35 (t, *J* = 7.1 Hz, 3H, H₁).

¹³C NMR of the major product I.17d (101 MHz, CDCl₃) δ 166.5 (s, C₃), 143.1 (s, C₅), 134.7 (s, C₆), 133.6 (s, C_{Ar}), 131.3 (s, C_{Ar}), 127.9 (s, C_{Ar}), 127.8 (s, C_{Ar}), 125.4 (s, C₁₁), 121.3 (s, C₄), 60.8 (s, C₂), 14.4 (s, C₁).

MS *m/z* (relative intensity): 256 (M⁺, 7), 254 (7), 209 (17), 181 (7), 175 (36), 147 (100), 130 (7), 102 (45), 91 (11), 75 (18), 63 (3), 51 (18).

ethyl (*E*)-3-(3-bromophenyl)acrylate (I.17e)⁶⁰



MW: 253.9942 g.mol⁻¹

Molecular Formula: C₁₁H₁₁BrO₂

Prepared according to the general procedure from *m*-bromobenzaldehyde **I.13e** (0.933 mL, 8 mmol, 1.0 equiv) and **I.14** (2.88 g, 8.4 mmol, 1.05 equiv) at rt for 15 h. After purification by flash column chromatography on silica gel (EtOAc/petroleum ether = 1:20 to 1:15), the compound **I.17e** was obtained (1.890 g, 93%).

IR (neat): 2980, 1710, 1639, 1592, 1562, 1475, 1445, 1418, 1392, 1366, 1312, 1270, 1197, 1177, 1093, 1073, 1037, 980 cm⁻¹.

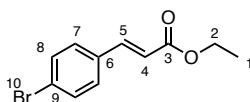
¹H NMR (400 MHz, CDCl₃) δ 7.63 (s, 1H, H₁₁), 7.57 (d, *J* = 16.0 Hz, 1H, H₅), 7.46 (d, *J* = 8.0 Hz, 1H, H₇ or H₉), 7.40 (d, *J* = 7.8 Hz, 1H, H₇ or H₉), 7.22 (t, *J* = 7.9 Hz, 1H, H₈), 6.40 (d, *J* = 16.0 Hz, 1H, H₄), 4.25 (q, *J* = 7.1 Hz, 2H, H₂), 1.32 (t, *J* = 7.1 Hz, 3H, H₁).

¹³C NMR (100 MHz, CDCl₃) δ 166.5 (s, C₃), 142.8 (s, C₅), 136.6 (s, C₆ or C₁₀), 133.0 (s, C₇ or C₉), 130.8 (s, C₁₁), 130.4 (s, C₈), 126.7 (s, C₇ or C₉), 123.1 (s, C₆ or C₁₀), 119.8 (s, C₄), 60.7 (s, C₂), 14.4 (s, C₁).

MS *m/z* (relative intensity): 256 (M⁺, 37), 254 (37), 228 (23), 226 (23), 211 (69), 209 (73), 183 (18), 181 (17), 157 (5), 147 (13), 130 (26), 129 (25), 102 (100), 91 (8), 75 (24), 63 (6), 51 (33).

⁶⁰ Fontán, N.; García-Domínguez, P.; Álvarez, R.; de Lera, Á. R. *Bioorg. Med. Chem.* **2013**, *21*, 2056-2067.

ethyl (*E*)-3-(4-bromophenyl)acrylate (I.17f**)⁶¹**



MW: 253.9942 g.mol⁻¹

Molecular Formula: C₁₁H₁₁BrO₂

Prepared according to the general procedure from *p*-bromobenzaldehyde **I.13f** (1.480 g, 8 mmol, 1.0 equiv) and **I.14** (2.88 g, 8.4 mmol, 1.05 equiv) at rt for 15 h. After purification by flash column chromatography on silica gel (EtOAc/petroleum ether = 1:20 to 1:15), the compound **I.17f** was obtained (1.930 g, 95%).

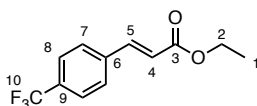
IR (neat): 1708, 1636, 1488, 1308, 1269, 1166, 1072, 1036, 817 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.61 (d, *J* = 16.0 Hz, 1H, H₅), 7.51 (d, *J* = 8.5 Hz, 2H, H₈), 7.38 (d, *J* = 8.4 Hz, 2H, H₇), 6.42 (d, *J* = 16.0 Hz, 1H, H₄), 4.26 (q, *J* = 7.1 Hz, 2H, H₂), 1.33 (t, *J* = 7.1 Hz, 3H, H₁).

¹³C NMR (100 MHz, CDCl₃) δ 167.0 (s, C₃), 139.7 (s, C₅), 137.2 (s, C₆), 130.9 (s, 2C, C₈), 128.5 (s, 2C, C₇), 128.2 (s, C₉), 117.2 (s, C₄), 60.6 (s, C₂), 14.5 (s, C₁).

MS *m/z* (relative intensity): 256 (M⁺, 19), 254 (19), 226 (13), 209 (43), 182 (11), 157 (4), 147 (6), 130 (20), 102 (100), 91 (6), 75 (28), 63 (6), 51 (30).

ethyl (*E*)-3-(4-(trifluoromethyl)phenyl)acrylate (I.17g**)⁶²**



MW: 244.0711 g.mol⁻¹

Molecular Formula: C₁₂H₁₁F₃O₂

Prepared according to the general procedure from *p*-trifluoromethylbenzaldehyde **I.13g** (1.093 mL, 8 mmol, 1.0 equiv) and **I.14** (2.88 g, 8.4 mmol, 1.05 equiv) at rt for 15 h. After purification by flash column chromatography on silica gel (EtOAc/petroleum ether = 1:20 to 1:15), the compound **I.17g** was obtained (1.796 g, 92%).

⁶¹ Felpin, F.-X.; Miqueu, K.; Sotiropoulos, J.-M.; Fouquet, E.; Ibarguren, O.; Laudien, J. *Chem. Eur. J.* **2010**, *16*, 5191-5204.

⁶² Su, Y.-H.; Wu, Z.; Tian, S.-K. *Chem. Commun.* **2013**, *49*, 6528-6530

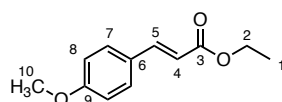
IR (neat): 1714, 1641, 1322, 1284, 1167, 1125, 1112, 1067, 1038, 1016 cm^{-1} .

^1H NMR (400 MHz, CDCl_3) δ 7.69 (d, $J = 16.0$ Hz, 1H, H_5), 7.67 – 7.60 (m, 4H, H_{Ar}), 6.50 (d, $J = 16.0$ Hz, 1H, H_4), 4.28 (q, $J = 7.1$ Hz, 2H, H_2), 1.34 (t, $J = 7.1$ Hz, 3H, H_1).

^{13}C NMR (100 MHz, CDCl_3) δ 166.5 (s, C_3), 142.8 (s, C_5), 138.0 (s, C_6), 131.8 (d, $J = 32.9$ Hz, C_9), 128.3 (s, 2C, C_7), 126.0 (q, $J = 3.9$ Hz, 2C, C_8), 124.0 (q, $J = 272.1$ Hz, C_{10}), 121.0 (s, C_{Ar}), 60.9 (s, C_2), 14.4 (s, C_1).

MS m/z (relative intensity): 244 (M^+ , 24), 225 (7), 216 (25), 199 (100), 171 (38), 159 (2), 151 (46), 131 (8), 120 (4), 102 (14), 95 (5), 75 (8), 63 (2), 51 (5).

ethyl (*E*)-3-(4-methoxyphenyl)acrylate (I.17h**)**⁵⁶



MW: 206.0943 $\text{g}\cdot\text{mol}^{-1}$

Molecular Formula: $\text{C}_{12}\text{H}_{14}\text{O}_3$

Prepared according to the general procedure from *p*-methoxybenzaldehyde **I.13h** (0.972 mL, 8 mmol, 1.0 equiv) and **I.14** (2.88 g, 8.4 mmol, 1.05 equiv) at rt for 15 h. After purification by flash column chromatography on silica gel (EtOAc/petroleum ether = 1:20 to 1:15), the compound **I.17h** was obtained (1.533 g, 93%).

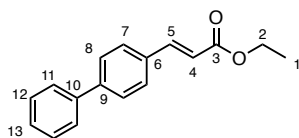
IR (neat): 2980, 1706, 1637, 1599, 1580, 1488, 1455, 1433, 1392, 1366, 1308, 1292, 1259, 1247, 1161, 1036, 980 cm^{-1} .

^1H NMR (400 MHz, CDCl_3) δ 7.63 (d, $J = 15.9$ Hz, 1H), 7.47 – 7.45 (m, 2H), 6.91 – 6.88 (m, 2H), 6.30 (d, $J = 15.9$ Hz, 1H), 4.24 (q, $J = 7.1$ Hz, 2H), 3.82 (s, 3H), 1.32 (t, $J = 7.1$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3) δ 167.4 (s, C_3), 161.4 (s, C_9), 144.3 (s, C_5), 129.8 (s, 2C, C_7), 127.3 (s, C_6), 115.8 (s, C_4), 114.4 (s, 2C, C_8), 60.4 (s, C_2), 55.4 (s, C_{10}), 14.5 (s, C_1).

MS m/z (relative intensity): 206 (M^+ , 61), 191 (2), 161 (100), 147 (7), 134 (81), 118 (19), 103 (10), 89 (24), 77 (23), 63 (14), 51 (8).

ethyl (*E*)-3-([1,1'-biphenyl]-4-yl)acrylate (I.17i**)**⁵⁹



MW: 252.1150 g.mol⁻¹

Molecular Formula: C₁₇H₁₆O₂

Prepared according to the general procedure from 4-Biphenylcarboxaldehyde **I.17i** (1.458 g, 8 mmol, 1.0 equiv) and **I.14** (2.88 g, 8.4 mmol, 1.05 equiv) at rt for 15 h. After purification by flash column chromatography on silica gel (EtOAc/petroleum ether = 1:20 to 1:15), the compound **I.17i** was obtained (1.311 g, 65%).

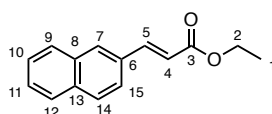
IR (neat): 1759, 1653, 1344, 1326, 1220, 1185, 1031 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.73 (d, *J* = 15.9 Hz, 1H, H₅), 7.64 – 7.59 (m, 6H, H_{Ar}), 7.46 (t, *J* = 7.5 Hz, 2H, H_{Ar}), 7.39 – 7.36 (m, 1H, H_{Ar}), 6.48 (d, *J* = 15.9 Hz, 1H, H₄), 4.28 (q, *J* = 7.1 Hz, 2H, H₂), 1.35 (t, *J* = 7.1 Hz, 3H, H₁).

¹³C NMR (100 MHz, CDCl₃) δ 167.2 (s, C₃), 144.3 (s, C₁), 143.1 (s, C₅), 140.3 (s, C_{Ar}), 133.6 (s, C_{Ar}), 129.0 (s, 2C, C_{Ar}), 128.7 (s, 2C, C_{Ar}), 128.0 (s, C_{Ar}), 127.7 (s, 2C, C_{Ar}), 127.2 (s, 2C, C_{Ar}), 118.3 (s, C₄), 60.7 (s, C₂), 14.5 (s, C₁).

MS *m/z* (relative intensity): 252 (M⁺, 100), 234 (2), 224 (17), 191 (3), 178 (59), 165 (34), 152 (20), 127 (2), 104 (11), 89 (27), 76 (16), 63 (4), 51 (4).

ethyl (*E*)-3-(naphthalen-2-yl)acrylate (I.17j**)**⁵⁹



MW: 226.0994 g.mol⁻¹

Molecular Formula: C₁₅H₁₄O₂

Prepared according to the general procedure from 2-Naphthaldehyde **I.13j** (1.249 g, 8 mmol, 1.0 equiv) and **I.14** (2.88 g, 8.4 mmol, 1.05 equiv) at rt for 15 h. After purification by flash column chromatography on silica gel (EtOAc/petroleum ether = 1:20 to 1:15), the compound **I.17j** was obtained (1.266 g, 70%).

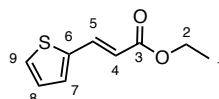
IR (neat): 2980, 1707, 1634, 1392, 1368, 1308, 1293, 1259, 1240, 1221, 1199, 1172, 1125, 1096, 1039, 987, 967 cm^{-1} .

^1H NMR (400 MHz, CDCl_3) δ 7.95 – 7.78 (m, 5H, H_{Ar} and H_5), 7.67 (dd, J = 8.8, 1.6 Hz, 1H, H_{Ar}), 7.56 – 7.47 (m, 2H, H_{Ar}), 6.56 (d, J = 16.2 Hz, 1H, H_4), 4.30 (q, J = 7.2 Hz, 2H, H_2), 1.37 (t, J = 7.1 Hz, 3H, H_1).

^{13}C NMR (100 MHz, CDCl_3) δ 167.2 (s, C_3), 144.8 (s, C_5), 134.3 (s, C_{Ar}), 133.4 (s, C_{Ar}), 132.1 (s, C_{Ar}), 130.0 (s, C_{Ar}), 128.8 (s, C_{Ar}), 128.7 (s, C_{Ar}), 127.9 (s, C_{Ar}), 127.3 (s, C_{Ar}), 126.8 (s, C_{Ar}), 123.6 (s, C_{Ar}), 118.5 (s, C_4), 60.7 (s, C_2), 14.5 (s, C_1).

MS m/z (relative intensity): 226 (M^+ , 100), 198 (15), 181 (98), 152 (65), 141 (6), 127 (13), 101 (3), 91 (9), 76 (38), 69 (3), 63 (8), 51 (3).

ethyl (*E*)-3-(thiophen-2-yl)acrylate (I.17K)⁵⁵



MW: 182.0402 $\text{g}\cdot\text{mol}^{-1}$

Molecular Formula: $\text{C}_9\text{H}_{10}\text{O}_2\text{S}$

Prepared according to the general procedure from 2-thenaldehyde **I.13k** (0.748 mL, 8 mmol, 1.0 equiv) and **I.14** (2.88 g, 8.4 mmol, 1.05 equiv) at rt for 15 h. After purification by flash column chromatography on silica gel (EtOAc/petroleum ether = 1:20 to 1:15), the compound **I.17k** was obtained (1.310 g, 90%).

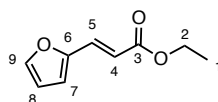
IR (neat): 1703, 1625, 1369, 1304, 1261, 1229, 1202, 1159, 1041, 969, 856, 704 cm^{-1} .

^1H NMR (400 MHz, CDCl_3) δ 7.78 (d, J = 15.7 Hz, 1H, H_5), 7.36 (d, J = 5.1 Hz, 1H, H_9), 7.24 (d, J = 3.2 Hz, 1H, H_7), 7.04 (dd, J = 5.1, 3.6 Hz, 1H, H_8), 6.24 (d, J = 15.7 Hz, 1H, H_4), 4.24 (q, J = 7.1 Hz, 2H, H_2), 1.32 (t, J = 7.1 Hz, 3H, H_1).

^{13}C NMR (100 MHz, CDCl_3) δ 167.0 (s, C_3), 139.7 (s, C_6), 137.2 (s, C_5), 130.9 (s, C_7), 128.5 (s, C_9), 128.2 (s, C_8), 117.2 (s, C_4), 60.6 (s, C_2), 14.5 (s, C_1).

MS m/z (relative intensity): 182 (M^+ , 30), 167 (2), 154 (9), 137 (100), 121 (7), 109 (42), 97 (5), 82 (3), 65 (29), 51 (6).

ethyl (*E*)-3-(furan-2-yl)acrylate (I.17I)⁵⁵



MW: 166.0630 g.mol⁻¹

Molecular Formula: C₉H₁₀O₃

Prepared according to the general procedure from Furfural **I.13I** (0.663 mL, 8 mmol, 1.0 equiv) and **I.14** (2.88 g, 8.4 mmol, 1.05 equiv) at rt for 15 h. After purification by flash column chromatography on silica gel (EtOAc/petroleum ether = 1:20 to 1:15), the compound **I.17I** was obtained (1.156 g, 87%).

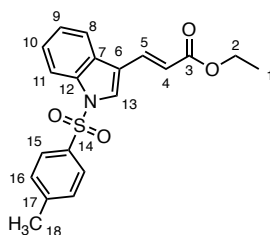
IR (neat): 1703, 1638, 1303, 1259, 1208, 1160, 1017, 972, 748 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.48 – 7.47 (m, 1H, H₉), 7.42 (d, *J* = 15.8 Hz, 1H, H₅), 6.59 (d, *J* = 3.2 Hz, 1H, H₇), 6.47 – 6.45 (m, 1H, H₈), 6.31 (d, *J* = 15.8 Hz, 1H, H₄), 4.24 (q, *J* = 7.1 Hz, 2H, H₂), 1.31 (t, *J* = 7.1 Hz, 3H, H₁).

¹³C NMR (100 MHz, CDCl₃) δ 167.2 (s, C₃), 151.1 (s, C₉), 144.8 (s, C₆), 131.1 (s, C₅), 116.1 (s, C₄), 114.7 (s, C₇), 112.4 (s, C₈), 60.6 (s, C₂), 14.4 (s, C₁).

MS *m/z* (relative intensity): 166 (M⁺, 28), 138 (29), 121 (100), 110 (13), 94 (38), 82 (7), 65 (47), 53 (5).

ethyl (*E*)-3-(1-tosyl-1*H*-indol-3-yl)acrylate (**I.17m**)⁶³



MW: 369.1035 g.mol⁻¹

Molecular Formula: C₂₀H₁₉NO₄S

Prepared according to the general procedure from 1-tosyl-1*H*-indole-3-carbaldehyde **I.13m** (2.392 g, 8 mmol, 1.0 equiv) and **I.14** (2.88 g, 8.4 mmol, 1.05 equiv) at rt for 15 h. After purification by flash column chromatography on silica gel (EtOAc/petroleum ether = 1:20 to 1:15), the compound **I.17m** was obtained (2.805 g, 95%).

⁶³ Kinsman, A. C.; Kerr, M. A. *J. Am. Chem. Soc.* **2003**, 125, 14120-14125.

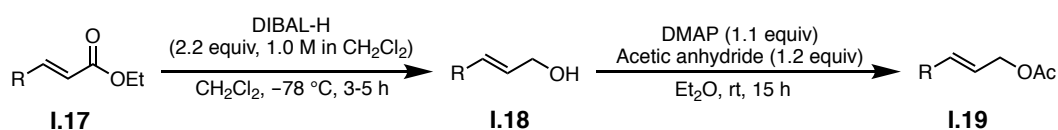
IR (neat): 1707, 1637, 1447, 1371, 1334, 1313, 1291, 1268, 1241, 1175, 1125, 1103, 1087, 1036, 977 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 8.00 (d, *J* = 8.3 Hz, 1H, H₅), 7.84 (s, 1H, H₁₃), 7.80 – 7.76 (m, 4H, H_{Ar}), 7.39 – 7.29 (m, 2H, H_{Ar}), 7.24 (d, *J* = 8.1 Hz, 2H, H_{Ar}), 6.51 (d, *J* = 16.1 Hz, 1H, H₄), 4.27 (q, *J* = 7.1 Hz, 2H, H₂), 2.34 (s, 3H, H₁₈), 1.34 (t, *J* = 7.1 Hz, 3H, H₁).

¹³C NMR (100 MHz, CDCl₃) δ 167.2 (s, C₃), 145.7 (s, C_{Ar}), 135.7 (s, 2C, C_{Ar}), 134.8 (s, C_{Ar}), 130.2 (s, 2C, C_{Ar}), 128.5 (s, C_{Ar}), 128.2 (s, C_{Ar}), 127.1 (s, 2C, C_{Ar}), 125.6 (s, C_{Ar}), 124.2 (s, C_{Ar}), 120.8 (s, C_{Ar}), 118.5 (s, C₄), 118.3 (s, C_{Ar}), 113.9 (s, C₅), 60.7 (s, C₂), 21.7 (s, C₁₈), 14.5 (s, C₁).

MS *m/z* (relative intensity): 369 (M⁺, 100), 324 (11), 297 (6), 214 (36), 186 (49), 169 (15), 158 (50), 155 (26), 140 (23), 130 (20), 114 (18), 91 (74), 65 (17), 55 (3)

The general procedure of preparation allylic alcohols **I.18** and allyl acetates **I.19h-t**:

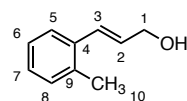


To a stirred solution of the α,β-unsaturated ester (*E*)-**I.17** (5.0 mmol, 1.0 equiv) in anhydrous CH₂Cl₂ (0.2 M) at -78 °C was added DIBAL-H (11 mL, 1.0 M in CH₂Cl₂, 2.2 equiv) drop-wise. The reaction was stirred for 3 h at -78 °C, and quenched with 10% aqueous NaOH. The resulting mixture was allowed to warm to rt and stirred for 1 h. The layers were separated and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give the pure allylic alcohols (*E*)-**I.18** which was used for next step directly without further purification.

Acetic anhydride (1.2 equiv) was added to a solution of allylic alcohol (*E*)-**I.18** (1.0 equiv) and 4-dimethylaminopyridine (1.1 equiv) in Et₂O (0.2 M), the reaction mixture was stirred at rt. After 15 h, the reaction mixture was washed with saturated aqueous

NaHCO₃ solution (3 × 10 mL) and HCl (1 M) solution (3 × 10 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give the allyl acetates (*E*)-**1.19**.

(*E*)-3-(*o*-tolyl)prop-2-en-1-ol (I.18a)⁶⁴



MW: 148.0888 g.mol⁻¹

Molecular Formula: C₁₀H₁₂O

Prepared according to the general procedure from **1.17a** (0.950 g, 5 mmol, 1.0 equiv) and DIBAL-H (11 mL, 11 mmol, 2.2 equiv) at rt for 15 h. The title compound **1.18a** was obtained (0.689 g, 93%).

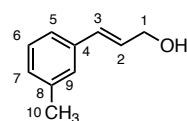
IR (neat): 3373, 1722, 1678, 1486, 1460, 1110, 1084, 1033, 968 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.46 – 7.44 (m, 1H, H_{Ar}), 7.19 – 7.16 (m, 3H, H_{Ar}), 6.84 (dt, *J* = 15.8, 1.6 Hz, 1H, H₃), 6.26 (dt, *J* = 15.8, 5.8 Hz, 1H, H₂), 4.35 (dd, *J* = 5.8, 1.5 Hz, 2H, H₁), 2.36 (s, 3H, H₁₀), 2.22 (s_{br}, 1H, OH).

¹³C NMR (100 MHz, CDCl₃) δ 135.9 (s, C₄ or C₉), 135.6 (s, C₄ or C₉), 130.4 (s, C₃), 130.0 (s, C_{Ar}), 129.1 (s, C₂), 127.7 (s, C_{Ar}), 126.2 (s, C_{Ar}), 125.8 (s, C_{Ar}), 64.0 (s, C₁), 19.9 (s, C₁₀).

MS *m/z* (relative intensity): 148 (M⁺, 25), 133 (14), 130 (100), 115 (57), 105 (52), 104 (37), 91 (59), 89 (8), 79 (12), 77 (20), 65 (15), 55 (24), 51 (13).

(*E*)-3-(*m*-tolyl)prop-2-en-1-ol (I.18b)⁶⁵



MW: 148.0888 g.mol⁻¹

Molecular Formula: C₁₀H₁₂O

Prepared according to the general procedure from **1.17b** (0.950 g, 5 mmol, 1.0 equiv) and DIBAL-H (11 mL, 11 mmol, 2.2 equiv) at rt for 15 h. The title compound **1.18b** was obtained (0.696 g, 94%).

⁶⁴ Peng, D.-J.; Zhang, M.-T.; Huang, Z. *Chem. Eur. J.* **2015**, *21*, 14737-14741.

⁶⁵ Shintai, R.; Takatsu, K.; Takeda, M.; Hayashi, T. *Angew. Chem., Int. Ed.* **2011**, *50*, 8656-8659

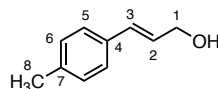
IR (neat): 3367, 2920, 1722, 1673, 1605, 1487, 1453, 1379, 1310, 1277, 1160, 1085, 1040, 999, 968, 908 cm^{-1} .

^1H NMR (400 MHz, CDCl_3) δ 7.24 – 7.19 (m, 3H, H_{Ar}), 7.08 – 7.07 (m, 1H, H_{Ar}), 6.59 (dt, $J = 16.0, 1.5$ Hz, 1H, H_3), 6.36 (dt, $J = 15.9, 5.7$ Hz, 1H, H_2), 4.32 (dd, $J = 5.8, 1.5$ Hz, 2H, H_1), 2.35 (s, 3H, H_{10}), 1.70 (s_{br} , 1H, OH).

^{13}C NMR (100 MHz, CDCl_3) δ 138.3 (s, C_4 or C_8), 136.7 (s, C_4 or C_8), 131.4 (s, C_3), 128.6 (s, 2C, C_{Ar}), 128.4 (s, C_{Ar}), 127.3 (s, C_2), 123.7 (s, C_{Ar}), 63.9 (s, C_1), 21.5 (s, C_{10}).

MS m/z (relative intensity): 148 (M^+ , 93), 133 (17), 129 (17), 119 (55), 115 (56), 105 (95), 91 (100), 89 (10), 77 (30), 65 (23), 55 (36), 51 (18).

(*E*)-3-(*p*-tolyl)prop-2-en-1-ol (I.18c)⁶⁶



MW: 148.0888 $\text{g}\cdot\text{mol}^{-1}$

Molecular Formula: $\text{C}_{10}\text{H}_{12}\text{O}$

Prepared according to the general procedure from **I.17c** (0.950 g, 5 mmol, 1.0 equiv) and DIBAL-H (11 mL, 11 mmol, 2.2 equiv) at rt for 15 h. The title compound **I.18c** was obtained (0.711 g, 96%).

IR (neat): 3302, 1679, 1514, 1484, 1460, 1261, 1234, 1110, 1084, 1007, 966 cm^{-1} .

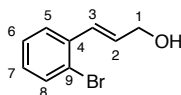
^1H NMR (400 MHz, CDCl_3) δ 7.47 – 7.43 (m, 1H, H_{Ar}), 7.20 – 7.13 (m, 3H, H_{Ar}), 6.84 (dt, $J = 15.8, 1.6$ Hz, 1H, H_3), 6.26 (dt, $J = 15.6, 5.7$ Hz, 1H, H_2), 4.35 (dd, $J = 5.7, 1.6$ Hz, 2H, H_1), 2.36 (s, 3H, H_8), 1.64 (s_{br} , 1H, OH)

^{13}C NMR (100 MHz, CDCl_3) δ 135.9 (s, C_9), 135.6 (s, C_6), 130.4 (s, C_2), 130.0 (s, C_{Ar}), 129.1 (s, C_3), 127.7 (s, C_{Ar}), 126.3 (s, C_{Ar}), 125.9 (s, C_{Ar}), 64.1 (s, C_1), 19.9 (s, C_8).

MS m/z (relative intensity): 148 (M^+ , 20), 130 (100), 115 (62), 105 (61), 91 (66), 77 (25), 65 (18), 55 (28).

(*E*)-3-(2-bromophenyl)prop-2-en-1-ol (I.18d)⁶³

⁶⁶ Kim, E.; Koh, M.; Lim, B. J.; Park, S. B.; *J. Am. Chem. Soc.* **2011**, *133*, 6642-6649.



MW: 211.9837 g.mol⁻¹

Molecular Formula: C₉H₉BrO

Prepared according to the general procedure from **I.17d** (1.270 g, 5 mmol, 1.0 equiv) and DIBAL-H (11 mL, 11 mmol, 2.2 equiv) at rt for 15 h. The title compound **I.18d** was obtained (1.007 g, 97%).

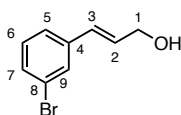
IR (neat): 3002, 1466, 1436, 1117, 1088, 1021, 966 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.42 (ddd, *J* = 14.3, 7.9, 1.5 Hz, 2H, H_{Ar}), 7.15 (t, *J* = 7.5 Hz, 1H, H_{Ar}), 6.99 (td, *J* = 7.6, 1.7 Hz, 1H, H_{Ar}), 6.85 (d, *J* = 15.8 Hz, 1H, H₃), 6.20 (dt, *J* = 15.9, 5.6 Hz, 1H, H₂), 4.25 (d, *J* = 5.1 Hz, 2H, H₁), 1.97 (s_{br}, 1H, OH).

¹³C NMR (100 MHz, CDCl₃) δ 136.7 (s, C₄), 133.1 (s, C₂), 131.8 (s, C₃), 129.7 (s, C_{Ar}), 129.0 (s, C_{Ar}), 127.6 (s, C_{Ar}), 127.2 (s, C_{Ar}), 123.7 (s, C_{Ar}), 63.6 (s, C₁)

MS *m/z* (relative intensity): 214 (M⁺, 6), 212 (6), 171 (9), 169 (10), 158 (5), 156 (5), 133 (100), 115 (25), 105 (42), 91 (36), 77 (30), 66 (11), 55 (18), 51 (23).

(E)-3-(3-bromophenyl)prop-2-en-1-ol (I.18e)⁶³



MW: 211.9837 g.mol⁻¹

Molecular Formula: C₉H₉BrO

Prepared according to the general procedure from **I.17d** (1.270 g, 5 mmol, 1.0 equiv) and DIBAL-H (11 mL, 11 mmol, 2.2 equiv) at rt for 15 h. The title compound **I.18e** was obtained (0.996 g, 95%).

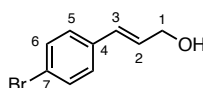
IR (neat): 3232, 2924, 1683, 1675, 1561, 1541, 1457, 1422, 1373, 1096, 995 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.54 – 7.53 (m, 1H, H_{Ar}), 7.39 – 7.36 (m, 1H, H_{Ar}), 7.31 – 7.28 (m, 1H, H_{Ar}), 7.19 (t, *J* = 7.8 Hz, 1H, H_{Ar}), 6.55 (dt, *J* = 15.9, 1.7 Hz, 1H, H₃), 6.36 (dt, *J* = 15.9, 5.4 Hz, 1H, H₂), 4.33 (dd, *J* = 5.4, 1.6 Hz, 2H, H₁), 2.05 (s_{br}, 1H, OH)

¹³C NMR (100 MHz, CDCl₃) δ 139.0 (s, C₄), 130.6 (s, C₇), 130.24 (s, C₂), 130.2 (s, C₆), 129.4 (s, 2C, C₃ and C₉), 125.2 (s, C₅), 122.9 (s, C₈), 63.4 (s, C₁).

MS m/z (relative intensity): 214 (M⁺, 53), 212 (57), 185 (11), 183 (12), 172 (58), 170 (62), 158 (16), 133 (43), 115 (66), 104 (89), 102 (44), 91 (100), 89 (22), 77 (73), 63 (28), 55 (45), 51 (52).

(E)-3-(4-bromophenyl)prop-2-en-1-ol (I.18f)⁶⁷



MW: 211.9837 g.mol⁻¹

Molecular Formula: C₉H₉BrO

Prepared according to the general procedure from **I.17f** (1.270 g, 5 mmol, 1.0 equiv) and DIBAL-H (11 mL, 11 mmol, 2.2 equiv) at rt for 15 h. The title compound **I.18f** was obtained (0.996 g, 94%).

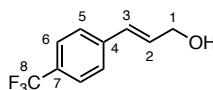
IR (neat): 3304, 1585, 1486, 1401, 1086, 1072, 1008, 971 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.43 (dd, *J* = 8.5, 1.7 Hz, 2H, H_{Ar}), 7.24 – 7.21 (m, 2H, H_{Ar}), 6.54 (dd, *J* = 15.9, 1.7 Hz, 1H, H₃), 6.37 – 6.30 (m, 1H, H₂), 4.30 (s_{app}, 2H, H₁), 1.81 (s_{br}, 1H, OH).

¹³C NMR (100 MHz, CDCl₃) δ 135.7 (s, C₄), 131.8 (s, 2C, C_{Ar}), 129.9 (s, C₃), 129.4 (s, C₂), 128.1 (s, 2C, C_{Ar}), 121.5 (s, C₇), 63.6 (s, C_{Ar}).

MS m/z (relative intensity): 214 (M⁺, 46), 212 (49), 195 (3), 183 (6), 171 (45), 156 (18), 133 (100), 115 (54), 104 (36), 91 (71), 77 (50), 66 (32), 55 (43), 51 (45).

(E)-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-ol (I.18g)⁶⁸



MW: 202.0605 g.mol⁻¹

Molecular Formula: C₁₀H₉F₃O

⁶⁷ Jobson, N. K.; Spike, R.; Crawford, A. R.; Dewar, D.; Pimlott, S. L.; Sutherland, A. *Org. Biomol. Chem.* **2008**, *6*, 2369-2376.

⁶⁸ Vyas, D. J.; Oestreich, M. *Chem. Commun.* **2010**, *46*, 568-570.

Prepared according to the general procedure from **I.17g** (1.220 g, 5 mmol, 1.0 equiv) and DIBAL-H (11 mL, 11 mmol, 2.2 equiv) at rt for 15 h. The title compound **I.18g** was obtained (0.940 g, 94%).

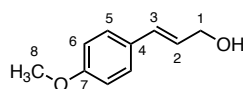
IR (neat): 3332, 1414, 1332, 1169, 1124, 1088, 1069, 1016, 974, 954, 920 cm^{-1} .

^1H NMR (400 MHz, CDCl_3) δ 7.57 (d, J = 8.1 Hz, 2H, H_{Ar}), 7.47 (d, J = 8.1 Hz, 2H, H_{Ar}), 6.67 (d, J = 15.9 Hz, 1H, H_3), 6.46 (dt, J = 15.9, 5.3 Hz, 1H, H_2), 4.37 (dd, J = 5.4, 1.8 Hz, 2H, H_1), 1.60 (s_{br} , 1H, OH)

^{13}C NMR (100 MHz, CDCl_3) δ 140.3 (s, C_4), 131.4 (s, C_2), 129.6 (d, J = 29.4 Hz, C_7), 129.4 (s, C_3), 126.7 (s, 2C, C_5), 125.68 (q, J = 3.9 Hz, 2C, C_6), 124.3 (q, J = 272.8 Hz, C_8), 63.4 (s, C_1)

MS m/z (relative intensity): 202 (M^+ , 52), 183 (16), 173 (11), 161 (9), 160 (100), 153 (13), 151 (19), 146 (17), 145 (11), 133 (55), 127 (15), 115 (29), 105 (15), 91 (48), 77 (11), 69 (4), 55 (27).

(*E*)-3-(4-methoxyphenyl)prop-2-en-1-ol (I.18h**)**⁶⁹



MW: 164.0837 $\text{g}\cdot\text{mol}^{-1}$

Molecular Formula: $\text{C}_{10}\text{H}_{12}\text{O}_2$

Prepared according to the general procedure from **I.17h** (1.030 g, 5 mmol, 1.0 equiv) and DIBAL-H (11 mL, 11 mmol, 2.2 equiv) at rt for 15 h. The title compound **I.18h** was obtained (0.763 g, 93%).

IR (neat): 3259, 1605, 1576, 1511, 1459, 1444, 1422, 1305, 1269, 1243, 1189, 1174, 1086, 1025, 1007, 970 cm^{-1} .

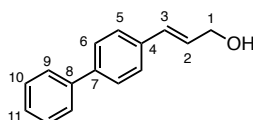
^1H NMR (400 MHz, CDCl_3) δ 7.34 – 7.31 (m, 2H, H_{Ar}), 6.88 – 6.84 (m, 2H, H_{Ar}), 6.56 (d, J = 15.9 Hz, 1H, H_3), 6.24 (dt, J = 15.9, 6.0 Hz, 1H, H_2), 4.30 (s_{app} , 2H, H_1), 3.81 (s, 3H, H_8), 1.45 (s_{br} , 1H, OH).

⁶⁹ Schmidt, B.; Hölter, F.; Kelling, A.; Schilde, U. *J. Org. Chem.* **2011**, 76, 3357-3365.

¹³C NMR (100 MHz, CDCl₃) δ 159.5 (s, C₇), 131.1 (s, C₃), 129.6 (s, C₄), 127.8 (s, 2C, C_{Ar}), 126.4 (s, C₂), 114.2 (s, 2C, C_{Ar}), 64.1 (s, C₁), 55.4 (s, C₈).

MS m/z (relative intensity): 164 (M⁺, 39), 145 (3), 135 (4), 131 (5), 121 (100), 115 (6), 108 (37), 103 (9), 91 (16), 89 (5), 77 (16), 75 (1), 65 (7), 55 (13), 51 (6).

(E)-3-([1,1'-biphenyl]-4-yl)prop-2-en-1-ol (I.18i)⁷⁰



MW: 210.1045 g.mol⁻¹

Molecular Formula: C₁₅H₁₄O

Prepared according to the general procedure from **I.17i** (1.260 g, 5 mmol, 1.0 equiv) and DIBAL-H (11 mL, 11 mmol, 2.2 equiv) at rt for 15 h. The title compound **I.18i** was obtained (0.945 g, 90%).

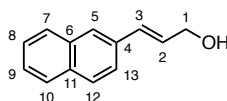
IR (neat): 3276, 1487, 1449, 1409, 1090, 1018, 1003, 966 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.62 – 7.56 (m, 4H, H_{Ar}), 7.48 – 7.42 (m, 4H, H_{Ar}), 7.37 – 7.33 (m, 1H, H_{Ar}), 6.67 (d, *J* = 16.1 Hz, 1H, H₃), 6.42 (dt, *J* = 15.8, 5.7 Hz, 1H, H₂), 4.36 (dd, *J* = 5.6, 1.5 Hz, 2H, H₁), 1.59 (s_{br}, 1H, OH).

¹³C NMR (100 MHz, CDCl₃) δ 140.8 (s, C₈), 140.6 (s, C₇), 135.8 (s, C₄), 130.9 (s, C₃), 128.9 (s, 2C, C_{Ar}), 128.7 (s, C₂), 127.5 (s, C₁₁), 127.4 (s, 2C, C_{Ar}), 127.1 (s, 2C, C_{Ar}), 127.0 (s, 2C, C_{Ar}), 63.9 (s, C₁).

MS m/z (relative intensity): 210 (M⁺, 79), 191 (8), 178 (20), 167 (100), 154 (43), 152 (20), 139 (3), 115 (10), 105 (6), 95 (4), 89 (6), 77 (9), 63 (4), 55 (9), 51 (5).

(E)-3-(naphthalen-2-yl)prop-2-en-1-ol (I.18j)⁷¹



MW: 184.0888 g.mol⁻¹

Molecular Formula: C₁₃H₁₂O

⁷⁰ Miyamura, H.; Choo, G. C. Y.; Yasukawa, T.; Yoo, W.-J.; Kobayashi, S.; *Chem. Commun.* **2013**, 49, 9917-9919.

⁷¹ Reichl, K.; Dunn, N. L.; Fastuca, N. J.; Radosevich, A. T. *J. Am. Chem. Soc.* **2015**, 137, 5292-5295

Prepared according to the general procedure from **I.17j** (1.130 g, 5 mmol, 1.0 equiv) and DIBAL-H (11 mL, 11 mmol, 2.2 equiv) at rt for 15 h. The title compound **I.18j** was obtained (0.838 g, 91%).

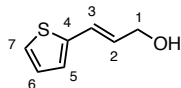
IR (neat): 3316, 1692, 1436, 1363, 1167, 1124, 1092, 1067, 1015, 963, 907 cm^{-1} .

^1H NMR (400 MHz, CDCl_3) δ 7.81 – 7.73 (m, 4H, H_{Ar}), 7.63 – 7.60 (m, 1H, H_{Ar}), 7.49 – 7.45 (m, 2H, H_{Ar}), 6.78 (d, J = 16.1 Hz, 1H, H_3), 6.49 (dt, J = 15.9, 5.8 Hz, 1H, H_2), 4.38 (d, J = 5.6 Hz, 2H, H_1), 1.75 (s_{br} , 1H, OH).

^{13}C NMR (100 MHz, CDCl_3) δ 134.2 (s, C_{Ar}), 133.7 (s, C_{Ar}), 133.1 (s, C_{Ar}), 131.3 (s, C_2), 129.0 (s, C_3), 128.4 (s, C_{Ar}), 128.1 (s, C_{Ar}), 127.8 (s, C_{Ar}), 126.6 (s, C_{Ar}), 126.4 (s, C_{Ar}), 126.0 (s, C_{Ar}), 123.7 (s, C_{Ar}), 63.9 (s, C_1).

MS m/z (relative intensity): 184 (M^+ , 79), 165 (38), 155 (41), 152 (37), 142 (100), 128 (75), 115 (25), 102 (3), 91 (4), 82 (10), 76 (12), 63 (9), 55 (12), 51 (6).

(E)-3-(thiophen-2-yl)prop-2-en-1-ol (I.18k)⁶⁷



MW: 140.0296 $\text{g}\cdot\text{mol}^{-1}$

Molecular Formula: $\text{C}_7\text{H}_8\text{OS}$

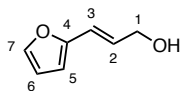
Prepared according to the general procedure from **I.17k** (0.910 g, 5 mmol, 1.0 equiv) and DIBAL-H (11 mL, 11 mmol, 2.2 equiv) at rt for 15 h. The title compound **I.18k** was obtained (0.658 g, 94%).

IR (neat): 3337, 1650, 1432, 1371, 1205, 1088, 1039, 1005, 956, 919 cm^{-1} .

^1H NMR (400 MHz, CDCl_3) δ 7.17 – 7.15 (m, 1H, H_6), 6.97 – 6.95 (m, 2H, H_7 and H_5), 6.74 (d, J = 15.3 Hz, 1H, H_3), 6.20 (dt, J = 15.7, 5.8 Hz, 1H, H_2), 4.28 (dd, J = 5.8, 1.6 Hz, 2H, H_1), 1.67 (s_{br} , 1H, OH).

^{13}C NMR (100 MHz, CDCl_3) δ 141.9 (s, C_4), 128.2 (s, C_2), 127.5 (s, C_5 or C_7), 126.0 (s, C_5 or C_7), 124.54 (s, C_6), 124.48 (s, C_3), 63.5 (s, C_1)

(E)-3-(furan-2-yl)prop-2-en-1-ol (I.18l)⁷²



MW: 124.0524 g.mol⁻¹

Molecular Formula: C₇H₈O₂

Prepared according to the general procedure from **I.17l** (0.772 g, 5 mmol, 1.0 equiv) and DIBAL-H (11 mL, 11 mmol, 2.2 equiv) at rt for 15 h. The title compound **I.18l** was obtained (0.577 g, 93%).

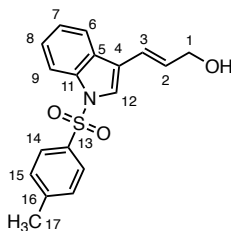
IR (neat): 3338, 1653, 1629, 1365, 1150, 1010, 962 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.35 (d, *J* = 1.8 Hz, 1H, H₇), 6.44 (dt, *J* = 15.8, 1.5 Hz, 1H, H₃), 6.37 (dd, *J* = 3.3, 1.8 Hz, 1H, H₆), 6.29 (dt, *J* = 15.8, 5.6 Hz, 1H, H₂), 6.24 (d, *J* = 3.3 Hz, 1H, H₅), 4.29 (dd, *J* = 5.5, 1.5 Hz, 2H, H₁), 1.64 (s_{br}, 1H, OH).

¹³C NMR (100 MHz, CDCl₃) δ 152.5 (s, C₄), 142.2 (s, C₇), 127.3 (s, C₂), 119.4 (s, C₃), 111.4 (s, C₆), 108.1 (s, C₅), 63.4 (s, C₁).

MS *m/z* (relative intensity): 124 (M⁺, 89), 107 (6), 95 (34), 81 (73), 77 (33), 68 (100), 62 (5), 53 (26), 51 (18).

(E)-3-(1-tosyl-1*H*-indol-3-yl)prop-2-en-1-ol (I.18m)⁷³



MW: 327.0929 g.mol⁻¹

Molecular Formula: C₁₈H₁₇NO₃S

Prepared according to the general procedure from **I.17m** (1.846 g, 5 mmol, 1.0 equiv) and DIBAL-H (11 mL, 11 mmol, 2.2 equiv) at rt for 15 h. The title compound **I.18m** was obtained (1.472 g, 90%).

⁷² Bober, Ashley.; Proto, Justin. T.; Brummond, K. M. *Org. Lett.* **2017**, *19*, 1500-1503

⁷³ Kinsman, A. C.; Beutner, G. L.; Grubbs, R. H. *J. Org. Chem.* **2006**, *71*, 7813-7825.

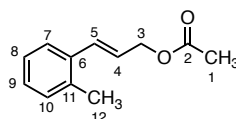
IR (neat): 1597, 1446, 1369, 1188, 1173, 1124, 1092, 977 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 8.01 (d, *J* = 8.3 Hz, 1H, H₆), 7.79 – 7.73 (m, 3H, H_{Ar}), 7.61 (s, 1H, H₁₂), 7.37 – 7.26 (m, 2H, H_{Ar}), 7.23 (d, *J* = 8.5 Hz, 2H, H_{Ar}), 6.71 (d, *J* = 16.1 Hz, 1H, H₃), 6.46 (dt, *J* = 16.1, 5.7 Hz, 1H, H₂), 4.37 (dd, *J* = 5.8, 1.7 Hz, 2H, H₁), 2.35 (s, 3H, H₁₇), 1.64 (s_{br}, 1H, OH).

¹³C NMR (100 MHz, CDCl₃) δ 145.2 (s, C_{Ar}), 135.6 (s, C_{Ar}), 135.2 (s, C_{Ar}), 130.0 (s, 2C, C_{Ar}), 129.9 (s, C₂), 129.1 (s, C_{Ar}), 127.0 (s, 2C, C_{Ar}), 125.1 (s, C_{Ar}), 124.1 (s, C₁₂), 123.7 (s, C_{Ar}), 121.9 (s, C₃), 120.4 (s, C_{Ar}), 120.1 (s, C_{Ar}), 113.9 (s, C₆), 64.1 (s, C₁), 21.7 (s, C₁₇).

MS *m/z* (relative intensity): 327 (M⁺, 70), 311 (5), 271 (39), 172 (20), 154 (54), 143 (53), 127 (19), 115 (37), 101 (5), 91 (74), 77 (11), 65 (26), 55 (100), 51 (7).

(*E*)-3-(*o*-Tolyl)allyl acetate (I.19h)⁷⁴



MW: 190.0994 g.mol⁻¹

Molecular Formula: C₁₂H₁₄O₂

Prepared according to the general procedure from the allylic alcohol **I.18a** (4 mmol, 1.0 equiv), acetic anhydride (0.453 mL, 4.8 mmol, 1.2 equiv) and DMAP (0.538 mg, 4.4 mmol, 1.1 equiv). Compound **I.19h** (0.715 g, 94%) was isolated as a colorless oil.

IR (neat): 1736, 1486, 1459, 1375, 1363, 1224, 1024, 965 cm⁻¹.

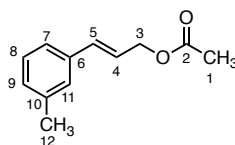
¹H NMR (400 MHz, CDCl₃) δ 7.46 – 7.43 (m, 1H, H_{Ar}), 7.19 – 7.15 (m, 3H, H_{Ar}), 6.88 (d, *J* = 15.8 Hz, 1H, H₅), 6.18 (dt, *J* = 15.7, 6.5 Hz, 1H, H₄), 4.75 (dd, *J* = 6.5, 1.4 Hz, 2H, H₃), 2.36 (s, 3H, H₁₂), 2.11 (s, 3H, H₁).

¹³C NMR (100 MHz, CDCl₃) δ 170.9 (s, C₂), 135.7 (s, C₁₁), 135.4 (s, C₆), 132.2 (s, C_{Ar}), 130.4 (s, C_{Ar}), 128.0 (s, C_{Ar}), 126.2 (s, C_{Ar}), 125.9 (s, C_{Ar}), 124.6 (s, C_{Ar}), 65.4 (s, C₃), 21.1 (s, C₁₂), 19.8 (s, C₁).

MS *m/z* (relative intensity): 190 (M⁺, 27), 147 (20), 130 (100), 115 (55), 104 (8), 91 (30), 77 (8), 65 (8), 51 (6)

⁷⁴ Su, Y.; Jiao, N. *Org. Lett.* **2009**, *11*, 2980-2983.

(E)-3-(*m*-Tolyl)allyl acetate (I.19i)⁷⁵



MW: 190.0994 g.mol⁻¹

Molecular Formula: C₁₂H₁₄O₂

Prepared according to the general procedure from the allylic alcohol **I.18b** (4 mmol, 1.0 equiv), acetic anhydride (0.453 mL, 4.8 mmol, 1.2 equiv) and DMAP (0.538 mg, 4.4 mmol, 1.1 equiv). Compound **I.19i** (0.722 g, 95%) was isolated as a colorless oil

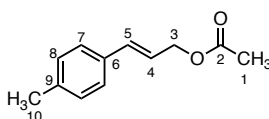
IR (neat): 1736, 1487, 1444, 1379, 1361, 1225, 1025, 964 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.24 – 7.19 (m, 3H, H_{Ar}), 7.08 (d, *J* = 6.8 Hz, 1H, H₉), 6.63 (d, *J* = 15.9 Hz, 1H, H₅), 6.28 (dt, *J* = 15.9, 6.5 Hz, 1H, H₄), 4.73 (dd, *J* = 6.5, 1.3 Hz, 2H, H₃), 2.35 (s, 3H, H₁₂), 2.10 (s, 3H, H₁).

¹³C NMR (100 MHz, CDCl₃) δ 171.0 (s, C₂), 138.3 (s, C₆), 136.3 (s, C₁₀), 134.5 (s, C₅), 129.0 (s, C_{Ar}), 128.6 (s, C_{Ar}), 127.4 (s, C_{Ar}), 123.9 (s, C_{Ar}), 123.1 (s, C_{Ar}), 65.3 (s, C₃), 21.5 (s, C₁₂), 21.1 (s, C₁).

MS *m/z* (relative intensity): 190 (M⁺, 74), 148 (72), 129 (63), 115 (100), 106 (67), 91(58), 77 (15), 65 (16), 51 (12)

(E)-3-(*p*-Tolyl)allyl acetate (I.19j)⁷²



MW: 190.0994 g.mol⁻¹

Molecular Formula: C₁₂H₁₄O₂

Prepared according to the general procedure from the allylic alcohol **I.18c** (4 mmol, 1.0 equiv), acetic anhydride (0.453 mL, 4.8 mmol, 1.2 equiv) and DMAP (0.538 mg, 4.4 mmol, 1.1 equiv). Compound **I.19j** (0.745 g, 98%) was isolated as a yellow oil.

⁷⁵ Pan, D.; Yu, M.; Chen, W.; Jiao, N. *Chem. Asian J.* **2010**, *5*, 1090-1093.

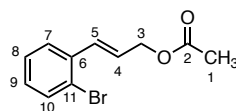
IR (neat): 1734, 1513, 1444, 1378, 1361, 1224, 1102, 1073, 1022, 964 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.29 (d, *J* = 8.1 Hz, 2H, H₇), 7.14 (d, *J* = 8.0 Hz, 2H, H₈), 6.63 (d, *J* = 15.9 Hz, 1H, H₅), 6.24 (dt, *J* = 15.9, 6.5 Hz, 1H, H₄), 4.72 (dd, *J* = 6.5, 1.2 Hz, 2H, H₃), 2.34 (s, 3H, H₁₀), 2.10 (s, 3H, H₁).

¹³C NMR (100 MHz, CDCl₃) δ 171.0 (s, C₂), 138.1 (s, C₉), 134.4 (s, C₅), 133.5 (s, C₆), 129.4 (s, 2C, C₈), 126.6 (s, 2C, C₇), 122.2 (s, C₄), 65.3 (s, C₃), 21.3 (s, C₁₀), 21.1 (s, C₁).

MS *m/z* (relative intensity): 190 (M⁺, 77), 148 (78), 129 (60), 115 (100), 106 (41), 91(64), 77 (17), 65 (17), 51 (12).

(*E*)-3-(2-bromophenyl)allyl acetate (19k)⁷⁶



MW: 253.9942 g.mol⁻¹

Molecular Formula: C₁₁H₁₁BrO₂

Prepared according to the general procedure from the allylic alcohol **I.18d** (4 mmol, 1.0 equiv), acetic anhydride (0.453 mL, 4.8 mmol, 1.2 equiv) and DMAP (0.538 mg, 4.4 mmol, 1.1 equiv). Compound **I.19k/19k'** (*E/Z* = 7:1) (0.985 g, 97%) were isolated as a yellow oil. The information of (*E*)-isomer is reported here.

IR (neat):1736, 1467, 1436, 1377, 1362, 1222, 1022, 963 cm⁻¹.

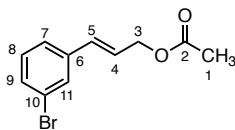
¹H NMR (400 MHz, CDCl₃) δ 7.56 – 7.51 (m, 2H, H_{Ar}), 7.32 – 7.10 (m, 2H, H_{Ar}), 7.00 (d, *J* = 15.8 Hz, 1H, H₅), 6.23 (dt, *J* = 15.8, 6.3 Hz, 1H, H₄), 4.76 (d, *J* = 6.3 Hz, 2H, H₃), 2.12 (s, 3H, H₁).

¹³C NMR (100 MHz, CDCl₃) δ 170.9 (s, C₂), 136.2 (s, C₆), 133.1 (s, C₅), 132.7 (s, C_{Ar}), 129.4 (s, C_{Ar}), 127.7 (s, C₄), 127.3 (s, C_{Ar}), 126.3 (s, C_{Ar}), 123.9 (s, C_{Ar}), 64.9 (s, C₃), 21.1 (s, C₁).

MS *m/z* (relative intensity): 256 (M⁺, 8), 254 (M⁺, 8), 213 (22), 197 (1), 183 (5), 175 (21), 133 (91), 115 (100), 104 (28), 89 (11), 77 (20), 63 (10), 51 (11).

⁷⁶ Ding, F. Q.; William, R.; Wang, F.; Liu, W. X. *Chem. Commun.*, **2012**, 48, 8709-8711.

(E)-3-(3-Bromophenyl)allyl acetate (I.19l)⁷³



MW: 253.9942 g.mol⁻¹

Molecular Formula: C₁₁H₁₁BrO₂

Prepared according to the general procedure from the allylic alcohol **I.18e** (4 mmol, 1.0 equiv), acetic anhydride (0.453 mL, 4.8 mmol, 1.2 equiv) and DMAP (0.538 mg, 4.4 mmol, 1.1 equiv). Compound **I.19l** (0.965 g, 95%) was isolated as a colorless oil.

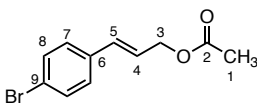
IR (neat): 1736, 1591, 1562, 1474, 1424, 1375, 1364, 1223, 1069, 1027, 963 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.53 (t_{app}, *J* = 1.8 Hz, 1H, H_{Ar}), 7.39 – 7.36 (m, 1H, H_{Ar}), 7.29 (m, 1H, H_{Ar}), 7.18 (t_{app}, *J* = 7.8 Hz, 1H, H_{Ar}), 6.57 (d, *J* = 15.9 Hz, 1H, H₅), 6.28 (dt, *J* = 15.9, 6.3 Hz, 1H, H₄), 4.72 (dd, *J* = 6.3, 1.4 Hz, 2H, H₃), 2.1 (s, 3H, H₁).

¹³C NMR (100 MHz, CDCl₃) δ 170.8 (s, C₂), 138.5 (s, C₆), 132.5 (s, C₅), 131.0 (s, C_{Ar}), 130.2 (s, C_{Ar}), 129.6 (s, C_{Ar}), 125.4 (s, C_{Ar}), 125.0 (s, C₅), 122.9 (s, C₁₀), 64.8 (s, C₃), 21.1 (s, C₁).

MS *m/z* (relative intensity): 255 (M⁺, 19), 254 (M⁺, 20), 212 (28), 196 (7), 170 (13), 133 (14), 115 (100), 104 (19), 89 (10), 77 (13), 58 (11), 51 (9).

(E)-3-(4-Bromophenyl)allyl acetate (I.19m)⁷⁷



MW: 253.9942 g.mol⁻¹

Molecular Formula: C₁₁H₁₁BrO₂

Prepared according to the general procedure from the allylic alcohol **I.18f** (4 mmol, 1.0 equiv), acetic anhydride (0.453 mL, 4.8 mmol, 1.2 equiv) and DMAP (0.538 mg, 4.4 mmol, 1.1 equiv). Compound **I.19m** (0.965 g, 95%) was isolated as a colorless oil.

IR (neat): 1735, 1487, 1441, 1402, 1378, 1361, 1223, 1070, 1024, 1008, 964 cm⁻¹.

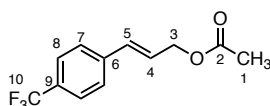
⁷⁷ a) Engman, M.; Diesen, J. S.; Paptchikhine, A.; Andersson, P. G. J. *Am. Chem. Soc.* **2007**, *129*, 4536-4537; b) Procopiou, P. A.; Baugh, S. P. D.; Flack, S.; Inglis, G. A. *J. Org. Chem.* **1998**, *63*, 2342-2347.

¹H NMR (400 MHz, CDCl₃) δ 7.46 – 7.42 (m, 2H, H_{Ar}), 7.26 – 7.23 (m, 2H, H_{Ar}), 6.58 (d, *J* = 15.6 Hz, 1H, H₅), 6.27 (dt, *J* = 15.8 Hz, 1H, H_{Ar}), 4.71 (dd, *J* = 6.4, 1.3 Hz, 2H, H₃), 2.1 (s, 3H, H₁).

¹³C NMR (100 MHz, CDCl₃) δ 170.9 (s, C₂), 135.3 (s, C₆), 133.0 (s, C₃), 131.9 (s, 2C, C₇ and C₁₁), 128.2 (s, 2C, C₈ and C₁₀), 124.2 (s, C₄), 122.0 (s, C₉), 64.9 (s, C₃), 21.1 (s, C₁).

MS *m/z* (relative intensity): 256 (M⁺, 20) 254 (M⁺, 21), 212 (31), 197 (4), 183 (6), 170 (4), 133 (26), 115 (100), 104 (28), 89 (12), 77 (15), 63 (11), 51 (10).

(*E*)-3-(4-(Trifluoromethyl)phenyl)allyl acetate (I.19n)⁷⁸



MW: 244.0711 g.mol⁻¹

Molecular Formula: C₁₂H₁₁F₃O₂

Prepared according to the general procedure from the allylic alcohol **I.18g** (4 mmol, 1.0 equiv), acetic anhydride (0.453 mL, 4.8 mmol, 1.2 equiv) and DMAP (0.538 mg, 4.4 mmol, 1.1 equiv). Compound **I.19n** (0.937 g, 96%) was isolated as a colorless oil

IR (neat): 1740, 1619, 1415, 1368, 1323, 1227, 1163, 1119, 1065, 1017, 969 cm⁻¹.

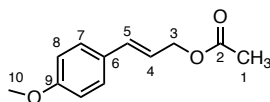
¹H NMR (400 MHz, CDCl₃) δ 7.56 (d, *J* = 8.3 Hz, 2H, H_{Ar}), 7.46 (d, *J* = 8.3 Hz, 2H, H_{Ar}), 6.66 (d, *J* = 16.0 Hz, 1H, H₅), 6.37 (dt, *J* = 15.9, 6.2 Hz, 1H, H₄), 4.75 (dd, *J* = 6.2, 1.3 Hz, 2H, H₃), 2.11 (s, 3H, H₁).

¹³C NMR (100 MHz, CDCl₃) δ 170.8 (s, C₂), 139.8 (s, C₆), 132.4 (s, C₅), 129.9 (q, *J* = 32.4 Hz, C₁₀), 126.9 (s, 2C, C₇), 126.1 (s, C₄), 125.7 (q, *J* = 3.8 Hz, 2C, C₈), 124.2 (q, *J* = 271.9 Hz, C₉), 64.7 (s, C₃), 21.0 (s, C₁).

MS *m/z* (relative intensity): 241 (M⁺, 3), 217 (51), 201 (10), 188 (6), 173 (28), 159 (42), 145 (21), 127 (35), 119 (10), 109 (11), 86 (100), 75 (7), 63 (11), 51 (6).

(*E*)-3-(4-Methoxyphenyl)allyl acetate (I.19o)⁷⁵

⁷⁸ Al-Masum, M.; Yamamoto, Y. *J. Am. Chem. Soc.*, **1998**, 120, 3809-3810.



MW: 206.0943 g.mol⁻¹

Molecular Formula: C₁₂H₁₄O₃

Prepared according to the general procedure from the allylic alcohol **I.18h** (4 mmol, 1.0 equiv), acetic anhydride (0.453 mL, 4.8 mmol, 1.2 equiv) and DMAP (0.538 mg, 4.4 mmol, 1.1 equiv). Compound **I.19o** (0.783 g, 95%) was isolated as a colorless oil

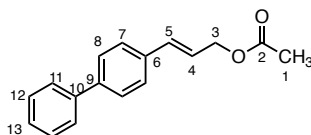
IR (neat): 1734, 1607, 1511, 1450, 1442, 1379, 1362, 1224, 1175, 1101, 1072, 1025, 961 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.35 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 6.86 (d, *J* = 1.7 Hz, 2H, H_{Ar}), 6.60 (d, *J* = 15.9 Hz, 1H, H₅), 6.15 (dt, *J* = 15.8 Hz, 1H, H₄), 4.70 (dd, *J* = 6.6, 1.3 Hz, 2H, H₃), 3.81 (s, 3H, H₁₀), 2.09 (s, 3H, H₁).

¹³C NMR (100 MHz, CDCl₃) δ 171.0 (s, C₂), 159.7 (s, C₉), 134.2 (s, C₅), 129.1 (s, C₆), 128.0 (s, 2C, C₇), 121.0 (s, C₄), 114.1 (s, 2C, C₈), 65.5 (s, C₃), 55.4 (s, C₁₀), 21.2 (s, C₁).

MS *m/z* (relative intensity): 206 (M⁺, 69) 163 (79), 147 (100), 135 (78), 121 (55), 103 (77), 91 (66), 77 (42), 65 (16), 51 (16).

(*E*)-3-([1,1'-Biphenyl]-4-yl)allyl acetate (I.19p**)**⁷¹



MW: 252.1150 g.mol⁻¹

Molecular Formula: C₁₇H₁₆O₂

Prepared according to the general procedure from the allylic alcohol **I.18i** (4 mmol, 1.0 equiv), acetic anhydride (0.453 mL, 4.8 mmol, 1.2 equiv) and DMAP (0.538 mg, 4.4 mmol, 1.1 equiv). Compound **I.19p** (0.948 g, 94%) was isolated as a white solid.

Mp: 96–97 °C.

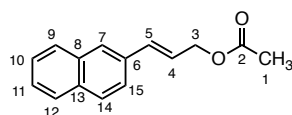
IR (neat): 1735, 1487, 1227, 1024, 1075, 1023, 967 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.62 – 7.57 (m, 4H, H_{Ar}), 7.48 – 7.33 (m, 5H, H_{Ar}), 6.70 (d, *J* = 15.9 Hz, 1H, H₅), 6.34 (dt, *J* = 15.8, 6.5 Hz, 1H, H₄), 4.76 (d, *J* = 6.4 Hz, 2H, H₃), 2.12 (s, 3H, H₁).

¹³C NMR (100 MHz, CDCl₃) δ 171.0 (s, C₂), 141.0 (s, C₁₀), 140.7 (s, C₉), 135.3 (s, C₆), 133.9 (s, C₅), 128.9 (s, 2C, C_{Ar}), 127.5 (s, C_{Ar}), 127.4 (s, 2C, C_{Ar}), 127.2 (s, 2C, C_{Ar}), 127.1 (s, 2C, C_{Ar}), 123.4 (s, C_{Ar}), 65.2 (s, C₃), 21.2 (s, C₁).

MS *m/z* (relative intensity): 252 (M⁺, 100), 210 (62), 209 (50), 191 (50), 178 (51), 165 (37), 152 (15), 126 (3), 115 (18), 95 (8), 83 (9), 63 (4), 51 (5).

(*E*)-3-(Naphthalen-2-yl)allyl acetate (I.19q)⁷¹



MW/: 226.0994 g.mol⁻¹

Molecular Formula: C₁₅H₁₄O₂

Prepared according to the general procedure from the allylic alcohol **I.18j** (4 mmol, 1.0 equiv), acetic anhydride (0.453 mL, 4.8 mmol, 1.2 equiv) and DMAP (0.538 mg, 4.4 mmol, 1.1 equiv). Compound **I.19q** (0.850 g, 94%) was isolated as a white solid.

Mp: 83–84 °C.

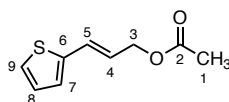
IR (neat): 1727, 1383, 1366, 1242, 1116, 1025, 977, 969, 902 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.83 – 7.79 (m, 3H, H_{Ar}), 7.76 (s, 1H, H_{Ar}), 7.61 (dd, *J* = 8.6, 1.5 Hz, 1H, H_{Ar}), 7.50 – 7.44 (m, 2H, H_{Ar}), 6.82 (d, *J* = 15.9 Hz, 1H, H₅), 6.42 (dt, *J* = 15.8, 6.4 Hz, 1H, H₄), 4.80 (dd, *J* = 6.4, 1.0 Hz, 2H, H₃), 2.14 (s, 3H, H₁).

¹³C NMR (100 MHz, CDCl₃) δ 171.0 (s, C₂), 134.4 (s, C₅), 133.7 (s, C_{Ar}), 133.6 (s, C_{Ar}), 133.3 (s, C_{Ar}), 128.4 (s, C_{Ar}), 128.2 (s, C_{Ar}), 127.8 (s, C_{Ar}), 127.0 (s, C_{Ar}), 126.4 (s, C_{Ar}), 126.2 (s, C_{Ar}), 123.60 (s, C_{Ar}), 123.56 (s, C₄), 65.3 (s, C₃), 21.1 (s, C₁).

MS *m/z* (relative intensity): 226 (M⁺, 83), 184 (60), 165 (100), 142 (45), 128 (29), 115 (11), 101 (2), 89 (2), 82 (18), 70 (6), 55 (5).

(E)-3-(Thiophen-2-yl)allyl acetate (I.19r)⁷⁹



MW: 182.0402 g.mol⁻¹

Molecular Formula: C₉H₁₀O₂S

Prepared according to the general procedure from the allylic alcohol **I.18k** (4 mmol, 1.0 equiv), acetic anhydride (0.453 mL, 4.8 mmol, 1.2 equiv) and DMAP (0.538 mg, 4.4 mmol, 1.1 equiv). Compound **I.19r** (0.692 g, 95%) was isolated as a yellow oil.

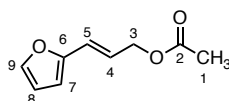
IR (neat): 1733, 1672, 1418, 1366, 1226, 1025, 955 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.18 (d, *J* = 4.9 Hz, 1H, H₉), 6.99 – 6.95 (m, 2H, H₈ and H₇), 6.78 (d, *J* = 15.7 Hz, 1H, H₅), 6.11 (dt, *J* = 15.7, 6.5 Hz, 1H, H₄), 4.68 (dd, *J* = 6.5, 1.2 Hz, 2H, H₃), 2.09 (s, 3H, H₁).

¹³C NMR (100 MHz, CDCl₃) δ 171.0 (s, C₂), 141.3 (s, C₆), 127.54 (s, C₇ or C₉), 127.52 (s, C₇ or C₉), 126.6 (s, C₅), 125.1 (s, C₈), 122.7 (s, C₄), 64.9 (s, C₃), 21.1 (s, C₁).

MS *m/z* (relative intensity): 182 (M⁺, 100), 140 (77), 139 (90), 123 (92), 111 (90), 84 (33), 77 (38), 65 (17), 55 (13).

(E)-3-(Furan-2-yl)allyl acetate (I.19s)⁸⁰



MW: 166.0630 g.mol⁻¹

Molecular Formula: C₉H₁₀O₃

Prepared according to the general procedure from the allylic alcohol **I.18l** (4 mmol, 1.0 equiv), acetic anhydride (0.453 mL, 4.8 mmol, 1.2 equiv) and DMAP (0.538 mg, 4.4 mmol, 1.1 equiv). Compound **I.19s** (0.638 g, 96%) was isolated as a colorless oil.

IR (neat): 1733, 1366, 1225, 1018, 961 cm⁻¹.

⁷⁹ a) Saha, A.; Ranu, B. C. *Tetrahedron Lett.* **2010**, 51, 1902-1905; b) Pan, D.; Chen, A.; Su, Y.; Zhou, W.; Li, S.; Jia, W.; Xiao, J.; Liu, Q.; Zhang, L.; Jiao, N. *Angew. Chem. Int. Ed.* **2008**, 47, 4729-4732; c) You, S.-L.; Z, X-Z; L, Y-M; Hou, X.-L.; Dai, L.-X. *J. Am. Chem. Soc.* **2001**, 123, 7471-7472; d) Iwasaki, M.; Kobayashi, Y.; Li, J.-P.; Matsuzaka, H.; Ishii, Y.; Hidai, M. *J. Org. Chem.* **1991**, 56, 1922-1927.

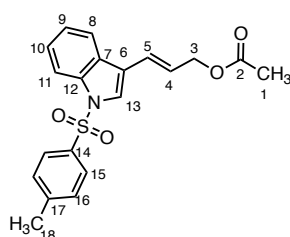
⁸⁰ a) L, L; Chase, C. E.; West, F. G. *Chem. Commun.* **2008**, 34, 4025-4027; b) Cooper, J. A.; Cornwall, P.; Dell, C. P.; Knight, D. W. *Tetrahedron Lett.* **1988**, 29, 2107-2110.

¹H NMR (400 MHz, CDCl₃) δ 7.35 (s, 1H, H₉), 6.46 – 6.15 (m, 4H, H₅, H₇, H₈ and H₄), 4.69 (d_{app}, *J* = 6.0 Hz, 2H, H₃), 2.08 (s, 3H, H₁);

¹³C NMR (100 MHz, CDCl₃) δ 170.9 (s, C₂), 152.0 (s, C₆), 142.5 (s, C₉), 122.3 (s, C₄), 121.8 (s, C₅), 111.5 (s, C₇), 109.0 (s, C₈), 64.7 (s, C₃), 21.1 (s, C₁).

MS *m/z* (relative intensity): 166 (M⁺, 100), 123 (90), 107 (59), 95 (49), 77 (56), 68 (28), 51 (18).

(*E*)-3-(1-Tosyl-1H-indol-3-yl)allyl acetate (I.19t)



MW: 369.1035 g.mol⁻¹

Molecular Formula: C₂₀H₁₉NO₄S

Prepared according to the general procedure from the allylic alcohol **I.18m** (4 mmol, 1.0 equiv), acetic anhydride (0.453 mL, 4.8 mmol, 1.2 equiv) and DMAP (0.538 mg, 4.4 mmol, 1.1 equiv). Compound **I.19t** (1.388 g, 94%) was isolated as a colorless oil

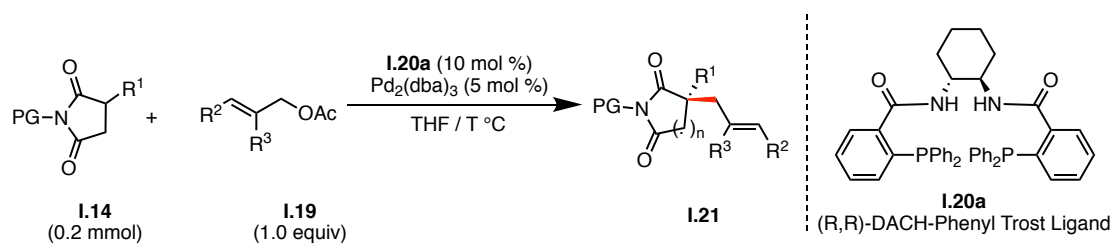
IR (neat): 1735, 1660, 1596, 1446, 1366, 1228, 1173, 1123, 1094, 1023, 964, 909 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 8.01 – 7.98 (m, 1H, H₈), 7.78 – 7.71 (m, 3H, H_{Ar}), 7.62 (s, 1H, H₁₃), 7.36 – 7.21 (m, 4H, H_{Ar}), 6.73 (d, *J* = 16.1 Hz, 1H, H₅), 6.36 (dt, *J* = 16.1, 6.4 Hz, 1H, H₄), 4.75 (dd, *J* = 6.5, 1.3 Hz, 2H, H₃), 2.34 (s, 3H, H₁₈), 2.11 (s, 3H, H₁).

¹³C NMR (101 MHz, CDCl₃) δ 171.0 (s, C₂), 145.3 (s, C₁₇), 135.6 (s, C₁₂), 135.2 (s, C₁₄), 130.2 (s, 2C, C_{Ar}), 128.9 (s, C₇), 127.0 (s, 2C, C_{Ar}), 125.21 (s, C_{Ar}), 125.18 (s, C_{Ar}), 124.8 (s, C_{Ar}), 124.4 (s, C_{Ar}), 123.7 (s, C_{Ar}), 120.5 (s, C_{Ar}), 119.6 (s, C₆), 113.9 (s, C_{Ar}), 65.5 (s, C₃), 21.7 (s, C₁₈), 21.2 (s, C₁).

HRMS (ESI) *m/z*: calcd for C₂₀H₁₉NO₄S Na [M+Na]⁺: 392.0927, found: 392.0928

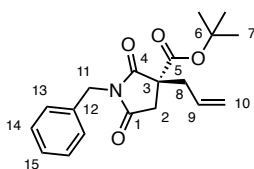
4. Scope and limitation



General Method: To a solution of Pd₂(dba)₃ (9 mg, 0.01 mmol, 0.05 equiv) in THF (1.0 mL) at rt was added the (*R,R*)-DACH phenyl Trost ligand **I.20a** (14 mg, 0.02 mmol, 0.1 equiv) and the mixture was stirred for 30 min at rt. In parallel, a solution of the succinimide-derivative **I.14** (0.2 mmol, 1.0 equiv) in THF (1.0 mL) at rt was prepared. Both mixtures were cooled to −20 °C and the solution containing the catalyst was transferred *via* cannula. The reaction mixture was stirred for an additional 10 min at the same temperature before allyl acetate **I.19** (0.2 mmol, 1.0 equiv) was added. The reaction was stirred at −20 °C until complete consumption of the starting material (reaction monitored by TLC). Once completed, a saturated aqueous solution of NH₄Cl (2 mL) was added and the aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic phases were washed with brine, dried over anhydrous Na₂SO₄, filtered and evaporated under reduced pressure to afford a crude residue, which was purified by flash column chromatography over silica gel to afford the corresponding α-quaternary succinimide **I.21**.

General procedure for the racemic allylic alkylation: To a solution of the succinimide-derivative **I.14** (0.2 mmol, 1.0 equiv), Pd(PPh₃)₄ (12 mg, 0.01 mmol, 0.05 equiv) and Na₂CO₃ (42 mg, 0.4 mmol, 2.0 equiv) in THF (1 mL) at rt was added allyl acetate **I.19** (0.2 mmol, 1.0 equiv) and the reaction mixture was stirred at rt for 15 h until complete consumption of the starting material (reaction monitored by TLC). The reaction mixture was then filtered through Celite[®] to remove the Pd salts and evaporated under reduced pressure to afford a crude residue, which was purified by flash column chromatography over silica gel to afford the corresponding racemic α-quaternary succinimide **I.21**.

(S)-tert-Butyl-3-allyl-N-benzyl-2,5-dioxopyrrolidine-3-carboxylate (I.21a)



MW: 329.1627 g.mol⁻¹

Molecular Formula: C₁₉H₂₃NO₄

Compound **I.21a** was synthesized according to the general method from *tert*-butyl *N*-benzyl-2,5-dioxopyrrolidine-3-carboxylate **I.14a** (58 mg, 0.2 mmol, 1.0 equiv) and allyl acetate **I.19a** (22 μL, 0.2 mmol, 1.0 equiv). Compound **I.21a** was obtained as a white solid (58 mg, 88%) after purification by flash column chromatography over silica gel (PE/Et₂O = 95:5).

Mp: 40–41 °C.

[α]²⁰_D = +26.5 (*c* = 0.2, CHCl₃), ee = 87% (determined by SFC).

SFC: OD-H column, pressure = 100 bar, eluent = CO₂/MeOH (99:1), flow rate = 4.0 mL/min, detection wavelength = 220 nm, *t*_{R1} = 5.90 (minor), *t*_{R2} = 6.64 (major).

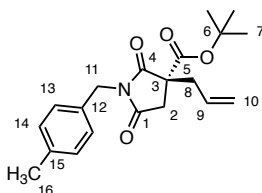
IR (neat): 2980, 1739, 1703, 1433, 1396, 1369, 1344, 1252, 1147, 1067, 1030, 998, 960, 927 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ 7.37 – 7.34 (m, 2H, H_{Ar}), 7.31 – 7.23 (m, 3H, H_{Ar}), 5.58 – 5.48 (m, 1H, H₉), 5.17 – 5.08 (m, 2H, H₁₀), 4.66 (s, 2H, H₁₁), 2.98 (d, *J*_{AB} = 18.2 Hz, 1H, H₂), 2.73 – 2.65 (m, 3H, H₂ and H₈), 1.32 (s, 9H, H₇).

¹³C NMR (100 MHz, CDCl₃): δ 175.4 (s, C₄), 174.9 (s, C₁), 168.0 (s, C₅), 135.5 (s, C₁₂), 131.2 (s, C₉), 128.7 (s, 2C, C_{Ar}), 128.6 (s, 2C, C_{Ar}), 128.0 (s, C_{Ar}), 121.1 (s, C₁₆), 83.3 (s, C₆), 55.1 (s, C₃), 42.8 (s, C₁₁), 37.3 (s, C₈), 37.3 (s, C₂), 27.6 (s, 3C, C₇).

HRMS (ESI) *m/z*: calcd for C₁₉H₂₃NO₄Na [M+Na]⁺: 352.1519, found: 352.1520.

(S)-tert-Butyl-3-allyl-N-(4-methylbenzyl)-2,5-dioxopyrrolidine-3-carboxylate (I.21b)



MW: 343.1784 g.mol⁻¹

Molecular Formula: C₂₀H₂₅NO₄

Compound **I.21b** was synthesized according to the general method from *tert*-butyl *N*-(4-methylbenzyl)-2,5-dioxopyrrolidine-3-carboxylate **I.14b** (61 mg, 0.2 mmol, 1.0 equiv) and allyl acetate **I.19a** (22 μ L, 0.2 mmol, 1.0 equiv). Compound **I.21b** was obtained as a yellow solid (57 mg, 83%) after purification by flash column chromatography over silica gel (PE/Et₂O = 95:5).

Mp: 51–53 °C.

[α]²⁰_D = +49.2 (*c* = 0.12, CDCl₃), ee = 85% (determined by HPLC).

HPLC: IE-H column, eluent = Hexane/*i*-PrOH (97/3), flow rate = 1.0 ml/min, detection wavelength = 220 nm, *t*_{R1} = 14.36 (major), *t*_{R2} = 20.09 (minor).

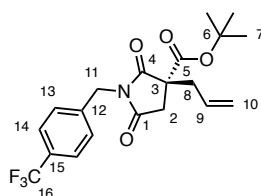
IR (neat): 1739, 1705, 1518, 1432, 1395, 1369, 1342, 1310, 1253, 1149, 961, 926 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ 7.23 (d, *J* = 8.0 Hz, 2H, H_{Ar}), 7.09 (d, *J* = 8.0 Hz, 2H, H_{Ar}), 5.58 – 5.47 (m, 1H, H₉), 5.16 – 5.08 (m, 2H, H₁₀), 4.61 (s, 2H, H₁₁), 2.97 (d, *J*_{AB} = 18.1 Hz, 1H, H₂), 2.68 – 2.63 (m, 2H, H₂ and H₈), 2.60 (d, *J*_{AB} = 18.0 Hz, 1H, H₂), 2.30 (s, 3H, H₁₆), 1.33 (s, 9H, H₇).

¹³C NMR (100 MHz, CDCl₃): δ 175.4 (s, C₄), 175.0 (s, C₁), 168.1, (s, C₅) 137.7 (s, C₁₅), 132.6 (s, C₁₂), 131.3 (s, C₉), 129.3 (s, 2C, C₁₄ or C₁₅), 128.7 (s, 2C, C₁₄ or C₁₅), 121.1 (s, C₁₀), 83.4 (s, C₆), 55.1 (s, C₃), 42.6 (s, C₁₁), 37.5 (s, C₈), 37.3 (s, C₂), 27.7 (s, 3C, C₇), 21.2 (s, C₁₆).

HRMS (ESI) *m/z*: calcd for C₂₀H₂₅NO₄Na [*M*+Na]⁺: 366.1676, found: 366.1677.

(*S*)-*tert*-Butyl-3-allyl-2,5-dioxo-*N*-(4-(trifluoromethyl)benzyl)pyrrolidine-3-carboxylate (I.21c**)**



MW: 397.1501 g.mol⁻¹

Molecular Formula: C₂₀H₂₂F₃NO₄

Compound **I.21c** was synthesized according to the general method from *tert*-butyl 2,5-dioxo- *N*-[4-(trifluoromethyl)benzyl]pyrrolidine-3-carboxylate **I.19c** (71 mg, 0.2 mmol, 1.0 equiv) and allyl acetate **I.19a** (22 μ L, 0.2 mmol, 1.0 equiv). Compound **I.19c** was

obtained as a yellow solid (64 mg, 81%) after purification by flash column chromatography over silica gel (PE/Et₂O = 95:5).

Mp: 44–45 °C.

[α]²⁰_D = +44.2 (*c* = 0.12, CHCl₃), ee = 86% (determined by HPLC).

HPLC: IA-H column, eluent = Hexane/*i*-PrOH (97/3), flow rate = 1.0 ml/min, detection wavelength = 220 nm, *t*_{R1} = 8.694 (major), *t*_{R2} = 9.778 (minor).

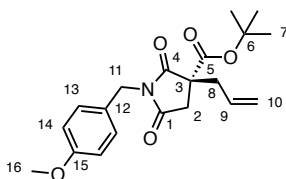
IR (neat): 2983, 1742, 1710, 1435, 1396, 1371, 1325, 1255, 1152, 1127, 1068, 1019, 928 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ 7.56 (d, *J* = 8.0 Hz, 2H, H_{Ar}), 7.47 (d, *J* = 8.0 Hz, 2H, H_{Ar}), 5.58 – 5.48 (m, 1H, H₉), 5.17 – 5.10 (m, 2H, H₁₀), 4.70 (s, 2H, H₁₁), 2.99 (d, *J* = 18.2 Hz, 1H, H₂), 2.73 – 2.63 (m, 2H, H₂ and H₈), 2.65 (d, *J*_{AB} = 18.4 Hz, 1H, H₂), 1.31 (s, 9H, H₇).

¹³C NMR (100 MHz, CDCl₃): δ 175.4 (s, C₄), 174.8 (s, C₁), 168.0 (s, C₅), 139.4 (s, C₁₂), 131.1 (s, C₉), 130.4 (q, *J* = 32.5 Hz, C₁₆), 129.1 (s, 2C, C_{Ar}), 125.7 (q, *J* = 3.8 Hz, 2C, C₁₄), 124.1 (d, *J* = 271.0 Hz, C₁₅), 121.3 (s, C₁₀), 83.6 (s, C₆), 55.2 (s, C₃), 42.3 (s, C₁₁), 37.4 (s, C₂), 37.3 (s, C₈), 27.7 (s, 3C, C₇).

HRMS (ESI) *m/z*: calcd for C₂₀H₂₂F₃NO₄Na [M+Na]⁺: 420.1393, found: 420.1386.

***tert*-butyl (*R*)-3-allyl-1-(4-methoxybenzyl)-2,5-dioxopyrrolidine-3-carboxylate (I.21d)**



MW: 359.1733 g.mol⁻¹

Molecular Formula: C₂₀H₂₅NO₅

Compound **I.21d** was synthesized according to the general method from *tert*-butyl 2,5-dioxo- *N*-[4-(methoxyl)benzyl]pyrrolidine-3-carboxylate **I.19d** (71 mg, 0.2 mmol, 1.0 equiv) and allyl acetate **I.19a** (22 μL, 0.2 mmol, 1.0 equiv). Compound **I.19d** was obtained as a colourless oil (64.6 mg, 90%) after purification by flash column chromatography over silica gel (PE/Et₂O = 95:5).

$[\alpha]_D^{20} = +44.0$ ($c = 1.67$, CHCl_3), $ee = 84\%$ (determined by HPLC).

SFC: OD-H column, pressure = 100 bar, eluent = CO_2/MeOH (99:1), flow rate = 3.5 mL/min, detection wavelength = 220 nm, $t_{R1} = 14.39$ (minor), $t_{R2} = 15.46$ (major).

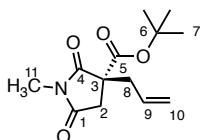
IR (neat): 2979, 1738, 1703, 1613, 1514, 1434, 1395, 1370, 1343, 1299, 1247, 1176, 1148, 1111, 1069, 1034, 998, 960 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ 7.31 – 7.27 (m, 2H, H_{13}), 6.82 – 6.78 (m, 2H, H_{14}), 5.55 – 5.45 (m, 1H, H_9), 5.15 – 5.04 (m, 2H, H_{10}), 4.58 (s, 2H, H_{11}), 3.76 (s, 3H, H_{16}), 2.95 (d, $J = 18.1\text{ Hz}$, 1H, H_2), 2.67 – 2.64 (m, 2H, H_8), 2.63 (d, $J = 18.1\text{ Hz}$, 1H, H_2), 1.32 (s, 9H, H_7).

^{13}C NMR (100 MHz, CDCl_3): δ 175.6 (s, C_4), 175.0 (s, C_1), 168.1 (s, C_5), 159.4 (s, C_{15}), 131.2 (s, C_9), 130.3 (s, C_{13}), 127.9 (s, C_{12}), 121.1 (s, C_{10}), 114.0 (s, C_{14}), 83.4 (s, C_6), 55.4 (s, C_6), 55.1 (s, C_3), 42.3 (s, C_{11}), 37.4 (s, C_8), 37.3 (s, C_2), 27.7 (s, C_7).

HRMS (ESI) m/z : calcd for $\text{C}_{20}\text{H}_{22}\text{F}_3\text{NO}_4\text{Na}$ $[\text{M}+\text{Na}]^+$: 382.1625, found: 382.1626.

(S)-tert-Butyl-3-allyl-N-methyl-2,5-dioxopyrrolidine-3-carboxylate (I.21e)



MW: 253.1314 $\text{g}\cdot\text{mol}^{-1}$

Molecular Formula: $\text{C}_{13}\text{H}_{19}\text{NO}_4$

Compound **I.21e** was synthesized according to the general method from *tert*-butyl *N*-methyl-2,5-dioxopyrrolidine-3-carboxylate **I.14e** (43 mg, 0.2 mmol, 1.0 equiv) and allyl acetate **I.19a** (22 μL , 0.2 mmol, 1.0 equiv). Compound **I.21e** was obtained as a colorless oil (42 mg, 83%) after purification by flash column chromatography over silica gel ($\text{PE}/\text{Et}_2\text{O} = 95:5$).

$[\alpha]_D^{20} = +41.7$ ($c = 0.3$, CHCl_3), $ee = 87\%$ (determined by HPLC).

HPLC: IC-H column, eluent = Hexane/*i*-PrOH (97/3), flow rate = 1.0 mL/min, detection wavelength = 220 nm, $t_{R1} = 9.96$ (major), $t_{R2} = 12.18$ (minor).

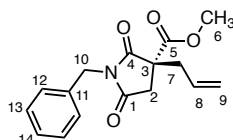
IR (neat): 2980, 1739, 1702, 1435, 1383, 1370, 1281, 1254, 1149, 1103, 1065, 994, 926 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ 5.62 – 5.52 (m, 1H, H_9), 5.20 – 5.13 (m, 2H, H_{10}), 3.00 (d, $J_{AB} = 17.8\text{ Hz}$, 1H, H_2), 2.90 (s, 3H, H_{11}), 2.70 – 2.60 (m, 3H, H_2 and H_8), 1.41 (s, 9H, C_7).

¹³C NMR (100 MHz, CDCl₃): δ 175.7 (s, C₄), 175.3 (s, C₁), 168.2 (s, C₅), 131.3 (s, C₉), 121.0 (s, C₁₀), 83.4 (s, C₆), 55.3 (s, C₃), 37.7 (s, C₈), 37.2 (s, C₂), 27.8 (s, 3C, C₇), 25.3 (s, C₁₁).

HRMS (ESI) *m/z*: calcd for C₁₃H₁₉NO₄Na [M+Na]⁺: 276.1206, found: 276.1206.

(S)-Methyl-3-allyl-N-benzyl-2,5-dioxopyrrolidine-3-carboxylate (I.21f)



MW: 287.1158 g.mol⁻¹

Molecular Formula: C₁₆H₁₇NO₄

Compound **I.21f** was synthesized according to the general method from methyl *N*-benzyl-2,5-dioxopyrrolidine-3-carboxylate **I.14f** (49 mg, 0.2 mmol, 1.0 equiv) and allyl acetate **I.19a** (22 μL, 0.2 mmol, 1.0 equiv). Compound **I.21f** was obtained as a colorless oil (55 mg, 96%) after purification by flash column chromatography over silica gel (PE/Et₂O = 95:5).

[α]_D²⁰ = −7.5 (*c* = 0.58, CHCl₃), ee = 18% (determined by SFC).

SFC: OD-H column, pressure = 100 bar, eluent = CO₂/MeOH (95:5), flow rate = 4.0 mL/min, detection wavelength = 220 nm, *t*_{R1} = 1.29 (major), *t*_{R2} = 1.39 (minor).

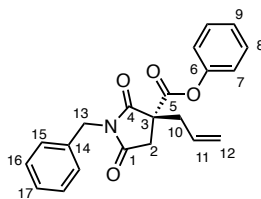
IR (neat): 2954, 1746, 1703, 1642, 1497, 1433, 1394, 1343, 1250, 1174, 1068, 973, 931 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ 7.27 – 7.18 (m, 5H, H_{Ar}), 5.45 – 5.35 (m, 1H, H₈), 5.09 – 4.99 (m, 2H, H₉), 4.61 (d, *J*_{AB} = 14.0 Hz, 1H, H₁₀), 4.57 (d, *J*_{AB} = 14.0 Hz, 1H, H₁₀), 3.65 (s, 3H, H₆), 3.02 (d, *J*_{AB} = 18.3 Hz, 1H, H₂), 2.67 – 2.61 (m, 3H, H₂ and H₇).

¹³C NMR (100 MHz, CHCl₃): δ 175.0 (s, C₄), 174.6 (s, C₁), 169.7 (s, C₅), 135.4 (s, C₁₁), 130.7 (s, C₈), 128.7 (s, 2C, C_{Ar}), 128.6 (s, 2C, C_{Ar}), 128.1 (s, C_{Ar}), 121.5 (s, C₉), 54.5 (s, C₃), 53.5 (s, C₆), 43.0 (s, C_{Ar}), 37.9 (s, C₇), 37.2 (s, C₂).

HRMS (ESI) *m/z*: calcd for C₁₆H₁₇NO₄Na [M+Na]⁺: 310.1050, found: 310.1049.

(S)-Phenyl-3-allyl-N-benzyl-2,5-dioxopyrrolidine-3-carboxylate (I.21g)



MW: 349.1314 g.mol⁻¹

Molecular Formula: C₂₁H₁₉NO₄

Compound **I.21g** was synthesized according to the general method from phenyl *N*-benzyl-2,5-dioxopyrrolidine-3-carboxylate **I.14g** (62 mg, 0.2 mmol, 1.0 equiv) and allyl acetate **I.19a** (22 μ L, 0.2 mmol, 1.0 equiv). Compound **I.21g** was obtained as a white solid (66 mg, 95%) after purification by flash column chromatography over silica gel (PE/Et₂O = 95:5).

Mp: 63–65 °C.

[α]_D²⁰ = +33.0 (*c* = 0.1, CDCl₃), ee = 44% (determined by SFC).

SFC: OD-H column, pressure = 100 bar, eluent = CO₂/MeOH (95:5), flow rate = 4.0 mL/min, detection wavelength = 220 nm, *t*_{R1} = 5.67 (major), *t*_{R2} = 6.19 (minor).

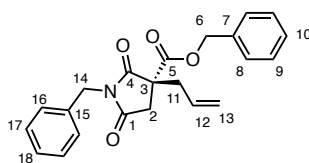
IR (neat): 2360, 1763, 1706, 1591, 1493, 1433, 1396, 1344, 1294, 1234, 1187, 1166, 960, 923 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ 7.30 – 7.25 (m, 4H, H_{Ar}), 7.23 – 7.14 (m, 4H, H_{Ar}), 6.90 – 6.83 (m, 2H, H_{Ar}), 5.55 – 5.45 (m, 1H, H₁₁), 5.13 – 5.0 (m, 2H, H₁₂), 4.65 (s, 2H, H₁₃), 3.20 (d, *J*_{AB} = 18.4 Hz, 1H, H₂), 2.78 (s, 2H, H₁₀), 2.75 (d, *J*_{AB} = 10.8 Hz, 1H, H₂).

¹³C NMR (100 MHz, CDCl₃): δ 174.7 (s, C₄), 174.4 (s, C₁), 167.9 (s, C₅), 150.3 (s, C₆), 135.3 (s, C₁₄), 130.5 (s, C₁₁), 129.7 (s, 2C, C_{Ar}), 128.8 (s, 2C, C_{Ar}), 128.7 (s, 2C, C_{Ar}), 128.2 (s, C_{Ar}), 126.6 (s, C_{Ar}), 121.8 (s, C₁₂), 121.1 (s, 2C, C_{Ar}), 54.8 (s, C₃), 43.2 (s, C₁₃), 37.9 (s, C₁₂), 37.2 (s, C₁₀).

HRMS (ESI) *m/z*: calcd for C₂₁H₁₉NO₄Na [M+Na]⁺: 372.1206, found: 372.1205.

(*S*)-Benzyl-3-allyl-*N*-benzyl-2,5-dioxopyrrolidine-3-carboxylate (**I.21h**)



MW: 363.1471 g.mol⁻¹

Molecular Formula: C₂₂H₂₁NO₄

Compound **I.21h** was synthesized according to the general method from benzyl *N*-benzyl-2,5-dioxopyrrolidine-3-carboxylate **I.14h** (65 mg, 0.2 mmol, 1.0 equiv) and allyl acetate **I.19a** (22 μ L, 0.2 mmol, 1.0 equiv). Compound **I.21h** was obtained as a colorless oil (70 mg, 96%) after purification by flash chromatography over silica gel (PE/Et₂O = 95:5).

$[\alpha]^{20}_{\text{D}} = -4.3$ ($c = 0.23$, CHCl₃), ee = 11% (determined by SFC).

SFC: OD-H column, pressure = 100 bar, eluent = CO₂/MeOH (95:5), flow rate = 4.0 mL/min, detection wavelength = 220 nm, $t_{\text{R}1} = 5.55$ (major), $t_{\text{R}2} = 6.54$ (minor).

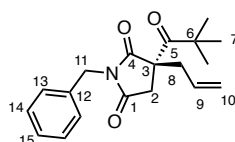
IR (neat): 3034, 1745, 1703, 1642, 1497, 1395, 1343, 1240, 1173, 961, 923 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ 7.39 – 7.31 (m, 5H, H_{Ar}), 7.30 – 7.24 (m, 5H, H_{Ar}), 5.56 – 5.46 (m, 1H, H₁₂), 5.21 – 5.09 (m, 4H, H₆ and C₁₃), 4.71 (d, $J_{\text{AB}} = 14.0$ Hz, 1H, H₁₄), 4.66 (d, $J_{\text{AB}} = 14.0$ Hz, 1H, H₁₄), 3.10 (d, $J_{\text{AB}} = 18.3$ Hz, 1H, H₂), 2.84 – 2.70 (m, 2H, H₁₁), 2.73 (d, $J_{\text{AB}} = 18.4$ Hz, 1H, H₂).

¹³C NMR (100 MHz, CDCl₃): δ 174.8 (s, C₄), 174.5 (s, C₁), 169.0 (s, C₅), 135.3 (s, C₁₅), 134.9 (s, C₇), 130.6 (s, C₁₂), 128.7 (s, 2C, C_{Ar}), 128.65 (s, 2C, C_{Ar}), 128.61 (s, C_{Ar}), 128.5 (s, 2C, C_{Ar}), 128.1 (s, 2C, C_{Ar}), 128.0 (s, C_{Ar}), 121.5 (s, C₁₃), 68.0 (s, C₆), 54.4 (s, C₃), 42.9 (s, C₁₄), 37.8 (s, C₂), 37.1 (s, C₄).

HRMS (ESI) m/z : calcd for C₂₂H₂₁NO₄Na [M+Na]⁺: 386.1363, found: 386.1361.

(S)-3-Allyl-*N*-benzyl-3-pivaloylpyrrolidine-2,5-dione (**I.21i**)



MW: 313.1678 g.mol⁻¹

Molecular Formula: C₁₉H₂₃NO₃

Compound **I.21i** was synthesized according to the general method from *N*-benzyl-3-pivaloylpyrrolidine-2,5-dione **I.14i** (55 mg, 0.2 mmol, 1.0 equiv) and allyl acetate **I.19a** (22 μ L, 0.2 mmol, 1.0 equiv). Compound **I.21i** was obtained as a white solid (47 mg, 75%) after purification by flash column chromatography over silica gel (PE/Et₂O = 95:5).

Mp: 55–58 °C.

[α] $^{20}_D$ = –11.6 (c = 0.17, CHCl₃), ee = 80% (determined by HPLC).

HPLC: IB-H column, eluent = Hexane/*i*-PrOH (97/3), flow rate = 1.0 ml/min, detection wavelength = 220 nm, t_{R1} = 6.66 (major), t_{R2} = 7.41 (minor).

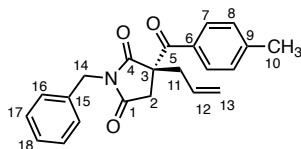
IR (neat): 2971, 1777, 1705, 1640, 1437, 1394, 1345, 1315, 1173, 1082, 1055, 931 cm⁻¹.

^1H NMR (400 MHz, CDCl₃): δ 7.33 – 7.31 (m, 2H, H_{Ar}), 7.24 – 7.17 (m, 3H, H_{Ar}), 5.31 – 5.21 (m, 1H, H₉), 5.01 (d, J = 16.9 Hz, 1H, H₁₀), 4.92 (d, J = 10.1 Hz, 1H, H₁₀), 4.62 (d, J_{AB} = 14.0 Hz, 1H, H₁₁), 4.57 (d, J_{AB} = 14.0 Hz, 1H, H₁₁), 2.83 (d, J_{AB} = 18.7 Hz, 1H, H₂), 2.64 – 2.53 (m, 2H, H₈), 2.60 (d, J_{AB} = 18.7 Hz, 1H, H₂), 1.01 (s, 9H, H₇).

^{13}C NMR (100 MHz, CDCl₃): δ 208.8 (s, C₅), 176.9 (s, C₄), 174.3 (s, C₁), 134.9 (s, C₁₂), 130.6 (s, C₉), 129.4 (s, 2C, C_{Ar}), 128.6 (s, 2C, C_{Ar}), 128.2 (s, C₁₅), 121.6 (s, C₁₀), 59.2 (s, C₃), 46.0 (s, C₆), 43.0 (s, C₁₁), 40.5 (s, C₈), 37.5 (s, C₂), 27.5 (s, 3C, C₇).

HRMS (ESI) m/z : calcd for C₁₉H₂₃NO₃Na [M+Na]⁺: 336.1570, found: 336.1570.

(S)-3-Allyl-N-benzyl-3-(4-methylbenzoyl)pyrrolidine-2,5-dione (I.21j)



MW: 347.1521 g.mol⁻¹

Molecular Formula: C₂₂H₂₁NO₃

Compound **I.21j** was synthesized according to the general method from *N*-benzyl-3-(4-methylbenzoyl)pyrrolidine-2,5-dione **I.14j** (61 mg, 0.2 mmol, 1.0 equiv) and allyl acetate **I.19a** (22 μ L, 0.2 mmol, 1.0 equiv). Compound **I.21j** was obtained as a yellow solid (61 mg, 88%) after purification by flash column chromatography over silica gel (PE/Et₂O = 95:5).

Mp: 107–109 °C.

[α] $^{20}_D$ = –29.2 (c = 0.12, CHCl₃), ee = 48% (determined by SFC).

SFC: OD-H column, pressure = 100 bar, eluent = CO₂/MeOH (95:5), flow rate = 4.0 mL/min, detection wavelength = 220 nm, t_{R1} = 5.89 (major), t_{R2} = 7.95 (minor).

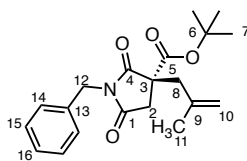
IR (neat): 2925, 1777, 1703, 1677, 1606, 1496, 1433, 1392, 1343, 1313, 1256, 1172, 927 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ 7.49 – 7.42 (m, 4H, H_{Ar}), 7.37 – 7.33 (m, 3H, H_{Ar}), 7.02 (d, *J* = 8.4 Hz, 2H, H_{Ar}), 5.53 – 5.43 (m, 1H, H₁₂), 5.12–5.07 (m, 2H, H₁₃), 4.75 (d, *J*_{AB} = 13.6 Hz, 1H, H₁₄), 4.71 (d, *J*_{AB} = 13.6 Hz, 1H, H₁₄), 3.18 (d, *J*_{AB} = 18.5 Hz, 1H, H₂), 2.90 – 2.82 (m, 2H, H₁₁), 2.77 (d, *J*_{AB} = 18.5 Hz, 1H, H₂), 2.34 (s, 3H, H₁₀).

¹³C NMR (100 MHz, CDCl₃): δ 195.1 (s, C₅), 176.3 (s, C₄), 174.5 (s, C₁), 144.1 (s, C₉), 135.1 (s, C₁₅), 132.2 (s, C₆), 130.7 (s, C₁₂), 129.4 (s, 2C, C_{Ar}), 129.3 (s, 2C, C_{Ar}), 128.8 (s, 2C, C_{Ar}), 128.6 (s, 2C, C_{Ar}), 128.3 (s, C_{Ar}), 121.5 (s, C₁₃), 59.1 (s, C₃), 43.1 (s, C₁₄), 39.8 (s, C₁₁), 38.2 (s, C₂), 21.6 (s, C₁₀).

HRMS (ESI) *m/z* : calcd for C₁₉H₂₃NO₄Na [M+Na]⁺: 370.1414, found: 370.1413.

(S)-tert-Butyl-N-benzyl-3-(2-methylallyl)-2,5-dioxopyrrolidine-3-carboxylate (I.21k)



MW/g (mol): 343.1784 g.mol⁻¹

Molecular Formula: C₂₀H₂₅NO₄

Compound **I.21k** was synthesized according to the general method from *tert*-butyl *N*-benzyl-2,5-dioxopyrrolidine-3-carboxylate **I.14a** (58 mg, 0.2 mmol, 1.0 equiv) and 2-methylallyl acetate **I.19b** (23 mg, 0.2 mmol, 1.0 equiv). Compound **I.21k** was obtained as a white solid (37 mg, 54%) after purification by flash column chromatography over silica gel (PE/Et₂O = 95:5).

Mp: 51–53 °C.

[α]²⁰_D = +68.0 (*c* = 0.2, CHCl₃), ee = 89% (determined by SFC).

SFC: OD-H column, pressure = 100 bar, eluent = CO₂/MeOH (99:1), flow rate = 4.0 mL/min, detection wavelength = 220 nm, *t*_{R1} = 6.32 (minor), *t*_{R2} = 7.00 (major).

IR (neat): 2978, 1740, 1706, 1432, 1395, 1369, 1344, 1253, 1149, 1075, 955, 905 cm⁻¹.

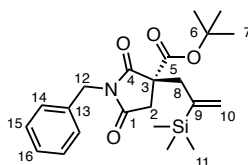
¹H NMR (400 MHz, CDCl₃): δ 7.38 – 7.35 (m, 2H, H_{Ar}), 7.32 – 7.24 (m, 3H, H_{Ar}), 4.86 – 4.85 (m, 1H, H₈), 4.66 (s_{app}, 3H, H₁₀ and H₁₂), 3.06 (d, *J*_{AB} = 18.1 Hz, 1H, H₂), 2.75 (d,

$J_{AB} = 14.8$ Hz, 1H, H_2), 2.70 (d, $J_{AB} = 18.1$ Hz, 1H, H_2), 2.66 (d, $J_{AB} = 14.7$ Hz, 1H, H_8), 1.55 (s, 3H, H_{11}), 1.33 (s, 9H, H_7).

^{13}C NMR (100 MHz, CDCl_3): δ 175.8 (s, C_4), 175.3 (s, C_1), 168.1 (s, C_5), 140.3 (s, C_9), 135.4 (s, C_{13}), 128.9 (s, 2C, C_{Ar}), 128.7 (s, 2C, C_{Ar}), 128.1 (s, C_{Ar}), 116.0 (s, C_{10}), 83.4 (s, C_6), 55.0 (s, C_3), 42.9 (s, C_{12}), 40.2 (s, C_8), 37.1 (s, C_2), 27.6 (s, 3C, C_7), 23.4 (s, C_{11}).

HRMS (ESI) m/z : calcd for $\text{C}_{20}\text{H}_{25}\text{NO}_4 \text{Na}$ [$\text{M}+\text{Na}$] $^+$: 366.1676, found: 366.1675.

(S)-tert-Butyl-N-benzyl-2,5-dioxo-3-(2-(trimethylsilyl)allyl)pyrrolidine-3-carboxylate (I.211)



MW: 401.2022 g.mol $^{-1}$

Molecular Formula: $\text{C}_{22}\text{H}_{31}\text{NO}_4\text{Si}$

Compound **I.211** was synthesized according to the general method from *tert*-butyl *N*-benzyl-2,5-dioxopyrrolidine-3-carboxylate **I.14a** (58 mg, 0.2 mmol, 1.0 equiv) and 2-(trimethylsilyl)allyl acetate **I.19c** (34 mg, 0.2 mmol, 1.0 equiv). Compound **I.211** was obtained as a white solid (49 mg, 61%) after purification by flash column chromatography over silica gel (PE/Et $_2$ O = 95:5).

Mp: 61–63 °C.

$[\alpha]_D^{20} = +53.8$ ($c = 0.08$, CHCl_3), ee = 87% (determined by SFC).

SFC: OD-H column, pressure = 100 bar, eluent = CO_2/MeOH (99:1), flow rate = 4.0 mL/min, detection wavelength = 220 nm, $t_{R1} = 4.94$ (minor), $t_{R2} = 6.19$ (major).

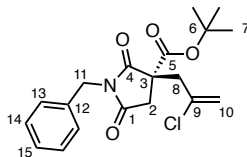
IR (neat): 2954, 1741, 1705, 1432, 1394, 1364, 1342, 1247, 1148, 1054, 963, 930 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ 7.29 – 7.26 (m, 2H, H_{Ar}), 7.24 – 7.16 (m, 3H, H_{Ar}), 5.33 (d, $J = 1.2$ Hz, 1H, H_{10}), 5.22 (d, $J = 1.6$ Hz, 1H, H_{10}), 4.58 (s, 2H, H_{12}), 3.15 (d, $J_{AB} = 18.1$ Hz, 1H, H_2), 2.97 (d, $J_{AB} = 16.6$, 1H, H_8), 2.58 (d, $J_{AB} = 18.1$ Hz, 1H, H_2), 2.49 (dt, $J_{AB} = 16.7$, 1.7 Hz, 1H, H_8), 1.24 (s, 9H, H_7), 0.00 (s, 9H, H_{11}).

^{13}C NMR (100 MHz, CDCl_3): δ 176.0 (s, C_4), 175.4 (s, C_1), 168.0 (s, C_5), 146.7 (s, C_{Ar}), 135.5 (s, C_9), 128.8 (s, 2C, C_{13}), 128.7 (s, 2C, C_{Ar}), 128.1 (s, C_{Ar}), 126.1 (s, C_{10}), 83.2 (s, C_6), 55.6 (s, C_3), 42.9 (s, C_{12}), 37.7 (s, C_2), 37.0 (s, C_8), 27.6 (s, 3C, C_7), -1.7 (s, 3C, C_{11}).

HRMS (ESI) m/z : calcd for $C_{22}H_{31}NO_4Si Na [M+Na]^+$: 424.1915, found: 424.1910.

(S)-tert-Butyl-N-benzyl-3-(2-chloroallyl)-2,5-dioxopyrrolidine-3-carboxylate (I.21m)



MW: 363.1237 g.mol⁻¹

Molecular Formula: $C_{19}H_{22}ClNO_4$

Compound **I.21m** was synthesized according to the general method from *tert*-butyl *N*-benzyl-2,5-dioxopyrrolidine-3-carboxylate **I.14a** (58 mg, 0.2 mmol, 1.0 equiv) and 2-chloroallyl acetate **I.19d** (27 mg, 0.2 mmol, 1.0 equiv). Compound **I.21m** was obtained as a yellow solid (22 mg, 30%) after purification by flash column chromatography over silica gel (PE/Et₂O = 95:5).

Mp: 69–72 °C.

$[\alpha]_D^{20}$ = +42.9 (c = 0.08, CHCl₃), ee = 85% (determined by SFC).

SFC: OJ-H column, pressure = 100 bar, eluent = CO₂/MeOH (99:1), flow rate = 4.0 mL/min, detection wavelength = 220 nm, t_{R1} = 2.48 (minor), t_{R2} = 2.84 (major).

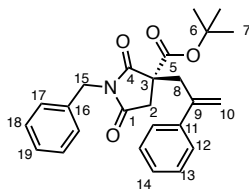
IR (neat): 1740, 1709, 1632, 1432, 1396, 1370, 1345, 1248, 1150, 967 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ 7.42 – 7.36 (m, 2H, H_{Ar}), 7.32 – 7.22 (m, 3H, H_{Ar}), 5.27 – 5.22 (m, 2H, H₁₀), 4.71 (s_{app}, 1H, H₁₁), 4.67 (s_{app}, 1H, H₁₁), 3.18 – 2.91 (m, 4H), 1.32 (s, 9H, H₇).

¹³C NMR (100 MHz, CDCl₃): δ 175.5 (s, C₄), 174.9 (s, C₁), 167.5 (s, C₅), 136.7 (s, C₁₂), 135.3 (s, C₉), 129.0 (s, 2C, C_{Ar}), 128.7 (s, 2C, C_{Ar}), 128.1 (s, C_{Ar}), 118.4 (s, C₁₀), 84.0 (s, C₆), 54.7 (s, C₃), 43.1 (s, C₁₁), 40.9 (s, C₂), 36.8 (s, C₈), 27.6 (s, 3C, C₇).

HRMS (ESI) m/z : calcd for $C_{19}H_{22}ClNO_4Na [M+Na]^+$: 386.1130, found: 386.1130.

(S)-tert-Butyl-N-benzyl-2,5-dioxo-3-(2-phenylallyl)pyrrolidine-3-carboxylate (I.21n)



MW: 405.1940 g.mol⁻¹

Molecular Formula: C₂₅H₂₇NO₄

Compound **I.21n** was synthesized according to the general method from *tert*-butyl *N*-benzyl-2,5-dioxopyrrolidine-3-carboxylate **I.14a** (58 mg, 0.2 mmol, 1.0 equiv) and 2-phenylallyl acetate **I.19e** (35 mg, 0.2 mmol, 1.0 equiv). Compound **I.21n** was obtained as a colorless oil (45 mg, 55%) after purification by flash column chromatography over silica gel (PE/Et₂O = 95:5).

[α]²⁰_D = +30.0 (*c* = 0.16, CHCl₃), ee = 47% (determined by SFC).

SFC: OJ-H column, pressure = 100 bar, eluent = CO₂/MeOH (99:1), flow rate = 4.0 mL/min, detection wavelength = 220 nm, *t*_{R1} = 5.61 (minor), *t*_{R2} = 7.25 (major).

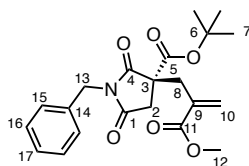
IR (neat): 2980, 1739, 1704, 1494, 1431, 1395, 1368, 1344, 1254, 1221, 1149, 1062, 966, 911 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ 7.26 – 7.15 (m, 10H, H_{Ar}), 5.18 (s_{app}, 1H, H₁₀), 5.03 (s_{app}, 1H, H₁₀), 4.26 (d, *J*_{AB} = 14.2 Hz, 1H, H₁₅), 4.08 (d, *J*_{AB} = 14.2 Hz, 1H, H₁₅), 3.31 (d, *J*_{AB} = 14.6 Hz, 1H, H₂), 3.10 (d, *J*_{AB} = 14.6 Hz, 1H, H₂), 2.80 (d, *J*_{AB} = 18.2 Hz, 1H, H₈), 2.63 (d, *J*_{AB} = 18.2 Hz, 1H, H₈), 1.25 (s, 9H, H₇).

¹³C NMR (100 MHz, CDCl₃): δ 175.6 (s, C₄), 175.0 (s, C₁), 168.4 (s, C₅), 143.9 (s, C₉), 140.6 (s, C₁₁), 135.5 (s, C₁₆), 128.62 (s, 2C, C_{Ar}), 128.59 (s, 2C, C_{Ar}), 128.55 (s, 2C, C_{Ar}), 128.2 (s, C_{Ar}), 127.9 (s, C_{Ar}), 126.8 (s, 2C, C_{Ar}), 119.1 (s, C₁₀), 83.4 (s, C₆), 55.2 (s, C₃), 42.5 (s, C₁₅), 37.8 (s, C₂), 37.0 (s, C₈), 27.7 (s, 3C, C₇).

HRMS (ESI) *m/z*: calcd for C₂₅H₂₇NO₄ Na [M+Na]⁺: 428.1832, found: 428.1829.

(S)-tert-Butyl-N-benzyl-3-[2-(methoxycarbonyl)allyl]-2,5-dioxopyrrolidine-3-carboxylate (I.21o)



MW: 387.1682 g.mol⁻¹

Molecular Formula: C₂₁H₂₅NO₆

Compound **I.21o** was synthesized according to the general method from *tert*-butyl *N*-benzyl-2,5-dioxopyrrolidine-3-carboxylate **I.14a** (61 mg, 0.2 mmol, 1.0 equiv) and methyl 2-(acetoxymethyl)acrylate **I.19f** (32 mg, 0.2 mmol, 1.0 equiv). Compound **I.21o** was obtained as a white solid (66 mg, 85%) after purification by flash column chromatography over silica gel (PE/Et₂O = 95:5).

Mp: 59–62 °C.

[α]²⁰_D = +39.0 (*c* = 0.2, CHCl₃), ee = 55% (determined by SFC).

SFC: OD-H column, pressure = 100 bar, eluent = CO₂/MeOH (97:3), flow rate = 4.0 mL/min, detection wavelength = 220 nm, *t*_{R1} = 3.41 (minor), *t*_{R2} = 3.80 (major).

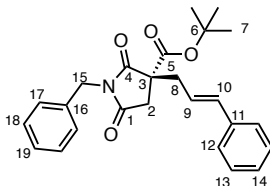
IR (neat): 1750, 1704, 1434, 1396, 1369, 1343, 1253, 1147, 1066, 965 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ 7.34 – 7.31 (m, 2H, H_{Ar}), 7.29 – 7.21 (m, 3H, H_{Ar}), 6.15 (s_{app}, 1H, H₁₀), 5.59 (d, *J* = 1.0 Hz, 1H, H₁₀), 4.63 (d, *J*_{AB} = 14.0 Hz, 1H, H₁₃), 4.60 (d, *J*_{AB} = 14.0 Hz, 1H, H₁₃), 3.69 (s, 3H, H₁₂), 3.13 (d, *J* = 14.6 Hz, 1H, H₂), 3.00 (d, *J*_{AB} = 18.4 Hz, 1H, H₈), 2.95 (d, *J*_{AB} = 14.4 Hz, 1H, H₂), 2.76 (d, *J*_{AB} = 18.4 Hz, 1H, H₈), 1.29 (s, 9H, H₇).

¹³C NMR (100 MHz, CDCl₃): δ 175.3 (s, C₄), 175.1 (s, C₁), 167.9 (s, C₅), 167.5 (s, C₁₁), 135.4 (s, C₁₄), 134.6 (s, C₉), 130.5 (s, C₁₀), 128.8 (s, 2C, C_{Ar}), 128.6 (s, 2C, C_{Ar}), 128.0 (s, C_{Ar}), 83.6 (s, C₆), 55.8 (s, C₃), 52.4 (s, C₁₂), 42.8 (s, C₁₃), 37.3 (s, C₈), 33.1 (s, C₂), 27.6 (s, 3C, C₇).

HRMS (ESI) *m/z*: calcd for C₂₁H₂₅NO₆Na [M+Na]⁺: 410.1574, found: 410.1575.

(*S*)-*tert*-Butyl-*N*-benzyl-3-cinnamyl-2,5-dioxopyrrolidine-3-carboxylate (**I.21p**)



MW: 405.1940 g.mol⁻¹

Molecular Formula: C₂₅H₂₇NO₄

Compound **I.21p** was synthesized according to the general method from *tert*-butyl 1-benzyl-2,5-dioxopyrrolidine-3-carboxylate **I.14a** (58 mg, 0.2 mmol, 1.0 equiv) and

cinnamyl acetate **I.19g** (33 μ L, 0.2 mmol, 1.0 equiv). Compound **I.21p** was obtained as a white solid (62 mg, 77%) after purification by flash column chromatography over silica gel (PE/Et₂O = 95:5).

Mp: 99–100 °C.

[α]²⁰_D = +57.5 (*c* = 0.2, CHCl₃), ee = 92% (determined by SFC).

SFC: OJ-H column, pressure = 100 bar, eluent = CO₂/MeOH (99:1), flow rate = 4.0 mL/min, detection wavelength = 220 nm, *t*_{R1} = 17.32 (major), *t*_{R2} = 19.25 (minor).

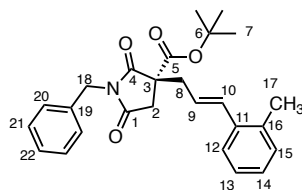
IR (neat): 1738, 1705, 1496, 1432, 1396, 1368, 1343, 1256, 1150, 1070, 970 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ 7.28 – 7.23 (m, 2H, H_{Ar}), 7.20 – 7.06 (m, 8H, H_{Ar}), 6.39 (d, *J* = 15.8 Hz, 1H, H₁₀), 5.77 (dt, *J* = 15.4, 7.6 Hz, 1H, H₉), 4.58 (s, 2H, H₁₅), 2.93 (d, *J*_{AB} = 18.2 Hz, 1H, H₂), 2.82 (ddd, *J*_{AB} = 14.0, 6.9, 1.3 Hz, 1H, H₈), 2.71 (dd, *J*_{AB} = 14.2, 8.2 Hz, 1H, H₈), 2.65 (d, *J*_{AB} = 18.2 Hz, 1H, H₂), 1.28 (s, 9H, H₇).

¹³C NMR (100 MHz, CDCl₃): δ 175.5 (s, C₄), 174.8 (s, C₁), 168.1 (s, C₅), 136.4 (s, C₁₇), 136.0 (s, C₁₀), 135.5 (s, C₁₁), 128.7 (s, 2C, C_{Ar}), 128.65 (s, 2C, C_{Ar}), 128.6 (s, 2C, C_{Ar}), 128.0 (s, C_{Ar}), 127.9 (s, C_{Ar}), 126.4 (s, 2C, C_{Ar}), 122.2 (s, C₉), 83.5 (s, C₆), 55.4 (s, C₃), 42.8 (s, C₁₅), 37.3 (s, C₂), 36.7 (s, C₈), 27.7 (s, 3C, C₇).

HRMS (ESI) *m/z*: calcd for C₂₅H₂₇NO₄ Na [M+Na]⁺: 428.1832, found: 428.1829.

(S)-tert-Butyl-(E)-N-benzyl-2,5-dioxo-3-[3-(o-tolyl)allyl]pyrrolidine-3-carboxylate
(I.21q)



MW: 419.2097 g.mol⁻¹

Molecular Formula: C₂₆H₂₉NO₄

Compound **I.21q** was synthesized according to the general method from *tert*-butyl *N*-benzyl-2,5-dioxopyrrolidine-3-carboxylate **I.14a** (58 mg, 0.2 mmol, 1.0 equiv) and (*E*)-3-(*o*-tolyl)allyl acetate **I.19h** (38 mg, 0.2 mmol, 1.0 equiv). Compound **I.21q** was obtained as a white solid (46 mg, 55%) after purification by flash column chromatography over silica gel (PE/Et₂O = 95:5).

Mp: 93–95 °C.

[α]²⁰_D = +26.7 (*c* = 0.1, CHCl₃), ee = 76% (determined by SFC).

SFC: AD-H column, pressure = 100 bar, eluent = CO₂/MeOH (95:5), flow rate = 4.0 mL/min, detection wavelength = 220 nm, *t*_{R1} = 4.20 (major), *t*_{R2} = 6.24 (minor).

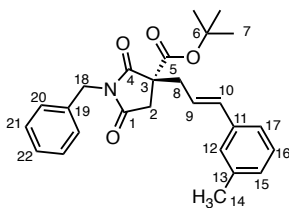
IR (neat): 2361, 1740, 1708, 1396, 1151, 749 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ 7.37 – 7.34 (m, 2H, H_{Ar}), 7.25 – 7.20 (m, 3H, H_{Ar}), 7.18 – 7.08 (m, 4H, H_{Ar}), 6.70 (d, *J* = 15.6 Hz, 1H, H₁₀), 5.75 (m, 1H, H₉), 4.68 (s, 2H, H₁₈), 3.05 (d, *J*_{AB} = 18.1 Hz, 1H, H₂), 2.95 (ddd, *J*_{AB} = 14.0, 7.0, 1.3 Hz, 1H, H₈), 2.83 (ddd, *J*_{AB} = 14.0, 8.1, 1.0 Hz, 1H, H₈), 2.77 (d, *J*_{AB} = 18.1 Hz, 1H, H₂), 2.29 (s, 3H, H₁₇), 1.38 (s, 9H, H₇).

¹³C NMR (100 MHz, CDCl₃): δ 175.4 (s, C₄), 174.9 (s, C₁), 168.1 (s, C₅), 135.7 (s, C₁₉), 135.5 (s, C₁₆), 135.3 (s, C₁₁), 134.0 (s, C₁₀), 130.3 (s, C_{Ar}), 128.7 (s, 2C, C_{Ar}), 128.6 (s, 2C, C_{Ar}), 128.0 (s, C_{Ar}), 127.8 (s, C_{Ar}), 126.2 (s, C₉), 125.8 (s, C_{Ar}), 123.6 (s, C₉), 83.4 (s, C₆), 55.5 (s, C₃), 42.8 (s, C₁₈), 37.4 (s, C₂), 36.9 (s, C₈), 27.7 (s, 3C, C₇), 19.8 (s, C₁₇).

HRMS (ESI) *m/z*: calcd for C₂₆H₂₉NO₄ Na [M+Na]⁺: 442.1989, found: 442.1985.

(S)-tert-Butyl-(E)-N-benzyl-2,5-dioxo-3-[3-(*m*-tolyl)allyl]pyrrolidine-3-carboxylate (I.21r)



MW: 419.2097 g.mol⁻¹

Molecular Formula: C₂₆H₂₉NO₄

Compound **I.21r** was synthesized according to the general method from *tert*-butyl *N*-benzyl-2,5-dioxopyrrolidine-3-carboxylate **I.14a** (58 mg, 0.2 mmol, 1.0 equiv) and (*E*)-3-(*m*-tolyl)allyl acetate **I.19i** (38 mg, 0.2 mmol, 1.0 equiv). Compound **I.21r** was obtained as a white solid (75 mg, 89%) after purification by flash column chromatography over silica gel (PE/Et₂O = 95:5).

Mp: 102–104 °C.

$[\alpha]_D^{20} = +60.7$ ($c = 0.3$, CHCl_3), $ee = 92\%$ (determined by SFC).

SFC: AD-H column, pressure = 100 bar, eluent = CO_2/MeOH (92:8), flow rate = 4.0 mL/min, detection wavelength = 220 nm, $t_{R1} = 3.40$ (major), $t_{R2} = 5.77$ (minor).

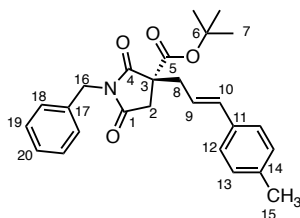
IR (neat): 1739, 1707, 1432, 1396, 1369, 1343, 1254, 1151, 970 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ 7.37 – 7.33 (m, 2H, H_{Ar}), 7.27 – 7.22 (m, 3H, H_{Ar}), 7.20 – 7.14 (m, 1H, H_{Ar}), 7.07–6.98 (m, 3H, H_{Ar}), 6.47 (d, $J = 15.7\text{ Hz}$, 1H, H_{10}), 5.88 (m, 1H, H_9), 4.68 (s, 2H, H_{18}), 3.02 (d, $J_{AB} = 18.2\text{ Hz}$, 1H, H_2), 2.91 (ddd, $J_{AB} = 14.0, 7.0, 1.3\text{ Hz}$, 1H, H_8), 2.83 (ddd, $J_{AB} = 14.0, 7.0, 1.3\text{ Hz}$, 1H, H_8), 2.76 (d, $J_{AB} = 16.2\text{ Hz}$, 1H, H_2), 2.33 (s, 3H, H_{14}), 1.37 (s, 9H, H_7).

^{13}C NMR (101 MHz, CDCl_3) δ 175.4 (s, C_4), 174.9 (s, C_1), 168.1 (s, C_5), 138.1 (s, C_{11}), 136.4 (s, C_{13}), 136.1 (s, C_{10}), 135.5 (s, C_{19}), 128.7 (s, 2C, C_{Ar}), 128.7 (s, C_{Ar}), 128.6 (s, 2C, C_{Ar}), 128.5 (s, C_{Ar}), 128.0 (s, C_{Ar}), 127.1 (s, C_{Ar}), 123.5 (s, C_{Ar}), 121.9 (s, C_9), 83.4 (s, C_6), 55.5 (s, C_3), 42.8 (s, C_{18}), 37.3 (s, C_2), 36.6 (s, C_8), 27.7 (s, 3C, C_7), 21.4 (s, C_{14}).

HRMS (ESI) m/z : calcd for $\text{C}_{26}\text{H}_{29}\text{NO}_4\text{Na}$ $[\text{M}+\text{Na}]^+$: 442.1989, found: 442.1988.

(S)-tert-Butyl-(E)-N-benzyl-2,5-dioxo-3-[3-(p-tolyl)allyl]pyrrolidine-3-carboxylate (I.21s)



MW: 419.2097 $\text{g}\cdot\text{mol}^{-1}$

Molecular Formula: $\text{C}_{26}\text{H}_{29}\text{NO}_4$

Compound **I.21s** was synthesized according to the general method from *tert*-butyl *N*-benzyl-2,5-dioxopyrrolidine-3-carboxylate **I.14a** (58 mg, 0.2 mmol, 1.0 equiv) and (*E*)-3-(*p*-tolyl)allyl acetate **I.19j** (38 mg, 0.2 mmol, 1.0 equiv). Compound **I.21s** was obtained as a white solid (66 mg, 79%) after purification by flash column chromatography over silica gel ($\text{PE}/\text{Et}_2\text{O} = 95:5$).

Mp: 107–108 °C.

$[\alpha]_D^{20} = +59.5$ ($c = 0.2$, CHCl_3), $ee = 96\%$ (determined by SFC).

SFC: AD-H column, pressure = 100 bar, eluent = CO₂/MeOH (95:5), flow rate = 4.0 mL/min, detection wavelength = 220 nm, *t*_{R1} = 5.22 (major), *t*_{R2} = 6.36 (minor).

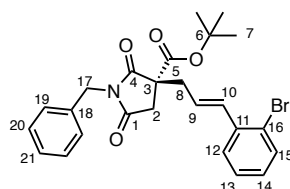
IR (neat): 2978, 1737, 1704, 1512, 1432, 1395, 1368, 1343, 1228, 1150, 1078, 1026, 969 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ 7.39 – 7.35 (m, 2H, H_{Ar}), 7.29 – 7.26 (m, 3H, H_{Ar}), 7.11 – 7.07 (m, 4H, H_{Ar}), 6.47 (d, *J* = 15.7 Hz, 1H, H₁₀), 5.86 – 5.78 (m, 1H, H₉), 4.69 (s, 2H, H₁₆), 3.03 (d, *J* = 18.2 Hz, 1H, H₂), 2.91 (ddd, *J*_{AB} = 14.0, 6.9, 1.3 Hz, 1H, H₈), 2.69 (ddd, *J*_{AB} = 14.0, 6.9, 1.3 Hz, 1H, H₈), 2.64 (d, *J*_{AB} = 18.6 Hz, 1H, H₂), 2.35 (s, 3H, H₁₅), 1.39 (s, 9H, H₇).

¹³C NMR (100 MHz, CDCl₃): δ 175.5 (s, C₄), 174.9 (s, C₁), 168.2 (s, C₅), 137.7 (s, C₁₄), 135.9 (s, C₁₀), 135.6 (s, C₁₇), 133.7 (s, C₁₁), 129.3 (s, 2C, C_{Ar}), 128.7 (s, 2C, C_{Ar}), 128.66 (s, 2C, C_{Ar}), 128.0 (s, C_{Ar}), 126.3 (s, 2C, C_{Ar}), 121.1 (s, C₉), 83.4 (s, C₆), 55.5 (s, C₃), 42.8 (s, C₁₆), 37.3 (s, C₂), 36.8 (s, C₈), 27.7 (s, 3C, C₇), 21.3 (s, C₁₅).

HRMS (ESI) *m/z*: calcd for C₂₆H₂₉NO₄ Na [M+Na]⁺: 442.1989, found: 442.1984.

(*S*)-*tert*-Butyl-(*E*)-*N*-benzyl-3-[3-(2-bromophenyl)allyl]-2,5-dioxopyrrolidine-3-carboxylate (I.21t)



MW: 483.1045 g.mol⁻¹

Molecular Formula: C₂₅H₂₆BrNO₄

Compound **I.21t** was synthesized according to the general method from *tert*-butyl 1-benzyl-2,5-dioxopyrrolidine-3-carboxylate **I.14a** (58 mg, 0.2 mmol, 1.0 equiv) and (*E*)-3-(2-bromophenyl)allyl acetate **I.19k** (51 mg, 0.2 mmol, 1.0 equiv). Compound **I.21t** was obtained as a white solid (29 mg, 30%) after purification by flash column chromatography over silica gel (PE/Et₂O = 95:5).

Mp: 109–110 °C.

[α]²⁰_D = +26.7 (*c* = 0.1, CHCl₃), ee = 76% (determined by SFC).

SFC: AD-H column, pressure = 100 bar, eluent = CO₂/MeOH (95:5), flow rate = 4.0 mL/min, detection wavelength = 220 nm, *t*_{R1} = 6.68 (major), *t*_{R2} = 9.32 (minor).

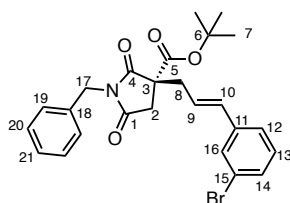
IR (neat): 1781, 1738, 1704, 1466, 1433, 1395, 1369, 1342, 1256, 1148, 1074, 1022, 968 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.51 (dd, *J* = 7.9, 1.1 Hz, 1H, H_{Ar}), 7.38 – 7.05 (m, 8H, H_{Ar}), 6.80 (d, *J* = 15.7 Hz, 1H, H₁₀), 5.83 – 5.75 (m, 1H, H₉), 4.67 (s, 2H, H₁₇), 3.04 (d, *J*_{AB} = 18.2 Hz, 1H, H₂), 2.93 (ddd, *J*_{AB} = 14.0, 6.9, 1.4 Hz, 1H, H₈), 2.84 (ddd, *J*_{AB} = 14.1, 8.3, 1.1 Hz, 1H, H₈), 2.76 (d, *J*_{AB} = 18.2 Hz, 1H, H₂), 1.36 (s, 9H, H₇).

¹³C NMR (101 MHz, CDCl₃) δ 175.3 (s, C₄), 174.8 (s, C₁), 168.0 (s, C₅), 136.4 (s, C₁₈), 135.5 (s, C₁₁), 134.82 (s, C₁₀), 132.9 (s, C_{Ar}), 129.1 (s, C_{Ar}), 128.7 (s, 2C, C_{Ar}), 128.7 (s, 2C, C_{Ar}), 128.0 (s, C_{Ar}), 127.6 (s, C_{Ar}), 127.2 (s, C₉), 125.6 (s, C_{Ar}), 123.4 (s, C₁₆), 83.5 (s, C₆), 55.3 (s, C₃), 42.9 (s, C₁₇), 37.4 (s, C₂), 36.7 (s, C₈), 27.7 (s, 3C, C₇).

HRMS (ESI) *m/z*: calcd for C₂₅H₂₆BrNO₄ Na [M+Na]⁺: 506.0937 and 508.0917, found: 506.0938 and 508.0918.

(S)-tert-Butyl-(E)-1-benzyl-3-[3-(3-bromophenyl)allyl]-2,5-dioxopyrrolidine-3-carboxylate (I.21u)



MW: 483.1045 g.mol⁻¹

Molecular Formula: C₂₅H₂₆BrNO₄

Compound **I.21u** was synthesized according to the general method from *tert*-butyl *N*-benzyl-2,5-dioxopyrrolidine-3-carboxylate **I.14a** (58 mg, 0.2 mmol, 1.0 equiv) and (*E*)-3-(3-bromophenyl)allyl acetate **I.19l** (51 mg, 0.2 mmol, 1.0 equiv). Compound **I.21u** was obtained as a white solid (82 mg, 85%) after purification by flash column chromatography over silica gel (PE/Et₂O = 95:5).

Mp: 101–103 °C.

[α]²⁰_D = +58.1 (*c* = 0.16, CHCl₃), ee = 77% (determined by SFC).

SFC: AD-H column, pressure = 100 bar, eluent = CO₂/MeOH (95:5), flow rate = 4.0 mL/min, detection wavelength = 220 nm, *t*_{R1} = 11.59 (major), *t*_{R2} = 18.12 (minor).

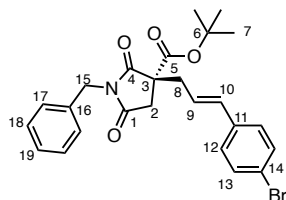
IR (neat): 1739, 1707, 1431, 1396, 1369, 1343, 1256, 1150, 1071, 969 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ 7.31 – 7.26 (m, 4H, H_{Ar}), 7.21 – 7.17 (m, 3H, H_{Ar}), 7.09 – 7.01 (m, 2H, H_{Ar}), 6.34 (d, *J* = 15.7 Hz, 1H, H₁₀), 5.83 (dt, *J* = 15.4, 7.6 Hz, 1H, H₉), 4.62 (s, 2H, H₁₇), 2.97 (d, *J*_{AB} = 18.2 Hz, 1H, H₂), 2.84 (ddd, *J*_{AB} = 14.0, 7.1, 1.0 Hz, 1H, H₈), 2.74 (dd, *J*_{AB} = 14.1, 8.1 Hz, 1H, H₈), 2.66 (d, *J*_{AB} = 18.2 Hz, 1H, H₂), 1.31 (s, 9H, H₇).

¹³C NMR (100 MHz, CDCl₃): δ 175.3 (s, C₄), 174.7 (s, C₁), 168.0 (s, C₅), 138.5 (s, C₁₁), 135.4 (s, C₁₈), 134.5 (s, C₁₀), 130.7 (s, C_{Ar}), 130.1 (s, C_{Ar}), 129.2 (s, C_{Ar}), 128.7 (s, 2C, C_{Ar}), 128.6 (s, 2C, C_{Ar}), 128.1 (s, C_{Ar}), 125.0 (s, C_{Ar}), 123.9 (s, C₉), 122.8 (s, C₁₅), 83.6 (s, C₆), 55.3 (s, C₃), 42.9 (s, C₁₇), 37.4 (s, C₂), 36.6 (s, C₈), 27.7 (s, 3C, C₇).

HRMS (ESI) *m/z*: calcd for C₂₅H₂₆BrNO₄ Na [M+Na]⁺: 506.0937 and 508.0917, found: 506.0938 and 508.0916.

(*S*)-*tert*-Butyl-(*E*)-*N*-benzyl-3-[3-(4-bromophenyl)allyl]-2,5-dioxopyrrolidine-3-carboxylate (I.21v**)**



MW: 483.1045 g.mol⁻¹

Molecular Formula: C₂₅H₂₆BrNO₄

Compound **I.21v** was synthesized according to method **B** from *tert*-butyl *N*-benzyl-2,5-dioxopyrrolidine-3-carboxylate **I.14a** (58 mg, 0.2 mmol, 1.0 equiv) and (*E*)-3-(4-bromophenyl)allyl acetate **I.19m** (51 mg, 0.2 mmol, 1.0 equiv). Compound **I.21v** was obtained as a white solid (83 mg, 86%) after purification by flash column chromatography over silica gel (PE/Et₂O = 95:5).

Mp: 117–119 °C.

[α]²⁰_D = +53.8 (*c* = 0.18, CHCl₃), ee = 89% (determined by SFC).

SFC: OD-H column, pressure = 100 bar, eluent = CO₂/MeOH (95:5), flow rate = 4.0 mL/min, detection wavelength = 220 nm, *t*_{R1} = 10.32 (minor), *t*_{R2} = 11.19 (major).

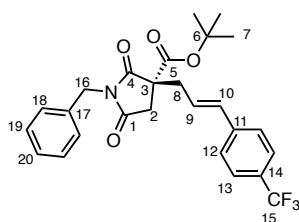
IR (neat): 1739, 1707, 1487, 1432, 1396, 1369, 1343, 1256, 1151, 1072, 1008, 971 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ 7.39 – 7.35 (m, 4H, H_{Ar}), 7.28 – 7.24 (m, 3H, H_{Ar}), 7.00 (d, $J = 7.2$ Hz, 2H, H_{Ar}), 6.41 (d, $J = 15.8$ Hz, 1H, H_{10}), 5.84 (dt, $J = 15.6, 7.5$ Hz, 1H, H_9), 4.68 (s, 2H, H_{15}), 3.04 (d, $J_{\text{AB}} = 18.1$ Hz, 1H, H_2), 2.91 (dd, $J_{\text{AB}} = 14.1, 6.9$ Hz, 1H, H_8), 2.79 (dd, $J_{\text{AB}} = 14.1, 8.2$ Hz, 1H, H_8), 2.72 (d, $J_{\text{AB}} = 18.2$ Hz, 1H, H_2), 1.38 (s, 9H, H_7).

^{13}C NMR (100 MHz, CDCl_3): δ 175.3 (s, C_4), 174.7 (s, C_1), 168.0 (s, C_5), 135.5 (s, C_{16}), 135.3 (s, C_{11}), 134.7 (s, C_{10}), 131.7 (s, 2C, C_{Ar}), 128.7 (s, 4C, C_{Ar}), 128.0 (s, C_{Ar}), 127.9 (s, 2C, C_{Ar}), 123.1 (s, C_9), 121.6 (s, C_{14}), 83.5 (s, C_6), 55.3 (s, C_3), 42.9 (s, C_{15}), 37.4 (s, C_2), 36.7 (s, C_8), 27.7 (s, 3C, C_7).

HRMS (ESI) m/z : calcd for $\text{C}_{25}\text{H}_{26}\text{BrNO}_4 \text{ Na}$ $[\text{M}+\text{Na}]^+$: 506.0937 and 508.0917, found: 506.0938 and 508.0978.

(S)-tert-Butyl-(E)-N-benzyl-2,5-dioxo-3-{3-[4(trifluoromethyl)phenyl]allyl}pyrrolidine-3-carboxylate (I.21w)



MW: 473.1814 $\text{g}\cdot\text{mol}^{-1}$

Molecular Formula: $\text{C}_{26}\text{H}_{26}\text{F}_3\text{NO}_4$

Compound **I.21w** was synthesized according to the general method from *tert*-butyl *N*-benzyl-2,5-dioxopyrrolidine-3-carboxylate **I.14a** (58 mg, 0.2 mmol, 1.0 equiv) and (*E*)-3-[4-(trifluoromethyl)phenyl]allyl acetate **I.19n** (49 mg, 0.2 mmol, 1.0 equiv). Compound **I.21w** was obtained as a white solid (90 mg, 95%) after purification by flash column chromatography over silica gel (PE/Et₂O = 95:5).

Mp: 127–129 °C.

$[\alpha]_{\text{D}}^{20} = +51.0$ ($c = 0.2$, CHCl_3), ee = 76% (determined by SFC).

SFC: AD-H column, pressure = 100 bar, eluent = CO_2/MeOH (95:5), flow rate = 4.0 mL/min, detection wavelength = 220 nm, $t_{\text{R}1} = 2.92$ (minor), $t_{\text{R}2} = 3.64$ (major).

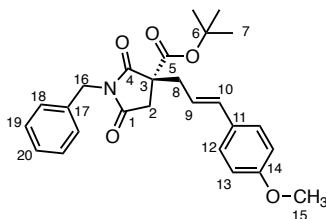
IR (neat): 1739, 1707, 1615, 1433, 1396, 1370, 1324, 1257, 1153, 1123, 1068, 1016, 972 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ 7.51 – 7.50 (m, 2H, H_{Ar}), 7.36 – 7.34 (m, 2H, H_{Ar}), 7.25 – 7.17 (m, 5H, H_{Ar}), 6.49 (d, *J* = 15.8 Hz, 1H, H₁₀), 5.95 (dt, *J* = 15.4, 7.6 Hz, 1H, H₉), 4.67 (s, 2H, H₁₆), 3.04 (d, *J*_{AB} = 18.2 Hz, 1H, H₈), 2.92 (dd, *J*_{AB} = 14.1, 7.0 Hz, 1H, H₂), 2.81 (dd, *J*_{AB} = 14.2, 8.1 Hz, 1H, H₂), 2.70 (d, *J*_{AB} = 18.2 Hz, 1H, H₈), 1.37 (s, 9H, H₇).

¹³C NMR (100 MHz, CDCl₃): δ 175.3 (s, C₄), 174.7 (s, C₁), 168.0 (s, C₅), 139.8 (s, C₁₁), 135.5 (s, C₁₇), 134.6 (s, C₁₀), 129.6 (d, *J* = 32.6 Hz, C₁₄), 128.8 (s, 2C, C_{Ar}), 128.7 (s, 2C, C_{Ar}), 128.1 (s, C_{Ar}), 126.6 (s, 2C, C_{Ar}), 125.6 (q, *J* = 32.6 Hz, 2C, C_{Ar}), 125.1 (s, C_{Ar}), 122.9 (s, C_{Ar}), 83.7 (s, C₆), 55.3 (s, C₃), 42.9 (s, C₁₀), 37.5 (s, C₈), 36.8 (s, C₂), 27.7 (s, 3C, C₇).

HRMS (ESI) *m/z*: calcd for C₂₆H₂₆F₃NO₄ Na [M+Na]⁺: 496.1706, found: 496.1705.

(*S*)-*tert*-Butyl-(*E*)-*N*-benzyl-3-[3-(4-methoxyphenyl)allyl]-2,5-dioxopyrrolidine-3-carboxylate (I.21x)



MW: 435.2046 g.mol⁻¹

Molecular Formula: C₂₆H₂₉NO₅

Compound **I.21x** was synthesized according to the general method from *tert*-butyl *N*-benzyl-2,5-dioxopyrrolidine-3-carboxylate **I.14a** (58 mg, 0.2 mmol, 1.0 equiv) and (*E*)-3-(4-methoxyphenyl)allyl acetate **I.19o** (41 mg, 0.2 mmol, 1.0 equiv). Compound **I.21x** was obtained as a white solid (79 mg, 91%) after purification by flash column chromatography over silica gel (PE/Et₂O = 95:5).

Mp: 96–99 °C.

[α]_D²⁰ = +55.0 (*c* = 0.16, CHCl₃), ee = 94% (determined by SFC).

SFC: AD-H column, pressure = 100 bar, eluent = CO₂/MeOH (95:5), flow rate = 4.0 mL/min, detection wavelength = 220 nm, *t*_{R1} = 8.01 (major), *t*_{R2} = 9.95 (minor).

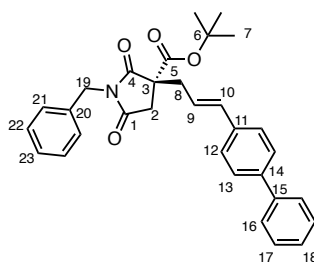
IR (neat): 1738, 1704, 1607, 1511, 1456, 1432, 1395, 1368, 1343, 1249, 1178, 1149, 1032, 970 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ 7.37 (dd, *J* = 6.6, 2.8 Hz, 2H, H_{Ar}), 7.27 – 7.26 (m, 3H, H_{Ar}), 7.11 (d, *J* = 8.7 Hz, 2H, H_{Ar}), 6.82 (d, *J* = 8.7 Hz, 2H, H_{Ar}), 6.44 (d, *J* = 15.7 Hz, 1H, H₁₀), 5.76 – 5.68 (m, 1H, H₉), 4.69 (s, 2H, H₁₆), 3.81 (s, 3H, H₁₅), 3.03 (d, *J*_{AB} = 18.1 Hz, 1H, H₂), 2.93 – 2.76 (m, 2H, H₈), 2.77 (d, *J*_{AB} = 18.0 Hz, 1H, H₂), 1.39 (s, 9H, H₇).

¹³C NMR (100 MHz, CDCl₃): δ 175.5 (s, C₄), 174.9 (s, C₁), 168.2 (s, C₅), 159.4 (s, C₁₄), 135.5 (s, C₁₇), 135.4 (s, C₁₀), 129.3 (s, C_{Ar}), 128.7 (s, 2C, C_{Ar}), 128.6 (s, 2C, C_{Ar}), 127.9 (s, C_{Ar}), 127.5 (s, 2C, C_{Ar}), 119.7 (s, C₉), 114.0 (s, 2C, C_{Ar}), 83.4 (s, C₆), 55.5 (s, C₁₅), 55.3 (s, C₃), 42.8 (s, C₁₆), 37.3 (s, C₂), 36.7 (s, C₈), 27.7 (s, 3C, C₇).

HRMS (ESI) *m/z*: calcd for C₂₆H₂₉NO₅ Na [M+Na]⁺: 458.1938, found: 458.1935.

(*S*)-*tert*-Butyl-(*E*)-3-{3-([1,1'-biphenyl]-4-yl)allyl}-*N*-benzyl-2,5-dioxopyrrolidine-3-carboxylate (I.21y**)**



MW: 481.2253 g.mol⁻¹

Molecular Formula: C₃₁H₃₁NO₄

Compound **I.21y** was synthesized according to the general method from *tert*-butyl *N*-benzyl-2,5-dioxopyrrolidine-3-carboxylate **I.14a** (58 mg, 0.2 mmol, 1.0 equiv) and (*E*)-3-([1,1'-biphenyl]-4-yl)allyl acetate **I.19p** (50 mg, 0.2 mmol, 1.0 equiv). Compound **I.21y** was obtained as a white solid (87 mg, 90%) after purification by flash column chromatography over silica gel (PE/Et₂O = 95:5).

Mp: 140–141 °C.

[α]_D²⁰ = +63.4 (*c* = 0.16, CHCl₃), ee = 92% (determined by SFC).

SFC: OD-H column, pressure = 100 bar, eluent = CO₂/MeOH (92:8), flow rate = 4.0 mL/min, detection wavelength = 220 nm, *t*_{R1} = 18.69 (minor), *t*_{R2} = 22.87 (major).

IR (neat): 1737, 1704, 1486, 1481, 1395, 1369, 1342, 1256, 1148, 1077, 971 cm⁻¹.

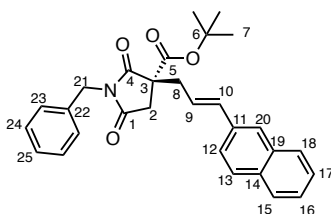
¹H NMR (400 MHz, CDCl₃): δ 7.64 – 7.61 (m, 2H, H_{Ar}), 7.55 – 7.53 (m, 2H, H_{Ar}), 7.50 – 7.46 (m, 2H, H_{Ar}), 7.41 – 7.36 (m, 3H, H_{Ar}), 7.30 – 7.25 (m, 5H, H_{Ar}), 6.55 (d, *J* = 15.8

Hz, 1H, H₁₀), 5.98 – 5.90 (m, 1H, H₉), 4.72 (s, 2H, H₁₉), 3.07 (d, J_{AB} = 18.2 Hz, 1H, H₂), 2.96 (ddd, J_{AB} = 14.0, 7.0, 1.3 Hz, 1H, H₈), 2.86 (ddd, J_{AB} = 14.9, 8.2, 1.1 Hz, 1H, H₈), 2.79 (d, J_{AB} = 18.2 Hz, 1H, H₂), 1.41 (s, 9H, H₇).

¹³C NMR (100 MHz, CDCl₃): δ 175.4 (s, C₄), 174.8 (s, C₁), 168.1 (s, C₅), 140.7 (s, C₁₅), 140.6 (s, C₁₄), 135.5 (s, 2C, C_{Ar}), 135.4 (s, C₁₀), 128.9 (s, 2C, C_{Ar}), 128.7 (s, 2C, C_{Ar}), 128.7 (s, 2C, C_{Ar}), 128.0 (s, C_{Ar}), 127.5 (s, C_{Ar}), 127.3 (s, 2C, C_{Ar}), 127.0 (s, 2C, C_{Ar}), 126.8 (s, 2C, C_{Ar}), 122.2 (s, C₉), 83.5 (s, C₆), 55.5 (s, C₃), 42.9 (s, C₁₉), 37.4 (s, C₂), 36.8 (s, C₈), 27.7 (s, 3C, C₇).

HRMS (ESI) m/z : calcd for C₃₁H₃₁NO₄ Na [M+Na]⁺: 504.2145, found: 504.2145.

(S)-tert-Butyl-(E)-N-benzyl-3-(3-(naphthalen-2-yl)allyl)-2,5-dioxopyrrolidine-3-carboxylate (I.21z)



MW: 455.2097 g.mol⁻¹

Molecular Formula: C₂₉H₂₉NO₄

Compound **I.21z** was synthesized according to the general method from *tert*-butyl *N*-benzyl-2,5-dioxopyrrolidine-3-carboxylate **I.14a** (58 mg, 0.2 mmol, 1.0 equiv) and (*E*)-3-(naphthalen-2-yl)allyl acetate **I.19q** (45 mg, 0.2 mmol, 1.0 equiv). Compound **I.21z** was obtained as a white solid (76 mg, 83%) after purification by flash column chromatography over silica gel (PE/Et₂O = 95:5).

Mp: 152–154 °C.

[α]²⁰_D = +65.0 (c = 0.16, CHCl₃), ee = 86% (determined by SFC).

SFC: OD-H column, pressure = 100 bar, eluent = CO₂/MeOH (92:8), flow rate = 4.0 mL/min, detection wavelength = 220 nm, t_{R1} = 12.76 (minor), t_{R2} = 15.92 (major).

IR (neat): 1735, 1703, 1431, 1398, 1366, 1341, 1287, 1274, 1226, 1179, 1148, 1074, 1042, 974, 950 cm⁻¹.

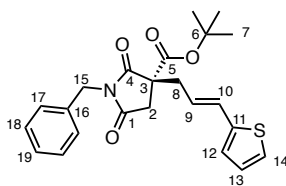
¹H NMR (400 MHz, CDCl₃): δ 7.69 – 7.65 (m, 2H, H_{Ar}), 7.61 (d, J = 8.6 Hz, 1H, H_{Ar}), 7.48 (s, 1H, H_{Ar}), 7.37 – 7.31 (m, 2H, H_{Ar}), 7.25 – 7.20 (m, 3H, H_{Ar}), 7.13 – 7.09 (m, 3H, H_{Ar}),

6.52 (d, $J = 15.7$ Hz, 1H, H_{10}), 5.89 (dt, $J = 15.4, 8.0$ Hz, 1H, H_9), 4.58 (s, 2H, H_{21}), 2.94 (d, $J_{AB} = 18.2$ Hz, 1H, H_2), 2.85 (ddd, $J_{AB} = 14.0, 7.0, 1.2$ Hz, 1H, H_8), 2.75 (ddd, $J_{AB} = 14.1, 8.1, 1.0$ Hz, 1H, H_8), 2.68 (d, $J_{AB} = 18.2$ Hz, 1H, H_2), 1.27 (s, 9H, H_7).

^{13}C NMR (100 MHz, CDCl_3): δ 175.4 (s, C_4), 174.8 (s, C_1), 168.1 (s, C_5), 136.1 (s, C_{10}), 135.5 (s, C_{22}), 133.8 (s, C_{Ar}), 133.5 (s, C_{Ar}), 133.1 (s, C_{Ar}), 128.7 (s, 2C, C_{Ar}), 128.6 (s, 2C, C_{Ar}), 128.3 (s, C_{Ar}), 128.0 (s, C_{Ar}), 128.0 (s, C_{Ar}), 127.7 (s, C_{Ar}), 126.4 (s, C_{Ar}), 126.38 (s, C_{Ar}), 126.1 (s, C_{Ar}), 123.4 (s, C_{Ar}), 122.5 (s, C_9), 83.5 (s, C_6), 55.5 (s, C_3), 42.8 (s, C_{21}), 37.4 (s, C_2), 36.8 (s, C_8), 27.7 (s, 3C, C_7).

HRMS (ESI) m/z : calcd for $\text{C}_{29}\text{H}_{29}\text{NO}_4\text{Na}$ $[\text{M}+\text{Na}]^+$: 478.1989, found: 478.1988.

(*S*)-*tert*-Butyl-(*E*)-*N*-benzyl-2,5-dioxo-3-[3-(thiophen-2-yl)allyl]pyrrolidine-3-carboxylate (I.21za**)**



MW/g (mol): 411.1504 g.mol⁻¹

Molecular Formula: $\text{C}_{23}\text{H}_{25}\text{NO}_4\text{S}$

Compound **I.21za** was synthesized according to the general method from *tert*-butyl *N*-benzyl-2,5-dioxopyrrolidine-3-carboxylate **I.14a** (58 mg, 0.2 mmol, 1.0 equiv) and (*E*)-3-(thiophen-2-yl)allyl acetate **I.19r** (36 mg, 0.2 mmol, 1.0 equiv). Compound **I.21za** was obtained as a white solid (77 mg, 94%) after purification by flash column chromatography over silica gel (PE/Et₂O = 95:5).

Mp: 86–87 °C.

$[\alpha]_{\text{D}}^{20} = +42.0$ ($c = 0.1$, CHCl_3), ee = 95% (determined by SFC).

SFC: AD-H column, pressure = 100 bar, eluent = CO_2/MeOH (95:5), flow rate = 4.0 mL/min, detection wavelength = 220 nm, $t_{\text{R}1} = 6.54$ (major), $t_{\text{R}2} = 11.92$ (minor).

IR (neat): 1738, 1706, 1432, 1394, 1369, 1343, 1256, 1150, 961 cm^{-1} .

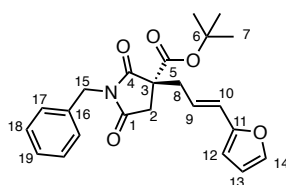
^1H NMR (400 MHz, CDCl_3): δ 7.25 – 7.23 (m, 2H, H_{Ar}), 7.16 – 7.12 (m, 3H, H_{Ar}), 7.04 (d, $J = 5.0$ Hz, 1H, H_{14}), 6.84 (dd, $J = 5.1, 3.6$ Hz, 1H, H_{13}), 6.76 (d, $J = 3.3$ Hz, 1H, H_{12}), 6.52 (d, $J = 15.5$ Hz, 1H, H_{10}), 5.67 (dt, $J = 15.4, 7.6$ Hz, 1H, H_9), 4.58 (s, 2H, H_{15}), 2.93 (d, J_{AB}

= 18.2 Hz, 1H, H₂), 2.80 – 2.68 (m, 2H, H₈), 2.64 (d, *J*_{AB} = 18.1 Hz, 1H, H₂), 1.27 (s, 9H, H₇).

¹³C NMR (100 MHz, CDCl₃): δ 175.3 (s, C₄), 174.8 (s, C₁), 168.0 (s, C₅), 141.4 (s, C₁₁), 135.4 (s, C₁₆), 128.9 (s, C₁₀), 128.7 (s, 2C, C_{Ar}), 128.5 (s, 2C, C_{Ar}), 127.9 (s, C_{Ar}), 127.4 (s, C_{Ar}), 125.8 (s, C_{Ar}), 124.5 (s, C_{Ar}), 121.8 (s, C₉), 85.5 (s, C₆), 55.5 (s, C₃), 42.8 (s, C₁₅), 37.3 (s, C₂), 36.4 (s, C₈), 27.7 (s, 3C, C₇).

HRMS (ESI) *m/z*: calcd for C₂₃H₂₅NO₄S Na [M+Na]⁺: 434.1397, found: 434.1393.

(*S*)-*tert*-Butyl-(*E*)-*N*-benzyl-3-[3-(furan-2-yl)allyl]-2,5-dioxopyrrolidine-3-carboxylate (I.21zb)



MW: 395.1733 g.mol⁻¹

Molecular Formula: C₂₃H₂₅NO₅

Compound **I.21zb** was synthesized according to the general method from *tert*-butyl 1-benzyl-2,5-dioxopyrrolidine-3-carboxylate **I.14a** (58 mg, 0.2 mmol, 1.0 equiv) and (*E*)-3-(thiophen-2-yl)allyl acetate **I.19s** (36 mg, 0.2 mmol, 1.0 equiv). Compound **I.21zb** was obtained as a white solid (60 mg, 76%) after purification by flash column chromatography over silica gel (PE/Et₂O = 95:5).

Mp: 77–79 °C.

[α]²⁰_D = +74.7 (*c* = 0.17, CHCl₃), ee = 96% (determined by SFC).

SFC: AD-H column, pressure = 100 bar, eluent = CO₂/MeOH (95:5), flow rate = 4.0 mL/min, detection wavelength = 220 nm, *t*_{R1} = 3.82 (major), *t*_{R2} = 5.79 (minor).

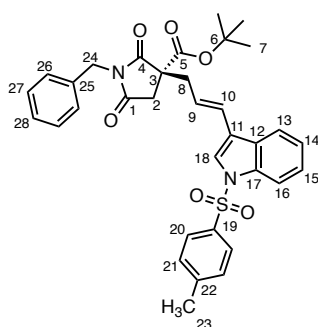
IR (neat): 1738, 1705, 1432, 1396, 1369, 1343, 1256, 1150, 1013, 965 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ 7.36 – 7.31 (m, 3H, H_{Ar}), 7.29 – 7.24 (m, 3H, H_{Ar}), 6.36 (dd, *J* = 3.3, 1.8 Hz, 1H, H_{Ar}), 6.31 (d, *J* = 15.7 Hz, 1H, H₁₃), 6.16 (d, *J* = 3.3 Hz, 1H, H₁₀), 5.87 (dt, *J* = 15.6, 7.7 Hz, 1H, H₉), 4.69 (s, 2H, H₁₅), 3.03 (d, *J*_{AB} = 18.2 Hz, 1H, H₂), 2.89 – 2.78 (m, 2H, H₈), 2.74 (d, *J*_{AB} = 18.2 Hz, 1H, H₂), 1.36 (s, 9H, H₇).

¹³C NMR (100 MHz, CDCl₃): δ 175.3 (s, C₄), 174.9 (s, C₁), 168.1 (s, C₅), 152.0 (s, C₁₁), 142.1 (s, C₁₄), 135.4 (s, C₁₆), 128.7 (s, 2C, C₁₇ or C₁₈), 128.5 (s, 2C, C₁₇ or C₁₈), 127.9 (s, C₁₉), 124.1 (s, C₁₀), 120.8 (s, C₉), 111.3 (s, C₁₃), 108.1 (s, C₁₂), 83.5 (s, C₆), 55.5 (s, C₃), 42.8 (s, C₁₅), 37.3 (s, C₂), 36.3 (s, C₈), 27.7 (s, 3C, C₇).

HRMS (ESI) *m/z*: calcd for C₂₃H₂₅NO₅ Na [M+Na]⁺: 418.1625, found: 418.1623.

(S)-tert-Butyl-(E)-N-benzyl-2,5-dioxo-3-[3-(1-tosyl-1H-indol-3-yl)allyl]pyrrolidine-3-carboxylate (I.21zc)



MW: 598.2138 g.mol⁻¹

Molecular Formula: C₃₄H₃₄N₂O₆S

Compound **I.21zc** was synthesized according to the general method from *tert*-butyl *N*-benzyl-2,5-dioxopyrrolidine-3-carboxylate **I.14a** (58 mg, 0.2 mmol, 1.0 equiv) and (*E*)-3-(1-tosyl-1H-indol-3-yl)allyl acetate **I.19t** (74 mg, 0.2 mmol, 1.0 equiv). Compound **I.21zc** was obtained as a white solid (97 mg, 81%) after purification by flash column chromatography over silica gel (PE/AcOEt = 90:10).

Mp: 138–139 °C.

[α]_D²⁰ = +35.7 (*c* = 0.2, CHCl₃), ee = 72% (determined by SFC).

SFC: AD-H column, pressure = 100 bar, eluent = CO₂/MeOH (80:20), flow rate = 4.0 mL/min, detection wavelength = 220 nm, *t*_{R1} = 8.36 (major), *t*_{R2} = 17.18 (minor).

IR (neat): 1737, 1704, 1596, 1445, 1432, 1396, 1368, 1342, 1265, 1172, 1149, 1123, 1094, 977 cm⁻¹.

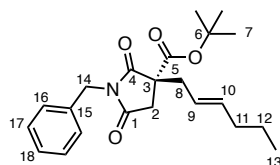
¹H NMR (400 MHz, CDCl₃): δ 7.99 (d, *J* = 8.3 Hz, 1H, H₁₄), 7.77 (d, *J* = 8.4 Hz, 2H, H₂₀), 7.53 (d, *J* = 7.9 Hz, 1H, H₂₁), 7.48 (s, 1H, H₁₂), 7.37 – 7.18 (m, 6H, H_{Ar}), 7.17 – 7.11 (m, 3H, H_{Ar}), 6.54 (d, *J* = 15.9 Hz, 1H, H₁₀), 6.00 (dt, *J* = 15.5, 7.5 Hz, 1H, H₉), 4.67 (s, 2H,

H₂₄), 3.05 (d, J_{AB} = 18.2 Hz, 1H, H₂), 2.95 – 2.82 (m, 2H, H₈), 2.78 (d, J_{AB} = 18.1 Hz, 1H, H₂), 2.32 (s, 3H, H₂₃), 1.36 (s, 9H, H₇).

¹³C NMR (101 MHz, CDCl₃): δ 175.4 (s, C₄), 174.8 (s, C₁), 168.1 (s, C₅), 145.2 (s, C₂₂), 135.4 (s, C_{Ar}), 135.4 (s, C_{Ar}), 135.1 (s, C_{Ar}), 130.0 (s, 2C, C_{Ar}), 128.8 (s, C_{Ar}), 128.6 (s, 2C, C_{Ar}), 128.5 (s, 2C, C_{Ar}), 128.0 (s, C_{Ar}), 126.9 (s, 2C, C_{Ar}), 126.5 (s, C₁₀), 125.0 (s, C₉), 124.0 (s, C_{Ar}), 123.7 (s, C_{Ar}), 123.6 (s, C_{Ar}), 120.3 (s, C₂₀), 119.7 (s, C_{Ar}), 113.8 (s, C₁₄), 83.6 (s, C₆), 55.5 (s, C₃), 42.9 (s, C₂₄), 37.5 (s, C₂), 37.2 (s, C₈), 27.7 (s, 3C, C₇), 21.6 (s, C₂₃).

HRMS (ESI) m/z : calcd for C₃₄H₃₄N₂O₆SNa [M+Na]⁺: 621.2030, found: 621.2040.

(S)-tert-Butyl-(E)-N-benzyl-3-(hex-2-en-1-yl)-2,5-dioxopyrrolidine-3-carboxylate (I.21zd)



MW: 371.2097 g.mol⁻¹

Molecular Formula: C₂₂H₂₉NO₄

Compound **I.21zd** was synthesized according to the general method from *tert*-butyl *N*-benzyl-2,5-dioxopyrrolidine-3-carboxylate **I.14a** (58 mg, 0.2 mmol, 1.0 equiv) and *trans*-2-hexenyl acetate **I.19u** (32 μL, 0.2 mmol, 1.0 equiv). Compound **I.21zd** was obtained as a yellow solid (33 mg, 45%) after purification by flash column chromatography over silica gel (PE/Et₂O = 95:5).

Mp: 55–57 °C.

[α]²⁰_D = +62.0 (c = 0.18, CHCl₃), ee = 90% (determined by SFC).

SFC: OD-H column, pressure = 100 bar, eluent = CO₂/MeOH (99:1), flow rate = 4.0 mL/min, detection wavelength = 220 nm, t_{R1} = 7.72 (minor), t_{R2} = 8.29 (major).

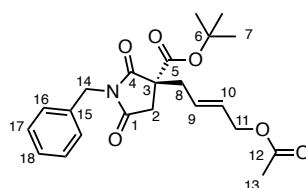
IR (neat): 2930, 1740, 1704, 1395, 1149, 843, 701 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): 7.37 – 7.34 (m, 2H, H_{Ar}), 7.32 – 7.26 (m, 3H, H_{Ar}), 5.54 (dt, J = 14.9, 6.8 Hz, 1H, H₁₀), 5.09 – 5.02 (m, 1H, H₉), 4.66 (s, 2H, H₁₄), 2.96 (d, J_{AB} = 18.1 Hz, 1H, H₂), 2.72 – 2.63 (m, 2H, H₂ and H₈), 2.55 (dd, J_{AB} = 13.9, 8.2 Hz, 1H, H₈), 1.84 (q_{app}, J = 7.2 Hz, 2H, H₁₁), 1.35 (s, 9H, H₇), 1.29 – 1.24 (m, 2H, H₁₂), 0.82 (t, J = 7.4 Hz, 3H, H₁₃).

¹³C NMR (100 MHz, CDCl₃): δ 175.7 (s, C₄), 175.2 (s, C₁), 168.4 (s, C₅), 137.6 (s, C₁₀), 135.6 (s, C₁₅), 128.8 (s, 2C, C_{Ar}), 128.7 (s, 2C, C_{Ar}), 128.1 (s, C₁₈), 122.3 (s, C₉), 83.3 (s, C₆), 55.4 (s, C₃), 42.8 (s, C₁₄), 37.3 (s, C₂), 36.4 (s, C₈), 34.7 (s, C₁₁), 27.8 (s, 3C, C₇), 22.4 (s, C₁₂), 13.7 (s, C₁₃).

HRMS (ESI) *m/z*: calcd for C₂₂H₂₉NO₄ Na [M+Na]⁺: 394.1989, found: 394.1990.

(S)-tert-Butyl-(E)-3-(4-acetoxybut-2-en-1-yl)-N-benzyl-2,5-dioxopyrrolidine-3-carbox-ylate (I.21ze)



MW/g (mol): 401.1838 g.mol⁻¹

Molecular Formula: C₂₂H₂₇NO₆

Compound **I.21ze** was synthesized according to the general method from *tert*-butyl *N*-benzyl-2,5-dioxopyrrolidine-3-carboxylate **I.14a** (57.8 mg, 0.2 mmol, 1.0 equiv) and *cis*-1,4-diacetoxy-2-butene **I.19v** (32 μL, 0.2 mmol, 1.0 equiv). Compound **I.21ze** was obtained as a colorless oil (21 mg, 26%) after purification by flash column chromatography over silica gel (PE/Et₂O = 95:5).

[α]²⁰_D = +37.9 (*c* = 0.42, CHCl₃), ee = 79% (determined by SFC).

SFC: AD-H column, pressure = 100 bar, eluent = CO₂/MeOH (95:5), flow rate = 4.0 mL/min, detection wavelength = 220 nm, *t*_{R1} = 2.53 (major), *t*_{R2} = 3.24 (minor).

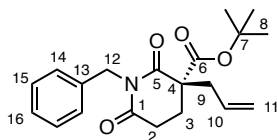
IR (neat): 1738, 1707, 1433, 1396, 1369, 1344, 1235, 1151, 1029, 972 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ 7.30 – 7.27 (m, 2H, H_{Ar}), 7.25 – 7.17 (m, 3H, H_{Ar}), 5.65 – 5.58 (m, 1H, H₉), 5.42 – 5.35 (m, 1H, H₁₀), 4.59 (s, 2H, H₁₄), 4.30 (d, *J* = 6.1 Hz, 2H, H₁₁), 2.92 (d, *J*_{AB} = 18.2 Hz, 1H, H₂), 2.66 – 2.56 (m, 2H, H₈), 2.56 (d, *J*_{AB} = 18.2 Hz, 1H, H₂), 1.96 (s, 3H, H₁₃), 1.26 (s, 9H, H₇).

¹³C NMR (100 MHz, CDCl₃): δ 175.3 (s, C₄), 174.8 (s, C₁), 170.7 (s, C₅), 168.0 (s, C₁₂), 135.5 (s, C₁₅), 130.5 (s, C₉), 128.75 (s, 2C, C_{Ar}), 128.73 (s, 2C, C_{Ar}), 128.1 (s, C_{Ar}), 127.8 (s, C₁₀), 83.6 (s, C₆), 64.3 (s, C₁₁), 55.1 (s, C₃), 42.9 (s, C₁₄), 37.4 (s, C₂), 35.9 (s, C₈), 27.7 (s, 3C, C₇), 21.0 (s, C₁₃).

HRMS (ESI) m/z : calcd for $C_{22}H_{27}NO_6 Na [M+Na]^+$: 424.1731, found: 424.1720.

(S)-tert-Butyl-3-allyl-1-benzyl-2,6-dioxopiperidine-3-carboxylate (I.22a)



MW: 343.1784 g.mol⁻¹

Molecular Formula: $C_{20}H_{25}NO_4$

Compound **I.22a** was synthesized according to the general method from *tert*-butyl *N*-benzyl-2,6-dioxopiperidine-3-carboxylate **I.12** (61 mg, 0.2 mmol, 1.0 equiv) and allyl acetate **I.19a** (22 μ L, 0.2 mmol, 1.0 equiv). Compound **I.22a** was obtained as a colorless oil (33 mg, 48%) after purification by flash column chromatography over silica gel (PE/Et₂O = 95:5).

$[\alpha]^{20}_D = -27.2$ ($c = 0.6$, CHCl₃), ee = 73% (determined by SFC).

SFC: OD-H column, pressure = 100 bar, eluent = CO₂/MeOH (99:1), flow rate = 4.0 mL/min, detection wavelength = 220 nm, $t_{R1} = 8.48$ (minor), $t_{R2} = 9.21$ (major).

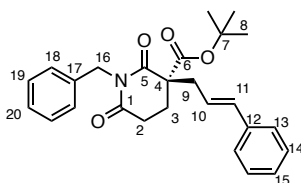
IR (neat): 1720, 1678, 1368, 1357, 1335, 1251, 1145, 1079, 997, 921 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ 7.40 – 7.38 (m, 2H, H_{Ar}), 7.30 – 7.21 (m, 3H, H_{Ar}), 5.78 – 5.67 (m, 1H, H₁₀), 5.17 – 5.12 (m, 2H, H₁₁), 4.98 (s, 2H, H₁₂), 2.85 – 2.62 (m, 4H, H₃ and H₉), 2.20 – 2.15 (m, 1H, H₂), 2.00 – 1.92 (m, 1H, H₂), 1.32 (s, 9H, H₈).

¹³C NMR (100 MHz, CDCl₃): δ 171.7 (s, C₅), 170.9 (s, C₁), 169.4 (s, C₆), 137.2 (s, C₁₃), 132.5 (s, C₁₀), 129.0 (s, 2C, C_{Ar}), 128.4 (s, 2C, C_{Ar}), 127.4 (s, C_{Ar}), 120.0 (s, C₁₁), 83.4 (s, C₇), 54.8 (s, C₄), 43.4 (s, C₁₂), 39.6 (s, C₉), 30.1 (s, C₃), 27.8 (s, 3C, C₈), 25.4 (s, C₂).

HRMS (ESI) m/z : calcd for $C_{20}H_{25}NO_4 Na [M+Na]^+$: 366.1676, found: 366.1676.

(S)-tert-Butyl-N-benzyl-3-cinnamyl-2,6-dioxopiperidine-3-carboxylate (I.22b)



MW: 419.2097 g.mol⁻¹

Molecular Formula: C₂₆H₂₉NO₄

Compound **I.22b** was synthesized according to the general method from *tert*-butyl *N*-benzyl-2,6-dioxopiperidine-3-carboxylate **I.12** (61 mg, 0.2 mmol, 1.0 equiv) and cinnamyl acetate **I.19g** (33 μ L, 0.2 mmol, 1.0 equiv). Compound **I.22b** was obtained as a colorless oil (8.5 mg, 10%) after purification by flash column chromatography over silica gel (PE/Et₂O = 95:5).

$[\alpha]_D^{20} = -6.0$ ($c = 0.3$, CHCl₃), ee = 44% (determined by SFC).

SFC: AD-H column, pressure = 100 bar, eluent = CO₂/MeOH (95:5), flow rate = 4.0 mL/min, detection wavelength = 220 nm, $t_{R1} = 5.78$ (major), $t_{R2} = 13.43$ (minor).

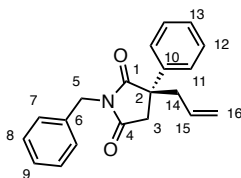
IR (neat): 1720, 1679, 1495, 1453, 1368, 1337, 1314, 1251, 1167, 1149, 1080, 1002, 971 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ 7.36 (d, $J = 6.6$ Hz, 2H, H_{Ar}), 7.29 – 7.19 (m, 8H, H_{Ar}), 6.45 (d, $J = 15.8$ Hz, 1H, H₁₁), 6.12 – 6.03 (m, 1H, H₁₀), 4.98 (s, 2H, H₁₆), 2.96 (dd, $J_{AB} = 13.7$, 6.9 Hz, 1H, H₉), 2.77 – 2.62 (m, 3H, H₉ and H₃), 2.26 – 2.17 (m, 1H, H₂), 2.05 – 1.96 (m, 1H, H₂), 1.31 (s, 9H, H₈).

¹³C NMR (100 MHz, CDCl₃): δ 171.7 (s, C₅), 171.0 (s, C₁), 169.6 (s, C₆), 137.2 (s, C₁₇), 136.9 (s, C₁₂), 135.0 (s, C₉), 129.0 (s, 2C, C_{Ar}), 128.7 (s, 2C, C_{Ar}), 128.5 (s, 2C, C_{Ar}), 127.7 (s, C_{Ar}), 127.5 (s, C_{Ar}), 126.4 (s, 2C, C_{Ar}), 124.0 (s, C₁₀), 83.6 (s, C₇), 55.4 (s, C₄), 43.4 (s, C₁₆), 39.1 (s, C₉), 30.2 (s, C₃), 27.9 (s, 3C, C₈), 25.7 (s, C₂).

HRMS (ESI) m/z : calcd for C₂₆H₂₉NO₄ Na [M+Na]⁺: 442.1989, found: 442.1986.

(S)-3-allyl-1-benzyl-3-phenylpyrrolidine-2,5-dione (I.23):



MW: 305.1416 g.mol⁻¹

Molecular Formula: C₂₀H₁₉NO₂

Compound **I.23** was synthesized according to the general method from (*S*)-1-benzyl-3-phenylpyrrolidine-2,5-dione **I.7** (61 mg, 0.2 mmol, 1.0 equiv) and allyl acetate **I.19a**

(33 μ L, 0.2 mmol, 1.0 equiv) at rt. Compound **1.23** was obtained as colourless oil (22 mg, 36%) after purification by flash column chromatography over silica gel (PE/Et₂O = 95:5).

$[\alpha]_D^{20}$ = 0.8 (c = 0.12, CHCl₃), ee = 6% (determined by SFC). **SFC**: AD-H column, pressure = 100 bar, eluent = CO₂/MeOH (95:5), flow rate = 4.0 mL/min, detection wavelength = 220 nm, t_{R1} = 5.89 (minor), t_{R2} = 7.97 (major).

IR (neat): 1774, 1698, 1496, 1393, 1343, 1174, 929, 698.

¹H NMR (400 MHz, CDCl₃): δ 7.40 – 7.27 (m, 10H, H_{Ar}), 5.54 – 5.40 (m, 1H, H₁₀), 5.14 (dd, J = 17.0, 1.3 Hz, 1H, H₁₁), 5.06 (dd, J = 10.1, 0.9 Hz, 1H, H₁₁), 4.74 – 4.66 (m, 2H, H₁₂), 3.08 – 2.98 (m, 2H, H₂), 2.84 (dd, J = 13.6, 6.7 Hz, 1H, H₈), 2.67 (dd, J = 13.6, 7.9 Hz, 1H, H₈).

¹³C NMR (100 MHz, CDCl₃): δ 179.5 (s, C₄), 175.2 (s, C₁), 140.8 (s, C₁₃), 135.8 (s, C₅), 131.7 (s, C₁₀), 129.0 (s, 2C, C_{Ar}), 128.8 (s, 2C, C_{Ar}), 128.7 (s, 2C, C_{Ar}), 128.0 (s, C_{Ar}), 127.7 (s, C_{Ar}), 126.2 (s, 2C, C_{Ar}), 121.0 (s, C₁₁), 51.5 (s, C₃), 43.7 (s, C₈), 42.7 (s, C₁₂), 40.9 (s, C₂).

HRMS (ESI) m/z : calcd for C₂₀H₁₉NO₂Na [M+Na]⁺: 328.1308, found: 328.1310.

5. Post-functionalization of allylated succinimides

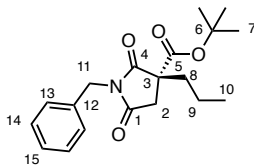
a) Hydrogenation of the allylated product **1.21a** and **1.21q**



To a solution of **1.21a** (66 mg, 0.2 mmol) in EtOAc (3 mL) was added Pd/C (20 mg, 0.02 mmol, 10 wt %). The reaction mixture was stirred under 1 atm of H₂ at rt. After 15 h, the hydrogen balloon was removed. The mixture solution was filtered through Celite and washed by CH₂Cl₂, the solvent was removed under reduced pressure and

purification of crude mixture product by flash column chromatography over silica gel (pentane/Et₂O = 10:1) afforded compound **I.24** (65 mg, 98%) as a colorless oil.

(S)-tert-Butyl-N-benzyl-2,5-dioxo-3-propylpyrrolidine-3-carboxylate (I.24)



MW: 331.1784 g.mol⁻¹

Molecular Formula: C₁₉H₂₅NO₄

[α]_D²⁰ = +31.9 (c = 0.58, CHCl₃). ee = 84% (determined by SFC).

SFC: OD–H column, pressure = 100 bar, eluent = CO₂/MeOH (99:1), flow rate = 4.0 mL/min, detection wavelength = 220 nm, t_{R1} = 5.31 (minor), t_{R2} = 6.01 (major).

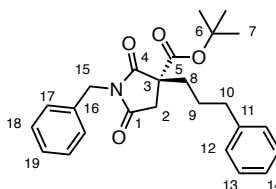
IR (neat): 1739, 1704, 1456, 1432, 1395, 1343, 1253, 1149, 1081, 951, 918 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ 7.37 – 7.34 (m, 2H, H_{Ar}), 7.32 – 7.24 (m, 3H, H_{Ar}), 4.67 (s, 2H, H₁₁), 3.07 (d, J_{AB} = 18.2 Hz, 1H, H₂), 2.61 (d, J_{AB} = 18.2 Hz, 1H, H₂), 1.97 – 1.84 (m, 2H, H₈), 1.33 (s, 9H, H₇), 1.28 (m, 1H, H₉), 1.15 (m, 1H, H₉), 0.93 (t, J = 7.2 Hz, 3H, H₁₀).

¹³C NMR (101 MHz, CDCl₃): δ 175.9 (s, C₄), 175.2 (s, C₁), 168.5 (s, C₅), 135.6, (s, C₁₂) 128.7 (s, 4C, C₁₃ and C₁₄), 128.0 (s, C₁₅), 83.2 (s, C₆), 55.8 (s, C₃), 42.8 (s, C₁₁), 38.0 (s, C₂), 36.4 (s, C₈), 27.7 (s, 3C, C₇), 17.7 (s, C₉), 14.3 (s, C₁₀).

HRMS (ESI) m/z : calcd for C₁₉H₂₅NO₄Na [M+Na]⁺: 354.1676, found: 354.1678.

Tert-butyl (R)-1-benzyl-2,5-dioxo-3-(3-phenylpropyl)pyrrolidine-3-carboxylate (I.25)



MW: 407.2097 g.mol⁻¹

Molecular Formula: C₂₅H₂₉NO₄

Compound **I.25** was synthesized according to the general method from the allylated product **I.21q** (40.5 mg, 0.1 mmol). After purification by flash column chromatography over silica gel (PE/Et₂O = 95:5), compound **I.25** was obtained as a colorless oil (40 mg, 98%).

$[\alpha]_D^{20} = +29.3$ ($c = 0.01$, CHCl_3). $ee = 94\%$ (determined by SFC).

SFC: AD-H, pressure = 100 bar, eluent = CO_2/MeOH (95:5), flow rate = 4.0 mL/min, detection wavelength = 220 nm, $t_{R1} = 3.23$ (major), $t_{R2} = 5.16$ (minor).

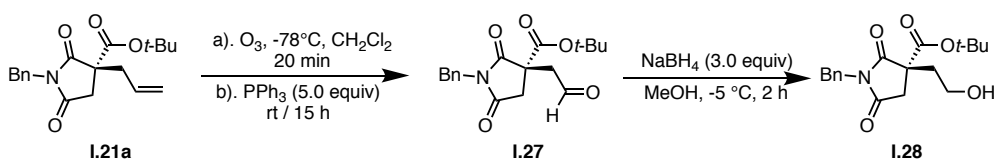
IR (neat): 2932, 1738, 1704, 1497, 1455, 1432, 1395, 1369, 1343, 1315, 1257, 1149, 1079, 1030, 947 cm^{-1} .

^1H NMR (400Hz, CDCl_3) δ 7.36 – 7.34 (m, 2H, H_{Ar}), 7.30 – 7.25 (m, 5H, H_{Ar}), 7.21 – 7.17 (m, 1H, H_{Ar}), 7.11 – 7.10 (m, 2H, H_{Ar}), 4.65 (s, 2H, H_{15}), 3.05 (d, $J = 18.2$ Hz, 1H, H_2), 2.64 – 2.58 (m, 2H, H_8), 2.56 (d, $J = 18.1$ Hz, 1H, H_2), 2.06 – 1.90 (m, 2H, H_{10}), 1.63 – 1.53 (m, 1H, H_9), 1.47 – 1.37 (m, 1H, H_9), 1.31 (s, 9H, H_7).

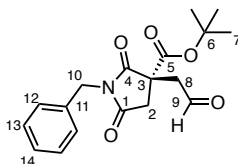
^{13}C NMR (101 Hz, CDCl_3) δ 175.8 (s, C_4), 175.1 (s, C_1), 168.3 (s, C_5), 141.4 (s, C_{Ar}), 135.6 (s, C_{Ar}), 128.75 (s, 2C, C_{Ar}), 128.73 (s, 2C, C_{Ar}), 128.6 (s, 2C, C_{Ar}), 128.5 (s, 2C, C_{Ar}), 128.1 (s, C_{Ar}), 126.2 (s, C_{Ar}), 83.3 (s, C_6), 55.6 (s, C_3), 42.8 (s, C_{15}), 38.1 (s, C_2), 35.9 (s, C_8), 32.9 (s, C_{10}), 27.7 (s, 3C, C_7), 26.2 (s, C_9).

HRMS (ESI) m/z : calcd for $\text{C}_{25}\text{H}_{29}\text{NO}_4\text{H}[\text{M}+\text{H}]^+$: 408.2169, found: 408.2168.

b) Synthesis of enantio-enriched primary alcohol from the allylated product **I.21a**⁸¹



(*S*)-*tert*-Butyl-*N*-benzyl-2,5-dioxo-3-(2-oxoethyl)pyrrolidine-3-carboxylate (**I.27**)



MW: 331.1420 $\text{g}\cdot\text{mol}^{-1}$

Molecular Formula: $\text{C}_{18}\text{H}_{21}\text{NO}_5$

To a solution of **I.21a** (66 mg, 0.2 mmol) in CH_2Cl_2 (5 mL) at -78°C was bubbled O_3 until the starting material was completely converted (20 min, as a deep blue solution,

⁸¹ Wang, T.L.; Yao, W. J.; Zhong, F. R.; Pang, G. H.; Lu, Y. X. *Angew. Chem. Int. Ed.* **2014**, 53, 2964-2968.

determined). Then, the reaction was allowed to warm to rt followed by the addition of PPh₃ (262 mg, 1 mmol). The mixture was stirred for 15 h until complete conversion of the starting material (reaction monitored by TLC). The solvent was eventually removed under reduced pressure to afford a crude residue, which was purified by flash column chromatography over silica gel (pentane /EtOAc= 10:1 to 5:1) to afford compound **1.27** (56 mg, 83%) as a colorless liquid.

[α]_D²⁰ = +39.7 (*c* = 0.76, CHCl₃).

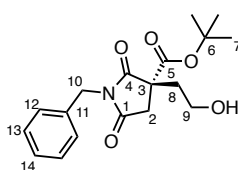
IR (neat): 1703, 1456, 1432, 1395, 1370, 1343, 1295, 1256, 1234, 1147, 1057, 936 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ 9.65 (s, 1H, H₉), 7.33 – 7.30 (m, 2H, H_{Ar}), 7.26 – 7.18 (m, 3H, H_{Ar}), 4.67 (d, *J*_{AB} = 14.4 Hz, 1H, H₁₀), 4.60 (d, *J*_{AB} = 14.0 Hz, 1H, H₁₀), 3.29 (d, *J*_{AB} = 19.1 Hz, 1H, H₂), 3.09 (d, *J*_{AB} = 17.6 Hz, 1H, H₈), 3.05 (d, *J*_{AB} = 19.2 Hz, 1H, H₂), 2.57 (d, *J*_{AB} = 18.0 Hz, 1H, H₈), 1.20 (s, 9H, H₇).

¹³C NMR (100 MHz, CDCl₃): δ 198.1 (s, C₉), 174.9 (s, C₄), 174.8 (s, C₁), 167.2 (s, C₅), 135.4 (s, C₁₁), 128.7 (s, 2C, C_{Ar}), 128.7 (s, 2C, C_{Ar}), 128.0 (s, C₁₄), 84.0 (s, C₆), 52.2 (s, C₃), 46.3 (s, C₂), 43.0 (s, C₁₀), 39.0 (s, C₈), 27.5 (s, 3C, C₇).

HRMS (ESI) *m/z*: calcd for C₁₈H₂₁NO₅Na [M+Na]⁺: 354.1312, found: 354.1314.

(*S*)-*tert*-Butyl *N*-benzyl-3-(2-hydroxyethyl)-2,5-dioxopyrrolidine-3-carboxylate (**1.28**)



MW: 333.1576 g.mol⁻¹

Molecular Formula: C₁₈H₂₃NO₅

To a solution of **1.27** (50 mg, 0.15 mmol) in MeOH (3 mL) at –5 °C was added NaBH₄ (17 mg, 0.45 mmol, 3.0 equiv). The reaction mixture was stirred at the same temperature for an additional 2 h until complete conversion of the starting material (reaction monitored by TLC). H₂O (10 ml) was then added and the reaction mixture was extracted with EtOAc (3 × 10 mL) and washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue was

purified by flash column chromatography over silica gel (pentane/ethyl acetate = 10:1 to 5:1) to afford compound **I.28** (15 mg, 30%) as a colorless oil.

$[\alpha]_D^{20} = +18.3$ ($c = 0.2$, CHCl_3). ee = 85% (determined by SFC).

SFC: AD-H column, pressure = 100 bar, eluent = CO_2/MeOH (93:7), flow rate = 4.0 mL/min, detection wavelength = 220 nm, $t_{R1} = 3.68$ (minor), $t_{R2} = 3.98$ (major).

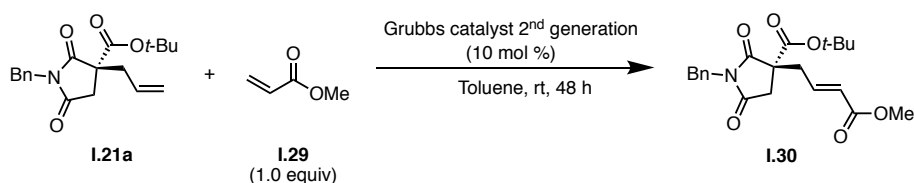
IR (neat): 1737, 1702, 1397, 1343, 1254, 1149, 841, 703 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ 7.31 – 7.29 (m, 2H, H_{Ar}), 7.25 – 7.15 (m, 3H, H_{Ar}), 4.60 (s, 2H, H_{10}), 3.70 – 3.67 (m, 2H, H_9), 2.90 (d, $J_{AB} = 18.1$ Hz, 1H, H_2), 2.80 (d, $J_{AB} = 18.0$ Hz, 1H, H_2), 2.22–2.11 (m, 2H, H_8), 1.78 (brs, 1H, OH), 1.23 (s, 9H, H_7).

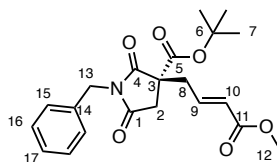
^{13}C NMR (101 MHz, CDCl_3): δ 176.4 (s, C_4), 175.2 (s, C_1), 168.8 (s, C_5), 135.6 (s, C_{11}), 128.8 (s, 2C, C_{Ar}), 128.7 (s, 2C, C_{Ar}), 128.1 (s, C_{14}), 83.6 (s, C_6), 59.0 (s, C_9), 54.5 (s, C_3), 42.9 (s, C_{10}), 38.4 (s, C_2), 34.9 (s, C_8), 27.7 (s, 3C, C_7).

HRMS (ESI) m/z : calcd for $\text{C}_{18}\text{H}_{23}\text{NO}_5\text{Na}$ $[\text{M}+\text{Na}]^+$: 356.1468, found: 356.1471.

c) Olefin metathesis of the allylated product **I.21a** with methyl acrylate (**I.30**)



(*S*)-*tert*-Butyl-(*E*)-*N*-benzyl-3-(4-methoxy-4-oxobut-2-en-1-yl)-2,5-dioxopyrrolidine-3-carboxylate (**I.30**)



MW: 387.1682 $\text{g}\cdot\text{mol}^{-1}$

Molecular Formula: $\text{C}_{21}\text{H}_{25}\text{NO}_6$

To a solution of **I.21a** (33 mg, 0.1 mmol) and the second generation of Grubbs' catalyst (9 mg, 0.01 mmol, 10 mol %) in toluene (2 mL), methyl acrylate **I.29** (9 μL , 0.1 mmol) was added. The solution was stirred at rt for 48 h until the starting material was

completely converted (determined by TLC). Then, the mixture solution was filtered through Celite and washed by CH₂Cl₂. The solvent was removed under reduced pressure and the mixture residue was purified by flash column chromatography over silica gel (pentane/Et₂O = 10:1–5:1) to afford compound **I.30** (21 mg, 55%) as a colorless oil.

[α]_D²⁰ = +32.5 (*c* = 0.32, CHCl₃). ee = 86% (determined by SFC).

SFC: OD–H column, pressure = 100 bar, eluent = CO₂/MeOH (97:3), flow rate = 4.0 mL/min, detection wavelength = 220 nm, *t*_{R1} = 4.54 (minor), *t*_{R2} = 4.89 (major).

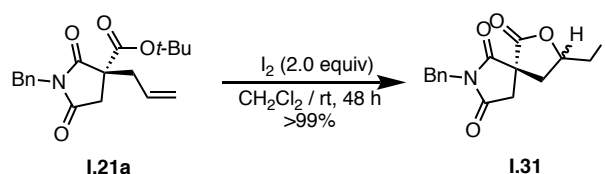
IR (neat): 1708, 1433, 1396, 1370, 1342, 1274, 1175, 1150, 985, 958 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ 7.29 – 7.26 (m, 2H, H_{Ar}), 7.25 – 7.19 (m, 3H, H_{Ar}), 6.65 (dt, *J* = 15.4, 7.6 Hz, 1H, H₉), 5.85 (dt, *J* = 15.6, 1.4 Hz, 1H, H₁₀), 4.63 (d, *J*_{AB} = 14.4 Hz, 1H, H₁₃), 4.60 (d, *J*_{AB} = 14.4 Hz, 1H), 3.64 (s, 3H, H₁₂), 2.94 (d, *J*_{AB} = 18.2 Hz, 1H, H₂), 2.82 (ddd, *J*_{AB} = 14.5, 7.8, 1.3 Hz, 1H, H₈), 2.70 (ddd, *J*_{AB} = 14.5, 7.4, 1.4 Hz, 1H, H₈), 2.53 (d, *J*_{AB} = 18.1 Hz, 1H, H₂), 1.23 (s, 9H, H₇).

¹³C NMR (101 MHz, CDCl₃): δ 174.8 (s, C₄), 174.4 (s, C₁), 167.5 (s, C₅), 166.0 (s, C₁₁), 141.3 (s, C₉), 136.4 (s, C₁₄), 128.8 (s, 4C, C_{Ar}), 128.2 (s, C₁₀), 126.4 (s, C₁₇), 84.0 (s, C₆), 54.8 (s, C₃), 51.8 (s, C₁₂), 43.1 (s, C₁₃), 37.7 (s, C₂), 36.5 (s, C₈), 27.7 (s, 3C, C₇).

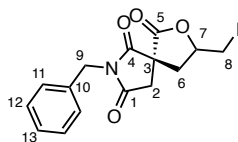
HRMS (ESI) *m/z*: calcd for C₂₁H₂₅NO₆Na [M+Na]⁺: 410.1574, found: 410.1572.

d) Synthesis of enantioenriched spirocyclic compound **I.31**⁸²:



(S)-7-benzyl-3-(iodomethyl)-2-oxa-7-azaspiro[4.4]nonane-1,6,8-trione (I.31) (major compound)

⁸² Rammah, M. M.; Othman, M.; Rammah, M. B. *Journal de la Société Chimique de Tunisie*, **2008**, 10, 11-21.



MW: 398.9968 g.mol⁻¹

Molecular Formula: C₁₅H₁₄INO₄

To a solution of the allylated product **1.21a** (50 mg, 0.125 mmol, 1.0 equiv) in CH₂Cl₂ (2 mL) was added iodine (63 mg, 0.25 mmol, 2.0 equiv). The reaction mixture was stirred at rt for 48 h. After the reaction was complete (reaction monitored by TLC), a saturated aqueous solution of Na₂S₂O₃ (10 mL) was added and the mixture was stirred for an additional 5 min. The reaction mixture was then extracted with CH₂Cl₂ (3 × 5 mL), washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. NMR analysis of the crude reaction mixture revealed the presence of two diastereomers with a 3.5:1 ratio. The crude residue was purified by the flash column chromatography over silica gel (pentane/EtOAc = 5:1) to afford the major cyclized product **1.31** (25 mg, 50%) as a white solid.

Mp: 133–134 °C.

[α]²⁰_D = +25.2 (*c* = 0.67, CHCl₃). ee = 86% (determined by SFC).

SFC: OD-H column, pressure = 100 bar, eluent = CO₂/MeOH (97:3), flow rate = 4.0 mL/min, detection wavelength = 220 nm, *t*_{R1} = 12.56 (minor), *t*_{R2} = 13.15 (major).

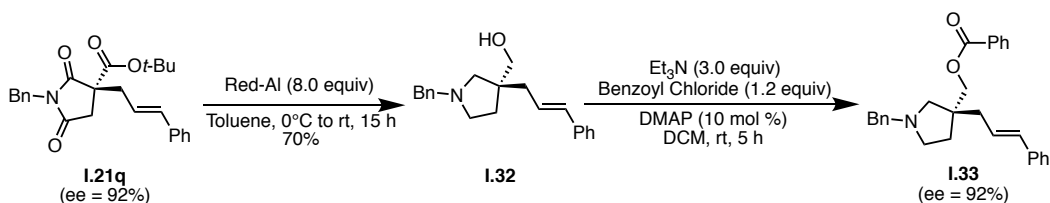
IR (neat): 1767, 1701, 1395, 1338, 1179, 994, 902, 733, 703, 631 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ 7.37 – 7.27 (m, 5H, H_{Ar}), 4.93 – 4.86 (m, 1H, H₇), 4.70 (d, *J*_{AB} = 14.0 Hz, 1H, H₉), 4.66 (d, *J*_{AB} = 14.0 Hz, 1H, H₈), 3.46 (dd, *J*_{AB} = 10.7, 4.1 Hz, 1H, H₈), 3.38 – 3.31 (m, 2H, H₂ and H₈), 2.95 (dd, *J*_{AB} = 13.2, 6.3 Hz, 1H, H₆), 2.70 (d, *J*_{AB} = 18.2 Hz, 1H, H₂), 2.08 (dd, *J*_{AB} = 13.3, 9.1 Hz, 1H, H₆).

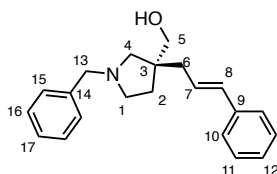
¹³C NMR (101 MHz, CDCl₃): δ 174.3 (s, C₄), 173.5 (s, C₁), 172.7 (s, C₅), 134.9 (s, C₁₀), 129.0 (s, 2C, C_{Ar}), 128.6 (s, 2C, C_{Ar}), 128.4 (s, C₁₃), 76.9 (s, C₇), 53.1 (s, C₃), 43.3 (s, C₉), 39.5 (s, C₆), 38.6 (s, C₁₂), 6.6 (s, C₈).

HRMS (ESI) *m/z*: calcd for C₁₅H₁₄INO₄Na [M+Na]⁺: 421.9860, found: 421.9857.

e) Synthesis of (*N*-benzyl-3-cinnamylpyrrolidin-3-yl)methanol (I.32**) and (*N*-benzyl-3-cinnamyl pyrrolidin-3-yl)methyl benzoate (**I.33**)⁸³**



(*N*-Benzyl-3-cinnamylpyrrolidin-3-yl)methanol (I.32**)**



MW: 307.1936 g.mol⁻¹

Molecular Formula: C₂₁H₂₅NO

To a solution of **I.21q** (55 mg, 0.136 mmol, 1.0 equiv) in toluene (2 mL) was cooled to 0 °C for 5 min, sodium bis(2-methoxyethoxy)aluminumhydride (Red-Al) (0.34 mL, 220 mg, 1.088 mmol, 8.0 equiv, 65% in toluene) was added drop-wise. After 5 min, the reaction mixture was stirred at rt. After 15 h, the reaction was quenched with a Rochelle's salt solution (10%), the aqueous layer was separated and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure to afford the crude product following. After purification by flash column chromatography over silica gel (CH₂Cl₂/MeOH = 15:1 to 10:1), compound **I.32** was isolated (29 mg, 70%) as a yellow solid.

Mp: 99–100 °C.

[α]_D²⁰ = +56.6 (*c* = 0.5, CHCl₃).

IR (neat): 2909, 2870, 2362, 2341, 1653, 1495, 1452, 1378, 1350, 1210, 1152, 1072, 1029, 967, 912 cm⁻¹.

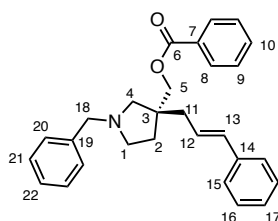
⁸³ Bao, D. H.; Gu, X. S.; Xie, J. H.; Zhou, Q. L. *Org. Lett.* **2017**, 19, 118-121.

¹H NMR (400 MHz, CDCl₃): δ 7.25 – 7.04 (m, 10H, H_{Ar}), 6.30 (d, *J* = 15.7 Hz, 1H, H₈), 6.04 (dt, *J* = 15.1, 7.5 Hz, 1H, H₇), 3.77 (s_{br}, 1H, OH), 3.52 (d, *J*_{AB} = 9.8 Hz, 1H, H₅), 3.48 (s, 2H, H₁₃), 3.35 (d, *J*_{AB} = 9.8 Hz, 1H, H₅), 2.92 – 2.86 (m, 1H, H₁), 2.73 (d, *J*_{AB} = 9.1 Hz, 1H, H₄), 2.24 – 2.17 (m, 4H, H₁, H₄ and H₆), 1.85 (m, 1H, H₂), 1.68 (m, 1H, H₂).

¹³C NMR (101 MHz, CDCl₃): δ 138.4 (s, C₁₄), 137.4 (s, C₉), 132.8 (s, C₈), 128.7 (s, 2C, C_{Ar}), 128.6 (s, 2C, C_{Ar}), 128.5 (s, 2C, C_{Ar}), 127.3 (s, 2C, C_{Ar}), 126.3 (s, C₇), 126.2 (s, 2C, C_{Ar}), 72.0 (s, C₅), 63.7 (s, C₄), 60.1 (s, C₁₃), 54.1 (s, C₁), 46.1 (s, C₃), 40.3 (s, C₆), 32.5 (s, C₂).

HRMS (ESI) *m/z*: calcd for C₂₁H₂₅NONa[M+H]⁺: 308.2009, found: 308.2008.

(*S*)-(N-Benzyl-3-cinnamylpyrrolidin-3-yl)methyl benzoate (**1.33**)



MW: 411.2198 g.mol⁻¹

Molecular Formula: C₂₈H₂₉NO₂

To a solution of **1.32** (29 mg, 0.095 mmol, 1.0 equiv) and DMAP (1.2 mg, 0.0095 mmol, 0.1 equiv) in CH₂Cl₂ (2 ml), Et₃N (40 μL, 0.285 mmol, 3.0 equiv) and benzoyl chloride (13 μL, 0.114 mmol, 1.2 equiv) were added. The reaction was stirred at rt for 5 h. After the reaction was completed finished (determined by TLC), the solvent was removed under reduced pressure. Purification of crude mixture product by flash column chromatography over silica gel (pentane/EtOAc = 10:1 to 5:1) afforded compound **1.33** (37 mg, 95%) as a color less oil.

[α]²⁰_D = +8.2 (*c* = 0.28, CHCl₃). ee = 92% (determined by SFC).

SFC: OD-H column, pressure = 120 bar, eluent = CO₂/MeOH (97:3), flow rate = 5.0 mL/min, detection wavelength = 220 nm, *t*_{R1} = 26.76 (major), *t*_{R2} = 29.05 (minor).

IR (neat): 1716, 1601, 1493, 1451, 1376, 1314, 1269, 1112, 1070, 966, 911 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ 7.96 (dd, *J* = 8.3, 1.2 Hz, 2H, H₈), 7.50 – 7.46 (m, 1H, H₁₀), 7.34 (t, *J* = 7.7 Hz, 2H, H₉), 7.26 – 7.09 (m, 10H, H_{Ar}), 6.35 (d, *J* = 15.7 Hz, 1H, H₁₃), 6.27 – 6.14 (m, 1H, H₁₂), 4.19 (s, 2H, H₁₈), 3.57 (d, *J*_{AB} = 13.2 Hz, 1H, H₅), 3.49 (d, *J*_{AB} = 13.2

Hz, 1H, H₁), 2.57 (t, J_{AB} = 7.0 Hz, 2H, H₁), 2.50 – 2.41 (m, 4H, H₄ and H₁₁), 1.78 – 1.66 (m, 2H, H₂).

¹³C NMR (101 MHz, CDCl₃): δ 166.7 (s, C₆), 139.4 (s, C₁₉), 137.6 (s, C₁₄), 133.08 (s, C_{Ar}), 133.06 (s, C_{Ar}), 130.4 (s, C₇), 129.7 (s, 2C, C_{Ar}), 128.62 (s, 2C, C_{Ar}), 128.60 (s, 2C, C_{Ar}), 128.5 (s, 2C, C_{Ar}), 128.3 (s, 2C, C_{Ar}), 127.2 (s, C₁₃), 127.0 (s, C₁₂), 126.6 (s, C_{Ar}), 126.2 (s, 2C, C_{Ar}), 70.2 (s, C₁₈), 62.2 (s, C₄), 60.2 (s, C₅), 53.9 (s, C₁), 45.4 (s, C₃), 41.3 (s, C₁₁), 33.5 (s, C₂).

HRMS (ESI) m/z : calcd for C₂₈H₂₉NO₂Na [M+Na]⁺: 412.2271, found: 412.2264.

Chapter II

Direct Palladium-Catalyzed Asymmetric Allylation of Cyclic Silyl Dienol Ethers: A Straightforward Entry to α -Quaternary γ -Lactams

1. γ -Lactams in natural products and/or bioactive compounds

1.1. Natural occurrence and biological activity

The γ -lactam ring, also known as pyrrolidin-2-one and γ -butyrolactam, is present in a number of biologically active natural products such as (–)-pramanicin, (+)-lactacystin, (–)-salinosporamide A and (–)-clausenamide (Figure 11).⁸⁴ In view of the plethora of compounds that bear this motif, a few chosen examples will be presented in the following section.

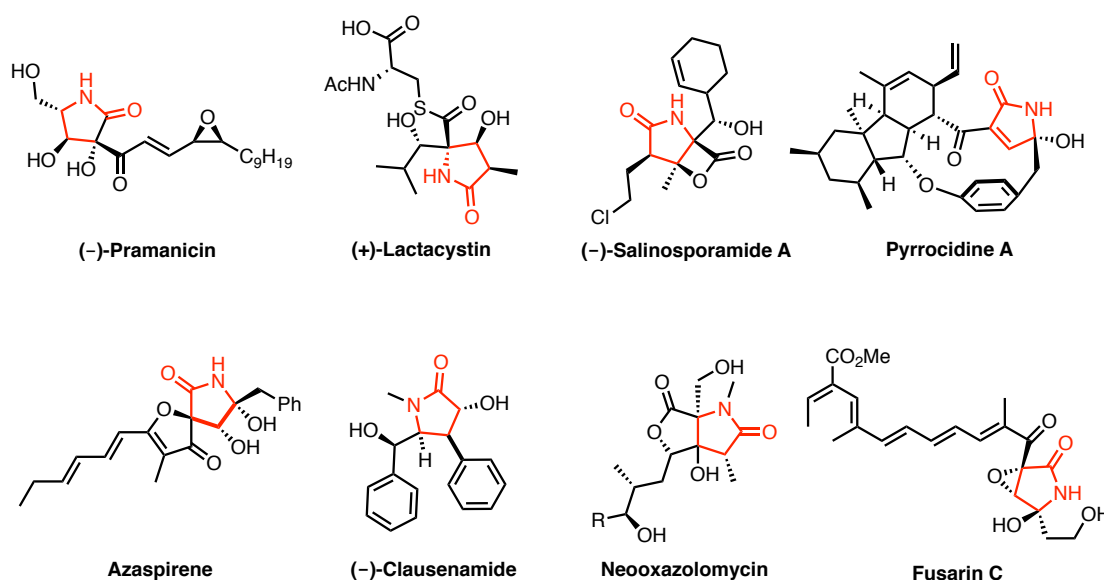


Figure 11. Typical examples of γ -lactam-containing natural products and pharmaceuticals.

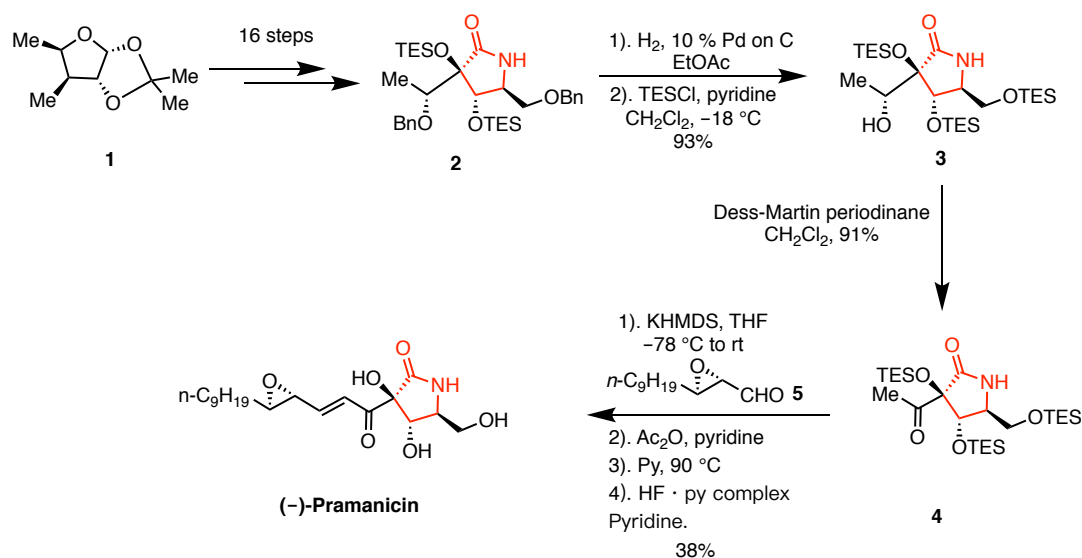
1.1.1. (–)-Pramanicin

(–)-Pramanicin, which was isolated from a fungus in 1994 by Schwartz *et al.*,⁸⁵ exhibits a good antimicrobial activity against the acapsular form of *Cryptococcus neoformans* (MIC = 0.062 μ M), and *Candida parapsilosis* (MIC = 4.0 μ M) in the Minimum Inhibitory Concentration (MIC) tests. A very good antibacterial activity was also observed against *Bacillus subtilis* (MIC = 4.0 μ M). Aoki and co-workers completed

⁸⁴ For a review, see: Caruano, J.; Muccioli, G. G.; Robiette, R. *Org. Biomol. Chem.* **2016**, *14*, 10134-10156.

⁸⁵ Schwartz, R. E.; Helms, G. L.; Bolessa, E. A.; Wilson, K. E.; Giacobbe, R. A.; Tkacz, J. S.; Bills, G. F.; Liesch, J. M.; Zink, D. L.; Curotto, J. E.; Pramanik, B.; Onishi, J. C. *Tetrahedron*, **1994**, *50*, 1675-1686.

the first total synthesis of (–)-pramanicin in 2006.⁸⁶ The synthesis started from the enantio-enriched acetal **1** to access the γ -lactam intermediate **2** in 16 steps. After debenzoylation of intermediate **2** followed by a selective protection of the primary alcohol by a TES group, γ -lactam **3** was isolated, this latter was transformed to keto intermediate **4** by using a DMP oxidation. An aldol condensation between **4** and epoxyaldehyde (**5**) was achieved and the resulted mixture of the aldol product was acetylated, treated with pyridine at 90 °C, and the desilylation with HF·pyridine to produce (–)-pramanicin successfully (Scheme 40).



Scheme 40. Total synthesis of (–)-pramanicin.

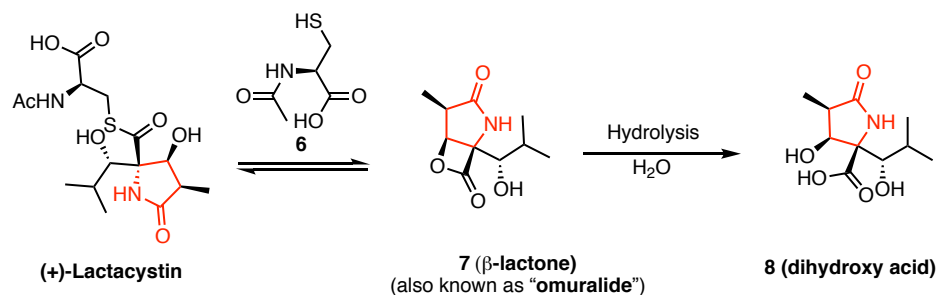
1.1.2. (+)-Lactacystin

(+)-Lactacystin is another very important γ -lactam-containing natural product, which was isolated from a *Streptomyces* strain by Ōmura *et al.* in 1991.⁸⁷ It is a cell-permeable and irreversible 20S proteasome inhibitor which can regulate the intracellular protein degradation.⁸⁸ Its inhibitory activity results from the hydrolysis of (+)-lactacystin into β -lactone **7**, also known as omuralide, which reacts with the *N*-terminal threonine residue of some proteasome subunit (Scheme 41).

⁸⁶ Aoki, S.-Y.; Tsukude, T.; Miyazaki, Y.; Takao, K.-I.; Tadano, K. I. *Heterocycles*. **2006**, 69, 49-54.

⁸⁷ Ōmura, S.; Fujimoto, T.; Otoguro, K.; Matsuzaki, K.; Moriguchi, R.; Tanaka, H.; Sasaki, Y. *J. Antibiot.* **1991**, 44, 113-117.

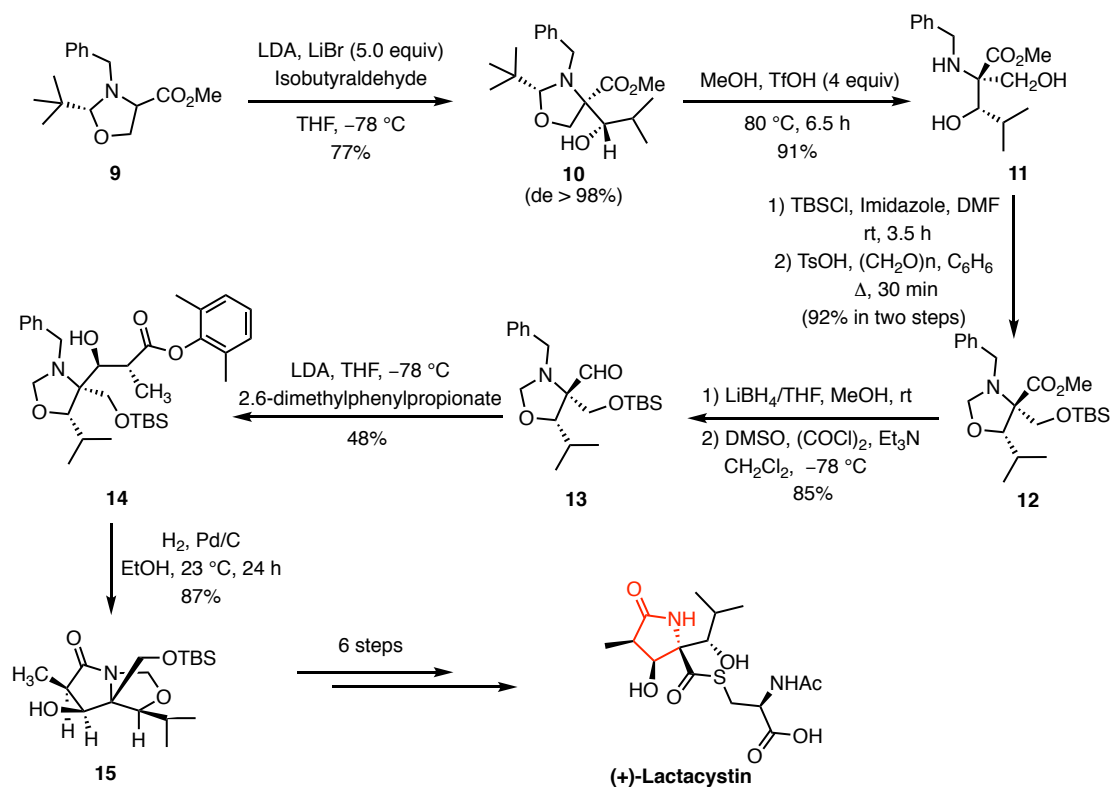
⁸⁸ a) Corey, E. J.; Reichard, G. A. *J. Am. Chem. Soc.* **1992**, 114, 10677-10678; b) Corey, E. J.; Li, W.; Nagamitsu, T. *Angew. Chem. Int. Ed.* **1998**, 37, 1676-1679; c) Corey, E. J.; Li, W.-D. *Z. Chem. Pharm. Bull.* **1999**, 47, 1-10.



Scheme 41. Hydrolysis of (+)-lactacystin.

Several groups have already developed different methods to complete the total synthesis of this important natural product.^{88,89} The first total synthesis was reported by Corey and Reichard in 1992.^{5a} They started from *cis*-oxazolidine **9**, which was first engaged in a highly diastereoselective aldol reaction (de > 98) with isobutyraldehyde. The aldol product **10** was obtained in good yield (77%) and excellent diastereoselectivity (>98%). A sequential amination cleavage/silylation/amination (CH₂O, TsOH), afforded the oxazolidine intermediate **12** bearing an ester moiety which was then reduced to the corresponding aldehyde and engaged in an aldol reaction to afford the desired *anti*-aldol product **14**. The latter was eventually converted to the bicyclic intermediate **15**. Six additional steps were necessary to complete the synthesis of (+)-lactacystin (Scheme 42).

⁸⁹ a) Ho Kang, S.; Jun, H.-S. *Chem. Commun.* **1998**, 1929-1930; b) Ooi, H.; Ishibashi, N.; Iwabuchi, Y.; Ishihara, J.; Hatakeyama, S. *J. Org. Chem.* **2004**, *69*, 7765-7768; c) Sunazuka, T.; Hirose, T.; Ōmura, S. *Acc. Chem. Res.* **2008**, *41*, 302-314.



Scheme 42. Total synthesis of (+)-lactacystin.

1.1.3. Salinosporamide A

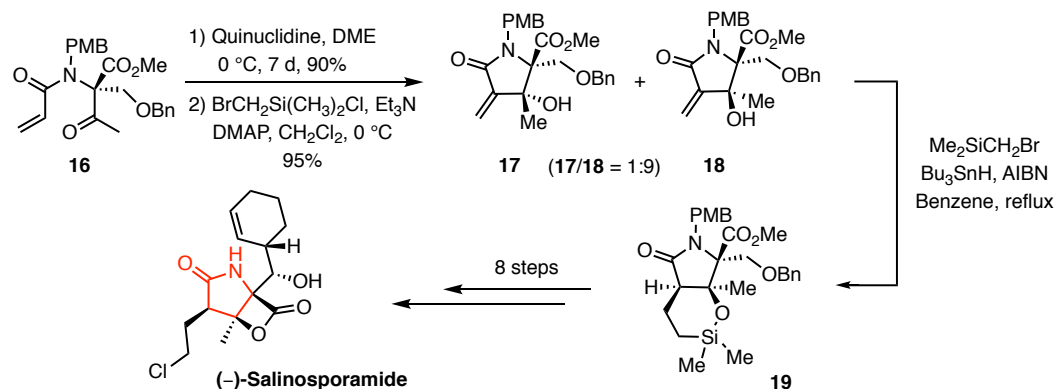
Salinosporamide A is another very important natural product bearing an unusual γ -lactam β -lactone unit, which was isolated from a marine bacterium by Fenical *et al.* in 2003.⁹⁰ Due to the high structural similarity of salinosporamide A with the active proteasome inhibitor omuralide (Scheme 41), it was immediately tested as a 20S proteasome inhibitor. As a result, salinosporamide A was shown to exhibit a better activity than omuralide. In addition, salinosporamide A was also found to inhibit many tumor cell lines such as colon cancer cell line (HCT-116), SF-539 CNS cancer, and MDA-MB-435 breast cancer. Salinosporamide A is actually currently in phase I of clinical trials.

In the past decade, various strategies have been envisioned in order to complete the total synthesis of this natural product,⁹¹ including the strategy developed by

⁹⁰ Feling, R. H.; Buchanan, G. O.; Mincer, T. J.; Kauffman, C. A.; Jensen, P. R.; Fenical, W. *Angew. Chem. Int. Ed.* **2003**, *42*, 355-357

⁹¹ a) Reddy, L. R.; Saravanan, P.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 6230-6231; b) Reddy, L. R.; Fournier, J.-F.; Subba Reddy, B. V.; Corey, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 8974-8976; c) Ma, G.; Nguyen, H.; Romo, D. *Org. Lett.* **2007**, *9*, 2143-2146; d) Takahashi, K.; Midori, M.; Kawano, K.; Ishihara, J.; Hatakeyama, S. *Angew. Chem. Int. Ed.* **2008**, *47*, 6244-6246; e) Satoh, N.; Yokoshima, S.; Fukuyama, T. *Org. Lett.* **2011**, *13*, 3028-3031.

Corey *et al.* that allowed to complete the first total synthesis of salinosporamide A using an intramolecular Morita-Baylis-Hillman reaction to form the γ -lactam moiety starting from the keto-amido ester intermediate **16** (Scheme 43).



Scheme 43. Synthesis of (–)-salinosporamide.

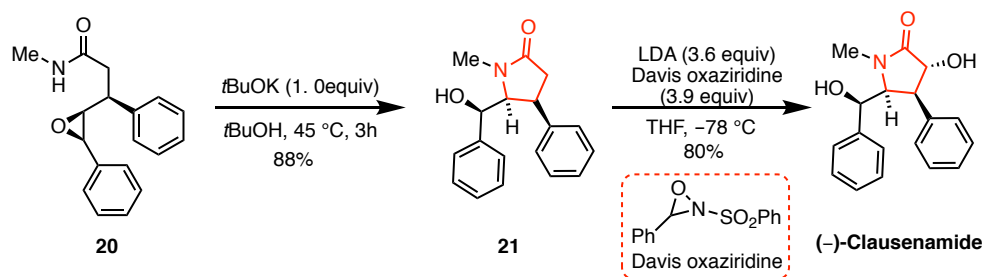
1.1.4. (–)-Clausenamide

Clausenamide is another important bioactive natural product bearing a γ -lactam motif. Racemic clausenamide was isolated from a traditional Chinese plant named *Clausena lansium*, but only (–)-clausenamide was found to exhibit interesting biological activities. This compound controls the intracellular calcium release to enable the CaMKII α -CREB signal pathway activation and thus improve learning and memory capacities to normal levels in amnesia animal models.⁹² This compound is currently in clinical trial in China for the treatment of Alzheimer's disease.⁹³ One of the most efficient and straightforward strategy to access (–)-clausenamide was developed by Huang *et al.* in 2013.⁹⁴ They constructed the γ -lactam ring through *t*-BuOK-promoted intramolecular epoxide ring-opening by an amide through a S_N2 type mechanism affording the corresponding γ -lactam **21** in high yield (88%). The latter was further converted to (–)-clausenamide through a Davis oxidation (Scheme 44).

⁹² a) Zhu, X. Z.; Li, X.-Y.; Liu, J. *Eur. J. Pharmacol.* **2004**, *500*, 221-230; b) Ning, N.; Hu, J.-F.; Sun, J.-D.; Han, N.; Zhang, J.-T.; Chen, N.-H. *Eur. J. Pharmacol.* **2012**, *682*, 50-55; c) Chu, S.; Zhang, J. *Acta Pharmaceutica Sinica B* **2014**, *4*, 417-423.

⁹³ Chu, S.; Liu, S.; Duan, W.; Cheng, Y.; Jiang, X.; Zhu, C.; Tang, K.; Wang, R.; Xu, L.; Wang, X.; Yu, X.; Wu, K.; Wang, Y.; Wang, M.; Huang, H.; Zhang, J. *Pharmacol. Ther.* **2016**, *162*, 179-187.

⁹⁴ Liu, D.; Yu, X.; Huang, L. *Chin. J. Chem.*, **2013**, *31*, 344-348.



Scheme 44. The structure of (–)-clausenamide.

2. Enantioselective synthesis of γ -lactam derivatives

As many of the natural products bearing a lactam unit were isolated as single enantiomers, chemists have been keen in developing efficient methods to access enantio-enriched γ -lactam derivatives bearing a tertiary or a quaternary stereogenic center. Some of the most representative ones are reported in the following section.

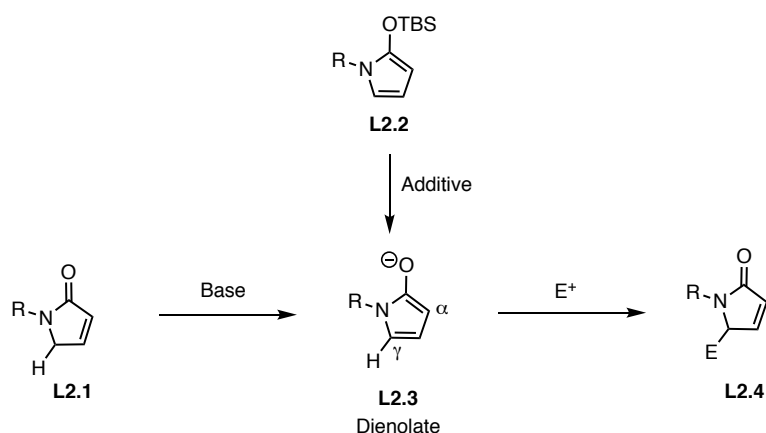
2.1 Enantioselective synthesis of γ -lactam derivatives bearing a tertiary stereogenic center

2.1.1. Asymmetric electrophilic substitution of α,β -unsaturated γ -lactams and 2-siloxypyrroles

One strategy to access enantio-enriched γ -lactams involves the asymmetric electrophilic substitution of α,β -unsaturated γ -lactams **L2.1** or 2-silyloxypyrroles **L2.2**, which emerged as good precursors to produce **L2.4**.⁹⁵ This is attributed to the facile formation of dienolate **L2.3** and the sufficient reactivity of this dienolate as a nucleophile (Scheme 45). Both the α,β -unsaturated γ -lactam **L2.1** and the 2-silyloxypyrrole **L2.2** have been successfully subjected to asymmetric vinylogous

⁹⁵ Selected examples, a) Barnes, D. M.; Bhagavatula, L.; DeMattei, J.; Gupta, A.; Hill, D. R.; Manna, S.; McLaughlin, M. A.; Nichols, P.; Premchandran, R.; Rasmussen, M. W.; Tian, Z.; Wittenberger, S. J. *Tetrahedron: Asymmetry* **2003**, *14*, 3541-3551; b) Gheorghe, A.; Schulte, M.; Reiser, O. *J. Org. Chem.* **2006**, *71*, 2173-2176; c) Suga, H.; Takemoto, H.; Kakehi, A. *Heterocycles* **2007**, *71*, 361-371; d) Sartori, A.; Curti, C.; Battistini, L.; Burreddu, P.; Rassu, G.; Pelosi, G.; Casiraghi, G.; Zanardi, F. *Tetrahedron* **2008**, *64*, 11697-11705; e) Curti, C.; Sartori, A.; Battistini, L.; Rassu, G.; Zanardi, F.; Casiraghi, G. *Tetrahedron Lett.* **2009**, *50*, 3428-3431.

Michael, Mannich addition and aldol-type reaction. Representative examples are shown below.⁹⁶



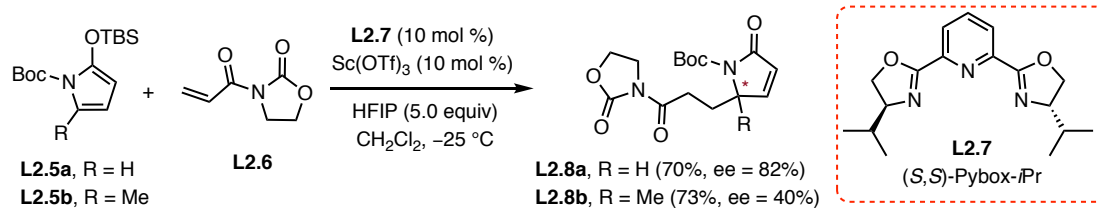
Scheme 45. The ambident nature of α,β -unsaturated γ -lactams and 2-silyloxypyrroles as nucleophiles.

2.1.1.1. Vinylogous Michael addition

In 2007, Suga *et al.*⁹⁷ developed the first example of a Lewis acid-catalyzed asymmetric Michael addition of *N*-Boc-2-silyloxypyrroles **L2.5** on 3-acryloyl-2-oxazolidinone **L2.6** to access optically active γ -lactams. They used the chiral (*S,S*)-Pybox-*i*-Pr ligand **L2.7** and $\text{Sc}(\text{OTf})_3$ as a catalyst to access the Michael addition product **L2.8a** in a good yield (70%) and high enantioselectivity (ee = 82%) from 2-silyloxypyrrole **L2.5a**. The 2-silyloxypyrrole derivative **L2.5b** bearing a methyl substituent at the γ -position was also examined under otherwise identical conditions. Interestingly, the corresponding product **L2.8b** bearing a γ -quaternary stereogenic center was isolated in good yield (73%) albeit with a moderate enantioselectivity (ee = 40%) (Scheme 46). Even though there were only two examples reported for this asymmetric vinylogous Michael addition, these examples showed that this reaction had a great potential to access optically active γ -lactams.

⁹⁶ For a review, see: Casiraghi, G.; Zanardi, F.; Battistini, L.; Rassu, G. *Synlett* **2009**, 10, 1525-1542.

⁹⁷ Suga, H.; Takemoto, H.; Kakehi, A. *Heterocycles* **2007**, 71, 361-371.



Scheme 46. Lewis acid-catalyzed asymmetric vinylogous Michael addition of 2-silyloxypyrroles to 3-acryloyl-2-oxazolidinone.

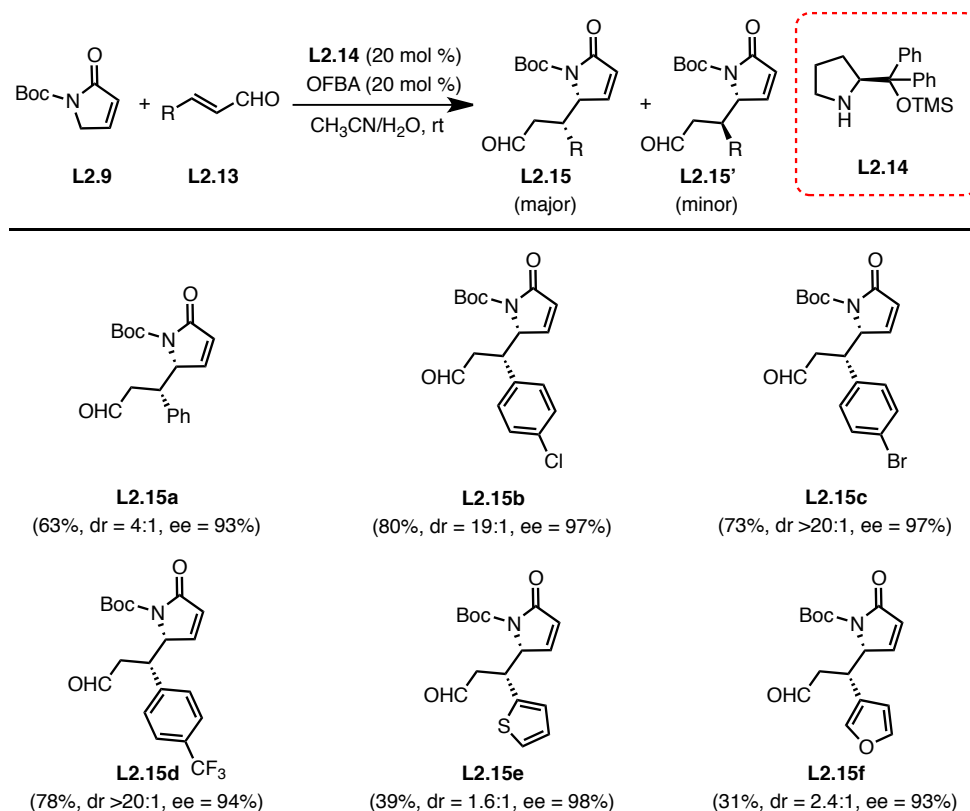
Subsequently, significant progress was made in the asymmetric vinylogous Michael addition approach. Thanks to the great efforts deployed by Shibasaki *et al.*,⁹⁸ the direct asymmetric vinylogous Michael addition of α,β -unsaturated γ -lactams to nitroalkenes was successfully developed. In 2010, the authors reported a nickel-catalyzed asymmetric vinylogous Michael addition of α,β -unsaturated γ -lactam **L2.9** to nitroalkenes affording the corresponding γ -lactams **L2.12** in good to high yields (83–98%), excellent diastereo- (up to >30:1) and enantioselectivities (ee = 93–99%) (Table 12).

Table 12. Ni-catalyzed asymmetric vinylogous Michael addition of α,β -unsaturated γ -lactam to nitroalkenes

Entry	R	t (h)	Yield of L2.12 (%)	dr	ee of L2.12 (%)
1	Ph	13	98	>30:1	97
2	2-Br-C ₆ H ₄	11	98	16:1	98
3	4-Br-C ₆ H ₄	12	96	29:1	99
4	4-Meo-C ₆ H ₄	25	98	>30:1	98
5	2-furyl	11	98	>30:1	98
6	2-thienyl	15	99	>30:1	98

⁹⁸ a) Shepherd, N.E.; Tanabe, H.; Xu, Y.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 3666–3667;
 b) Tanabe, H.; Xu, Y. J.; Sun, B.; Matsunaga, S.; Shibasaki, M. *Heterocycles* **2012**, *86*, 611–621.

Following this work, Chen *et al.*,^{16a} Wang *et al.*,^{16b} Ye *et al.*^{16c} and Yuan *et al.*,^{99d} applied this vinylogous Michael addition to other substrates including α,β -unsaturated aldehydes and ketones and 2-enoylpyridines, using various organocatalysts. For example, Chen *et al.* developed a direct vinylogous Michael addition of α,β -unsaturated γ -lactams to α,β -unsaturated aldehydes using a chiral prolinol derivative as the catalyst. The corresponding products were obtained in good to high yields (39-89%), moderate to high dr (1:1 to >20:1) and high levels of enantioselectivity (ee up to 98%) (Scheme 47).



Scheme 47. Selected examples of organocatalytic direct vinylogous Michael addition of α,β -unsaturated γ -lactam to α,β -unsaturated aldehydes.

2.1.1.2. Vinylogous Mannich-type addition

⁹⁹ Selected examples of asymmetric vinylogous Michael addition reaction, see: a) Feng, X.; Cui, H.-L.; Xu, S.; Wu, L.; Chen, Y.-C. *Chem. Eur. J.* **2010**, *16*, 10309-10312; b) Lin, J.; Zhang, J.; Ma, X.; Fu, X.; Wang, R. *Org. Lett.* **2011**, *13*, 6410-6413; c) Huang, H.; Jin, Z.; Zhu, K.; Liang, X.; Ye, J. *Angew. Chem. Int. Ed.* **2011**, *50*, 3232-3235; d) Wang, Z.-H.; Wu, Z.-J.; Yue, D.-F.; You, Y.; Xu, X.-Y.; Zhang, X.-M.; Yuan, W.-C. *Org. Biomol. Chem.* **2016**, *14*, 6568-6576.

Asymmetric vinylogous Mannich-type addition on α,β -unsaturated γ -lactams has also been reported by Shibasaki *et al.*^{13a} who used a dinuclear nickel-catalysts to generate γ -functionalized α,β -unsaturated γ -lactam **L2.14** from α,β -unsaturated lactams **L2.9**. The resulting substituted γ -lactams **L2.14** were obtained in good to high dr (up to >30:1) and good to high yields (61-95%), the ee of the major compound is 99% (Table 13).

Table 13. Asymmetric vinylogous Mannich-type reaction of α,β -unsaturated γ -butyrolactam to *N*-Boc imines

Entry	R	Yield of L2.14 (%)	dr	ee of L2.14 (%)
1	Ph	95	>30:1	99
2	2-naphthyl	76	30:1	99
3	1-naphthyl	93	26:1	99
4	2-Cl-C ₆ H ₄	95	>30:1	99
5	3-Me-C ₆ H ₄	87	>30:1	99
6	4-Cl-C ₆ H ₄	87	>30:1	99
7	4-MeO-C ₆ H ₄	85	23:1	99
8	2-furyl	61	5:1	99
9	3-thienyl	83	21:1	99

2.1.1.3. Vinylogous Mukaiyama aldol reaction

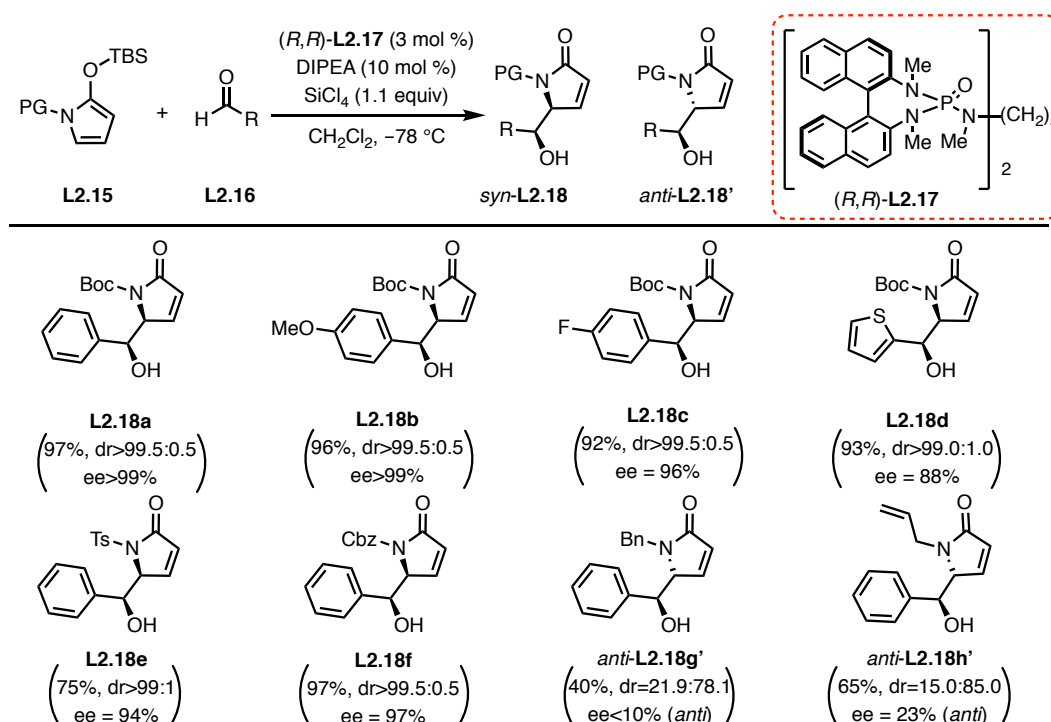
Besides asymmetric vinylogous Michael and Mannich-type additions, Casiraghi *et al.*¹⁰⁰ and Bolm *et al.*¹⁰¹ have successfully developed asymmetric

¹⁰⁰ a) Curti, C.; Sartori, A.; Battistini, L.; Rassu, G.; Zanardi, F.; Casiraghi, G. *Tetrahedron Lett.* **2009**, *50*, 3428-3431; b) Curti, C.; Ranieri, B.; Battistini, L.; Rassu, G.; Zambrano, V.; Pelosi, G.; Casiraghi, G.; Zanardi, F. *Adv. Synth. Catal.* **2010**, *352*, 2011-2022.

¹⁰¹ a) Frings, M.; Atodiresei, I.; Runsink, J.; Raabe, G.; Bolm, C. *Chem. Eur. J.* **2009**, *15*, 1566-1569; b) Frings, M.; Atodiresei, I.; Wang, Y.; Runsink, J.; Raabe, G.; Bolm, C. *Chem. Eur. J.* **2010**, *16*, 4577-4587.

vinyllogous Mukaiyama aldols¹⁰² between 2-silyloxypyrroles and aldehydes to access the corresponding optically pure γ -lactams bearing a tertiary center.

Casiraghi *et al.*¹⁷ used a similar catalytic system to the one developed by Denmark *et al.*¹⁰³ to catalyze the asymmetric vinyllogous Mukaiyama aldol reaction between 2-silyloxypyrroles and aldehydes. When a 2-silyloxypyrrole such as **L2.15** bearing a *N*-Boc, a *N*-Ts or a *N*-Cbz substituent on the nitrogen, was involved in the vinyllogous Mukaiyama aldol, a variety of aldehydes **L2.16** were well tolerated, affording the corresponding aldol products **L2.18** and **L2.18'** in good to high yields (75-97%), high diastereoselectivities (dr >99:1 in favor of *syn*-**L2.18**) and high enantioselectivities (ee = 88-99%) (Scheme 48). It is worth noting that 2-silyloxypyrroles **L2.15** bearing a *N*-benzyl or a *N*-allyl substituent on the nitrogen afford low yields, low diastereoselectivities and low enantioselectivities. In all these latter examples, the *anti*-products **L2.18g'** and **L2.18h'** were obtained as the major products (Scheme 48).

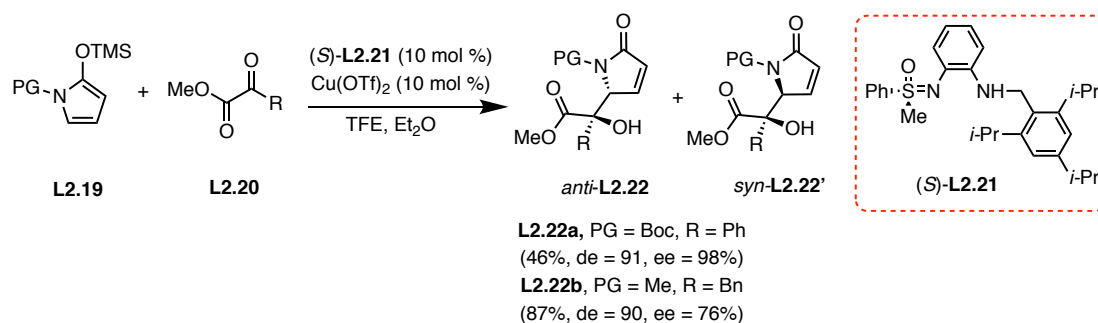


Scheme 48. Chiral biphosporamide/SiCl₄-catalyzed asymmetric vinyllogous Mukaiyama aldol reaction of 2-silyloxypyrroles to aromatic aldehydes.

¹⁰² For a review, see: Casiraghi, G.; Battistini, L.; Curti, C.; Rassu, G.; Zanardi, F. *Chem. Rev.* **2011**, *111*, 3076-3154.

¹⁰³ a) Denmark, S. E.; Beutner, G. L. *J. Am. Chem. Soc.* **2003**, *125*, 7800-7801. b) Denmark, S. E.; Heemstra, J. R., Jr. *Synlett* **2004**, 2411-2416. c) Denmark, S. E.; Beutner, G. L.; Wynn, T.; Eastgate, M. D. *J. Am. Chem. Soc.* **2005**, *127*, 3774-3789. d) Denmark, S. E.; Heemstra, J. R., Jr. *J. Am. Chem. Soc.* **2006**, *128*, 1038-1039; e) Denmark, S. E.; Heemstra, J. R., Jr. *J. Org. Chem.* **2007**, *72*, 5668-5688.

Roughly at the same time, Bolm *et al.*¹⁸ developed a C_1 -symmetric amino sulfoximide ligand **L2.21**, which upon copper-catalyzed asymmetric vinylogous Mukaiyama aldol reaction with 2-(trimethylsilyloxy)furan, thiophene and pyrrole afforded the corresponding *anti*-addition products **L2.22a** (46%, de = 91, ee = 98%) and **L2.22b** (87%, de = 90, ee = 76%) in good yields, high diastereoselectivities and good to excellent enantioselectivities (Scheme 49).



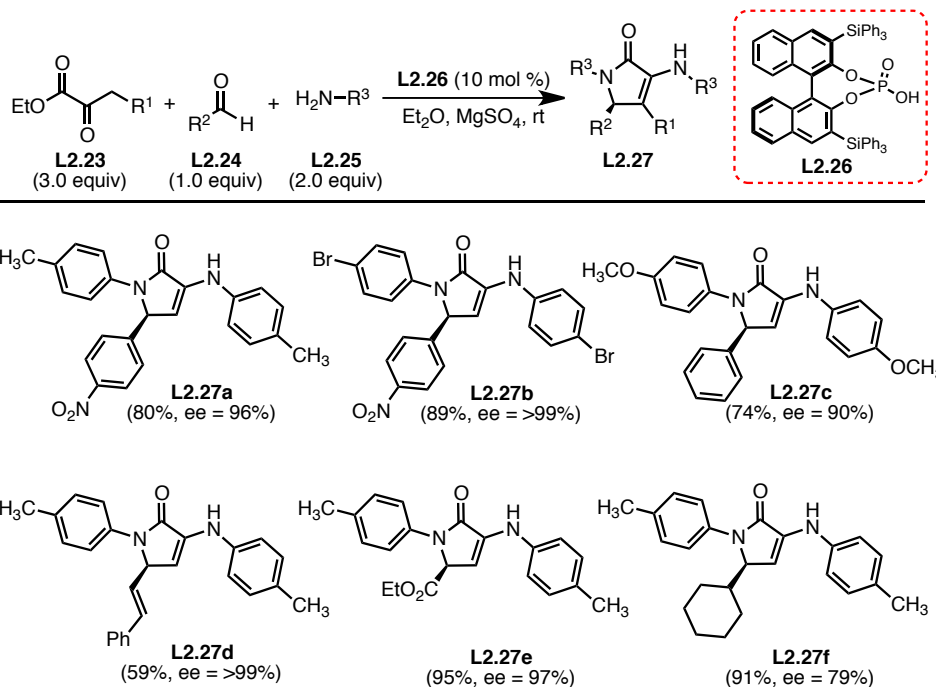
Scheme 49. Copper-catalyzed asymmetric vinylogous Mukaiyama aldol reaction of 2-silyloxypyrroles.

2.1.2. Brønsted-acid catalyzed asymmetric tandem reactions

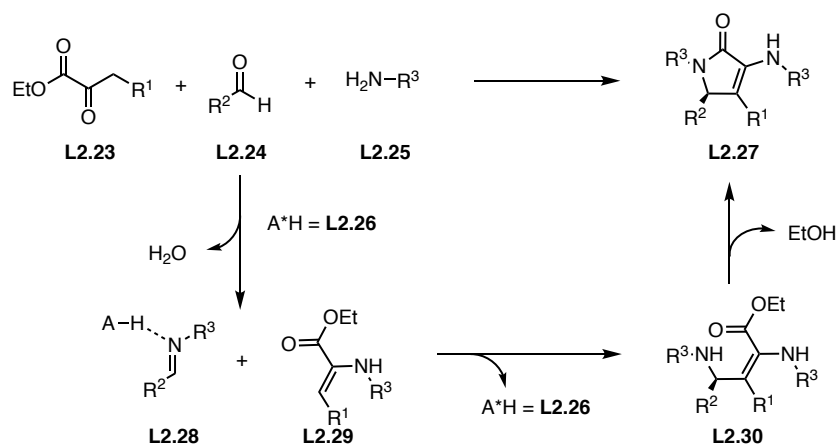
Besides the electrophilic substitution of α,β -unsaturated γ -lactams and 2-silyloxypyrroles, optically active γ -lactams can also be accessed *via* a Brønsted-acid catalyzed asymmetric tandem reaction. Recently, Marigorta *et al.*¹⁰⁴ successfully developed a chiral phosphoric acid catalyzed three-component reaction involving amines, aldehydes and pyruvate derivatives to construct highly functionalized optically active γ -lactam derivatives in good to high yields (59-98%) and high levels of enantioselectivity (ee up to 99%) (Scheme 50).

Mechanistically, the reaction was initiated by the *in situ* generation of the imine and enamine intermediates **L2.28** and **L2.29**, which could undergo a Mannich reaction to form intermediate **L2.30**. The latter would eventually undergo an intramolecular nucleophilic substitution to generate the amide bond and affording the desired γ -lactam **L2.27** (Scheme 51).

¹⁰⁴ Del Corte, X.; Maestro, A.; Vicario, J.; de Marigorta, E. M.; Palacios, F. *Org. Lett.* **2018**, *20*, 317-320.



Scheme 50. Selected examples of chiral phosphoric acid-catalyzed asymmetric tandem reaction to construct optically active γ -lactams.

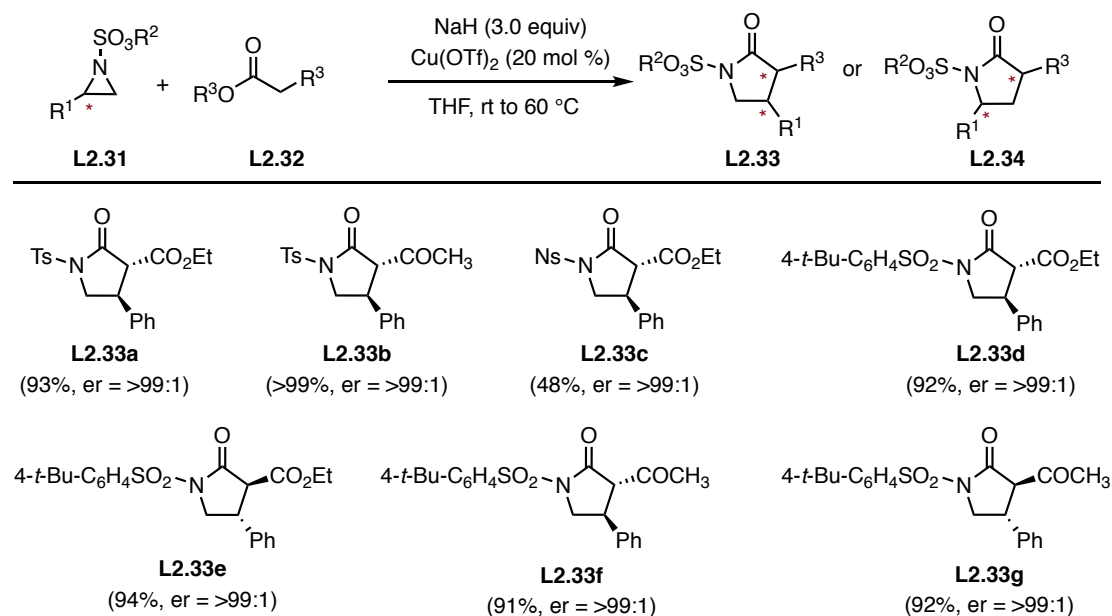


Scheme 51. Proposed catalytic cycle of chiral phosphoric-acid catalyzed asymmetric tandem reaction of amines, aldehydes and pyruvate derivatives.

2.1.3. Lewis-acid-catalyzed domino-ring-opening/cyclization from optically pure aziridines with enolates

Another interesting method to access optically active γ -lactams involves the ring opening of optically pure aziridines. In 2010, Ghorai and Tiwari developed a Lewis acid-

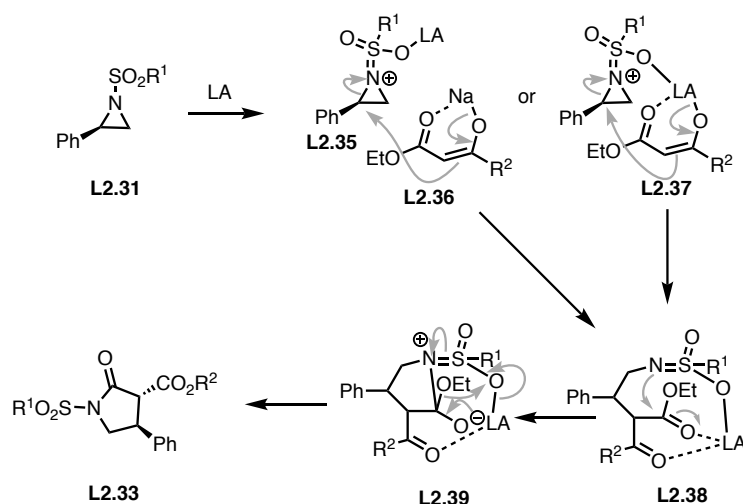
catalyzed stereoselective domino ring-opening/cyclization of activated aziridines with malonates to access the optically active γ -lactams.¹⁰⁵ Hence, by using an optically pure aziridine such as **L2.31** to react with 1,3-diester **L2.32** under their optimized conditions, the corresponding γ -lactams were obtained in high yields (48->99%). Most importantly, no erosion of the enantiomeric excess was observed on the optically active γ -lactams (er >99:1) (Scheme 52).



Scheme 52. Selected examples of Lewis-acid-catalyzed stereoselective domino ring-opening/cyclization of activated aziridines with enolates to synthesize γ -lactams.

Two possible mechanistic pathways can be envisaged: the first one involves a Lewis acid (LA) activation of aziridine **L2.31** *via* a coordination with the sulfonyl group to generate the ammonium intermediate **L2.35**. The enolate **L2.36** resulting from the deprotonation of 1,3-diester **L2.32** would then add onto the activated aziridine to form, after ring-opening, intermediate **L2.38** which can undergo an intramolecular nucleophilic addition. The second possible pathway involves the coordination of the Lewis acid with both the aziridine and the enolate intermediate followed by a nucleophilic addition to open the aziridine ring. The resulting intermediate **L2.38** then undergoes an intramolecular nucleophilic addition to form **L2.39** which, after decoordination from the Lewis acid, affords the desired product **L2.33** (Scheme 53).

¹⁰⁵ Ghorai, M. K.; Tiwari, D. P. *J. Org. Chem.* **2010**, 75, 6173-6181.



Scheme 53. Proposed mechanism of Lewis acid-catalyzed domino ring-opening/cyclization of activated aziridines with enolates to synthesize γ -lactams

2.1.4. Transition metal-catalyzed reaction

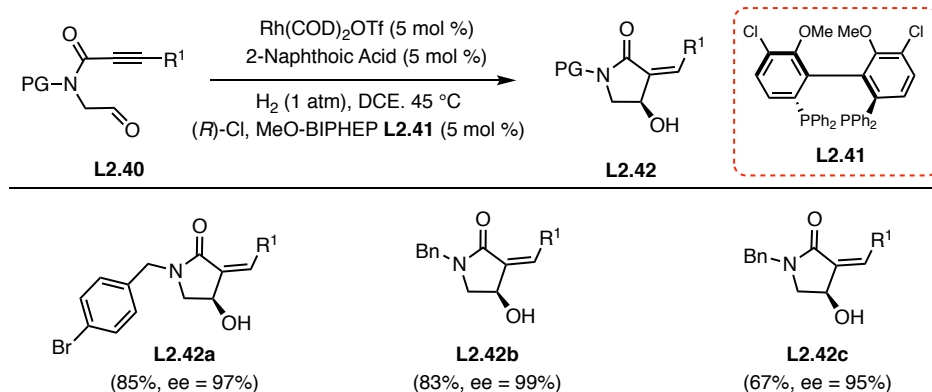
During the past two decades, transition metal-catalysis has been used to construct γ -lactam derivatives.¹⁰⁶

2.1.4.1. Rhodium-catalyzed intramolecular reductive cyclization

In 2006, Krische and Rhee developed a highly enantioselective Rh-catalyzed asymmetric reductive cyclization of acetylenic amide aldehydes **L2.40** *via* a hydrogenation process, which provides an efficient access to γ -lactam derivatives bearing a β -tertiary stereogenic center (**L2.42**) in good yields (67-85%) and excellent enantioselectivities (ee up to 99%) (Scheme 54).¹⁰⁷

¹⁰⁶ For a review, see: Ye, L.-W.; Shu, C.; Gagosz, F. *Org. Biomol. Chem.* **2014**, *12*, 1833-1845.

¹⁰⁷ Rhee, J. U.; J. Krische, M. *J. Am. Chem. Soc.* **2006**, *128*, 10674-10675.

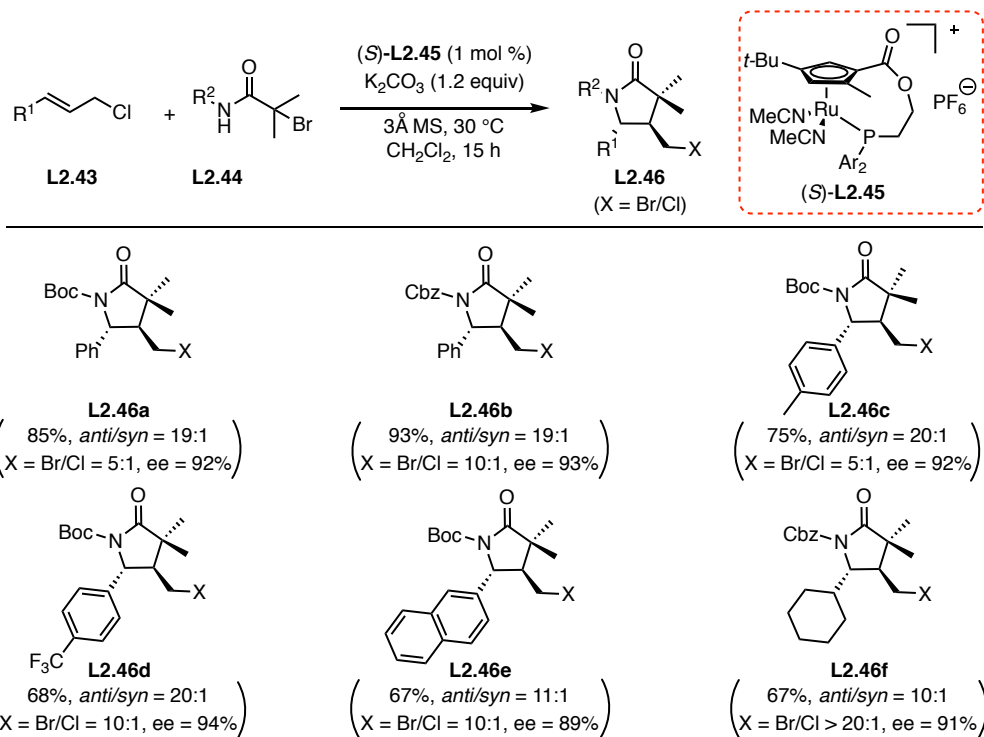


Scheme 54. Selected examples of Rh-catalyzed asymmetric reductive cyclization of acetylenic amide aldehydes.

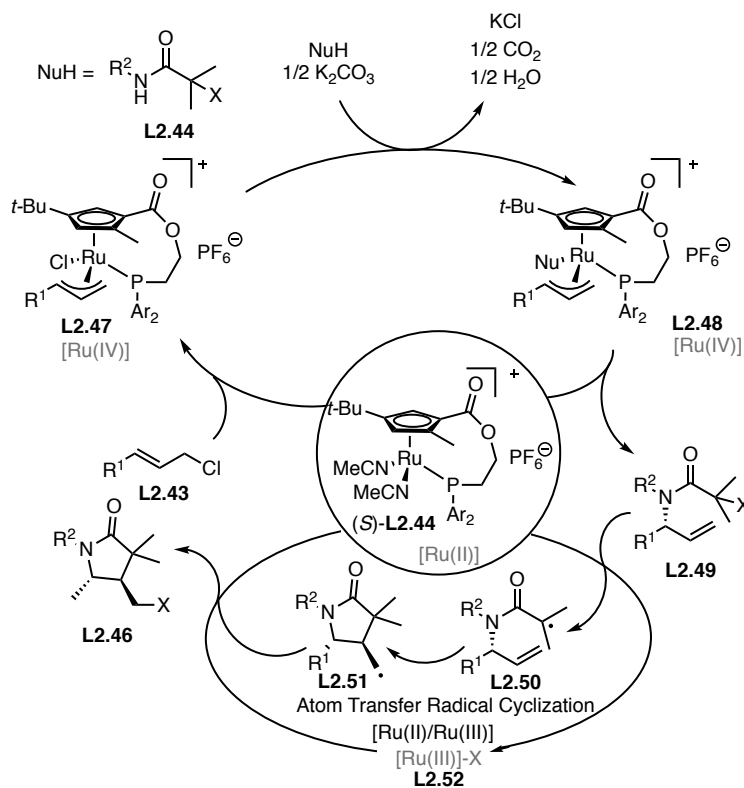
2.1.4.2. Ruthenium-catalyzed asymmetric auto-tandem allylic amidation

Recently, Okamura *et al.* reported another novel and efficient method for the asymmetric synthesis of optically active γ -lactams.¹⁰⁸ They successfully developed a Ru-catalyzed asymmetric auto-tandem allylic amidation to form γ -lactams using the planar chiral CpRu complex, (*S*)-**L2.45**. The corresponding optically active γ -lactams were obtained in high yields (67-85%), good to high diastereoselectivities (dr = 10:1-20:1) and excellent enantioselectivities (ee up to 99%) (**L2.46a-f**) (Scheme 55). This reaction involves a Ru-catalyzed asymmetric allylic substitution [Ru(II)/Ru(IV)] and a diastereoselective atom-transfer radical cyclization [Ru(II)/Ru(III)]. Indeed, the reaction may be initiated by the oxidative addition of **L2.43** onto the chiral Ru catalyst **L2.45** to form the key π -allylic intermediate **L2.47**. Subsequently, nucleophilic addition of the amide to the Ru- π allylic species forms the branched allylic amide intermediate **L2.49**, which can then undergo an atom transfer process. This would generate the [Ru(III)]-X intermediate **L2.52** and a tertiary radical **L2.50**, which can react with the terminal alkene in an intramolecular fashion to form the radical intermediate **L2.51**. Finally, the halogen atom on the [Ru(III)] complex **L2.52** can recombine with the radical intermediate **L2.51** to give the final product **L2.45** (Scheme 56).

¹⁰⁸ Kanbayashi, N.; Takenaka, K.; Okamura, T.-A.; Onitsuka, K. *Angew. Chem. Int. Ed.* **2013**, 52, 4997-5001.



Scheme 55. Selected examples of Ru-catalyzed asymmetric auto-tandem allylic amidation and atom-transfer radical cyclization.



Scheme 56. Proposed catalytic cycle of Ru-catalyzed asymmetric auto-tandem allylic amidation and atom-transfer radical cyclization.

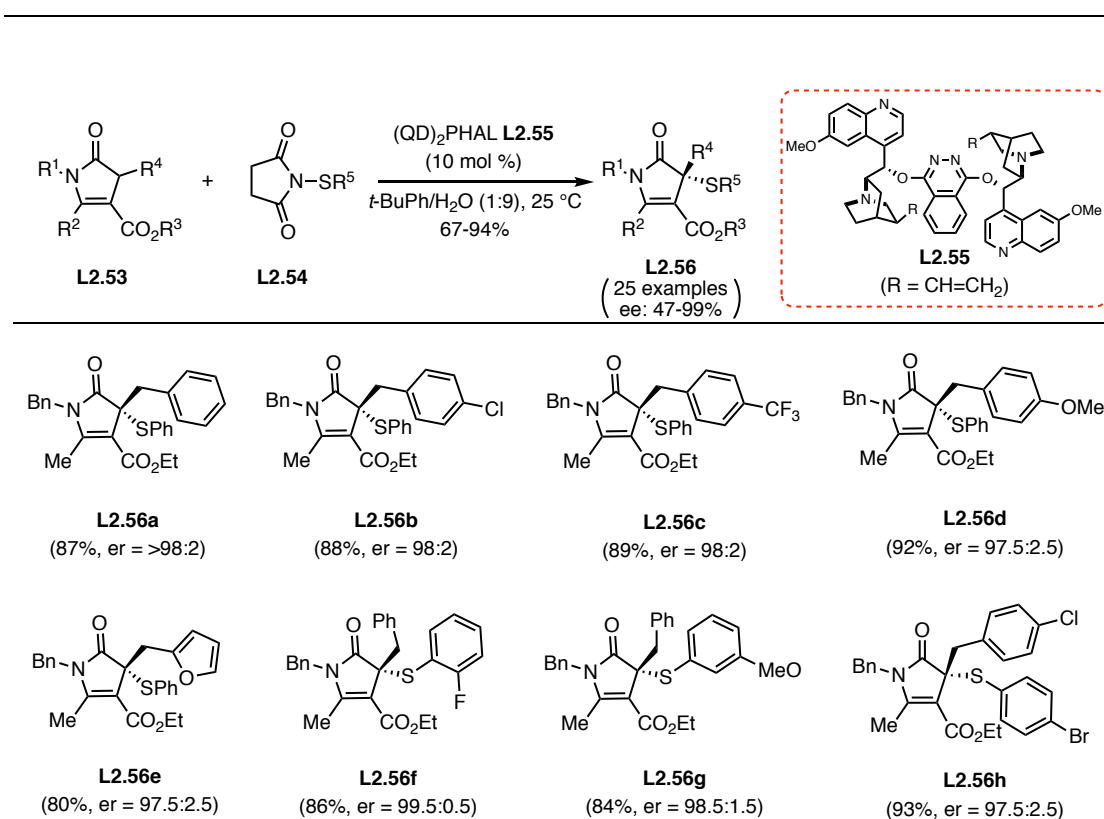
2.2. Enantioselective synthesis of γ -lactam derivatives bearing a quaternary stereogenic center

The asymmetric synthesis of cyclic and acyclic compounds bearing a quaternary stereogenic center remains a challenge in organic chemistry. To the best of our knowledge, there are only few methods that allow an efficient access to optically pure γ -lactams bearing a quaternary stereogenic center. In this section, we will present some of the most emblematic methods.

2.2.1. Organocatalytic enantioselective sulfenylation of deconjugated butyrolactams

Recently, Mukherjee and co-workers¹⁰⁹ developed an efficient organocatalytic enantioselective sulfenylation of β,γ -unsaturated γ -lactams using the dimeric cinchona alkaloid **L2.55**. Various substituents at the α -, β - and γ -position were well tolerated and the corresponding sulfenylated γ -lactam products bearing an α -quaternary stereogenic center were obtained in generally high yields and good to excellent enantioselectivities (ee up to 98%) (**L2.56a-h**) (Scheme 57). Interestingly, the use of a 9:1 H₂O/*t*-BuPh mixture afforded higher yields and enantioselectivities than the use of other organic solvents.

¹⁰⁹ Singha Roy, S. J.; Mukherjee, S. *Org. Biomol. Chem.* **2017**, *15*, 6921-6925.

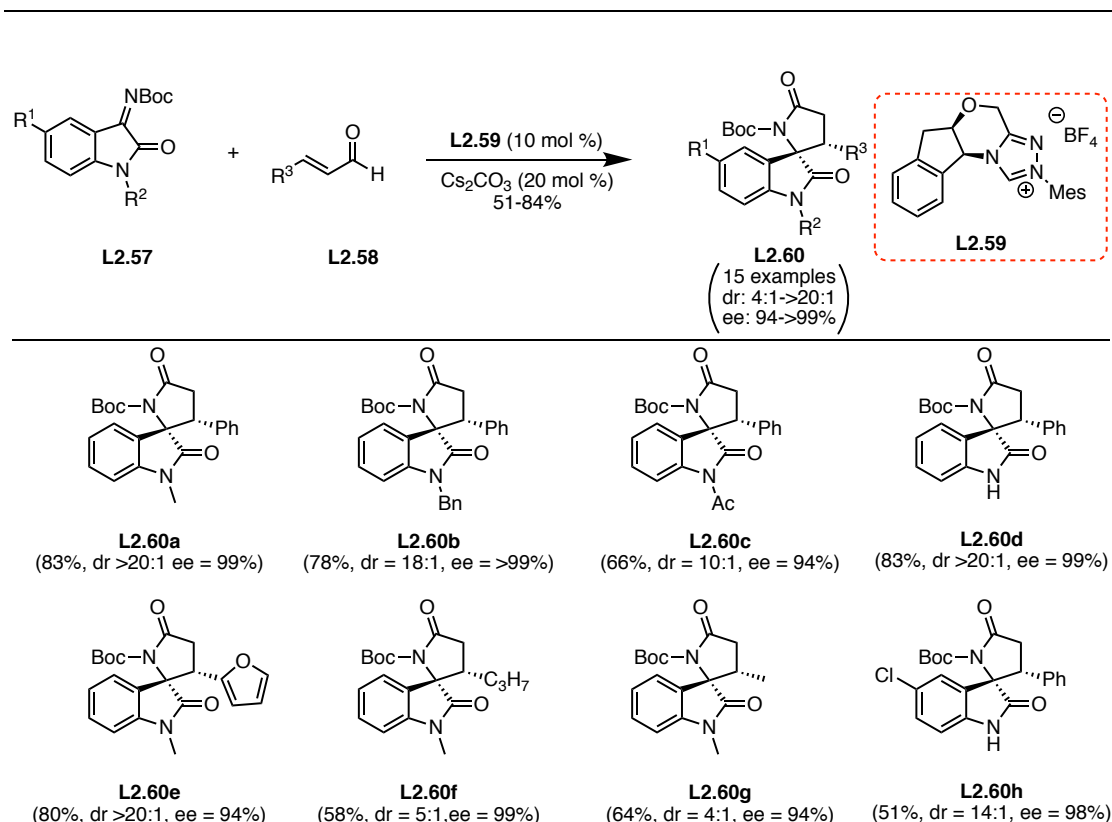


Scheme 57. Organocatalytic asymmetric sulfenylation of β,γ -unsaturated γ -lactams.

2.2.2. NHC-catalyzed enantioselective addition of enal to isatin-derived ketimines

Optically active γ -lactams can also be accessed *via* a stereoselective [3+2]-annulation. In 2012, Robin Chi *et al.*¹¹⁰ successfully used this method to synthesize various enantio-enriched spirocyclic γ -lactams through the enantioselective cyclization of enals **L2.58** with isatin-derived ketimines **L2.57** using an optically active *N*-heterocyclic carbene pre-catalyst, **L2.59**. The corresponding annulation products **L2.60** were obtained in good to high yields (51-84%), moderate to excellent diastereoselectivities (4:1 to >20:1) and high levels of enantioselectivity (ee up to >99%) (**L2.60a-h**) (Scheme 58).

¹¹⁰ Lv, H.; Tiwari, B.; Mo, J.; Xing, C.; Robin Chi, Y. *Org. Lett.* **2012**, *14*, 5412-5415.

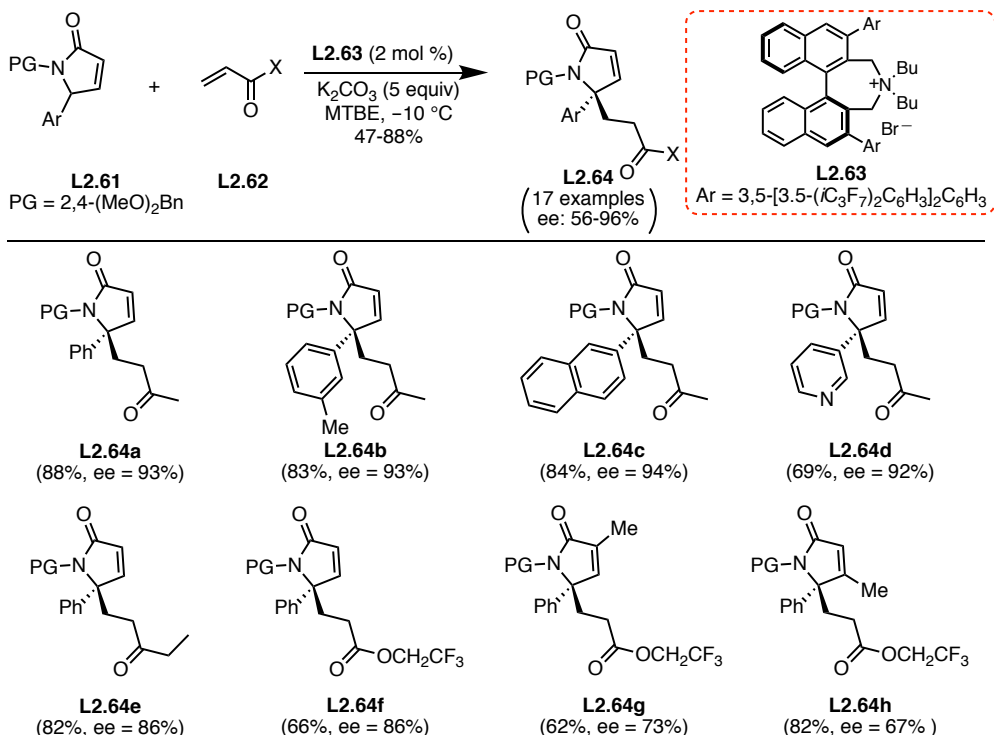


Scheme 58. Selected examples of asymmetric cyclization of enals to isatin-derived ketimines.

2.2.3. Asymmetric vinylogous Michael addition

The asymmetric vinylogous Michael addition of prochiral substrates is another possible and straightforward strategy to construct compounds bearing a quaternary stereogenic center. Inspired by the work of Suga *et al.*¹³ on the Lewis acid-catalyzed Michael addition of *N*-Boc-2-silyloxypyrroles onto 3-acryloyl 2-oxazolidinones to access optically active γ -lactams **L2.8** bearing a γ -quaternary stereogenic center (Chapter II, Section 2.1.1), Maruoka *et al.*¹¹¹ recently developed a phase-transfer catalyzed asymmetric vinylogous Michael addition of α,β -unsaturated γ -lactams **L2.61** onto methyl vinyl ketone and trifluoroethyl acrylate **L2.62**. The corresponding enantio-enriched γ -lactams **L2.64** bearing a γ -quaternary stereogenic center were isolated in good to high yields (47-88%) and moderate to excellent enantioselectivities (ee = 56-96%) (**L2.64a-h**) (Scheme 59).

¹¹¹ Arlt, A.; Toyama, H.; Takada, K.; Hashimoto, T.; Maruoka, K. *Chem. Commun.* **2017**, 53, 4779-4782.



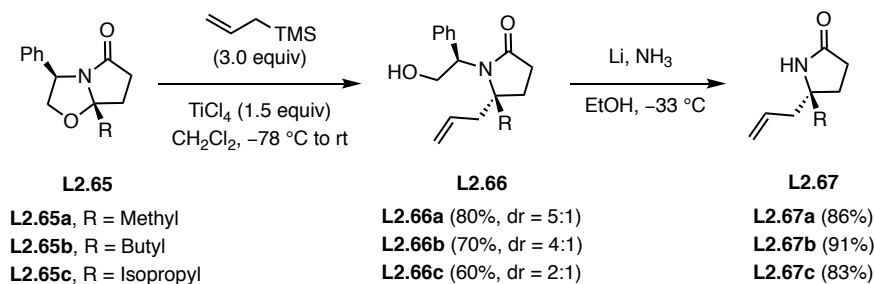
Scheme 59. Selected examples of phase-transfer catalyzed asymmetric vinylogous Michael addition to synthesize γ -lactams bearing a γ -quaternary center.

2.2.4. Auxiliary based stereoselective allylation of optically active bicyclic lactam

Optically active bicyclic lactams have been widely used to construct many optically active carbocycles and heterocycles.¹¹² In 1991, Burgess and Meyers synthesized optically pure 4,4-disubstituted pyrrolidinones **L2.66** (**L2.66a-c**) in good to high yields (60-80%) through a Lewis acid-catalyzed stereoselective allylation of chiral bicyclic lactams **L2.65** (Scheme 60).¹¹³ After reductive cleavage of the phenylglycinol moiety of **L2.66**, enantio-enriched 4,4-disubstituted pyrrolidinones **L2.67** (**L2.67a-c**) were isolated in generally high yields (83-91%) (Scheme 60).

¹¹² For a review, see: Groaning, M. D.; Meyers, A. I. *Tetrahedron* **2000**, *56*, 9843-9873.

¹¹³ a) Burgess, L. E.; Meyers, A. I. *J. Am. Chem. Soc.* **1991**, *113*, 9858-9859; b) Burgess, L. E.; Meyers, A. I. *J. Org. Chem.* **1992**, *57*, 1657-1662.



Scheme 60. Enantio-enriched bicyclic lactams auxiliary Lewis-acid catalyzed allylation to access optically active pyrrolidinones.

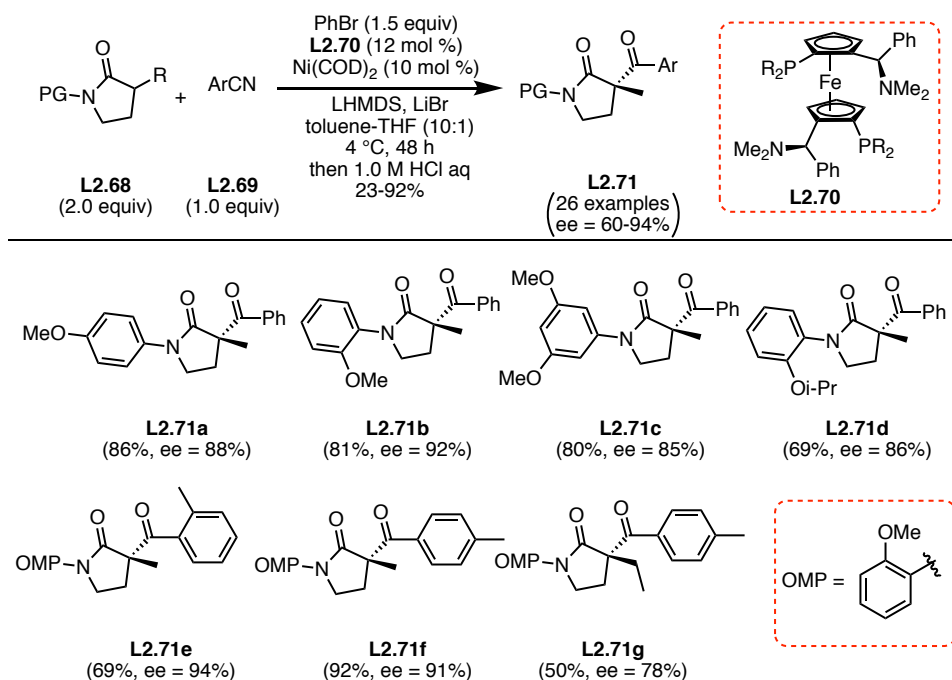
2.2.5. Transition metal-catalyzed asymmetric reactions

Besides these methods, transition metal-catalyzed asymmetric reactions were also successfully developed to construct enantio-enriched γ -lactams bearing a quaternary stereogenic center.

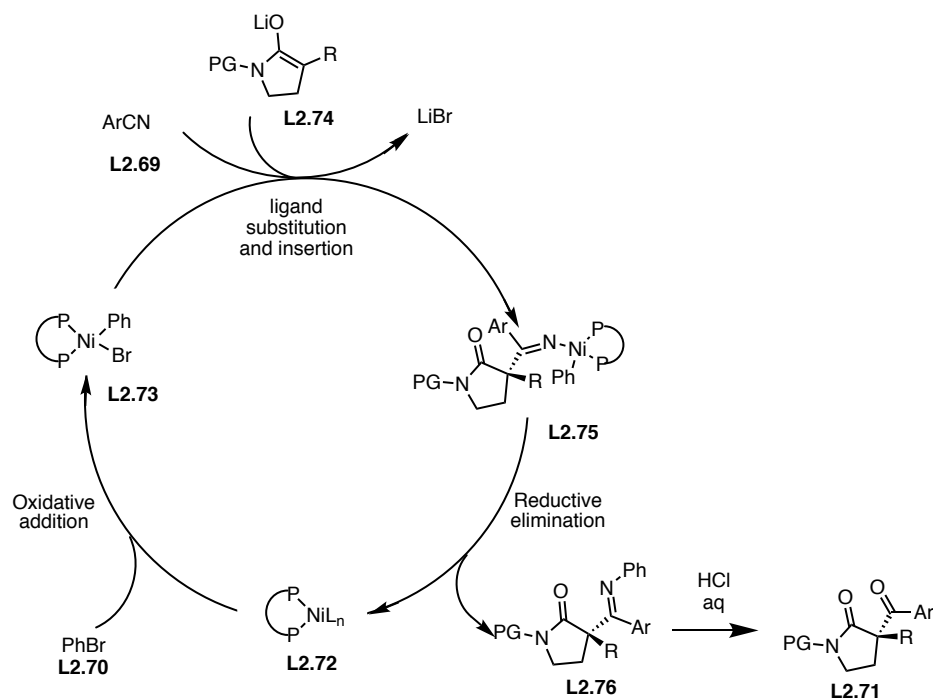
2.2.5.1. Ni-catalyzed enantioselective C-acylation

Recently, an efficient nickel-catalyzed enantioselective C-acylation of α -substituted lactams was developed by Stoltz and co-workers.¹¹⁴ The corresponding γ -lactam derivatives bearing an all-carbon α -quaternary stereogenic center were obtained in good to high yields (23-92%) and good to excellent enantioselectivities (ee = 60-94%) (Scheme 61). The proposed mechanism involves a $\text{Ni(0)}/\text{Ni(II)}$ catalytic cycle. Hence, the oxidative addition of the aryl bromide onto a Ni(0) complex **L2.72** produced the Ni(II) arene species **L2.73**. Ligand substitution and insertion of the benzonitrile then afforded intermediate **L2.75**, which was eventually converted to the primary imine **L2.76** after reductive elimination. The C-acylated product **L2.71** was finally obtained from the primary imine **L2.76** under acidic conditions (Scheme 62).

¹¹⁴ Hayashi, M.; Bachman, S.; Hashimoto, S.; Eichman, C. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2016**, *138*, 8997-9000.



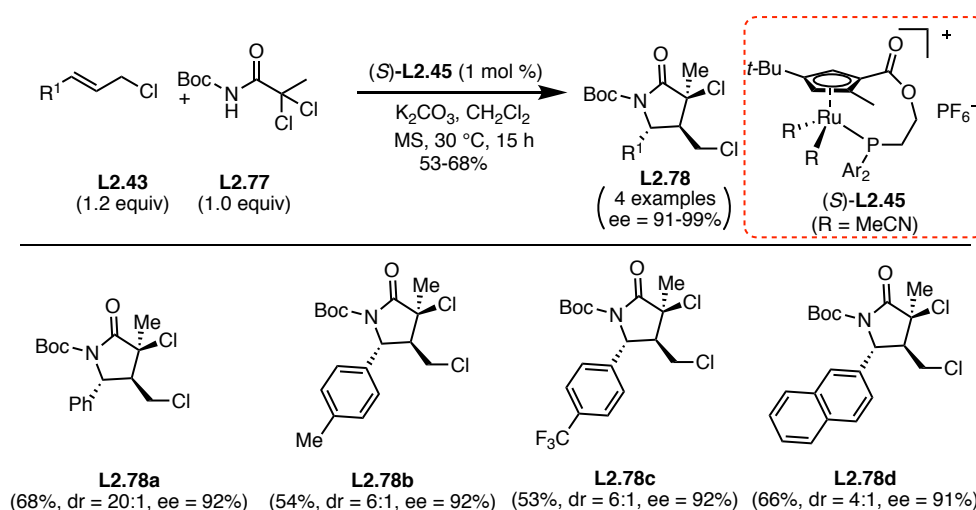
Scheme 61. Selected examples of Ni-catalyzed enantioselective C-acylation of α -substituted lactams.



Scheme 62. Proposed catalytic cycle of Ni-catalyzed enantioselective C-acylation of α -substituted lactams.

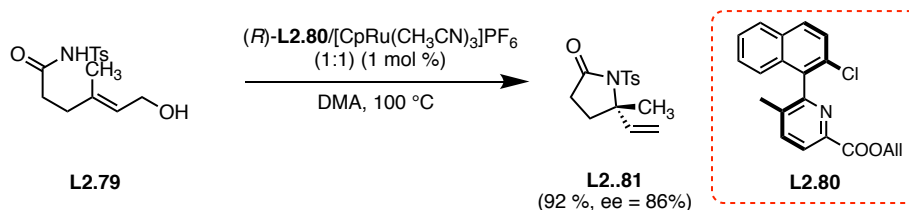
2.2.5.2. Ru-catalyzed dehydrative intramolecular *N*-allylation

In the previous section, we discussed the Ru-catalyzed asymmetric auto-tandem allylic amidation and atom transfer radical cyclization,²⁴ however optically active lactams containing a quaternary stereogenic can also be accessed using dichloro-substituted amide **L2.77**. The corresponding cyclization product **L2.78** can be obtained in good yield (53-68%) and high level of enantioselectivity (ee = 91-92%) (Scheme 63).



Scheme 63. Ru-catalyzed asymmetric auto-tandem allylic amidation and atom-transfer radical cyclization.

Kitamura *et al.*¹¹⁵ also developed a Ru-catalyzed dehydrative intramolecular *N*-allylation which provided another efficient protocol to synthesize γ -lactams bearing a quaternary stereogenic center in high yields (up to 93%) and very good enantioselectivities (ee up to 86%) (Scheme 64).

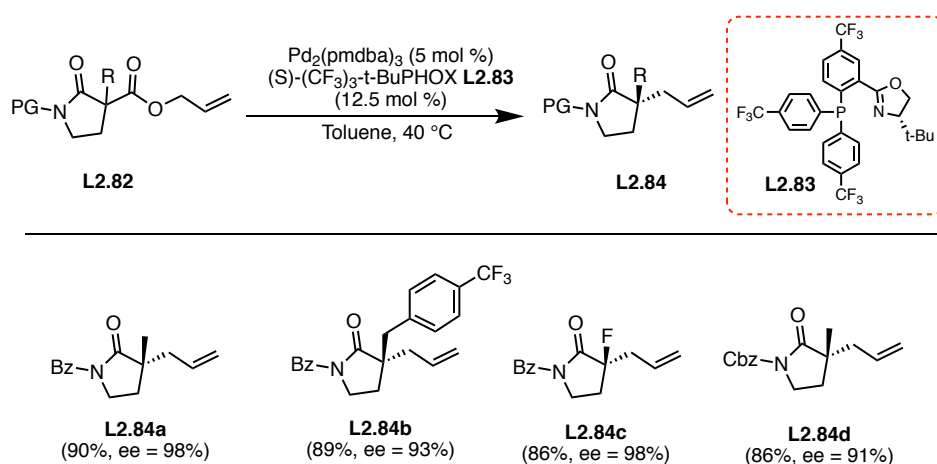


Scheme 64. Ru-catalyzed intramolecular *N*-allylation.

¹¹⁵ Seki, T.; Tanaka, S.; Kitamura, M. *Org. Lett.* **2012**, *14*, 608-611.

2.2.5.3. Pd-catalyzed asymmetric decarboxylative allylic alkylation

The Pd-catalyzed asymmetric allylation was also successfully utilized to access enantio-enriched γ -lactams bearing a quaternary stereogenic center. In 2012, Stoltz *et al.*¹¹⁶ developed an efficient Pd-catalyzed asymmetric decarboxylative allylation of five-, six- and seven-membered heterocyclic compounds using (*S*)-(CF₃)₃-*t*-BuPHOX ligand **L2.83** (12.5 mol %) and Pd₂(pmdba)₃ (5 mol %). The corresponding γ -lactams **L2.84** were obtained in high yields (86-90%) and excellent enantioselectivities (ee = 91-98%) (**L2.84a-d**) (Scheme 65).



Scheme 65. Pd-catalyzed asymmetric decarboxylative allylation of γ -lactams.

3. Results and discussion

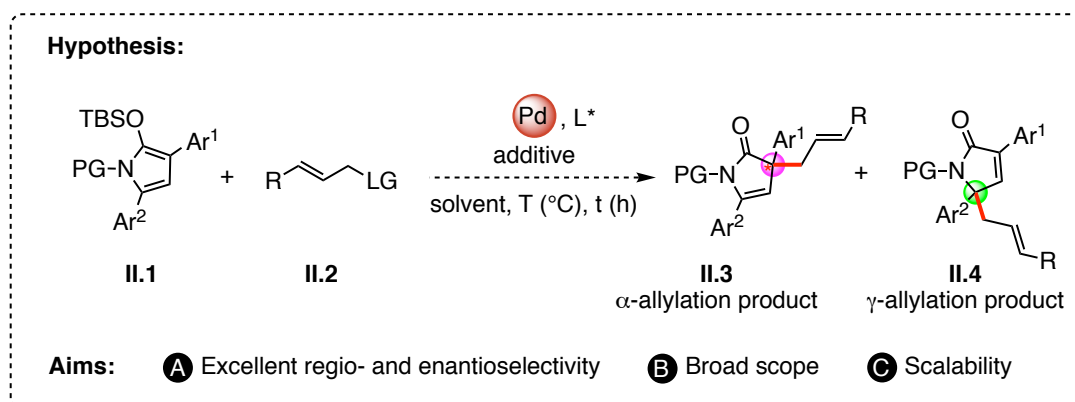
3.1. Context and objective

In view of the literature, the asymmetric synthesis of optically active γ -lactams has attracted considerable attention over the past decades. However, despite the various methods that have allowed a straightforward access to enantio-enriched γ -lactams bearing a quaternary stereogenic center, this field still remains particularly challenging.

Based on our previous results on the asymmetric synthesis of optically active succinimides bearing an all-carbon α -quaternary stereogenic center using a

¹¹⁶ Behenna D.C.; Liu, Y., Yurino, T.; Kim, J.; White, D. E.; Virgil, S. C.; Stoltz, B. M. *Nat Chem.* **2012**, 4, 130-133.

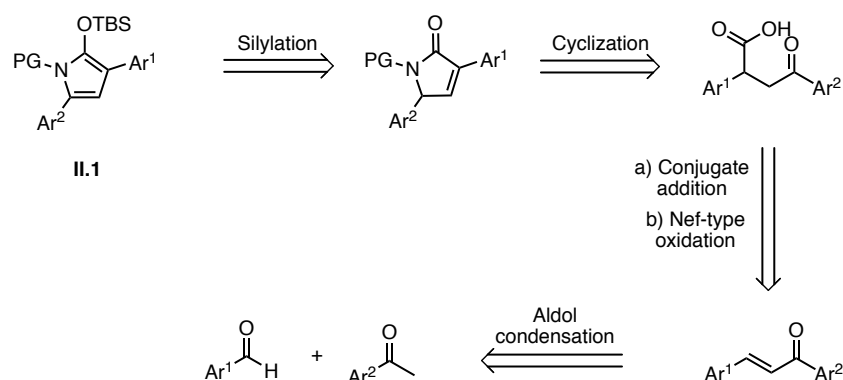
palladium-catalyzed **Asymmetric Allylic Alkylation** (Pd-AAA), we envisioned that optically active γ -lactams could be similarly accessed starting from α,γ -disubstituted 2-silyloxypyrroles. Indeed, if this approach was successful, it would probably be one of the most straightforward and efficient method developed to access enantio-enriched γ -lactams bearing a quaternary stereogenic center (Scheme 66).



Scheme 66. Synthesis of γ -lactams bearing a quaternary stereogenic center using a Pd-catalyzed asymmetric allylic alkylation.

3.2. Synthesis of α,γ -disubstituted 2-silyloxypyrrole substrates

The α,γ -disubstituted 2-silyloxypyrrole substrates **II.1** were planned in five steps starting from aromatic aldehydes and acetophenones using an “aldol condensation” / “conjugate addition”/“Nef-type oxidation”/“cyclization”/“silylation” sequence (Scheme 67).



Scheme 67. Hypothesis of the synthesis of α,γ -disubstituted 2-silyloxypyrroles.

3.2.1. Synthesis of α,β -unsaturated ketones (Aldol condensation)

A variety of α,β -unsaturated ketones **II.7** bearing two different aromatic groups were successfully synthesized from the corresponding aromatic aldehydes **II.8** and acetophenones **II.9** through a typical aldol condensation [NaOH (2.0 equiv), EtOH/H₂O=1:1, rt, 15 - 24 h].¹¹⁷ Various aromatic aldehydes bearing a 2-, 3-, or 4-methyl, a 2- or 4-methoxy, a 4-trifluoromethyl or a 4-bromo substituent were involved in the aldol condensation with acetophenone, affording the corresponding α,β -unsaturated ketones **II.7b-j** in high yields ranging from 85% to 92% (Table 14, entries 1-9). 2-Methylacetophenone **II.9b** and 2,4,6-trimethylacetophenone **II.9c** were also used in conjunction with benzaldehyde to synthesize the corresponding α,β -unsaturated ketone. The corresponding α,β -unsaturated ketones **II.7k** and **II.7l** were obtained in 80% and 75% yield, respectively (Table 14, entries 10 and 11).

Table 14. Synthesis of α,β -unsaturated ketone **II.7**

Entry	II.8, R ¹	II.9, R ²	II.7 ^a (Isolated yield)
1	II.8a , 2-Me	II.9a , H	II.7b (90%)
2	II.8b , 3-Me	II.9a , H	II.7c (91%)
3	II.8c , 4-Me	II.9a , H	II.7d (88%)
4	II.8d , 2-MeO	II.9a , H	II.7e (85%)
5	II.8e , 4-MeO	II.9a , H	II.7f (88%)
6	II.8f , 4-CF ₃	II.9a , H	II.7g (85%)
7	II.8g , 4-Br	II.9a , H	II.7h (90%)
8	II.8h , 4-Ph	II.9a , H	II.7i (92%)
9	II.8i , 2-naphthyl	II.9a , H	II.7j (90%)
10	II.8j , H	II.9b , 2-Me	II.7k (80%)
11	II.8k , H	II.9c , 2,4,6-trimethyl	II.7l (75%)

^a **II.7a** chalcone is commercially available.

3.2.2. Synthesis of γ -ketoacides (Conjugate addition and Nef-type oxidation)

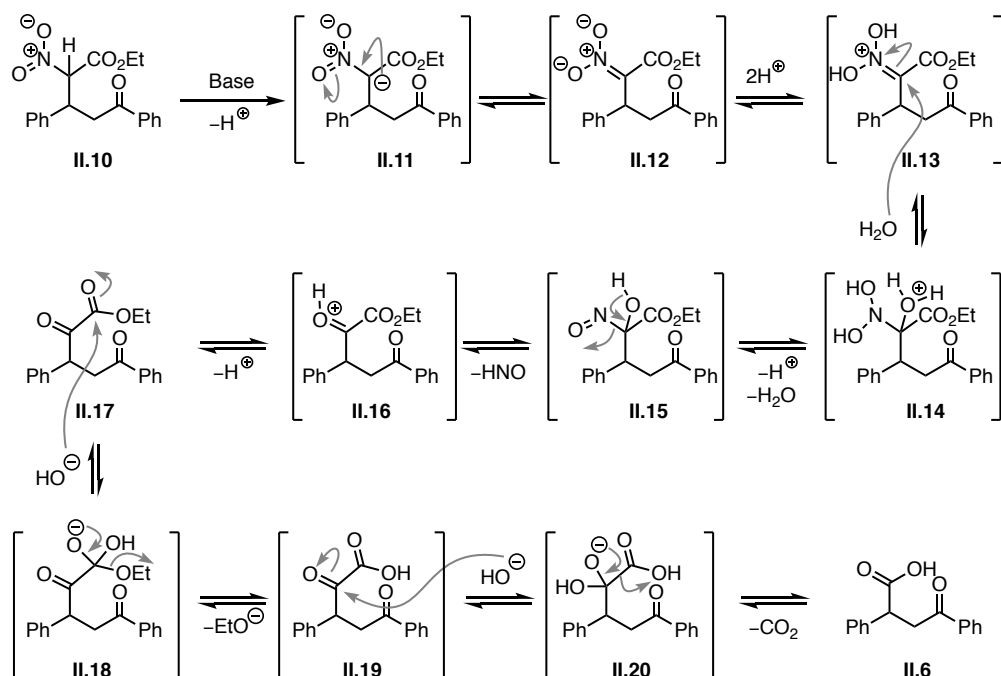
All of the α,β -unsaturated ketones prepared were subjected to the conjugate addition condition with ethyl nitroacetate (1.0 equiv) under basic conditions [Et_3N (3.0 equiv), 75 °C, 24 h]. The crude reaction mixtures were used in the Nef-type oxidation [H_2O_2 (20.0 equiv), K_2CO_3 (4.8 equiv), MeOH] without any purification. The resulting γ -ketoacides **II.6a-l** were successfully obtained in good to high yields ranging from 38% to 70% (Table 15, entries 1-12).³³

Table 15. Synthesis of ketoacids from α,β -unsaturated ketones.

Entry	R ¹	R ²	II.6 (Isolated yield)
1	H	H	II.6a (70%)
2	2-Me	H	II.6b (41%)
3	3-Me	H	II.6c (46%)
4	4-Me	H	II.6d (40%)
5	2-MeO	H	II.6e (45%)
6	4-MeO	H	II.6f (38%)
7	4-CF ₃	H	II.6g (50%)
8	4-Br	H	II.6h (40%)
9	4-Ph	H	II.6i (48%)
10	2-naphthyl	H	II.6j (45%)
11	H	2-Me	II.6k (46%)
12	H	2,4,6-trimethyl	II.6l (40%)

The mechanism of this oxidation involves the deprotonation of the keto nitro ester **II.10** to afford intermediate **II.11**, which is in resonance with **II.12**. After protonation of the latter, the nitronic acid intermediate **II.13** is formed which can then react with H_2O to form intermediate **II.14**. After losing a proton and H_2O , the latter is converted to the 1-nitroso intermediate **II.15**, which rearranges to form the hyponitrous acid and the oxonium ion intermediate **II.16**, which can lose a proton to

form **II.17**. Hydrolysis of the latter under basic conditions eventually affords the ketoacid product **II.6** (Scheme 68).

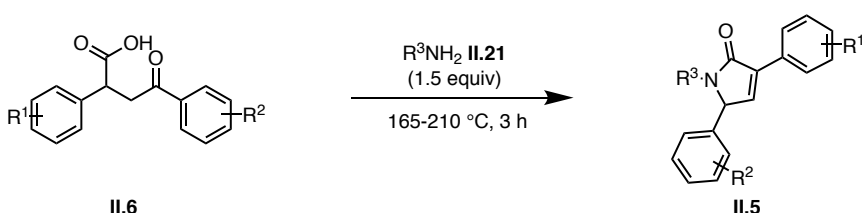


Scheme 68. Proposed mechanism of “Nef-type oxidation”

3.2.3. Synthesis of α,γ -disubstituted- α,β -unsaturated lactams (Cyclization)

α,β -Unsaturated γ -lactams **II.5** can also be synthesized through the cyclization of a ketoacide (**II.6**) in the presence of an amine or an aniline.³³ By heating the compound **II.6** with an amine (1.5 equiv) at 165 - 210 °C for 3 h, without any solvent, led to **II.5**, we therefore prepared a series of α,β -unsaturated γ -lactams **II.5** with different *N*-protecting groups such as *N*-benzyl, *N*-PMB and *N*-Ph group by using the corresponding amines, which were all obtained in good yields (50-75%) (Table 16, entries 1-5). This method could also be used to prepare α,β -unsaturated γ -lactams **II.5** bearing different aromatic substituents at the α - or the γ -position in good to excellent yields ranging from 49% to 90% (**II.5f-o**) (Table 16, entries 6-15). Unfortunately, ketoacide **II.6h** bearing a 4-bromo substituent on the phenyl ring at the C2-position was not suitable for this cyclization and only traces of the corresponding cyclized product **II.5l** were observed (Table 16, entry 12).

Table 16. Synthesis of α,β -unsaturated γ -lactams **II.5a-p**.

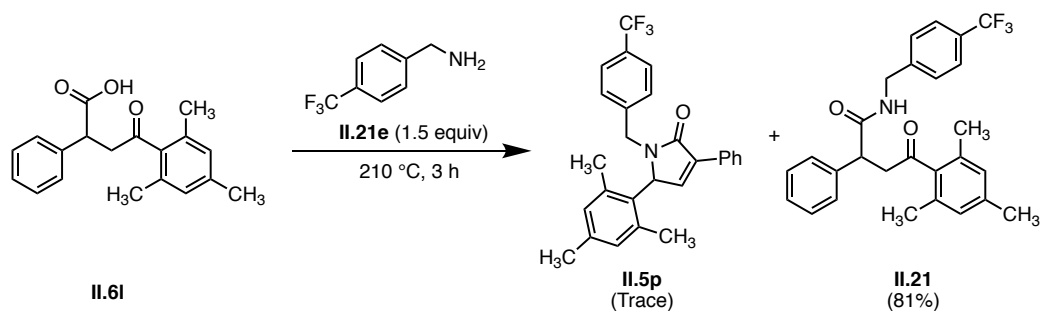


II.6 R³NH₂ **II.21**
(1.5 equiv) II.5

165-210 °C, 3 h

Entry	R ¹	R ²	II.21, R ³	II.5 (Isolated yield)
1	H	H	II.21a , Bn	II.5a (75%)
2	H	H	II.21b , (2-MeO)-PhCH ₂	II.5b (50%)
3	H	H	II.21c , (4-MeO)-PhCH ₂	II.5c (55%)
4	H	H	II.21d , Ph	II.5d (52%)
5	H	H	II.21e , (4-CF ₃)-PhCH ₂	II.5e (65%)
6	2-Me	H	II.21e , (4-CF ₃)-PhCH ₂	II.5f (51%)
7	3-Me	H	II.21e , (4-CF ₃)-PhCH ₂	II.5g (52%)
8	4-Me	H	II.21e , (4-CF ₃)-PhCH ₂	II.5h (60%)
9	2-MeO	H	II.21e , (4-CF ₃)-PhCH ₂	II.5i (49%)
10	4-MeO	H	II.21e , (4-CF ₃)-PhCH ₂	II.5j (50%)
11	4-CF ₃	H	II.21e , (4-CF ₃)-PhCH ₂	II.5k (60%)
12	4-Br	H	II.21e , (4-CF ₃)-PhCH ₂	II.5l (Trace)
13	4-Ph	H	II.21e , (4-CF ₃)-PhCH ₂	II.5m (55%)
14	2-naphthyl	H	II.21e , (4-CF ₃)-PhCH ₂	II.5n (61%)
15	H	2-Me	II.21e , (4-CF ₃)-PhCH ₂	II.5o (90%)
16	H	2,4,6-trimethyl	II.21e , (4-CF ₃)-PhCH ₂	II.5p (Trace)

We also tried to synthesize the α,β -unsaturated γ -lactam **II.5p** bearing a 2,4,6-trimethyl substituents on the γ -phenyl ring under the similar conditions [210 °C, neat, 3 h], however the corresponding cyclization product **II.5p** was not observed, only the amide intermediate **II.21** could be isolated in 81% yield. A reasonable explanation for this result is probably the steric hindrance induced by the 2,4,6-trimethyl substituted phenyl ring, which must prevent the cyclization to take place (Scheme 69).



Scheme 69. Synthesis of α,β -unsaturated γ -lactam **II.5p**.

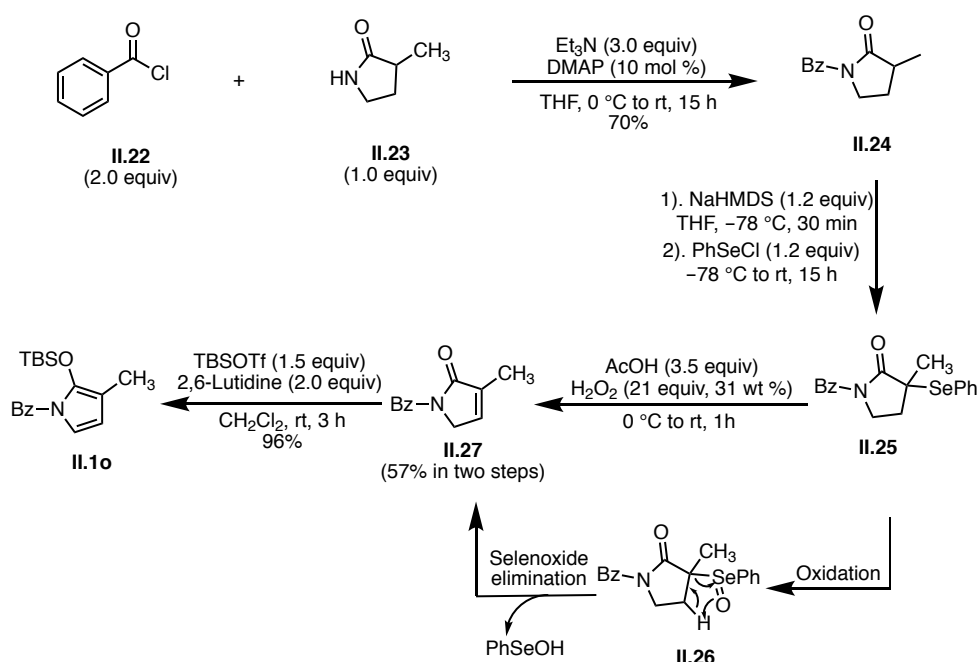
3.2.4. Synthesis of α,γ -disubstituted 2-silyloxypyrroles (Silylation)

All the α,β -unsaturated lactams **II.5** were transformed to the corresponding α,γ -disubstituted 2-silyloxypyrroles **II.1** [TBSOTf (1.2 equiv), 2,6-lutidine (2.0 equiv), CH_2Cl_2 , rt, 3 h]. 2-Silyloxypyrroles bearing a phenyl group at both the α - and the γ -position (**II.1a-e**) and different *N*-protecting groups, such as a *N*-benzyl (**II.1a**, 95%), *N*-*ortho*-methoxy-benzyl (**II.1b**, 96%), *N*-*para*-methoxy-benzyl (**II.1c**, 95%) and a *N*-phenyl group (**II.1d**, 95%) were first prepared (Table 17, entries 1-5). The 2-silyloxypyrroles bearing a *N*-*para*-trifluoromethyl-benzyl group and a phenyl group at the γ -position and various aromatic groups at the α -position were prepared next (**II.1f-l**, 95-97%) (Table 17, entries 6-13). Finally, 2-silyloxypyrrole **II.1n** bearing a phenyl group at the α -position and a 2-methyl phenyl group at the γ -position was also obtained in 95% yield (Table 17, entry 14).

Table 17. Synthesis of α,γ -disubstituted 2-silyloxypyrroles

Entry	R ¹	R ²	R ³	II.1 (Isolated yield)
1	H	H	PhCH ₂	II.1a (95%)
2	H	H	(2-MeO)-PhCH ₂	II.1b (96%)
3	H	H	(4-MeO)-PhCH ₂	II.1c (95%)
4	H	H	Ph	II.1d (95%)
5	H	H	(4-CF ₃)-PhCH ₂	II.1e (96%)
6	2-Me	H	(4-CF ₃)-PhCH ₂	II.1f (95%)
7	3-Me	H	(4-CF ₃)-PhCH ₂	II.1g (96%)
8	4-Me	H	(4-CF ₃)-PhCH ₂	II.1h (96%)
9	2-MeO	H	(4-CF ₃)-PhCH ₂	II.1i (95%)
10	4-MeO	H	(4-CF ₃)-PhCH ₂	II.1j (96%)
11	4-CF ₃	H	(4-CF ₃)-PhCH ₂	II.1k (95%)
12	4-Ph	H	(4-CF ₃)-PhCH ₂	II.1l (97%)
13	2-naphthyl	H	(4-CF ₃)-PhCH ₂	II.1m (95%)
14	H	2-Me	(4-CF ₃)-PhCH ₂	II.1n (95%)

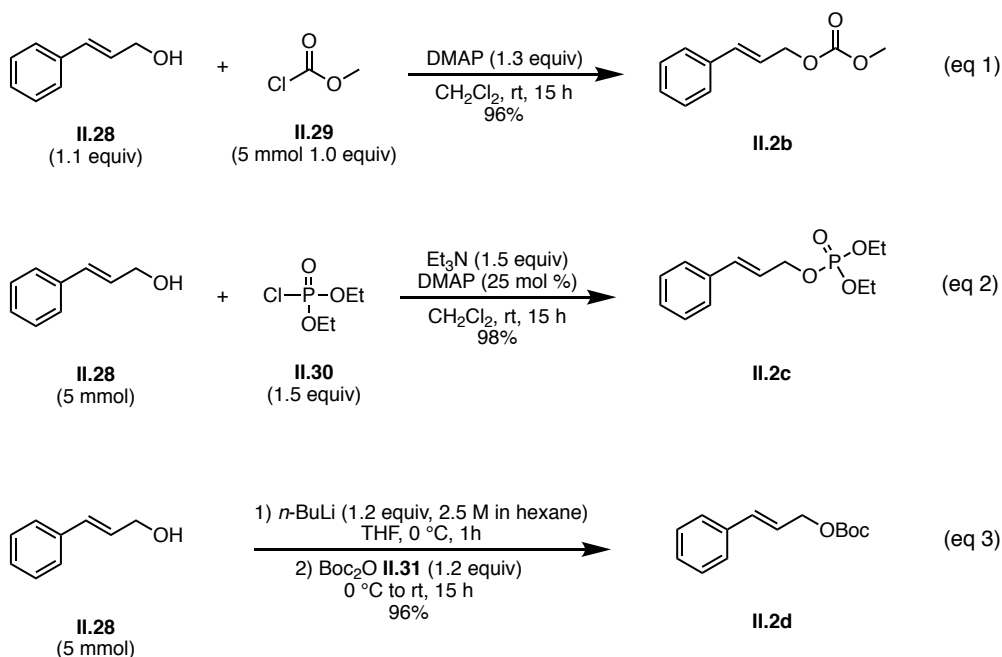
Besides these α,γ -disubstituted 2-silyloxypyrroles, **II.1a-n**, a final 2-silyloxypyrrole bearing a *N*-benzoyl group and a methyl substituent at the α -position (**II.1o**) was prepared in four steps starting from 2-methyl-pyrrolidinone **II.23**. At first, a protection of 2-methyl pyrrolidinone **II.23** with benzoyl chloride **II.22** under base conditions [Et₃N (3.0 equiv), DMAP (10 mol %), THF, 0 °C to rt] afforded the *N*-benzoyl 2-methyl pyrrolidinone **II.24** in 70% yield. The latter was then converted to the corresponding α -selenide **II.25** [NaHMDS (1.2 equiv), PhSeCl (1.2 equiv), THF, -78 °C to rt], which was directly oxidized [AcOH (3.5 equiv), H₂O₂ (21 equiv) 0 °C to rt] without any purification to produce the α,β -unsaturated lactam **II.27**. The α,β -unsaturated lactam **II.27** was isolated in good yield (57% in two steps) and subsequently involved in the next step to access the corresponding 2-silyloxypyrrole **II.1o** under basic conditions [TBSOTf (1.5 equiv), 2,6-lutidine (2.0 equiv), CH₂Cl₂, rt, 3 h, 96%] (Scheme 70).



Scheme 70. Synthesis of 2-silyloxypyrrole derivative **II.10**.

3.3. Synthesis allylic reagents

To evaluate the influence of the leaving group of the allyl donor, besides the commercially available cinnamyl acetate **II.2a**, we also prepared the allylic reagents **II.2b-d**, derived from cinnamyl alcohol, such as the methyl carbonate **II.2b** (96%) which was prepared from cinnamyl alcohol **II.28** by using methyl chloroformate **II.29** under basic conditions [DMAP (1.3 equiv), CH_2Cl_2 , rt, 15 h] (Scheme 71, eq 1); ethyl phosphate **II.2c** (98%) which was prepared from cinnamyl alcohol **II.28** by using diethyl chlorophosphate **II.30** in the presence of Et_3N (1.5 equiv), DMAP (25 mol %), in CH_2Cl_2 at rt for 15 h (Scheme 71, eq 2); *tert*-butyl carbonate **II.2d** (96%) which was synthesized from cinnamyl alcohol and di-*tert*-butyl carbonate (Boc_2O) (96%) by using 1.2 equiv *n*-BuLi (2.5 M in hexane) and by running the reaction at 0°C to rt for 16 h in THF (Scheme 71, eq 3).



Scheme 71. Synthesis of different allyl donor reagents.

In the first Chapter (**I.3.2.2**), we described the synthesized of various allylic alcohols, which involved a sequential Wittig reaction [$\text{Ph}_3\text{PCH}_2\text{CO}_2\text{Et}$ (1.1 equiv), CH_2Cl_2 , rt, 15 h]/DIBAL-H mediated reduction [DIBAL-H (2.2 equiv, 1.0 M in CH_2Cl_2), CH_2Cl_2 , -78°C , 3-5 h] starting from aromatic aldehydes. To evaluate the reactivity of the allyl donor in the Pd-AAA of 2-silyloxypyrroles, a series of β -substituted allyl benzoates **II.2e-m** were prepared under standard acylating conditions [Et_3N (1.5 equiv), DMAP (10 mol %), CH_2Cl_2 , rt, 15 h] using benzoyl chloride (1.2 equiv) and by starting from the corresponding allylic alcohol precursor (Table 18).¹¹⁸ All of these allylating agents were eventually evaluated in the Pd-catalyzed asymmetric allylic alkylation of 2-silyloxypyrrole **II.1**.

¹¹⁸ a) Jiang, X. Y.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2017**, *56*, 8887-8891; b) Niwa, T.; Nakada, M. *J. Am. Chem. Soc.* **2012**, *134*, 13538-13541; c) Li, J.-Q.; Peters, B.; G. Andersson, P. *Chem. Eur. J.* **2011**, *17*, 11143-11145; d) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essensfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183-2186.

Table 18. Synthesis the β -substituted allyl benzoate derivatives

$\text{R-CH=CH-CH}_2\text{OH} + \text{Cl-CO-C}_6\text{H}_5 \xrightarrow[\text{CH}_2\text{Cl}_2, \text{rt, 15 h}]{\text{Et}_3\text{N (1.5 equiv), DMAP (10 mol \%)}} \text{R-CH=CH-CH}_2\text{O-CO-C}_6\text{H}_5$

II.28 **II.22** (1.2 equiv) **II.2**

Entry	II.28, R	II.2 (Isolated yield)
1	II.28a , Ph	II.2e (>99%)
2	II.28b , 4-CH ₃ -C ₆ H ₄	II.2f (>99%)
3	II.28c , 4-Br-C ₆ H ₄	II.2g (>99%)
4	II.28d , 4-CF ₃ -C ₆ H ₄	II.2h (>99%)
5	II.28e , (4-CO ₂ Me)-C ₆ H ₄	II.2i (>99%)
6	II.28f , 4-MeO-C ₆ H ₄	II.2j (>99%)
7	II.28g , 3-MeO-C ₆ H ₄	II.2k (>99%)
8	II.28h , 2-naphthyl	II.2l (>99%)
9	II.28i , biphenyl	II.2m (>99%)
10	II.28j , thiophene	II.2n (>99%)
11	II.28k , furan	II.2o (>99%)

3.4. Optimization of the Pd-AAA conditions

With various of α,γ -disubstituted 2-silyloxypyrroles and allylic reagents in hand, we started to explore the reaction conditions. The 2-silyloxypyrrole derivative **II.1a** bearing a phenyl-substituent at both the α - and the γ -position was chosen as a model substrate and (*R,R*)-DACH-Phenyl Trost ligand **II.32a** and Pd₂(dba)₃ were used as the initial catalytic system.

3.4.1. Influence of the leaving group of allylic reagent

We initiated our screening using 10 mol % of (*R,R*)-DACH-Phenyl Trost ligand **II.32a** and 5 mol % of Pd₂(dba)₃ and running the reaction at rt. However, no product could be obtained even after 36 h. We therefore decided to run the reaction at 60 °C. Under these conditions, we were pleased to observe the formation of a mixture of the desired products **II.3a** and **II.4a** in 19% yield and a 13:1 in favor of **II.3a**. The latter was

eventually isolated in 17% yield and 33% ee (Table 19, entry 2). To get a better understanding of the mechanism, and perhaps improve the reactivity, we ran a reaction using 1.0 equiv NaOAc under otherwise identical conditions. After 22 h, all of the starting material **II.1a** was completely converted to the desired products **II.3a** and **II.4a** (>99%), which were obtained in a 3.8:1 ratio in favor of **II.3a**. The major product **II.3a** was isolated in 76% yield but albeit in only 20% ee (Table 19, entry 3). These preliminary results clearly indicate that the acetate anion, which is generated *in situ* during the catalytic cycle, activates the substrate, making it more nucleophilic. To improve the regio- and enantioselectivity, a variety of allyl donors bearing different leaving groups, such as -OCO₂Me (**II.2b**), -OP(O)OEt₂ (**II.2c**) and -OBz (**II.2e**), were evaluated. The results are summarized in Table 19. To our delight, the benzoate derivative **II.2e** showed a higher reactivity than all the other allyl donors bearing a different leaving group [-OAc, -OCO₂Me, -OP(O)OEt₂ and -OBoc], affording complete conversion of the starting material to the corresponding allylated products **II.3a** and **II.4a** which were obtained in a 3.5:1 ratio in favor of **II.3a**. The latter was isolated in 76% yield and 58% ee. More importantly, the reaction also performed well at rt, as the corresponding allylated products were obtained in roughly the same yield (75%), the same regioselectivity (3.4:1 in favor of **II.3a**) and enantioselectivity (58% ee for **II.3a**) compared to the reaction performed at 60 °C (Table 19, entries 7-8).

Table 19. Influence of different leaving groups (LG), additives and temperatures

Ph-CH=CH-LG (II.2, 1.5 equiv)
Ph-CH=CH-Ph (II.32a, 10 mol %)
Pd2(dba)3 (5 mol %)
 THF, T °C, t (h)

II.1a (0.1 mmol) → **II.3a** (α-allylation product) + **II.4a** (γ-allylation product)

II.32a (structure shown in dashed box)

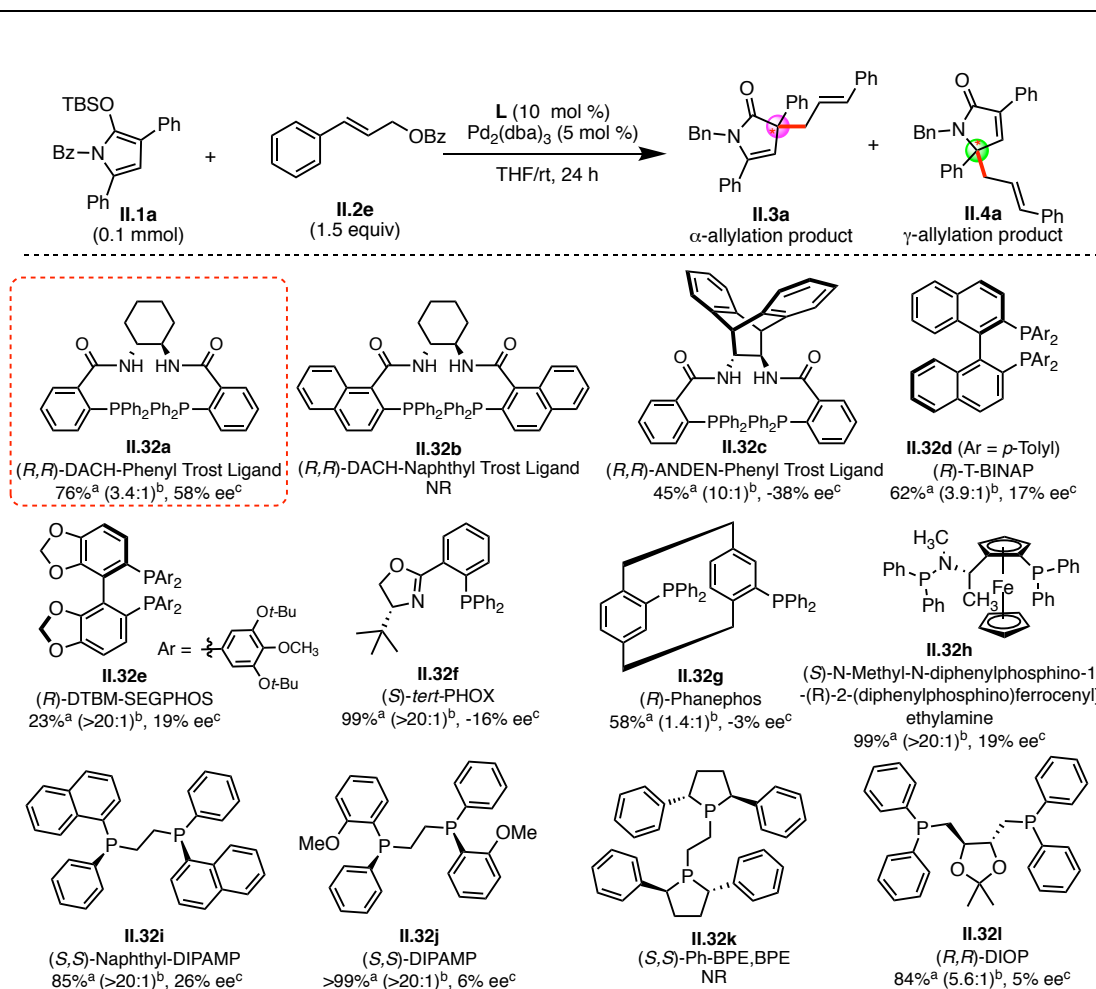
Entry	II.2, LG	T (°C)	t (h)	Conversion of (II.3a+II.4a) (II.3a/4a) ^a	Isolated yield of II.3a	ee ^b of II.3a
1	II.2a, OAc	rt	36	trace	-	-
2	II.2a, OAc	60	24	19% (13:1)	17%	33%
3 ^c	II.2a, OAc	60	22	>99% (3.8:1)	78%	20%
4	II.2b, OCO ₂ Me	60	24	57% (2.6:1)	40%	25%

5	II.2c , OP(O)OEt ₂	60	24	36% (2:1)	24%	20%
6	II.2d , OBoc	60	24	71% (5.5:1)	58%	-3%
7	II.2e , OBz	60	24	>99% (3.5:1)	76%	58%
8	II.2e , OBz	rt	22	>99% (3.4:1)	75%	58%

^a Determined by ¹H NMR on the crude reaction mixture; ^b Determined by SFC analysis. ^c 1.0 equiv of NaOAc was added.

3.4.2. Influence of the chiral phosphine ligand

Encouraged by these preliminary results, we decided to further optimize the reaction conditions using 2-silyloxypyrrole **II.1a** and cinnamyl benzoate as the allyl donor. To improve the regio- and enantioselectivity, eleven optically active phosphine ligands were examined (see results in Scheme 72), however, the best enantioselectivity was obtained when using (*R,R*)-DACH-Phenyl Trost ligand **II.32a**, even though some ligands, such as the chiral N/P-type oxzoline (PHOX) ligand **II.32f** (99%, **II.3a/II.4a** > 20:1), the ferrocenephosphine ligand **II.32h** (99%, **II.3a/II.4a** > 20:1) and naphthyl-DIPAMP **II.32i** (85%, **II.3a/II.4a** > 20:1) afforded high yields and excellent levels of regioselectivity (Scheme 72). Thus, the optically active ligand **II.32a** was still chosen for further optimizations.



^a Isolated yield; ^b Determined by ¹H NMR on the crude reaction mixture; ^c Determined by SFC analysis.

Scheme 72. Different chiral ligands in Pd-AAA

3.4.3. Influence of the solvent

The influence of the solvent was also evaluated, the results are summarized in Table 20. For solvents, such as Et₂O (65%, **II.3a/II.4a** = 4.3:1, 59% ee of **II.3a**), CH₃CN (68%, **II.3a/II.4a** = 3.3:1, 54% ee of **II.3a**) and DMF (62%, **II.3a/II.4a** = 2.3:1, 35% ee of **II.3a**), the desired products were obtained with similar yields, regio- and enantioselectivities. When CH₂Cl₂ (27%, **II.3a/II.4a** = 2.6:1, 47% ee of **II.3a**) and toluene (18%, **II.3a/II.4a** = 3.8:1, 43% ee of **II.3a**) were used as solvent, the desired products were obtained in low yields and regioselectivities, and a slight decrease in enantioselectivity was observed. Interestingly, when 2-Me-THF was chosen, a good yield (78%) and a high regioselectivity (**II.3a/II.4a** = 11.6:1) was observed, however, the major product **II.3a** was obtained in only 51% ee.

Table 20. Influence of different solvents

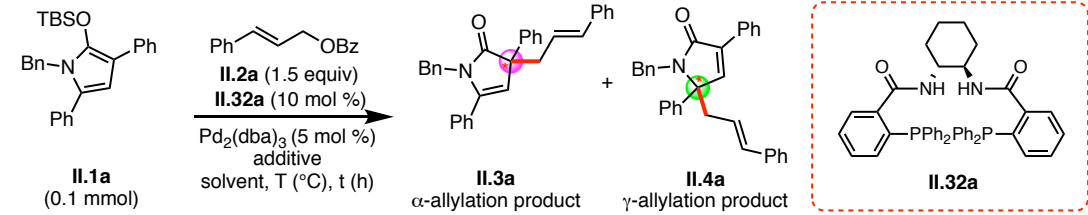
Entry	Solvent	Conversion of (II.3a+II.4a) (II.3a/II.4a) ^a	Isolated yield of II.3a	ee ^b of II.3a
1	THF	>99% (3.4:1)	75%	58%
2	2-Me-THF	85% (11.6:1)	78%	51%
3	Et ₂ O	81% (4.3:1)	65%	59%
4	CH ₂ Cl ₂	38% (2.6:1)	27%	47%
5	toluene	23% (3.8:1)	18%	43%
6	CH ₃ CN	89% (3.3:1)	68%	54%
7	DMF	89% (2.3:1)	62%	35%

^a Determined by ¹H NMR of the crude reaction mixture; ^b Determined by SFC analysis;

3.4.4. Influence of the temperature

Due to the high reactivity of cinnamyl benzoate, we decided to run a few reactions at a lower temperature in THF and 2-Me-THF as these solvents gave the most promising results. To our delight, we were able to improve the regioselectivity from 3.4:1 to 12:1 ratio in favor of **II.3a** as well as the enantioselectivity (from ee = 58% to 82%) by simply running the reaction at –20 °C instead of rt, in THF (Table 21, entry 1 vs 5). The reaction performed in 2-Me-THF at –20 °C also afforded the desired product **II.3a**, however in a much lower yield (54%) and a slightly lower enantioselectivity (ee = 70%) (Table 21, entry 6). We could further improve the selectivity without drastically impacting the yield by decreasing the temperature to –30 °C; the desired allylated products **II.3a** and **II.4a** were obtained with a good regioselectivity (12:1 ratio in favor of **II.3a**) and an improved enantioselectivity (ee = 84%) after 45 h (Table 21, entry 7). Unfortunately, we were not able to improve further the conditions without impacting both the yield and the enantioselectivity (Table 21, entries 8-10).

Table 21. Influence of different temperatures

						
Entry	Solvent	T (°C)	t (h)	Conversion of (II.3a+II.4a) (II.3a/4a) ^a	Isolated yield of II.3a	ee ^b of II.3a
1	THF	rt	24	>99% (3.4:1)	76%	58%
2	2-Me-THF	rt	24	85% (11.6:1)	78%	51%
3	THF	0	24	83% (4.5:1)	67%	74%
4	2-Me-THF	0	24	74% (14:1)	69%	68%
5	THF	−20	24	79% (12:1)	73%	82%
6	2-Me-THF	−20	24	54% (>20:1)	54%	70%
7	THF	−30	45	96% (12:1)	89%	84%
8 ^c	THF	−30	45	31% (>20:1)	31%	76%
9 ^d	THF	−40	65	52% (>20:1)	52%	78%
10 ^e	THF	−40	40	62% (6.6:1)	54%	67%

^a Determined by ¹H NMR of the crude reaction mixture; ^b Determined by SFC analysis; ^c *n*-BuNOBz (10 mol %) was used; ^d Molecular sieves (20 mg) were used; ^e NaOBz (20 mol %) was used.

3.4.5. Influence of catalyst loading

In addition to the influence of the solvent and the temperature, the impact of the catalyst loading was evaluated next (Table 22). Hence, when 1 mol % of Pd₂(dba)₃ and 3 mol % of **II.32a** were used, the two allylated products **II.3a** and **II.4a** were obtained in a 6:1 ratio in favor of **II.3a**. The latter was isolated in 27% yield and 74% ee (Table 22, entry 1). When 2.5 mol % of Pd₂(dba)₃ and 5 mol % of **II.32a** were used, the major allylated product **II.3a** was isolated in 59% yield and 84% ee without any change of the regioselectivity (**II.3a/4a** = 6:1) (Table 22, entry 2). The best regio- and enantioselectivity were obtained when 5 mol % of Pd₂(dba)₃ and 10 mol % of **II.32a** were used (Table 22, entry 3).

Table 22. Influence of catalysts loading

Entry	x	y	T (h)	Isolated yield of II.3a (II.3a/4a) ^a	ee ^b of II.3a	Note
1	3	1	65	27% (6:1)	74%	(<i>R,R</i>)-II.32a
2	5	2.5	65	59% (6:1)	84%	(<i>R,R</i>)-II.32a
3	10	5	45	89% (12:1)	84%	(<i>R,R</i>)-II.32a

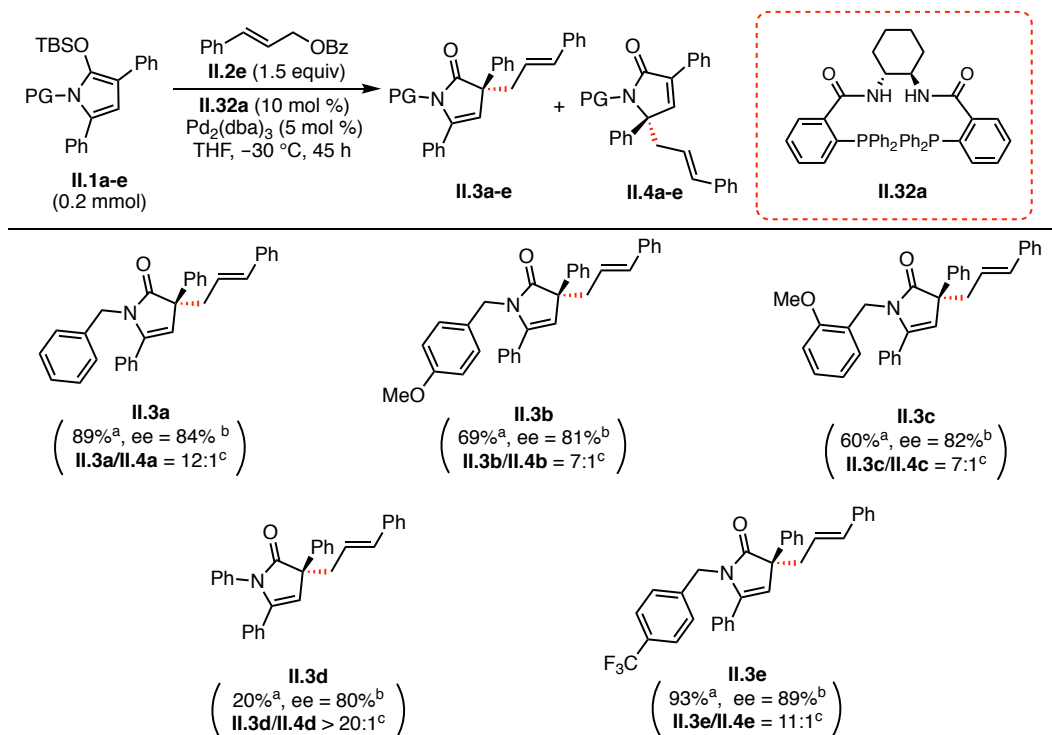
^a Determined by ¹H NMR on the crude reaction mixture; ^b Determined by SFC analysis.

3.5. Substrate scope and limitation

With the best conditions in hand [(*R,R*)-DACH-Phenyl Trost ligand **II.32a** (10 mol %), Pd₂(dba)₃ (5 mol %), THF, −30 °C], we next study the reactivity of various α,γ-disubstituted 2-silyloxypyrroles **II.1** and different allyl acetates **II.2**.

3.5.1. Substrate scope of *N*-protected 2-silyloxypyrroles

We first evaluated the influence of the *N*-protecting group. As depicted in Scheme 73, the best results were obtained with **II.1e** bearing a *para*-trifluoromethyl-benzyl *N*-protecting group; Indeed, the corresponding major α-allylated product **II.3e** was isolated in an excellent 93% yield and a high enantioselectivity (ee = 89%). Substrates **II.1b** and **II.1c**, respectively bearing a *para*- and an *ortho*-methoxy-benzyl group, were converted to the corresponding allylated products **II.3c** and **II.3d** in good yields (60–69%), good enantioselectivities (ee = 81–82%) and an interesting 7:1 regioselectivity in favor of the α-allylated product. In contrast, when the *N*-benzyl protecting group was replaced by a *N*-phenyl group, the allylated product **II.3e** was obtained with a similar enantioselectivity (ee = 80%), an excellent regioselectivity (>20:1) but a low yield of 20%.



^a Isolated yield of **II.3**; ^b Determined by SFC; ^c The ratio was determined by crude ^1H NMR.

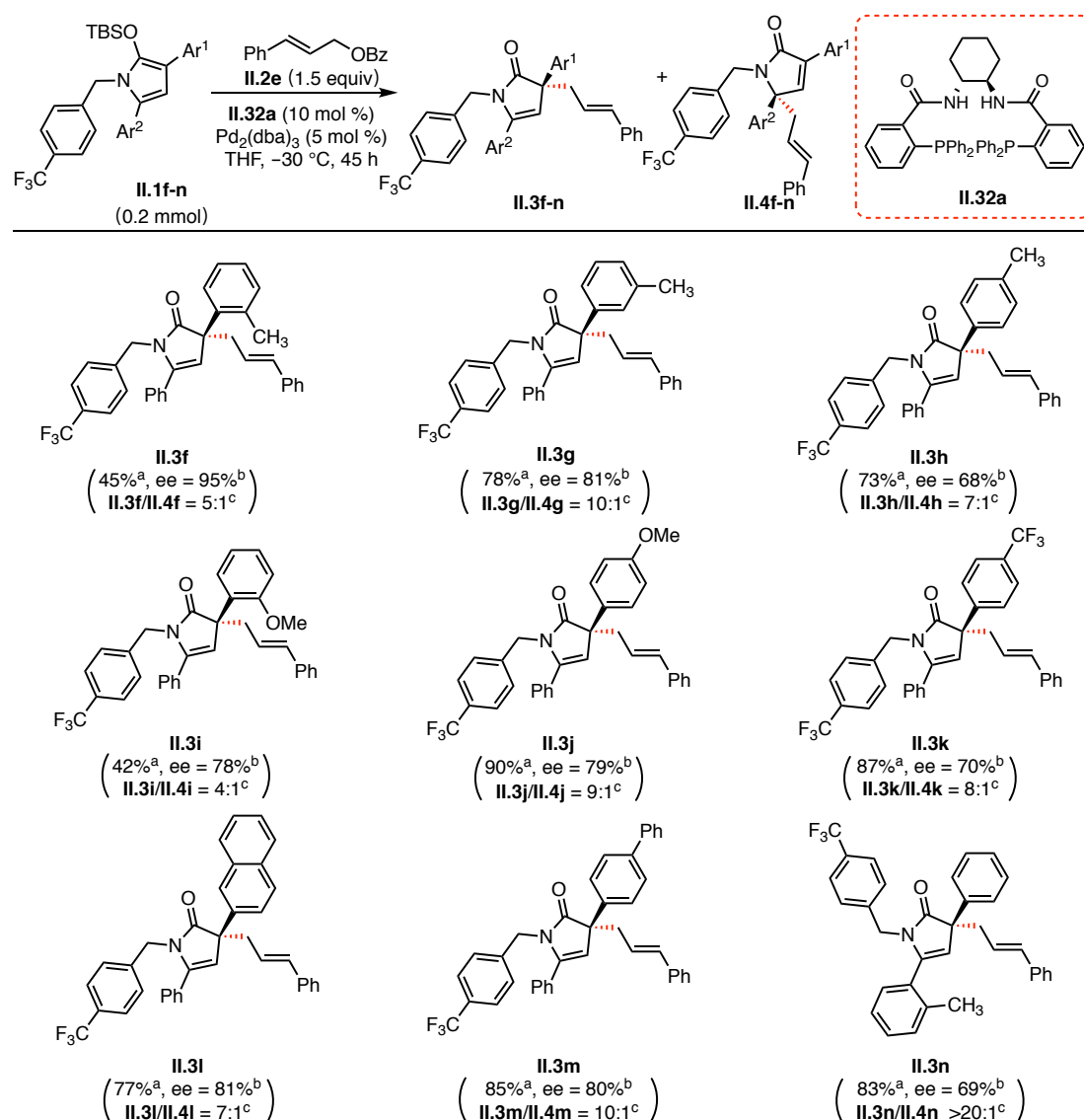
Scheme 73. Substrate scope of *N*-protected 2-silyloxypyrroles

3.5.2. Substrate scope of 2-silyloxypyrroles substituted at the α - and the γ -position

As the *para*-trifluoromethyl-benzyl derivative induced the highest enantioselectivity, a variety of 2-silyloxypyrroles incorporating this moiety, **II.1a-e**, were synthesized and evaluated under our optimized conditions. The results are summarized in Scheme 74.

We first started by evaluating the influence on the selectivity of the aromatic substituent at the C2 position of the pyrrole ring (Ar^1). The results showed that a higher enantioselectivity was obtained with **II.1f**, bearing an *ortho*-methyl substituted phenyl ring (**II.3f/II.4f** = 11/1, 95% ee), than with **II.3g** and **II.3h**, which have a *meta*- (**II.3g/II.4g** = 10/1, 81% ee) and a *para*-methyl-substituted (**II.3h/II.4h** = 7/1, 68% ee) aromatic ring, indicating that the steric hindrance may be an important parameter that accounts for the enantioselectivity. In order to confirm this hypothesis, we evaluated the analogous *ortho*- and *para*-methoxy-substituted

derivatives, however a different trend was observed; the corresponding α -allylated products **II.3i** (**II.3i**/**II.4i** = 4/1, ee = 78%) and **II.3j** (**II.3j**/**II.4j** = 9/1, ee = 79%) were obtained with roughly the same enantiomeric excess. Replacing the *para*-methoxy by an electron-withdrawing *para*-trifluoromethyl group (**II.1k**) gave the α -allylated product in 87% yield, however with a slightly lower 70% ee. Finally, the substrates bearing a naphthyl (**II.1l**) or a biphenyl (**II.1m**) also appeared to be suitable precursors as the corresponding α -allylated products **II.3l** and **II.3m** were both obtained in roughly 81% enantiomeric excess.



^a Isolated yield; ^b Determined by SFC analysis; ^c Determined by ^1H NMR on the crude reaction mixture. ^d Total yield of **II.3j** and **II.4j** (**II.3j**/**II.4j** = 5.5:1)

Scheme 74. Substrate scope of 2-silyloxypyrroles substituted at the α - and/or γ -position.

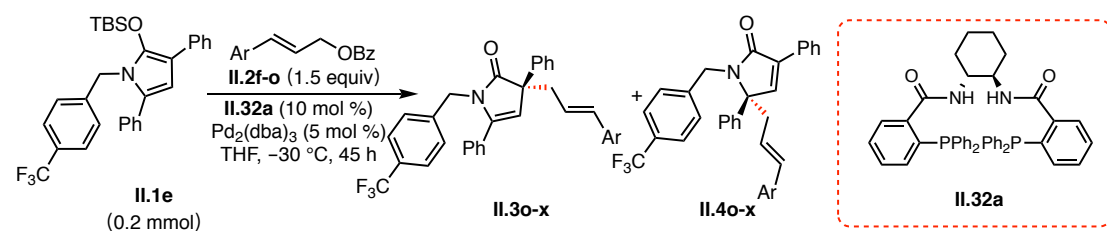
Finally, we evaluated the influence on the selectivity of the aromatic substituent at the C4 position of the pyrrole ring (Ar^2). Substrate **II.1n** bearing a methyl substituent at the *ortho*-position of the phenyl ring was thus synthesized and subjected to our optimized Pd-AAA conditions. Pleasingly, the regioselectivity improved from 11:1 (**II.3b**) to >20:1 in favor of the α -allylated product **II.3n**, however, the enantioselectivity dropped dramatically from 89% (**II.3b**) to 69% (**II.3n**).

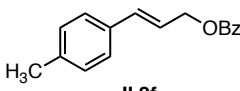
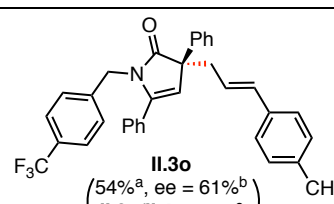
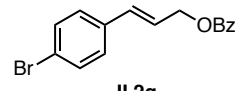
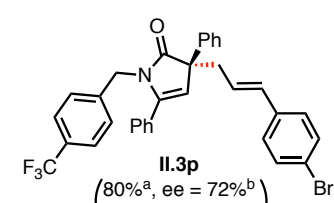
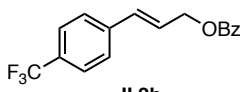
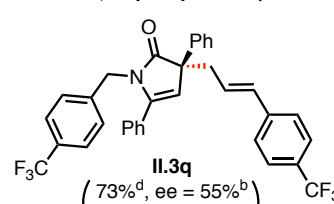
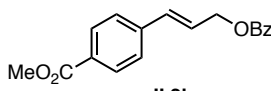
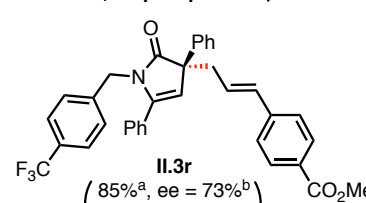
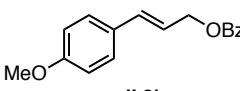
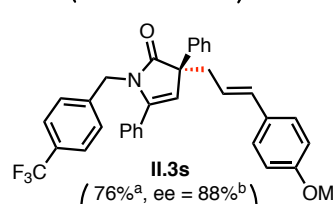
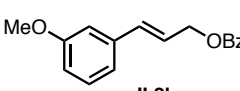
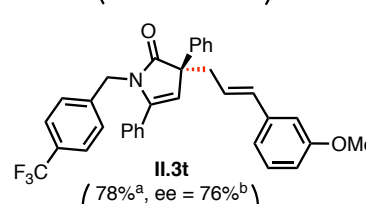
3.5.3. Substrate scope of different β -substituted allyl benzoates

After evaluating the substrate scope, we decided to vary the allyl donors in order to gain in structural diversity. A variety of 3-substituted allyl benzoates (**II.2f-o**) were thus prepared and engaged in the Pd-AAA of 2-silyloxypyrrole **II.1b**; the results are reported in Table 23.

We first evaluated various *para*-substituted cinnamyl benzoate derivatives (**II.2f-i**), which all afforded good levels of enantioselectivity ranging from 70% to 88% enantiomeric excess, except for the cinnamyl benzoate bearing a *para*-trifluoromethyl substituent, which led to the corresponding α -allylated product **II.3h** in only 55% ee. The cinnamyl benzoate bearing either a methoxy substituent at the *meta* position or a naphthalene in place of the phenyl ring also afforded high enantioselectivities ranging from 76% ee (**II.3t**) to 84% ee (**II.3u**). Most importantly, the 3-substituted allyl benzoates bearing a heterocyclic substituent such as a thiophene (**II.3w**, ee = 87%) or a furan (**II.3x**, ee = 94%) afforded the best selectivities.

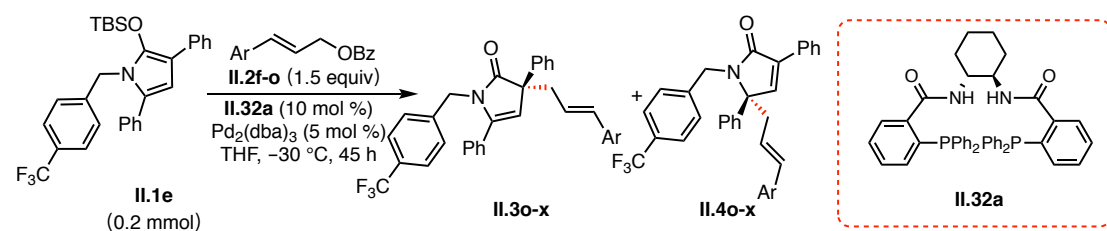
Table 23. Substrate scope of various β -substituted allyl benzoates.



Entry	II.2f-o	II.3o-x (yield, ee, II.3/II.4)
1	 II.2f	 II.3o (54% ^a , ee = 61% ^b) (II.3o / II.4o = 6:1 ^c)
2	 II.2g	 II.3p (80% ^a , ee = 72% ^b) (II.3p / II.4p = 5:1 ^c)
3	 II.2h	 II.3q (73% ^d , ee = 55% ^b) (II.3q / II.4q = 4.6:1 ^c)
4	 II.2i	 II.3r (85% ^a , ee = 73% ^b) (II.3r / II.4r = 11:1 ^c)
5	 II.2j	 II.3s (76% ^a , ee = 88% ^b) (II.3s / II.4s = 5:1 ^c)
6	 II.2k	 II.3t (78% ^a , ee = 76% ^b) (II.3t / II.4t = 6:1 ^c)

^a Isolated yield; ^b Determined by SFC analysis; ^c Determined by ^1H NMR on the crude reaction mixture.

Table 23. Substrate scope of various β -substituted allyl benzoates (continued).



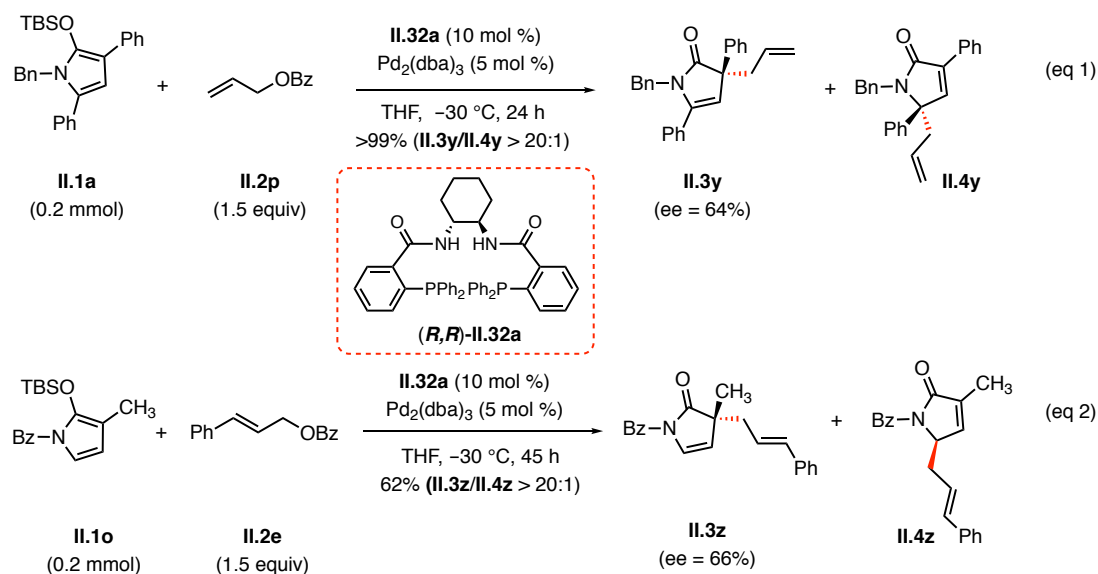
Entry	II.2	II.3 (yield, ee, II.3/II.4)
7		 II.3u (79% ^a , ee = 84% ^b) (II.3u/II.4u = 5:1 ^c)
8		 II.3v (78% ^e , ee = 76% ^b) (II.3v/II.4v = 6:1 ^c)
9		 II.3w (67% ^a , ee = 87% ^b) (II.3w/II.4w = 3:1 ^c)
10		 II.3x (68% ^a , ee = 94% ^b) (II.3x/II.4x = 10:1 ^c)

^a Isolated yield; ^b Determined by SFC analysis; ^c Determined by ^1H NMR on the crude reaction mixture. ^d Total yield of **II.3q** and **II.4q** (II.3q/II.4q = 4:1). ^e Total yield of **II.3v** and **II.4v** (II.3v/II.4v = 4:1).

3.5.4. Substrate scope with allyl benzoates and other 2-silyloxypyrroles

Substrate **II.1a** was also tested with allyl benzoate under the optimized conditions. The allylated product **II.3y** was obtained with an excellent yield (>99%), an excellent regioselectivity (>20:1) but a moderate enantioselectivity (ee = 64%) (Scheme 75, eq 1). Comparatively, substrate **II.1o**, which has only a methyl substituent at the α -

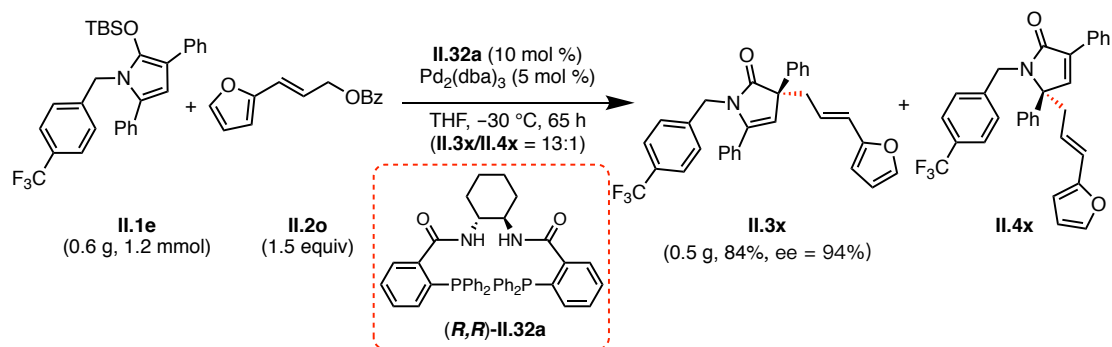
position, led to the allylated product **II.3z** in 62% yield and 66% enantiomeric excess in an excellent regioselectivity (>20:1) (Scheme 75, eq 2).



Scheme 75. Substrate scope (continued).

3.5.5. Scale-up of the reaction

To prove the robustness of the process, a reaction was run on a mmol scale (0.6 g) using 2-silyloxypyrrole **II.1e** and allyl donor **II.2o** (1.5 equiv). The resulting γ -lactam derivative **II.3x** was still obtained in a very good yield (84%), a high regioselectivity (**II.3x/II.4x** = 13:1) and an excellent enantioselectivity (ee = 94%) (Scheme 76).



Scheme 76. Scale-up reaction of 2-silyloxypyrrole derivative **II.1e** and allyl benzoate derivative **II.2o**.

3.6. Origin of the enantioselectivity

In the first chapter, we presented a cartoon model, which was first introduced by Trost *et al.*⁴⁸ for predicting the stereoselective outcome of an allylation when using an optically active Pd catalyst derived from **II.32a** (Figure 12). Hence, the enolate intermediate should be approaching the (*R,R*)-**II.32a**-Pd- π -allyl complex by its Re-face to avoid any disfavored steric interaction between the γ -aromatic substituent and the “wall” of the ligand, resulting in the formation of the (*R*)-allylated product (*R*)-**II.3** as the major enantiomer (Figure 12). This was confirmed by the single crystal X-ray analysis of the α -allylated product **II.3b**.

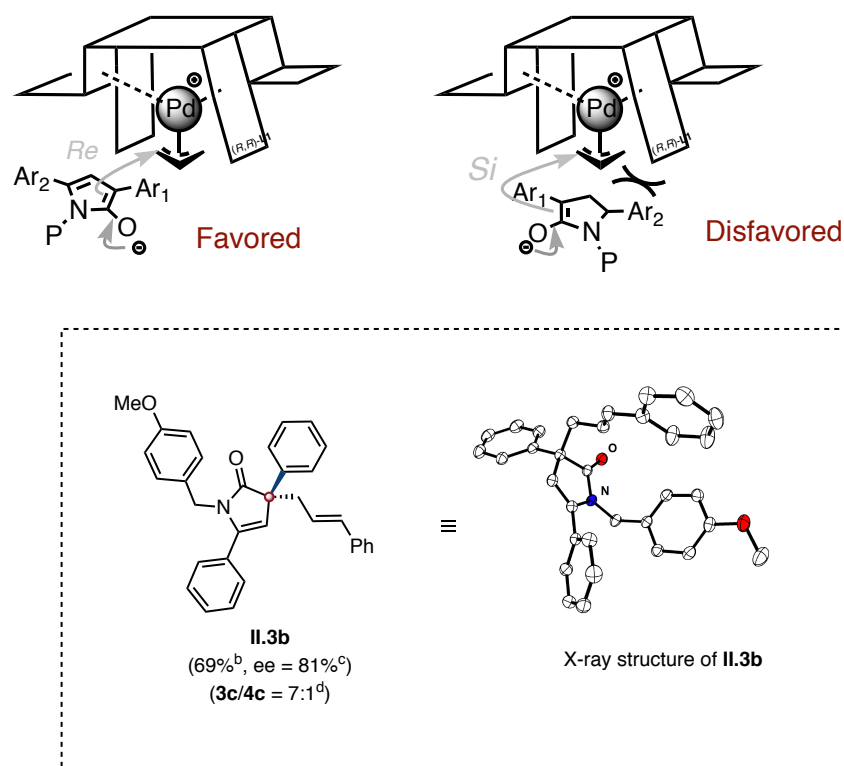


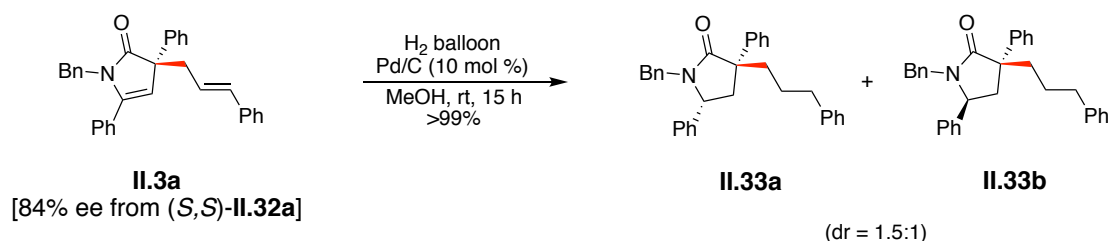
Figure 12. Proposed stereochemical pathway

3.7. Post-functionalizations

The γ -lactams prepared through this Pd-AAA process could be easily converted to various useful building blocks through simple synthetic transformations.

3.7.1. Synthesis of optically active pyrrolidinones

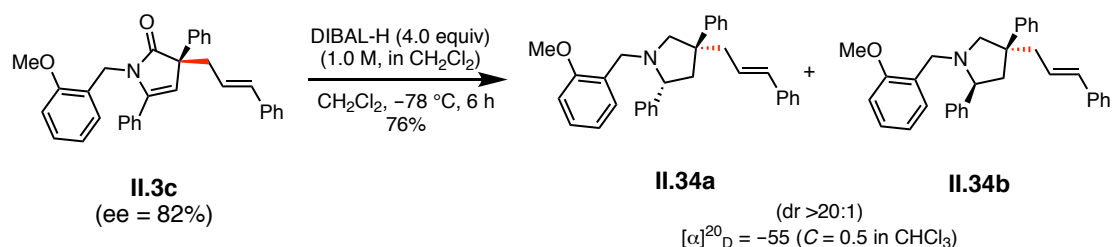
The optically active α -allylated γ -lactam **II.3a** [ee = 84% obtained from the (*S,S*)-**II.32a**] was first converted to the corresponding pyrrolidinone **II.33** by hydrogenation. The resulting pyrrolidine diastereoisomers **II.33a** and **II.33b** were obtained in quantitative yield (>99%) in 1.5:1 ratio. Both diastereomers were separated successfully, and the enantiomeric excesses of two diastereomers were determined by SFC which showed no any erosion compared to the allylate product **II.3a** (Scheme 77).



Scheme 77. Synthesis of chiral pyrrolidinone derivative **II.33** by a hydrogenation of the allylated product **II.3a**.

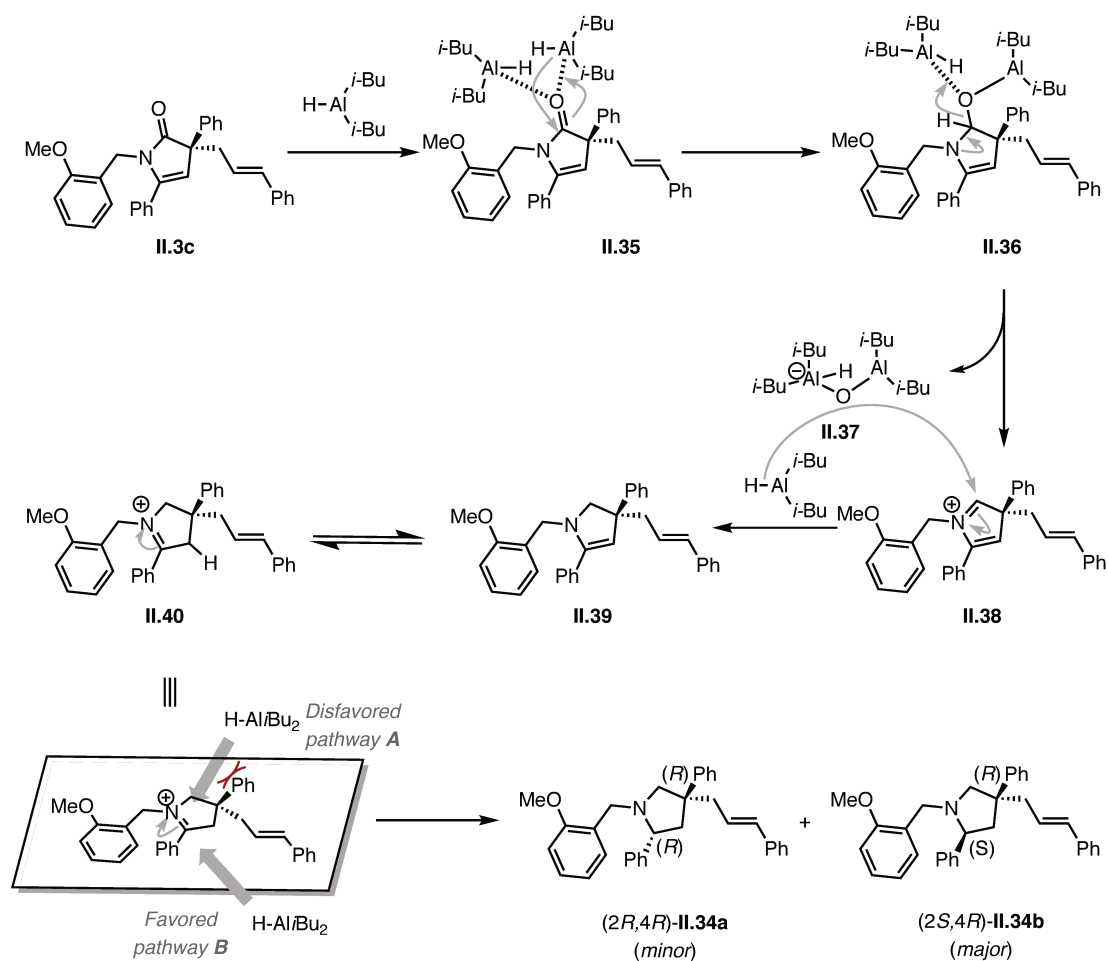
3.7.2. Synthesis of optically active pyrrolidines

In addition, we were also able to prepare the optically active pyrrolidines **II.34a** and **II.34b** from the allylated product **II.3c** by a DIBAL-H-mediated reduction [DIBAL-H (4.0 equiv), CH_2Cl_2 , -78°C , 6 h], The optically active pyrrolidine was obtained as a single diastereoisomer in a good yield, however, its relative configuration could not be determined unambiguously (Scheme 78).



Scheme 78. Synthesis of chiral pyrrolidine derivative **II.34** by DIBAL-H-mediated reduction.

A plausible mechanism for the DIBAL-H-mediated reduction, which could account for the diastereoselectivity, involves the complexation of the carbonyl moiety with two molecules of DIBAL-H to form intermediate **II.35**, which could undergo an intramolecular hydrogen transfer to yield intermediate **II.36**. The latter can then be converted to the corresponding imine intermediate **II.38** through a lone pair-assisted elimination and then reduced by another molecule of DIBAL-H. A new lone pair-promoted reduction could then take place to form the imine intermediate **II.40** which can eventually react with one molecule of DIBAL-H to obtain the two possible diastereomers **II.34a** and **II.34b**. We believe that the attack of the hydride from the top face could be disfavored due to a steric interaction with the phenyl group, however, we were not able to confirm this hypothesis (Scheme 79).



Scheme 79. Plausible mechanism of DIBAL-H-mediated reduction to synthesize compound **II.34**.

3.7.3. Cope rearrangement vs 1,3-migration of allylated products

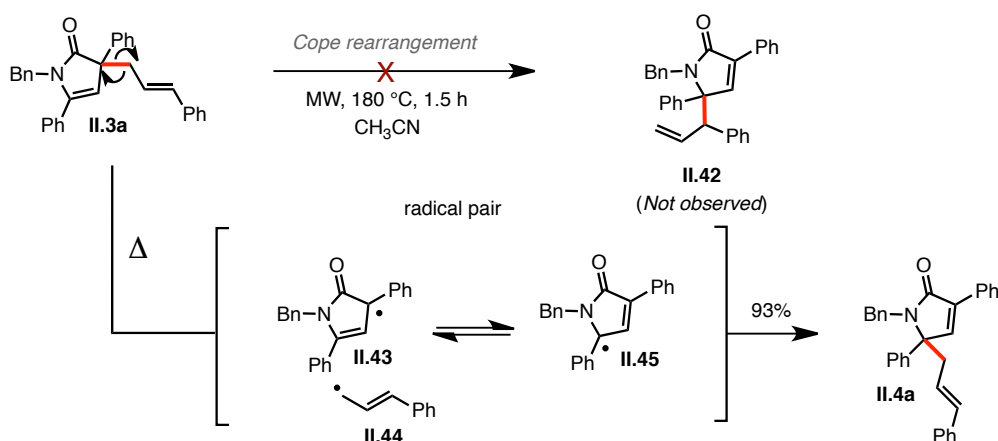
We also tried to perform a [3,3]-sigmatropic Cope rearrangement to access the corresponding γ -lactam derivative **II.42**, bearing two contiguous stereogenic centers. Indeed, as the Cope rearrangement should be stereospecific, the resulting γ -lactam **II.42** should be obtained with complete conservation of both ee and de. Unfortunately, whatever the conditions, we were never able to observe the formation of the desired Cope rearranged product **II.42**, but instead the linear γ -allylated product **II.4a**. This was most probably the result of a homolytic cleavage of the C–C bond connecting the allyl group to the γ -lactam in **II.3a** followed by a radical C–C bond formation with the most stable radical (Scheme 80). This hypothesis is strongly corroborated by the fact that when subjecting the optically active **II.3a** (70% ee) to thermal conditions (180 °C),

product **II.4a** was obtained quasi quantitatively (93%) as a racemic product (Table 23, entry 1). Lowering the temperature to 140 °C did not prevent the racemization and the reaction appeared to be more sluggish (Table 23, entry 2), while no reaction took place at 100 °C (Table 23, entry 3).

Table 23. The explored of Cope rearrangement.

Entry	T (°C)	Yield of II.42 / II.4a (%)	Recovery of II.3a (%)	Ee of II.4a (%)
1	180	-/93	7	0
2	140	-/68	32	0
3	100	NR	>99	-

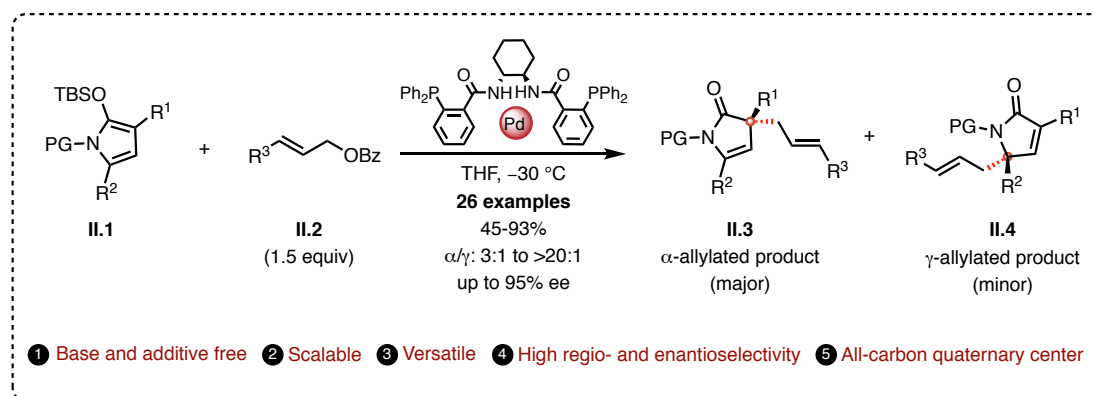
Based on these results, we propose the following mechanism: first, the homolytic cleavage of the C-C bond (in red) affords the two radicals **II.43** and **II.44**. The radical **II.43** can then rearrange to the more stable radical **II.45** by a single electron transfer (SET). After recombination, the 1,3-migration product **II.4a** is generated (Scheme 80).



Scheme 80. Proposed mechanism of the 1,3-migration of allylated product **II.3a** to afford the allylated product **II.4a**.

4. Conclusion

We have successfully developed a direct, highly regio- and enantioselective palladium-catalyzed allylic allylation of α,γ -disubstituted 2-silyloxypyrroles to access optically active γ -lactam derivatives bearing a quaternary stereogenic center. A variety of α,γ -disubstituted 2-silyloxypyrroles derived from the corresponding α,β -unsaturated lactam precursors were synthesized and evaluated under our optimized reaction conditions [$\text{Pd}_2(\text{dba})_3$ (5 mol %), **II.32a** (10 mol %), THF, $-30\text{ }^\circ\text{C}$]. The desired α -allylated γ -lactams were obtained in generally high yields, good to excellent regioselectivities (3:1 to >20:1) and good to excellent enantioselectivities (ee up to 95%). Most importantly, the allylated γ -lactams could be easily converted to useful building blocks including chiral pyrrolidinones and pyrrolidines through simple synthetic transformations (Scheme 81).



Scheme 81. Pd-catalyzed AAA of 2-silyloxypyrroles to access the optically active γ -lactams bearing a quaternary stereogenic center.

Experimental section-Chapter II

Table of Contents

1. General experimental methods.....	257
2. Synthesis of α,β -unsaturated ketones.....	259
3. Synthesis of γ -ketoacids.....	267
4. Synthesis of α,γ -disubstituted- α,β -unsaturated lactams.....	276
5. Synthesis of α,γ -disubstituted 2-silyloxypyrroles.....	290
6. Synthesis of β -substituted allyl benzoates.....	303
7. Substrate scope and limitation.....	315
8. Post-functionalization of allylated γ -lactams.....	343

1. General experimental methods

All reactions were run under an argon atmosphere in oven-dried glassware unless otherwise specified. All commercially available compounds were purchased from Aldrich Chemical Co. and used as received. Anhydrous solvents, such as tetrahydrofuran (THF) and diethyl ether (Et₂O) were distilled from sodium/benzophenone. Dichloromethane (CH₂Cl₂) was distilled from calcium hydride. The other anhydrous solvents, CH₃CN, 1,4-dioxane, DMF and 2-Me-THF, were purchased from Sigma Aldrich and used as received.

Analytical thin layer chromatography (TLC) was performed over silica gel plates (Merck 60F₂₅₄) visualized either with a UV lamp (254 nm) or by using solutions of *p*-anisaldehyde/sulfuric acid/acetic acid in ethanol or KMnO₄/K₂CO₃ in H₂O followed by heating. Flash chromatography was performed over silica gel (230-400 mesh).

Infrared spectra (IR) were recorded on a Bruker TENSOR™ 27 (IR-FT) with attenuated total reflectance (ATR) and wavenumbers are indicated in cm⁻¹.

¹H NMR spectra were recorded on a Bruker AVANCE 400 at 400 MHz in CDCl₃ (unless otherwise specified) and the observed signals are reported as follows: chemical shift in parts per million from tetramethylsilane with the solvent as an internal indicator (CDCl₃ δ 7.26 ppm, DMSO δ 2.50 ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quintet = quint, m = multiplet or overlap of non-equivalent resonances), integration. ¹³C NMR spectra were recorded at 100 MHz in CDCl₃ (unless otherwise specified) and the observed signals were reported as follows: chemical shift in parts per million from tetramethylsilane with the solvent as an internal indicator (CDCl₃ δ 77.16 ppm, DMSO δ 39.52 ppm), multiplicity on respect to proton. Coupling constants (*J*) are reported in Hertz (Hz). All NMR spectra were obtained at rt unless otherwise specified.

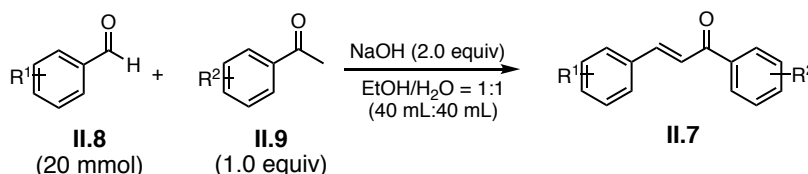
Mass spectra with electronic impact (EI-MS) were recorded with a Shimadzu GCM-QP 2010S gas chromatography-mass spectrometer. High-resolution mass spectra (HRMS) were performed by "Groupe de Spectrométrie de masse de l'Université Pierre et Marie Curie (Paris)".

Optical rotations were determined using a Perkin Elmer 343 polarimeter. The enantiomeric excesses were determined by supercritical fluid chromatography (SFC)

analysis on a chiral stationary phase using a Minigram Berger SFC-Mettler Toledo apparatus.

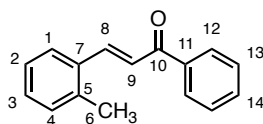
2. Synthesis of α,β -unsaturated ketones:

General procedure for synthesized the α,β -unsaturated ketone:



To a solution of acetophenone **II.9** (20 mmol, 2.33 mL, 1.0 equiv) in the mixture solvent EtOH/H₂O (40 mL/40 mL), NaOH (40 mmol, 1.6 g, 2.0 equiv) was added. Then, the mixture solution was stirred at rt for 10 min, and the corresponding aromatic aldehyde (20 mmol, 1.0 equiv) was added subsequently. The mixture was stirred at rt for 24 h. After the reaction was completely finished, HCl (1.0 M) solution was added until the PH to 4-5. The mixture was extracted by CH₂Cl₂ (3 $\times$ 30 mL), dried through Na₂SO₄ and filtered and concentrated under reduced pressure. The crude residue was purified by recrystallization (CH₂Cl₂/Hexane = 1:10) or flash column chromatography on silica gel (PE/EtOAc = 15:1) to afford the α,β -unsaturated ketone.

(E)-1-Phenyl-3-(o-tolyl)prop-2-en-1-one (II.7a)¹¹⁹



MW: 222.1045 g.mol⁻¹

Molecular Formula: C₁₆H₁₄O

Prepared according to the general procedure from 2-methylbenzaldehyde (2.313 mL, 20 mmol, 1.0 equiv) and acetophenone (2.333 mL, 20 mmol, 1.0 equiv). **II.7a** (3.997 g, 90%) was isolated as a green oil.

IR (neat): 1662, 1595, 1578, 1484, 1460, 1447, 1319, 1280, 1215, 1179, 1160, 1086, 1033, 1026, 979 cm⁻¹.

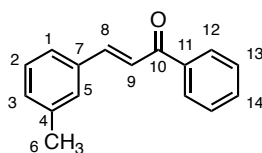
¹¹⁹ a) Fleige, M.; Glorius, F. *Chem. Eur. J.* **2017**, 23, 10773-10776; b) Jiang, Q.; Jia, J.; Xu, B.; Zhao, A.; Guo, C.-C. *J. Org. Chem.*, **2015**, 80, 3586-3596.

¹H NMR (400 MHz, CDCl₃) δ 8.03 (d, *J* = 15.5 Hz, 1H, H₈), 7.95 – 7.93 (m, 2H, H_{Ar}), 7.61 (d, *J* = 7.8 Hz, 1H, H_{Ar}), 7.51 – 7.47 (m, 1H, H_{Ar}), 7.43 – 7.39 (m, 3H, H_{Ar} and H₉), 7.23 – 7.13 (m, 3H, H_{Ar}), 2.38 (s, 3H, H₆).

¹³C NMR (101 MHz, CDCl₃) δ 190.5 (s, C₁₀), 142.5 (s, C₈), 138.5 (s, C_{Ar}), 138.3 (s, C_{Ar}), 134.0 (s, C_{Ar}), 132.9 (s, C_{Ar}), 131.0 (s, C_{Ar}), 130.4 (s, C_{Ar}), 128.7 (s, 2C, C_{Ar}), 128.6 (s, 2C, C_{Ar}), 126.5 (s, C_{Ar}), 126.4 (s, C_{Ar}), 123.2 (s, C₉), 20.0 (s, C₆).

MS *m/z* (relative intensity): 222 (M⁺, 40), 207 (100), 193 (5), 203 (4), 193 (5), 178 (10), 145 (19), 130 (7), 115 (42), 105 (44), 96 (11), 91 (35), 77 (58), 63 (5), 51 (17).

(*E*)-1-Phenyl-3-(*m*-tolyl)prop-2-en-1-one (II.7b)¹¹⁹



MW: 222.1045 g.mol⁻¹

Molecular Formula: C₁₆H₁₄O

Prepared according to the general procedure from 3-methylbenzaldehyde (2.358 mL, 20 mmol, 1.0 equiv) and acetophenone (2.333 mL, 20 mmol, 1.0 equiv). **II.7b** (4.004 g, 91%) was isolated as a yellow solid.

Mp: 64–65 °C.

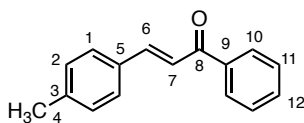
IR (neat): 1662, 1640, 1599, 1578, 1483, 1447, 1331, 1316, 1238, 1211, 1179, 1158, 1091, 1035, 1018, 982 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 8.03 (d, *J* = 7.4 Hz, 2H, H_{Ar}), 7.80 (d, *J* = 15.7 Hz, 1H, H₈), 7.61–7.45 (m, 6H, H_{Ar} and H₉), 7.32 (t, *J* = 7.9 Hz, 1H, H_{Ar}), 7.25 – 7.23 (m, 1H, H_{Ar}), 2.41 (s, 3H, H₆).

¹³C NMR (101 MHz, CDCl₃) δ 190.7 (s, C₁₀), 145.2 (s, C₈), 138.8 (s, C_{Ar}), 138.4 (s, C_{Ar}), 135.0 (s, C_{Ar}), 132.9 (s, C_{Ar}), 131.6 (s, C_{Ar}), 129.2 (s, C_{Ar}), 129.0 (s, C_{Ar}), 128.8 (s, 2C, C_{Ar}), 128.6 (s, 2C, C_{Ar}), 125.9 (s, C_{Ar}), 122.0 (s, C₉), 21.5 (s, C₆).

MS *m/z* (relative intensity): 222 (M⁺, 48), 207 (100), 193 (3), 179 (13), 165 (2), 145 (26), 130 (8), 115 (33), 91 (18), 77 (50), 65 (10), 51 (15).

(E)-1-Phenyl-3-(p-tolyl)prop-2-en-1-one (II.7c)¹²⁰



MW: 222.1045 g.mol⁻¹

Molecular Formula: C₁₆H₁₄O

Prepared according to the general procedure from 4-methylbenzaldehyde (2.358 mL, 20 mmol, 1.0 equiv) and acetophenone (2.333 mL, 20 mmol, 1.0 equiv). **II.7c** (3.907 g, 88%) was isolated as a white solid.

Mp: 95–96 °C

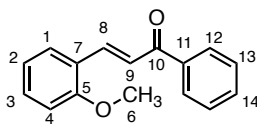
IR (neat): 2360, 2340, 1656, 1591, 1567, 1510, 1446, 1410, 1332, 1322, 1304, 1286, 1217, 1206, 1176, 1115, 1075, 1032, 1015, 983, 947, 928 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 8.02 (d, *J* = 7.2 Hz, 2H, H_{Ar}), 7.80 (d, *J* = 15.7 Hz, 1H, H₆), 7.60 – 7.48 (m, 6H, H_{Ar} and H₇), 7.22 (d, *J* = 7.9 Hz, 2H, H_{Ar}), 2.39 (s, 3H, H₄).

¹³C NMR (101 MHz, CDCl₃) δ 190.7 (s, C₈), 145.0 (s, C₆), 141.2 (s, C_{Ar}), 138.4 (s, C_{Ar}), 132.8 (s, C_{Ar}), 132.2 (s, C_{Ar}), 129.8 (s, 2C, C_{Ar}), 128.7 (s, 2C, C_{Ar}), 128.6 (s, 2C, C_{Ar}), 128.5 (s, 2C, C_{Ar}), 121.1 (s, C₇), 21.6 (s, C₄).

MS *m/z* (relative intensity): 222 (M⁺, 37), 221 (46), 207 (100), 193 (3), 179 (15), 145 (32), 130 (15), 115 (34), 105 (23), 96 (12), 91 (18), 77 (45), 63 (4), 51 (14).

(E)-3-(2-Methoxyphenyl)-1-phenylprop-2-en-1-one (II.7d)¹¹⁹



MW: 238.0994 g.mol⁻¹

Molecular Formula: C₁₆H₁₄O₂

Prepared according to the general procedure from *o*-anisaldehyde (2.416 mL, 20 mmol, 1.0 equiv) and acetophenone (2.333 mL, 20 mmol, 1.0 equiv). **II.7d** (4.047 g, 85%) was isolated as a white solid.

¹²⁰ Chan, C.-K.; Tsai, Y.-L.; Chang, M.-Y. *Tetrahedron*, **2017**, 73, 3368-3376

Mp: 59–60 °C.

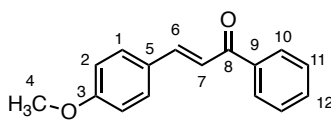
IR (neat): 1658, 1592, 1572, 1487, 1464, 1447, 1437, 1333, 1316, 1283, 1273, 1246, 1212, 1178, 1163, 1125, 1108, 1072, 1051, 1016, 987 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 8.13 (d, *J* = 15.9 Hz, 1H, H₈), 8.03 – 8.01 (m, 2H, H₁₂), 7.65 – 7.56 (m, 3H, H₉ and H_{Ar}), 7.52 – 7.48 (m, 2H, H_{Ar}), 7.41 – 7.36 (m, 1H, H_{Ar}), 7.00 (t, *J* = 7.5 Hz, 1H, H_{Ar}), 6.95 (d, *J* = 8.3 Hz, 1H, H₄), 3.92 (s, 3H, H₆).

¹³C NMR (101 MHz, CDCl₃) δ 191.3 (s, C₁₀), 158.9 (s, C_{Ar}), 140.5 (s, C₇), 138.7 (s, C_{Ar}), 132.7 (s, C_{Ar}), 131.9 (s, C_{Ar}), 129.4 (s, C_{Ar}), 128.7 (s, 4C, C_{Ar}), 124.0 (s, C_{Ar}), 123.0 (s, C₈), 120.9 (s, C_{Ar}), 111.4 (s, C₄), 55.7 (s, C₆).

MS *m/z* (relative intensity): 238 (M⁺, 100), 223 (11), 194 (10), 179 (10), 165 (9), 161 (32), 152 (5), 133 (18), 118 (19), 105 (38), 103 (7), 90 (14), 77 (73), 63 (8), 51 (17).

(*E*)-3-(4-Methoxyphenyl)-1-phenylprop-2-en-1-one (II.7e)¹²¹



MW: 238.0994 g.mol⁻¹

Molecular Formula: C₁₆H₁₄O₂

Prepared according to the general procedure from *p*-Anisaldehyde (2.438 mL, 20 mmol, 1.0 equiv) and acetophenone (2.333 mL, 20 mmol, 1.0 equiv). **II.7e** (4.189 g, 88%) was isolated as a white solid.

Mp: 63–64 °C

IR (neat): 1657, 1589, 1571, 1509, 1253, 1212, 1170, 1033, 1016, 982, 827, 777, 723, 692, 657 cm⁻¹.

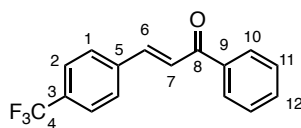
¹H NMR (400 MHz, CDCl₃) δ 8.03 – 8.00 (m, 2H, H₁₀), 7.79 (d, *J* = 15.6 Hz, 1H, H₆), 7.62 – 7.55 (m, 3H, H_{Ar}), 7.52 – 7.48 (m, 2H, H_{Ar}), 7.42 (d, *J* = 15.7 Hz, 1H, H₇), 6.96 – 6.92 (m, 2H, H₂), 3.85 (s, 3H, H₄).

¹²¹ a) Lin, C.; Achtenhagen, M.; Szostak, M. *Org. Lett.*, **2016**, *18*, 2375-2378; b) Zhang, S., Wang, L.; Feng, X.; Bao, M. *Org. Biomol. Chem.*, **2014**, *12*, 7233-7237.

¹³C NMR (101 MHz, CDCl₃) δ 190.7 (s, C₈), 161.8 (s, C₃), 144.8 (s, C₆), 138.6 (s, C₉), 132.7 (s, C_{Ar}), 130.4 (s, 2C, C_{Ar}), 128.7 (s, 2C, C_{Ar}), 128.5 (s, 2C, C₁₀), 127.7 (s, C₅), 119.9 (s, C₆), 114.5 (s, 2C, C₂), 55.5 (s, C₄).

MS m/z (relative intensity): 238 (M⁺, 100), 223 (23), 207 (18), 195 (10), 179 (6), 167 (7), 161 (48), 152 (5), 133 (27.7), 130 (4), 118 (11), 89 (13), 77 (56), 63 (7), 51 (15).

(E)-1-Phenyl-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-one (II.7f)¹¹⁹



MW: 276.0762 g.mol⁻¹

Molecular Formula: C₁₆H₁₁F₃

Prepared according to the general procedure from 4-(trifluoromethyl)benzaldehyde (2.731 mL, 20 mmol, 1.0 equiv) and acetophenone (2.333 mL, 20 mmol, 1.0 equiv). **II.7f** (4.693 g, 85%) was isolated as a white solid.

Mp: 125–126 °C

IR (neat): 1664, 1637, 1610, 1577, 1448, 1416, 1364, 1331, 1291, 1221, 1169, 1156, 1129, 1109, 1068, 1033, 1017, 984, 966, 935, 909 cm⁻¹.

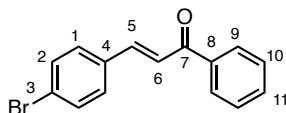
¹H NMR (400 MHz, CDCl₃) δ 8.03 (d, *J* = 7.3 Hz, 2H, H₁₀), 7.81 (d, *J* = 15.7 Hz, 1H, H₆), 7.74 (d, *J* = 8.2 Hz, 2H, H_{Ar}), 7.67 (d, *J* = 8.3 Hz, 2H, H_{Ar}), 7.63 – 7.50 (m, 4H, H_{Ar} and H₇).

¹³C NMR (101 MHz, CDCl₃) δ 190.2 (s, C₈), 142.9 (s, C₆), 138.4 (s, C_{Ar}), 137.9 (s, C_{Ar}), 133.3 (s, C_{Ar}), 132.0 (d, *J* = 32.8 Hz, C₃), 128.9 (s, 2C, C_{Ar}), 128.7 (s, 2C, C_{Ar}), 128.6 (s, 2C, C_{Ar}), 126.0 (q, *J* = 3.7 Hz, 2C, C₂), 124.4 (s, C₇), 124.0 (d, *J* = 273.0 Hz, C₄)

MS m/z (relative intensity): 276 (M⁺, 54), 257 (5), 207 (35), 171 (17), 151 (37), 105 (85), 77 (100), 51 (32).

(E)-3-(4-Bromophenyl)-1-phenylprop-2-en-1-one (II.7g)¹²²

¹²² Ganesan, P.; Ranganathan, R.; Chi, Y.; Liu, X.-K.; Lee, C.-S.; Liu, S.-H.; Lee, G.-H.; Lin, T.-C.; Chen, Y.-T.; Chou, P.-T. *Chem. Eur. J.* **2017**, *23*, 2858-2866.



MW: 285.993 g.mol⁻¹

Molecular Formula: C₁₅H₁₁BrO

Prepared according to the general procedure from 4-bromobenzaldehyde (2.000 mL, 20 mmol, 1.0 equiv) and acetophenone (2.333 mL, 20 mmol, 1.0 equiv). **II.7g** (5.148 g, 90%) was isolated as a white solid.

Mp: 122–123 °C.

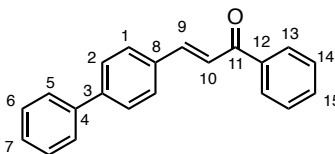
IR (neat): 1722, 1658, 1634, 1607, 1596, 1582, 1486, 1446, 1428, 1400, 1361, 1297, 1220, 1158, 1110, 1074, 1017, 1008, 980 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 8.01 (d, *J* = 7.4 Hz, 2H, H₉), 7.74 (d, *J* = 15.7 Hz, 1H, H₅), 7.62 – 7.49 (m, 8H, H_{Ar} and H₆).

¹³C NMR (101 MHz, CDCl₃) δ 190.4 (s, C₇), 143.5 (s, C₅), 138.1 (s, C_{Ar}), 133.9 (s, C_{Ar}), 133.1 (s, C_{Ar}), 132.3 (s, 2C, C_{Ar}), 129.9 (s, 2C, C_{Ar}), 128.8 (s, 2C, C_{Ar}), 128.6 (s, 2C, C_{Ar}), 124.9 (s, C_{Ar}), 122.7 (s, C₆).

MS *m/z* (relative intensity): 286 (M⁺, 34.8), 207 (53), 179 (26), 152 (3), 130 (31), 102 (94), 89 (36), 77 (100), 63 (7), 51 (42).

(E)-3-([1,1'-Biphenyl]-4-yl)-1-phenylprop-2-en-1-one (II.7h)¹²³



MW: 284.1201 g.mol⁻¹

Molecular Formula: C₂₁H₁₆O

Prepared according to the general procedure from 4-Biphenylcarboxyaldehyde (3.644 g, 20 mmol, 1.0 equiv) and acetophenone (2.333 mL, 20 mmol, 1.0 equiv). **II.7h** (5.228 g, 92%) was isolated as a white solid.

¹²³ Stroba, A.; Schaeffer, F.; Hindiel, V.; Lopez-Garcia, L.; Adrian, I.; Fröhner, H. R. W.; Biondil, R. M.; E, M. *J. Med. Chem.* **2009**, 52, 4683-4693.

Mp: 108–109 °C

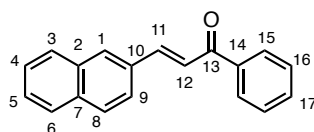
IR (neat): 2359, 2342, 1763, 1659, 1634, 1598, 1578, 1556, 1520, 1487, 1448, 1409, 1331, 1304, 1217, 1179, 1120, 1076, 1034, 1014, 1005 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 8.05 (d, *J* = 7.7 Hz, 2H, H₁₃), 7.87 (d, *J* = 15.7 Hz, 1H, H₉), 7.74 – 7.37 (m, 13H, H₁₀ and H_{Ar}).

¹³C NMR (101 MHz, CDCl₃) δ 190.6 (s, C₁₁), 144.5 (s, C₉), 143.4 (s, C_{Ar}), 140.2 (s, C_{Ar}), 138.4 (s, C_{Ar}), 134.0 (s, C_{Ar}), 132.9 (s, C₁₅), 129.1 (s, 2C, C_{Ar}), 129.06 (s, 2C, C_{Ar}), 128.8 (s, 2C, C_{Ar}), 128.6 (s, 2C, C_{Ar}), 128.0 (s, C_{Ar}), 127.7 (s, 2C, C_{Ar}), 127.2 (s, 2C, C_{Ar}), 122.0 (s, C₁₀).

MS *m/z* (relative intensity): 284 (M⁺, 100), 267 (3), 255 (8), 239 (5), 226 (0.9), 207 (56), 189 (0.5), 178 (45), 165 (20), 154 (27), 142 (2), 128 (4), 113 (2), 105 (22), 89 (3), 77 (46), 63 (2), 51 (10).

(*E*)-3-(Naphthalen-2-yl)-1-phenylprop-2-en-1-one (II.7i)¹²⁴



MW: 258.1045 g.mol⁻¹

Molecular Formula: C₁₉H₁₄O

Prepared according to the general procedure from 2-naphthaldehyde (3.124 g, 20 mmol, 1.0 equiv) and acetophenone (2.333 mL, 20 mmol, 1.0 equiv). **II.7i** (4.646 g, 90%) was isolated as a white solid.

Mp: 156–157 °C

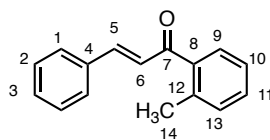
IR (neat): 2361, 1771, 1688, 1662, 1604, 1591, 1576, 1541, 1448, 1412, 1361, 1324, 1297, 1268, 1258, 1209, 1165, 1122, 1068, 1034, 1017, 982, 941 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 8.08 – 8.01 (m, 3H, H_{Ar}), 7.99 (d, *J* = 15.7 Hz, 1H, H₁₁), 7.90 – 7.79 (m, 4H, H_{Ar}), 7.65 (d, *J* = 15.7 Hz, 1H, H₁₂), 7.61 – 7.51 (m, 5H, H_{Ar}).

¹²⁴ Larionov, V. A.; Markelova, E. P.; Smol'yakov, A. F.; Savel'yeva, T.; Maleev, V. L.; Belokon, Y. N. *RSC. Adv.* **2015**, *5*, 72764-72771.

¹³C NMR (101 MHz, CDCl₃) δ 190.7 (s, C₁₃), 145.1 (s, C₁₁), 138.4 (s, C_{Ar}), 134.5 (s, C_{Ar}), 133.5 (s, C_{Ar}), 132.9 (s, C_{Ar}), 132.5 (s, C_{Ar}), 130.8 (s, C_{Ar}), 128.9 (s, C_{Ar}), 128.8 (s, 3C, C_{Ar}), 128.7 (s, 2C, C_{Ar}), 127.9 (s, C_{Ar}), 127.5 (s, C_{Ar}), 126.9 (s, C_{Ar}), 123.8 (s, C_{Ar}), 122.3 (s, C₁₂).
MS m/z (relative intensity): 258 (M⁺, 89), 257 (100), 241 (3), 229 (21), 215 (7), 202 (2), 181 (21), 152 (40), 128 (32), 114 (10), 105 (30), 87 (1), 77 (42), 63 (2), 51 (9).

(E)-3-Phenyl-1-(o-tolyl)prop-2-en-1-one (II.7j)¹²⁵



MW: 222.1045 g.mol⁻¹

Molecular Formula: C₁₆H₁₄O

Prepared according to the general procedure from benzaldehyde (2.033 mL, 20 mmol, 1.0 equiv) and 2'-methylacetophenone (2.616 mL, 20 mmol, 1.0 equiv). **II.7j** (3.776 g, 85%) was isolated as a green oil.

IR (neat): 1666, 1641, 1599, 1575, 1494, 1381, 1328, 1300, 1272, 1204, 1161, 1129, 1065, 1030, 1014, 979 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.57 – 7.56 (m, 2H, H_{Ar}), 7.52 – 7.45 (m, 2H, H_{Ar} and H₅), 7.41 – 7.37 (m, 4H, H_{Ar}), 7.29 (d, *J* = 7.2 Hz, 2H, H_{Ar}), 7.14 (d, *J* = 16.0 Hz, 1H, H₆), 2.46 (s, 3H, H₁₄).

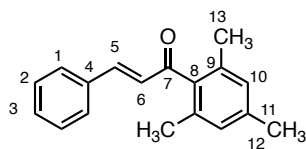
¹³C NMR (101 MHz, CDCl₃) δ 196.7 (s, C₇), 146.0 (s, C₅), 139.2 (s, C_{Ar}), 137.1 (s, C_{Ar}), 134.7 (s, C_{Ar}), 131.4 (s, C_{Ar}), 130.8 (s, C_{Ar}), 130.6 (s, C_{Ar}), 129.1 (s, 2C, C_{Ar}), 128.5 (s, 2C, C_{Ar}), 128.2 (s, C_{Ar}), 126.9 (s, C₆), 125.6 (s, C_{Ar}), 20.3 (s, C₁₄).

MS m/z (relative intensity): 222 (M⁺, 38), 207 (5), 203 (4), 193 (3), 178 (6), 144 (6), 131 (100), 119 (14), 105 (2), 103 (27), 91 (44), 77 (22), 63 (5), 51 (8).

(E)-1-Mesityl-3-phenylprop-2-en-1-one (II.7k)¹²⁶

¹²⁵ Wang, J.; Liu, C.; Yuan, J.; Lei, A. *Angew. Chem. Int. Ed.* **2013**, 52, 2256-2259.

¹²⁶ Frost, J. R.; Cheong, C. B.; Akhtar, W. M.; Caputo, D. F. J.; Stevenson, N. G.; Donohoe, T. J. *J. Am. Chem. Soc.*, **2015**, 137, 15664-15667.



MW: 250.1358 g.mol⁻¹

Molecular Formula: C₁₈H₁₈O

Prepared according to the general procedure from benzaldehyde (2.033 mL, 20 mmol, 1.0 equiv) and 2',4',6'-trimethylacetophenone (2.616 mL, 20 mmol, 1.0 equiv). **II.7k** (4.002 g, 80%) was isolated as a green oil.

Mp: 56–57 °C

IR (neat): 2917, 1641, 1623, 1599, 1575, 1495, 1448, 1379, 1327, 1300, 1269, 1215, 1203, 1166, 1124, 1063, 1022, 1014, 979, 910 cm⁻¹.

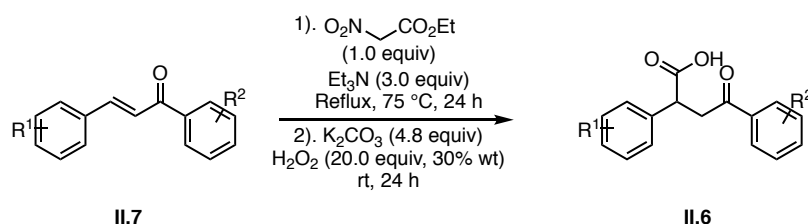
¹H NMR (400 MHz, CDCl₃) δ 7.53 – 7.50 (m, 2H, H_{Ar}), 7.40 – 7.37 (m, 3H, H_{Ar}), 7.21 (d, *J* = 16.3 Hz, 1H, H₅), 6.95 (dd, *J* = 16.3, 1.1 Hz, 1H, H₆), 6.90 (s, 2H, H₁₀), 2.34 (s, 3H, H₁₂), 2.21 (s, 6H, H₁₃).

¹³C NMR (101 MHz, CDCl₃) δ 201.5 (s, C₇), 146.8 (s, C₅), 138.5 (s, C_{Ar}), 137.2 (s, C_{Ar}), 134.5 (s, C_{Ar}), 134.2 (s, C_{Ar}), 130.9 (s, C_{Ar}), 129.0 (s, 2C, C_{Ar}), 128.6 (s, 2C, C_{Ar}), 128.50 (s, C₆), 128.47 (s, 2C, C_{Ar}), 21.2 (s, C₁₂), 19.4 (s, 3C, C₁₃).

MS *m/z* (relative intensity): 250 (M⁺, 30), 235 (7), 218 (1), 207 (2), 192 (3), 178 (0.9), 173 (6), 159 (100), 147 (12), 143 (1), 131 (10), 119 (11), 103 (16), 91 (21), 77 (16), 65 (3), 51 (5).

3. Synthesis of γ -ketoacids

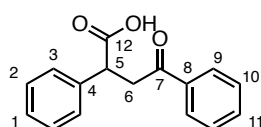
General procedure for synthesis the γ -ketoacid compound¹¹⁷:



To a mixture solution of chalcone **II.7a** (10 mmol) and Et₃N (4.17 mL, 3.0 equiv) in 100 mL dried-flask, ethyl nitroacetate (1.11 mL, 10 mmol, 1.0 equiv) was added subsequently. The mixture was refluxed at 75 °C for 24 h. When reaction was completely finished, the reaction was cooled to rt, and ethyl acetate (50 mL) was added into the mixture. The mixture was washed with HCl (1.0 M) solution, dried over Na₂SO₄ and concentrated in vacuo to give the crude residue which was used for next step without further purification.

To a solution of the crude residue in MeOH (30 mL) in an ice bath, K₂CO₃ (6.63 g, 48 mmol, 4.8 equiv) and H₂O₂ (22.6 mL, 200 mmol, 20 equiv, 30 wt. % in H₂O) were added at 0 °C, subsequently. After 10 min, the mixture solution was allowed to stir at rt for 24 h. when the reaction was completely finished, the concentrated HCl (12 M) solution was slowly added to the mixture solution at 0 °C until the PH to 1. Then, the mixture solution was extracted with CH₂Cl₂ (3 × 30 mL), dried over Na₂SO₄ and concentrated in vacuo to give the crude residue which was purified by flash column chromatography on silica gel (PE/ EtOAc = 5:1 to 3:1) to give the pure γ -ketoacid product **II.6a** (1.778 g, 70%) as a white solid.

4-oxo-2,4-diphenylbutanoic acid (**II.6a**)¹¹⁷



MW: 254.0943 g.mol⁻¹

Molecular Formula: C₁₆H₁₄O₃

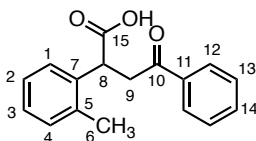
Mp: 138–139 °C

IR (neat): 2361, 2342, 1708, 1685, 1598, 1580, 1496, 1450, 1417, 1361, 1241, 1204, 1182, 992, 754, 691 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.98 – 7.92 (m, 2H, H₉), 7.59 – 7.53 (m, 1H, H₁₁), 7.47 – 7.43 (m, 2H, H₁₀), 7.39 – 7.27 (m, 5H, H_{Ar}), 4.32 (dd, J = 10.1, 4.2 Hz, 1H, H₅), 3.91 (dd, J = 18.1, 10.2 Hz, 1H, H₆), 3.29 (dd, J = 18.1, 4.2 Hz, 1H, H₆).

¹³C NMR (101 MHz, CDCl₃) δ 197.5 (s, C₇), 178.7 (s, C₁₂), 137.8 (s, C₄), 136.4 (s, C₈), 133.5 (s, C₁₁), 129.1 (s, 2C, C_{Ar}), 128.8 (s, 2C, C_{Ar}), 128.2 (s, 2C, C_{Ar}), 128.1 (s, 2C, C_{Ar}), 127.9 (s, C₁), 46.6 (s, C₅), 42.5 (s, C₆).

4-oxo-4-phenyl-2-(*o*-tolyl)butanoic acid (**II.6b**)



MW: 268.1099 g.mol⁻¹

Molecular Formula: C₁₇H₁₆O₃

The γ -ketoacid **II.6b** was synthesized from the α,β -unsaturated ketone **II.7b** (10 mmol, 1.0 equiv) followed the general procedure. **II.6b** (1.099 g, 41% in two steps) was isolated as a green oil.

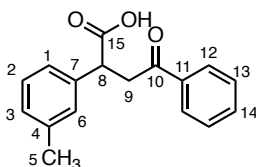
IR (neat): 1704, 1683, 1597, 1580, 1492, 1463, 1449, 1418, 1359, 1299, 1242, 1201, 1181, 1106, 1074, 1053, 1031, 992, 909.

¹H NMR (400 MHz, CDCl₃) δ 9.62 (s_{br}, 1H, -OH), 7.97 (d, J = 7.9 Hz, 2H, H_{Ar}), 7.57 (t, J = 7.5 Hz, 1H, H_{Ar}), 7.47-7.44 (m, 2H, H_{Ar}), 7.32 – 7.31 (m, 1H, H_{Ar}), 7.22 – 7.19 (m, 3H, H_{Ar}), 4.64 (dd, J = 9.8, 4.1 Hz, 1H, H₈), 3.91 (dd, J = 18.1, 9.8 Hz, 1H, H₉), 3.22 (dd, J = 18.1, 4.2 Hz, 1H, H₉), 2.48 (s, 3H, H₆).

¹³C NMR (101 MHz, CDCl₃) δ 197.7 (s, C₁₀), 179.5 (s, C₁₅), 136.5 (s, C_{Ar}), 136.4 (s, C_{Ar}), 133.5 (s, C_{Ar}), 131.0 (s, C_{Ar}), 128.7 (s, 3C, C_{Ar}), 128.2 (s, 2C, C_{Ar}), 127.7 (s, C_{Ar}), 126.9 (s, C_{Ar}), 126.7 (s, C_{Ar}), 41.9 (s, C₈), 41.8 (s, C₉), 19.9 (s, C₆).

HRMS (ESI) m/z : calculated for C₁₇H₁₆O₃H [M+H]⁺: 269.1172, found: 269.1175.

4-oxo-4-phenyl-2-(*m*-tolyl)butanoic acid (**II.6c**)



MW: 268.1099 g.mol⁻¹

Molecular Formula: C₁₇H₁₆O₃

The γ -ketoacid **II.6c** was synthesized from the α,β -unsaturated ketone **II.7c** (10 mmol, 1.0 equiv) followed the general procedure. **II.6c** (1.233 g, 46% in two steps) was isolated as a white solid.

Mp: 171–172 °C.

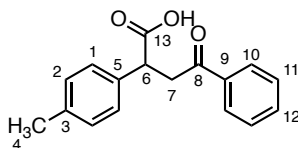
IR (neat): 1701, 1680, 1597, 1489, 1449, 1426, 1361, 1335, 1317, 1294, 1265, 1222, 1200, 1186, 1162, 1096, 1043, 992, 945, 909 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 10.09 (s_{br}, 1H, -OH), 7.97 (d, *J* = 7.4 Hz, 2H, H_{Ar}), 7.57 (t, *J* = 7.4 Hz, 1H, H_{Ar}), 7.47–7.43 (m, 2H, H_{Ar}), 7.26–7.23 (m, 1H, H_{Ar}), 7.18–7.16 (m, 2H, H_{Ar}), 7.11 (d, *J* = 7.4 Hz, 1H, H_{Ar}), 4.28 (dd, *J* = 10.2, 4.1 Hz, 1H, H₈), 3.91 (dd, *J* = 18.1, 10.2 Hz, 1H, H₉), 3.27 (dd, *J* = 18.1, 4.1 Hz, 1H, H₉), 2.36 (s, 3H, H₅).

¹³C NMR (101 MHz, CDCl₃) δ 197.6 (s, C₁₀), 179.1 (s, C₁₅), 138.8 (s, C_{Ar}), 137.7 (s, C_{Ar}), 136.4 (s, C_{Ar}), 133.5 (s, C_{Ar}), 129.0 (s, C_{Ar}), 128.8 (s, C_{Ar}), 128.74 (s, 2C, C_{Ar}), 128.71 (s, C_{Ar}), 128.2 (s, 2C, C_{Ar}), 125.2 (s, C_{Ar}), 46.3 (s, C₈), 42.5 (s, C₉), 21.6 (s, C₅).

HRMS (ESI) *m/z*: calculated for C₁₇H₁₆O₃H [M+H]⁺: 269.1172, found: 269.1180.

4-oxo-4-phenyl-2-(*p*-tolyl)butanoic acid (**II.6d**)



MW: 268.1099 g.mol⁻¹

Molecular Formula: C₁₇H₁₆O₃

The γ -ketoacid **II.6d** was synthesized from the α,β -unsaturated ketone **II.7d** (10 mmol, 1.0 equiv) followed the general procedure. **II.6d** (1.072 g, 40% in two steps) was isolated as a white solid.

Mp: 150–151 °C.

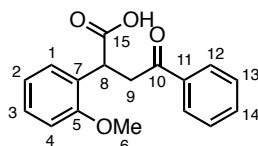
IR (neat): 1705, 1684, 1597, 1580, 1513, 1449, 1422, 1359, 1322, 1290, 1243, 1214, 1200, 1183, 1160, 1001, 992, 910 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 10.95 (s_{br}, 1H, -OH) 7.96 (d, *J* = 7.4 Hz, 2H, H_{Ar}), 7.56 (t, *J* = 7.4 Hz, 1H, H_{Ar}), 7.47–7.43 (m, 2H, H_{Ar}), 7.26 (d, *J* = 8.0 Hz, 2H, H_{Ar}), 7.16 (d, *J* = 7.9 Hz, 2H, H_{Ar}), 4.28 (dd, *J* = 10.0, 4.2 Hz, 1H, H₆), 3.89 (dd, *J* = 18.1, 10.0 Hz, 1H, H₇), 3.27 (dd, *J* = 18.1, 4.3 Hz, 1H, H₇), 2.34 (s, 3H, H₄).

^{13}C NMR (101 MHz, CDCl_3) δ 197.6 (s, C_8), 179.1 (s, C_{13}), 137.7 (s, C_{Ar}), 136.4 (s, C_{Ar}), 134.8 (s, C_{Ar}), 133.5 (s, C_{Ar}), 129.8 (s, 2C, C_{Ar}), 128.7 (s, 2C, C_{Ar}), 128.2 (s, 2C, C_{Ar}), 128.0 (s, 2C, C_{Ar}), 45.9 (s, C_6), 42.4 (s, C_7), 21.2 (s, C_4).

HRMS (ESI) m/z : calculated for $\text{C}_{17}\text{H}_{16}\text{O}_3\text{H}$ $[\text{M}+\text{H}]^+$: 269.1172, found: 269.1180.

2-(2-methoxyphenyl)-4-oxo-4-phenylbutanoic acid (**II.6e**)



MW: 284.1049 $\text{g}\cdot\text{mol}^{-1}$

Molecular Formula: $\text{C}_{17}\text{H}_{16}\text{O}_4$

The γ -ketoacid **II.6e** was synthesized from the α,β -unsaturated ketone **II.7e** (10 mmol, 1.0 equiv) followed the general procedure. **II.6e** (1.278 g, 45% in two steps) was isolated as a white solid.

Mp: 123–125 $^{\circ}\text{C}$.

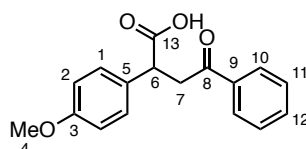
IR (neat): 1706, 1684, 1598, 1494, 1464, 1449, 1440, 1417, 1358, 1291, 1247, 1205, 1181, 1162, 1117, 1108, 1051, 1027, 1001, 992, 909 cm^{-1} .

^1H NMR (400 MHz, CDCl_3) δ 9.58 (s_{br}, 1H, -OH), 7.96 – 7.94 (m, 2H, H_{Ar}), 7.56 – 7.52 (m, 1H, H_{Ar}), 7.45 – 7.41 (m, 2H, H_{Ar}), 7.31 – 7.24 (m, 2H, H_{Ar}), 6.96 – 6.92 (m, 1H, H_{Ar}), 6.90 (d, J = 7.6 Hz, 1H, H_{Ar}), 4.73 (dd, J = 9.2, 4.4 Hz, 1H, H_8), 3.88 (dd, J = 18.0, 9.2 Hz, 1H, H_9), 3.83 (s, 3H, H_9), 3.20 (dd, J = 18.0, 4.5 Hz, 1H, H_6).

^{13}C NMR (101 MHz, CDCl_3) δ 198.0 (s, C_{10}), 179.2 (s, C_{15}), 156.9 (s, C_{Ar}), 136.7 (s, C_{Ar}), 133.3 (s, C_{Ar}), 129.3 (s, C_{Ar}), 128.9 (s, C_{Ar}), 128.7 (s, 2C, C_{Ar}), 128.2 (s, 2C, C_{Ar}), 126.9 (s, C_{Ar}), 121.1 (s, C_{Ar}), 111.2 (s, C_{Ar}), 55.7 (s, C_8), 41.0 (s, C_9), 40.8 (s, C_6).

HRMS (ESI) m/z : calculated for $\text{C}_{17}\text{H}_{16}\text{O}_4\text{H}$ $[\text{M}+\text{H}]^+$: 285.1121, found: 285.1128.

2-(4-methoxyphenyl)-4-oxo-4-phenylbutanoic acid (**II.6f**)¹¹⁷



MW: 284.1049 g.mol⁻¹

Molecular Formula: C₁₇H₁₆O₄

The γ -ketoacid **II.6f** was synthesized from the α,β -unsaturated ketone **II.7f** (10 mmol, 1.0 equiv) followed the general procedure. **II.6f** (1.080 g, 38% in two steps) was isolated as a white solid.

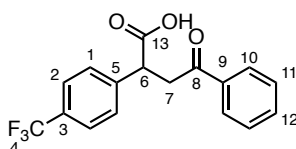
Mp: 137–138 °C.

IR (neat): 2922, 1684, 1604, 1578, 1512, 1449, 1427, 1300, 1261, 1204, 1179, 1107, 1028, 1001, 929 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.95 (d, J = 7.1 Hz, 2H, H_{Ar}), 7.56 (t, J = 7.4 Hz, 1H, H_{Ar}), 7.46 – 7.42 (m, 2H, H_{Ar}), 7.28 (d, J = 8.7 Hz, 2H, H_{Ar}), 6.87 (d, J = 8.7 Hz, 2H, H_{Ar}), 4.25 (dd, J = 9.9, 4.4 Hz, 1H, H₆), 3.86 (dd, J = 18.0, 9.9 Hz, 1H, H₇), 3.79 (s, 3H, H₄), 3.27 (dd, J = 18.1, 4.4 Hz, 1H, H₇).

¹³C NMR (101 MHz, CDCl₃) δ 197.6 (s, C₈), 178.8 (s, C₁₃), 159.3 (s, C₃), 136.5 (s, C_{Ar}), 133.5 (s, C_{Ar}), 129.8 (s, C_{Ar}), 129.2 (s, 2C, C_{Ar}), 128.8 (s, 2C, C_{Ar}), 128.2 (s, 2C, C_{Ar}), 114.5 (s, 2C, C_{Ar}), 55.4 (s, C₄), 45.5 (s, C₆), 42.5 (s, C₇).

4-oxo-4-phenyl-2-(4-(trifluoromethyl)phenyl)butanoic acid (II.6g)¹²⁷



MW: 322.0817 g.mol⁻¹

Molecular Formula: C₁₇H₁₃F₃O₃

The γ -ketoacid **II.6g** was synthesized from the α,β -unsaturated ketone **II.7g** (10 mmol, 1.0 equiv) followed the general procedure. **II.6g** (1.610 g, 50% in two steps) was isolated as a white solid.

Mp: 146–147 °C

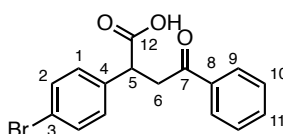
IR (neat): 1771, 1735, 1709, 1685, 1618, 1598, 1581, 1473, 1450, 1419, 1362, 1324, 1249, 1205, 1164, 1122, 1068, 1019, 993, 955, 909 cm⁻¹.

¹²⁷ Hino, K.; Nagai, Y.; Uno, H.; Masuda, Y.; Oka, M.; Karasawa, T. *J. Med. Chem.*, **1988**, 31, 107-117

¹H NMR (400 MHz, CDCl₃) δ 8.60 (s_{br}, 1H, -OH), 7.95 (d, *J* = 7.9 Hz, 2H, H_{Ar}), 7.63 – 7.56 (m, 3H, H_{Ar}), 7.51 – 7.44 (m, 4H, H_{Ar}), 4.40 (dd, *J* = 9.6, 4.5 Hz, 1H, H₆), 3.91 (dd, *J* = 18.1, 9.7 Hz, 1H, H₇), 3.33 (dd, *J* = 18.1, 4.5 Hz, 1H, H₇).

¹³C NMR (101 MHz, CDCl₃) δ 197.0 (s, C₈), 178.2 (s, C₁₃), 141.7 (s, C_{Ar}), 136.1 (s, C_{Ar}), 133.8 (s, C₁₂), 130.3 (d, *J* = 32.7 Hz, C₃), 128.9 (s, 2C, C_{Ar}), 128.6 (s, 2C, C_{Ar}), 128.2 (s, 2C, C_{Ar}), 126.1 (q, *J* = 3.8 Hz, 2C, C₂), 124.1 (q, *J* = 270.2 Hz, C₄), 46.2 (s, C₆), 42.1 (s, C₇).

2-(4-bromophenyl)-4-oxo-4-phenylbutanoic acid (II.6h)



MW: 332.0048 g.mol⁻¹

Molecular Formula: C₁₆H₁₃BrO₃

The γ-ketoacid **II.6h** was synthesized from the α,β-unsaturated ketone **II.7h** (10 mmol, 1.0 equiv) followed the general procedure. **II.6h** (1.328 g, 40% in two steps) was isolated as a white solid.

Mp: 154–155 °C

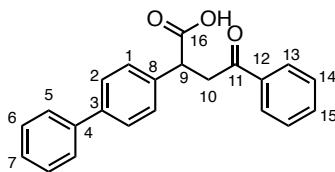
IR (neat): 1705, 1683, 1596, 1552, 1512, 1488, 1449, 1406, 1359, 1318, 1282, 1247, 1204, 1180, 1128, 1105, 1072, 1011, 1002, 993, 909 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 8.57 (s_{br}, 1H, -OH), 7.95 (d, *J* = 7.9 Hz, 2H, H_{Ar}), 7.63 – 7.56 (m, 3H, H_{Ar}), 7.52 – 7.44 (m, 4H, H_{Ar}), 4.40 (dd, *J* = 9.6, 4.5 Hz, 1H, H₅), 3.91 (dd, *J* = 18.1, 9.7 Hz, 1H, H₆), 3.33 (dd, *J* = 18.1, 4.5 Hz, 1H, H₆).

¹³C NMR (101 MHz, CDCl₃) δ 197.2 (s, C₇), 178.4 (s, C₁₂), 136.7 (s, C_{Ar}), 136.2 (s, C_{Ar}), 133.7 (s, C_{Ar}), 132.2 (s, 3C, C_{Ar}), 129.9 (s, 2C, C_{Ar}), 128.8 (s, 2C, C_{Ar}), 128.2 (s, 2C, C_{Ar}), 122.0 (s, C_{Ar}), 45.8 (s, C₅), 42.2 (s, C₆).

HRMS (ESI) *m/z*: calcd for C₁₆H₁₃BrO₃Na [M+Na]⁺: 354.9940 and 356.9920, found: 354.9946 and 356.9917.

2-([1,1'-biphenyl]-4-yl)-4-oxo-4-phenylbutanoic acid (II.6i)



MW: 330.1256 g.mol⁻¹

Molecular Formula: C₂₂H₁₈O₃

The γ -ketoacid **II.6i** was synthesized from the α,β -unsaturated ketone **II.7i** (10 mmol, 1.0 equiv) followed the general procedure. **II.6i** (1.585 g, 48% in two steps) was isolated as a white solid.

Mp: 145–147 °C.

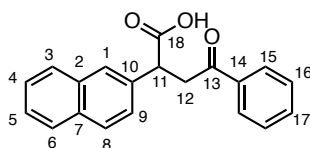
IR (neat): 3029, 1702, 1684, 1597, 1580, 1520, 1487, 1449, 1409, 1360, 1242, 1204, 1181, 1076, 992, 927 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.99 (d, J = 7.4 Hz, 2H, H_{Ar}), 7.59 – 7.56 (m, 5H, H_{Ar}), 7.48 – 7.42 (m, 6H, H_{Ar}), 7.35 (t, J = 7.6 Hz, 1H, H_{Ar}), 4.38 (dd, J = 10.0, 4.2 Hz, 1H, H₉), 3.96 (dd, J = 18.1, 10.0 Hz, 1H, H₁₀), 3.35 (dd, J = 18.1, 4.3 Hz, 1H, H₁₀).

¹³C NMR (101 MHz, CDCl₃) δ 197.5 (s, C₁₁), 178.7 (s, C₁₆), 141.0 (s, C_{Ar}), 140.7 (s, C_{Ar}), 136.8 (s, C_{Ar}), 136.4 (s, C_{Ar}), 133.6 (s, C_{Ar}), 128.9 (s, 2C, C_{Ar}), 128.8 (s, 2C, C_{Ar}), 128.6 (s, 2C, C_{Ar}), 128.3 (s, 2C, C_{Ar}), 127.9 (s, 2C, C_{Ar}), 127.2 (s, 3C, C_{Ar}), 46.1 (s, C₉), 42.4 (s, C₁₀).

HRMS (ESI) m/z : calcd for C₂₂H₁₈O₃H [M+H]⁺: 331.1329, found: 331.1332.

2-(naphthalen-2-yl)-4-oxo-4-phenylbutanoic acid (**II.6j**)



MW: 304.1099 g.mol⁻¹

Molecular Formula: C₂₀H₁₆O₃

The γ -ketoacid **II.6j** was synthesized from the α,β -unsaturated ketone **II.7j** (10 mmol, 1.0 equiv) followed the general procedure. **II.6j** (1.368 g, 46% in two steps) was isolated as a white solid.

Mp: 164–165 °C.

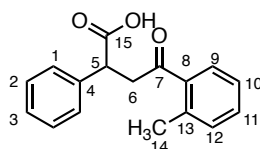
IR (neat): 3056, 1704, 1683, 1597, 1509, 1449, 1419, 1355, 1270, 1181, 992 cm^{-1} .

^1H NMR (400 MHz, CDCl_3) δ 8.01 – 7.94 (m, 2H, H_{Ar}), 7.84 – 7.81 (m, 4H, H_{Ar}), 7.56 (t, J = 7.4 Hz, 1H, H_{Ar}), 7.50 – 7.43 (m, 5H, H_{Ar}), 4.50 (dd, J = 9.9, 4.3 Hz, 1H, H_{11}), 4.01 (dd, J = 18.1, 9.9 Hz, 1H, H_{12}), 3.38 (dd, J = 18.1, 4.3 Hz, 1H, H_{12}).

^{13}C NMR (101 MHz, CDCl_3) δ 197.5 (s, C_{13}), 178.6 (s, C_{18}), 136.4 (s, C_{Ar}), 135.2 (s, C_{Ar}), 133.57 (s, C_{Ar}), 133.55 (s, C_{Ar}), 132.9 (s, C_{Ar}), 128.9 (s, C_{Ar}), 128.8 (s, 2C, C_{Ar}), 128.3 (s, 2C, C_{Ar}), 128.0 (s, C_{Ar}), 127.8 (s, C_{Ar}), 127.1 (s, C_{Ar}), 126.5 (s, C_{Ar}), 126.3 (s, C_{Ar}), 125.9 (s, C_{Ar}), 46.4 (s, C_{11}), 42.5 (s, C_{12}).

HRMS (ESI) m/z : calcd for $\text{C}_{20}\text{H}_{16}\text{O}_3\text{Na}$ [$\text{M}+\text{Na}$] $^+$: 305.1172, found: 305.1175.

4-oxo-2-phenyl-4-(*o*-tolyl)butanoic acid (**II.6k**)



MW: 268.1099 $\text{g}\cdot\text{mol}^{-1}$

Molecular Formula: $\text{C}_{17}\text{H}_{16}\text{O}_3$

The γ -ketoacid **II.6k** was synthesized from the α,β -unsaturated ketone **II.7k** (10 mmol, 1.0 equiv) followed the general procedure. **II.6k** (1.233 g, 46% in two steps) was isolated as a white solid.

Mp: 104–105 $^{\circ}\text{C}$

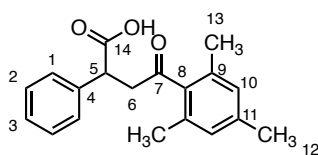
IR (neat): 3029, 1704, 1682, 1601, 1570, 1496, 1455, 1419, 1383, 1355, 1318, 1287, 1239, 1187, 1070, 1032, 979, 908 cm^{-1} .

^1H NMR (400 MHz, CDCl_3) δ 10.65 (s_{br} , 1H, -OH), 7.68 (d, J = 7.0 Hz, 1H, H_{Ar}), 7.43 – 7.20 (m, 8H, H_{Ar}), 4.32 (dd, J = 10.2, 4.4 Hz, 1H, H_5), 3.83 (dd, J = 17.9, 10.2 Hz, 1H, H_6), 3.22 (dd, J = 17.9, 4.4 Hz, 1H, H_6), 2.46 (s, 3H, H_{14}).

^{13}C NMR (101 MHz, CDCl_3) δ 201.3 (s, C_7), 179.4 (s, C_{15}), 138.6 (s, C_{Ar}), 137.7 (s, C_{Ar}), 137.2 (s, C_{Ar}), 132.1 (s, C_{Ar}), 131.7 (s, C_{Ar}), 129.1 (s, 2C, C_{Ar}), 128.7 (s, C_{Ar}), 128.1 (s, 2C, C_{Ar}), 127.9 (s, C_{Ar}), 125.8 (s, C_{Ar}), 46.7 (s, C_5), 45.0 (s, C_6), 21.4 (s, C_{14}).

HRMS (ESI) m/z : calcd for $\text{C}_{17}\text{H}_{16}\text{O}_3\text{H}$ [$\text{M}+\text{H}$] $^+$: 269.1172, found: 269.1172.

4-mesityl-4-oxo-2-phenylbutanoic acid (**II.6I**)



MW: 296.1412 g.mol⁻¹

Molecular Formula: C₁₉H₂₀O₃

The γ -ketoacid **II.6I** was synthesized from the α,β -unsaturated ketone **II.7I** (10 mmol, 1.0 equiv) followed the general procedure. **II.6I** (1.185 g, 40% in two steps) was isolated as a white solid.

Mp: 173–174 °C

IR (neat): 2918, 1699, 1611, 1495, 1455, 1423, 1389, 1358, 1325, 1294, 1238, 1208, 1183, 1152, 1068, 1032, 987, 910 cm⁻¹.

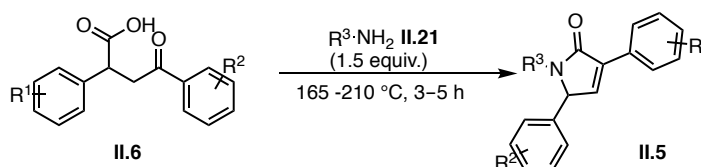
¹H NMR (400 MHz, CDCl₃) δ 7.40 – 7.25 (m, 5H, H_{Ar}), 6.81 (s, 2H, H₁₀), 4.30 (dd, J = 9.7, 4.4 Hz, 1H, H₅), 3.63 (dd, J = 19.1, 9.7 Hz, 1H, H₆), 3.05 (dd, J = 19.1, 4.4 Hz, 1H, H₆), 2.26 (s, 3H, H₁₂), 2.13 (s, 6H, H₁₃).

¹³C NMR (101 MHz, CDCl₃) δ 207.8 (s, C₇), 178.7 (s, C₁₄), 138.7 (s, C_{Ar}), 138.5 (s, C_{Ar}), 137.5 (s, C_{Ar}), 133.0 (s, C_{Ar}), 129.1 (s, 2C, C_{Ar}), 128.6 (s, 2C, C_{Ar}), 128.2 (s, 2C, C_{Ar}), 128.0 (s, C_{Ar}), 48.2 (s, C₆), 45.8 (s, C₅), 21.2 (s, C₁₂), 19.0 (s, 3C, C₁₃).

HRMS (ESI) m/z : calcd for C₁₉H₂₀O₃H [M+H]⁺: 297.1485, found: 297.1482.

4. Synthesis of α,γ -disubstituted- α,β -unsaturated lactams

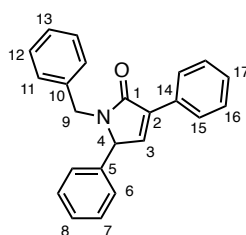
General Procedure for synthesis the α,β -unsaturated lactams **II.5a-o:**



The γ -ketoacid substrate **II.6a** (1.27 g, 5 mmol, 1.0 equiv) and benzylamine **II.21a** (0.874 mL, 8 mmol, 1.5 equiv) were added to a flamed dried 50 mL round bottom flask, the mixture was refluxed at 165 °C for 3 h. After the reaction completely finished, the mixture was cooled to rt, extracted with EtOAc (2 $\times$ 30 mL) and washed with brine (25

mL), dried through Na_2SO_4 and concentrated in vacuo to give the crude residue. The crude residue was purified by the flash column chromatography on silica gel ($\text{EtOAc/PE} = 1:10$ to $1:5$) to afford the α , β -unsaturated lactam **II.5a** (1.219 g, 75%) as a white solid.

1-Benzyl-3,5-diphenyl-1,5-dihydro-2H-pyrrol-2-one (II.5a)



MW: 325.1467 $\text{g}\cdot\text{mol}^{-1}$

Molecular Formula: $\text{C}_{23}\text{H}_{19}\text{NO}$

Mp: 121–122 $^{\circ}\text{C}$.

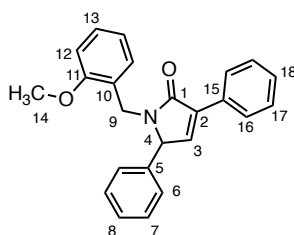
IR (neat): 1681, 1601, 1492, 1454, 1401, 1358, 1078, 1001, 940 cm^{-1} .

^1H NMR (400 MHz, CDCl_3) δ 8.02 – 7.95 (m, 2H, H_{Ar}), 7.45 – 7.26 (m, 9H, H_{Ar}), 7.20 – 7.12 (m, 5H, H_{Ar} and H_3), 5.29 (d, $J_{\text{AB}} = 14.9$ Hz, 1H, H_9), 4.91 (d, $J = 2.1$ Hz, 1H, H_4), 3.70 (d, $J_{\text{AB}} = 14.9$ Hz, 1H, H_9).

^{13}C NMR (101 MHz, CDCl_3) δ 170.2 (s, C_1), 140.9 (s, C_3), 137.5 (s, C_{Ar}), 135.3 (s, C_2), 135.2 (s, C_{Ar}), 131.6 (s, C_{Ar}), 129.3 (s, 2C, C_{Ar}), 128.88 (s, C_{Ar}), 128.86 (s, C_{Ar}), 128.82 (s, 2C, C_{Ar}), 128.6 (s, 2C, C_{Ar}), 128.5 (s, 2C, C_{Ar}), 127.8 (s, 2C, C_{Ar}), 127.6 (s, C_{Ar}), 127.4 (s, 2C, C_{Ar}), 63.4 (s, C_4), 44.0 (s, C_9).

HRMS (ESI) m/z : calculated for $\text{C}_{29}\text{H}_{33}\text{NOSiNa}$ $[\text{M}+\text{Na}]^+$: 348.1359, found: 348.1362.

1-(2-Methoxybenzyl)-3,5-diphenyl-1,5-dihydro-2H-pyrrol-2-one (II.5b)



MW: 355.1572 $\text{g}\cdot\text{mol}^{-1}$

Molecular Formula: $\text{C}_{24}\text{H}_{21}\text{NO}_2$

Compound **II.5b** was synthesized from the corresponding carboxylic acid **II.6a** (5 mmol, 1.0 equiv) and 2-methoxybenzylamine **II.21b** (8 mmol, 1.5 equiv) followed the general procedure. The α,β -unsaturated lactam **II.5b** (0.888 g, 50%) was isolated as a colourless oil.

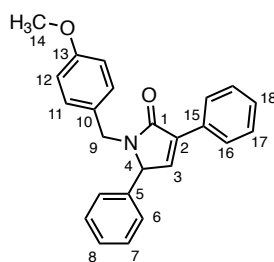
IR (neat): 1681, 1601, 1492, 1438, 1362, 1290, 1076, 1002, 755, 697.

^1H NMR (400 MHz, CDCl_3) δ 7.96 (d, $J = 7.4$ Hz, 2H, H_{Ar}), 7.42 – 7.32 (m, 6H, H_{Ar}), 7.24 – 7.21 (m, 2H, H_{Ar}), 7.16 – 7.14 (m, 3H, H_3 and H_{Ar}), 6.89 (t, $J = 7.5$ Hz, 1H, H_{Ar}), 6.83 (d, $J = 8.1$ Hz, 1H, H_{Ar}), 5.05 – 5.02 (m, 2H, H_4 and H_9), 4.04 (d, $J_{\text{AB}} = 15.1$ Hz, 1H, H_9), 3.74 (s, 3H, H_{14}).

^{13}C NMR (101 MHz, CDCl_3) δ 170.4 (s, C_1), 157.5 (s, C_{15}), 141.1 (s, C_3), 135.7 (s, C_{Ar}), 135.1 (s, C_2), 131.7 (s, C_{Ar}), 130.5 (s, C_{Ar}), 129.1 (s, 2C, C_{Ar}), 128.9 (s, C_{Ar}), 128.7 (s, C_{Ar}), 128.59 (s, C_{Ar}), 128.56 (s, 2C, C_{Ar}), 127.6 (s, 2C, C_{Ar}), 127.3 (s, 2C, C_{Ar}), 125.6 (s, C_{Ar}), 120.7 (s, C_{Ar}), 110.4 (s, C_{Ar}), 64.1 (s, C_4), 55.3 (s, C_{16}), 39.1 (s, C_9).

HRMS (ESI) m/z : calculated for $\text{C}_{24}\text{H}_{21}\text{NO}_2\text{Na}$ $[\text{M}+\text{Na}]^+$: 378.1464, found: 378.1472.

1-(4-Methoxybenzyl)-3,5-diphenyl-1,5-dihydro-2H-pyrrol-2-one (**II.5c**)



MW: 355.1572 $\text{g}\cdot\text{mol}^{-1}$

Molecular Formula: $\text{C}_{24}\text{H}_{21}\text{NO}$

Compound **II.5c** was synthesized from the corresponding carboxylic acid **II.6a** (5 mmol, 1.0 equiv) and 4-methoxybenzylamine **II.21c** (8 mmol, 1.5 equiv) followed the general procedure. The α,β -unsaturated lactam **II.5c** (0.977 g, 55%) was isolated as a yellow solid.

Mp: 108–109 $^{\circ}\text{C}$.

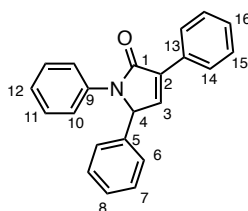
IR (neat): 1682, 1541, 1512, 1288, 1202, 1001, 868, 757, 697 cm^{-1} .

¹H NMR (400 MHz, CDCl₃) δ 7.97 (d, *J* = 8.0 Hz, 2H, H_{Ar}), 7.43 – 7.34 (m, 6H, H_{Ar}), 7.14 – 7.09 (m, 5H, H_{Ar} and H₃), 6.83 (d, *J* = 8.4 Hz, 2H, H_{Ar}), 5.22 (d, *J*_{AB} = 14.7 Hz, 1H, H₉), 4.88 (d, *J* = 2.1 Hz, 1H, H₄), 3.79 (s, 3H, H₁₄), 3.63 (d, *J*_{AB} = 14.5 Hz, 1H, H₉).

¹³C NMR (101 MHz, CDCl₃) δ 170.1 (s, C₁), 159.1 (s, C₁₃), 140.9 (s, C₃), 135.3 (s, C₂), 135.2 (s, C_{Ar}), 131.6 (s, C_{Ar}), 129.9 (s, 2C, C_{Ar}), 129.7 (s, C_{Ar}), 129.3 (s, 2C, C_{Ar}), 128.8 (s, 2C, C_{Ar}), 128.6 (s, 2C, C_{Ar}), 127.8 (s, 2C, C_{Ar}), 127.3 (s, 2C, C_{Ar}), 114.2 (s, 2C, C₁₂), 63.3 (s, C₄), 55.4 (s, C₁₄), 43.4 (s, C₉).

HRMS (ESI) *m/z*: calculated for C₂₄H₂₁NO₂Na [M+Na]⁺: 378.1465, found: 378.1470

1,3,5-Triphenyl-1,5-dihydro-2*H*-pyrrol-2-one (II.5d)



MW: 311.1310 g.mol⁻¹

Molecular Formula: C₂₂H₁₇NO

Compound **II.5d** was synthesized from the corresponding carboxylic acid **II.6a** (5 mmol, 1.0 equiv) and aniline **II.21d** (8 mmol, 1.5 equiv) followed the general procedure at 200 °C. The α,β-unsaturated lactam **II.5d** (0.809 g, 52%) was isolated as a yellow solid.

Mp: 183–185 °C.

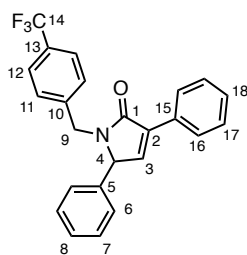
IR (neat): 1684, 1598, 1492, 1455, 1368, 1323, 1302, 1258, 1176, 1116, 1076, 1029, 1002, 980, 909 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.96 (d, *J* = 7.6 Hz, 2H, H_{Ar}), 7.59 (d, *J* = 7.9 Hz, 2H, H_{Ar}), 7.46 – 7.37 (m, 3H, H_{Ar}), 7.35 – 7.24 (m, 8H, H₃ and H_{Ar}), 7.09 (t, *J* = 7.5 Hz, 1H, H_{Ar}), 5.73 (d, *J* = 2.3 Hz, 1H, H₄).

¹³C NMR (101 MHz, CDCl₃) δ 169.5 (s, C₁), 141.3 (s, C₃), 137.7 (s, C_{Ar}), 135.7 (s, C_{Ar}), 135.1 (s, C_{Ar}), 131.3 (s, C_{Ar}), 129.3 (s, 2C, C_{Ar}), 129.00 (s, C_{Ar}), 128.98 (s, 2C, C_{Ar}), 128.6 (s, 2C, C_{Ar}), 128.6 (s, C_{Ar}), 127.5 (s, 2C, C_{Ar}), 127.0 (s, 2C, C_{Ar}), 124.8 (s, C_{Ar}), 121.8 (s, 2C, C_{Ar}), 64.9 (s, C₄).

HRMS (ESI) *m/z*: calculated for C₂₂H₁₇NONa [M+Na]⁺: 334.1202, found: 334.1204.

3,5-Diphenyl-1-(4-(trifluoromethyl)benzyl)-1,5-dihydro-2H-pyrrol-2-one (II.5e)



MW: 393.1340 g.mol⁻¹

Molecular Formula: C₂₄H₁₈F₃NO

Compound **II.5e** was synthesized from the corresponding carboxylic acid **II.6a** (5 mmol, 1.0 equiv) and 4-(trifluoromethyl)benzylamine **II.21e** (8 mmol, 1.5 equiv) followed the general procedure. The α,β -unsaturated lactam **II.5e** (1.277 g, 65%) was isolated as a yellow solid.

Mp: 121–122 °C.

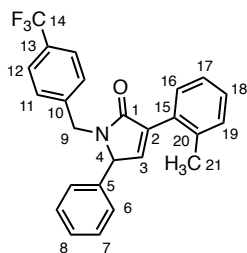
IR (neat): 1690, 1686, 1620, 1597, 1492, 1447, 1400, 1361, 1323, 1164, 1122, 1066, 1018, 967, 911 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.97 (d, J = 7.1 Hz, 2H, H_{Ar}), 7.55 (d, J = 8.0 Hz, 2H, H_{Ar}), 7.45 – 7.36 (m, 6H, H_{Ar}), 7.28 (d, J = 8.0 Hz, 2H, H_{Ar}), 7.19 (d, J = 2.2 Hz, 1H, H₃), 7.11 (dd, J = 6.7, 2.9 Hz, 2H, H_{Ar}), 5.24 (d, J_{AB} = 15.1 Hz, 1H, H₉), 4.90 (d, J = 2.1 Hz, 1H, H₄), 3.83 (d, J_{AB} = 15.2 Hz, 1H, H₉).

¹³C NMR (101 MHz, CDCl₃) δ 170.3 (s, C₁), 141.6 (s, C₂), 141.0 (s, C₃), 135.3 (s, C₉), 134.8 (s, C_{Ar}), 131.3 (s, C_{Ar}), 129.9 (d, J = 32.2 Hz, C₁₄), 129.4 (s, 2C, C_{Ar}), 129.1 (s, C_{Ar}), 129.0 (s, C_{Ar}), 128.74 (s, 2C, C_{Ar}), 128.68 (s, 2C, C_{Ar}), 127.8 (s, 2C, C_{Ar}), 127.3, (s, 2C, C_{Ar}) 125.8 (q, J = 3.7 Hz, 2C, C₁₂), 124.2 (d, J = 273.04 Hz, C₁₃), 63.7 (s, C₄), 43.7 (s, C₉)

HRMS (ESI) m/z : calculated for C₂₄H₁₈F₃NONa [M+Na]⁺: 416.1233, found: 416.1231.

5-Phenyl-3-(*o*-tolyl)-1-(4-(trifluoromethyl)benzyl)-1,5-dihydro-2H-pyrrol-2-one (II.5f)



MW: 407.1497 g.mol⁻¹

Molecular Formula: C₂₅H₂₀F₃NO

Compound **II.5f** was synthesized from the corresponding carboxylic acid **II.6b** (5 mmol, 1.0 equiv) and 4-(trifluoromethyl)benzylamine **II.21e** (8 mmol, 1.5 equiv) followed the general procedure. The α,β -unsaturated lactam **II.5f** (1.038 g, 51%) was isolated as a yellow solid.

Mp: 141–142 °C

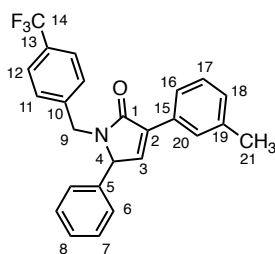
IR (neat): 1687, 1620, 1491, 1456, 1399, 1324, 1215, 1164, 1122, 1067, 1019, 938 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.56 (d, J = 8.0 Hz, 2H), 7.45 (d, J = 7.0 Hz, 1H), 7.41 – 7.38 (m, 3H), 7.30 – 7.23 (m, 5H), 7.15 – 7.13 (m, 2H), 6.96 (d, J = 1.9 Hz, 1H), 5.21 (d, J = 15.1 Hz, 1H), 4.94 (d, J = 1.8 Hz, 1H), 3.84 (d, J = 15.1 Hz, 1H), 2.40 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 170.4 (s, C₁), 144.1 (s, C₃), 141.7 (s, C₂), 137.6 (s, C_{Ar}), 136.8 (s, C_{Ar}), 134.8 (s, C_{Ar}), 131.2 (s, C_{Ar}), 130.6 (s, C_{Ar}), 130.0 (d, J = 32.2 Hz, C₁₄), 129.9 (s, C_{Ar}), 129.5 (s, 2C, C_{Ar}), 129.1 (s, C_{Ar}), 128.78 (s, 2C, C_{Ar}), 128.76 (s, C_{Ar}), 127.7 (s, 2C, C_{Ar}), 125.9 (s, C_{Ar}), 125.8 (q, J = 3.6 Hz, 2C, C₁₂), 124.2 (d, J = 273.4 Hz, C₁₃), 64.2 (s, C₄), 43.9 (s, C₉), 20.8 (s, C₂₁).

HRMS (ESI) m/z : calculated for C₂₅H₂₀F₃NONa [M+Na]⁺: 430.1389, found: 430.1384.

5-Phenyl-3-(*m*-tolyl)-1-(4-(trifluoromethyl)benzyl)-1,5-dihydro-2H-pyrrol-2-one
(II.5g)



MW: 407.1497 g.mol⁻¹

Molecular Formula: C₂₅H₂₀F₃NO

Compound **II.5g** was synthesized from the corresponding carboxylic acid **II.6c** (5 mmol, 1.0 equiv) and 4-(trifluoromethyl)benzylamine **II.21e** (8 mmol, 1.5 equiv) followed the

general procedure. The α,β -unsaturated lactam **II.5g** (1.058 g, 52%) was isolated as a white solid.

Mp: 151–152 °C.

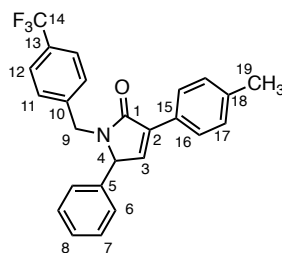
IR (neat): 1685, 1619, 1492, 1455, 1421, 1400, 1323, 1249, 1162, 1122, 1066, 1019, 1002, 960 cm^{-1} .

^1H NMR (400 MHz, CDCl_3) δ 7.82 (s, 1H, H_{Ar}), 7.74 (d, $J = 7.7$ Hz, 1H, H_{Ar}), 7.55 (d, $J = 8.0$ Hz, 2H, H_{Ar}), 7.38 – 7.27 (m, 6H, H_{Ar}), 7.19 (d, $J = 7.6$ Hz, 1H, H_3), 7.17 (d, $J = 1.6$ Hz, 1H, H_{Ar}), 7.12 – 7.10 (m, 2H, H_{Ar}), 5.23 (d, $J = 15.2$ Hz, 1H, H_9), 4.89 (s, 1H, H_4), 3.83 (d, $J = 15.2$ Hz, 1H, H_9), 2.40 (s, 3H, H_{21}).

^{13}C NMR (101 MHz, CDCl_3) δ 170.4 (s, C_1), 141.6 (s, C_2), 140.9 (s, C_3), 138.3 (s, C_{Ar}), 135.4 (s, C_{Ar}), 134.9 (s, C_{Ar}), 131.2 (s, C_{Ar}), 130.0 (d, $J = 31.9$ Hz, C_{14}), 129.8 (s, C_{Ar}), 129.4 (s, 2C, C_{Ar}), 129.1 (s, C_{Ar}), 128.7 (s, 2C, C_{Ar}), 128.6 (s, C_{Ar}), 128.0 (s, C_{Ar}), 127.8 (s, 2C, C_{Ar}), 125.8 (q, $J = 3.8$ Hz, 2C, C_{12}), 124.4 (s, C_{Ar}), 124.2 (d, $J = 270.3$ Hz, C_{13}), 63.7 (s, C_4), 43.8 (s, C_9), 21.6 (s, C_{21}).

HRMS (ESI) m/z : calculated for $\text{C}_{25}\text{H}_{20}\text{F}_3\text{NOH}$ $[\text{M}+\text{H}]^+$: 408.1570, found: 408.1566.

5-Phenyl-3-(*p*-tolyl)-1-(4-(trifluoromethyl)benzyl)-1,5-dihydro-2*H*-pyrrol-2-one (II.5h)



MW: 407.1497 $\text{g}\cdot\text{mol}^{-1}$

Molecular Formula: $\text{C}_{25}\text{H}_{20}\text{F}_3\text{NO}$

Compound **II.5h** was synthesized from the corresponding carboxylic acid **II.6d** (5 mmol, 1.0 equiv) and 4-(trifluoromethyl)benzylamine **II.21e** (8 mmol, 1.5 equiv) followed the general procedure. The α,β -unsaturated lactam **II.5h** (1.221 g, 60%) was isolated as a white solid.

Mp: 120–122 °C.

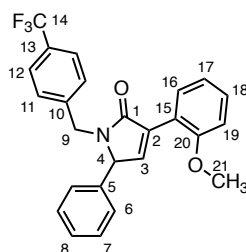
IR (neat): 1683, 1619, 1511, 1492, 1455, 1399, 1322, 1162, 1121, 1111, 1066, 1018, 1002, 938, 910 cm^{-1} .

^1H NMR (400 MHz, CDCl_3) δ 7.88 (d, J = 8.2 Hz, 2H, H_{Ar}), 7.55 (d, J = 8.1 Hz, 2H, H_{Ar}), 7.39 – 7.36 (m, 3H, H_{Ar}), 7.28 (d, J = 8.0 Hz, 2H, H_{Ar}), 7.23 (d, J = 8.0 Hz, 2H, H_{Ar}), 7.14 (d, J = 2.2 Hz, 1H, H_3), 7.12 – 7.10 (m, 2H, H_{Ar}), 5.23 (d, J_{AB} = 15.1 Hz, 1H, H_9), 4.88 (d, J = 2.1 Hz, 1H, H_4), 3.83 (d, J_{AB} = 15.2 Hz, 1H, H_9), 2.39 (s, 3H, H_{19}).

^{13}C NMR (101 MHz, CDCl_3) δ 170.4 (s, C_1), 141.6 (s, C_2), 140.0 (s, C_3), 139.0 (s, C_{Ar}), 135.1 (s, C_{Ar}), 134.9 (s, C_{Ar}), 129.9 (d, J = 32.6 Hz, C_{14}), 129.4 (s, 4C, C_{Ar}), 129.0 (s, C_{Ar}), 128.7 (s, 2C, C_{Ar}), 128.5 (s, C_{Ar}), 127.8 (s, 2C, C_{Ar}), 127.2 (s, 2C, C_{Ar}), 125.8 (q, J = 3.8 Hz, 2C, C_{12}), 124.2 (d, J = 271.9 Hz, C_{13}), 63.6 (s, C_4), 43.7 (s, C_9), 21.5 (s, C_{19}).

HRMS (ESI) m/z : calculated for $\text{C}_{25}\text{H}_{20}\text{F}_3\text{NOH}$ $[\text{M}+\text{H}]^+$: 408.1570, found: 408.1563.

3-(2-Methoxyphenyl)-5-phenyl-1-(4-(trifluoromethyl)benzyl)-1,5-dihydro-2H pyrrol-2-one (II.5i)



MW: 423.1446 $\text{g}\cdot\text{mol}^{-1}$

Molecular Formula: $\text{C}_{25}\text{H}_{20}\text{F}_3\text{NO}_2$

Compound **II.5i** was synthesized from the corresponding carboxylic acid **II.6e** (5 mmol, 1.0 equiv) and 4-(trifluoromethyl)benzylamine **II.21e** (8 mmol, 1.5 equiv) followed the general procedure. The α,β -unsaturated lactam **II.5i** (1.037 g, 49%) was isolated as a yellow solid.

Mp: 122–124 $^{\circ}\text{C}$.

IR (neat): 1679, 1619, 1598, 1577, 1492, 1455, 1434, 1422, 1400, 1322, 1291, 1249, 1214, 1199, 1161, 1120, 1110, 1066, 1019, 940, 909 cm^{-1} .

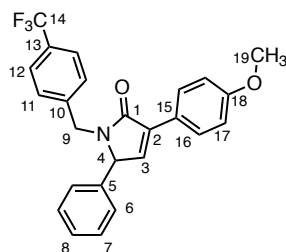
^1H NMR (400 MHz, CDCl_3) δ 8.40 (d, J = 7.8 Hz, 1H, H_{Ar}), 7.56 – 7.54 (m, 3H, H_3 and H_{Ar}), 7.38 – 7.28 (m, 6H, H_{Ar}), 7.15 – 7.10 (m, 2H, H_{Ar}), 7.08 (t, J = 7.6 Hz, 1H, H_{Ar}), 6.96 (d, J

= 8.5 Hz, 1H, H_{Ar}), 5.24 (d, J_{AB} = 15.2 Hz, 1H, H₉), 4.93 (s, 1H, H₄), 3.84 (d, J_{AB} = 15.6 Hz, 1H, H₉), 3.84 (s, 3H, H₂₁).

¹³C NMR (101 MHz, CDCl₃) δ 171.0 (s, C₁), 158.0 (s, C₂₀), 145.0 (s, C₃), 141.8 (s, C₂), 135.2 (s, C_{Ar}), 130.6 (s, C_{Ar}), 130.2 (s, C_{Ar}), 129.8 (d, J = 32.7 Hz, C₁₄), 129.7 (s, C_{Ar}), 129.3 (s, 2C, C_{Ar}), 128.9 (s, C_{Ar}), 128.7 (s, 2C, C_{Ar}), 127.8 (s, 2C, C_{Ar}), 125.7 (q, J = 3.8 Hz, 2C, C₁₂), 124.2 (d, J = 272.3 Hz, C₁₃), 120.6 (s, C_{Ar}), 120.2 (s, C_{Ar}), 110.8 (s, C_{Ar}), 63.9 (s, C₄), 55.5 (s, C₉), 43.7 (s, C₂₁)

HRMS (ESI) m/z : calculated for C₂₅H₂₀F₃NO₂Na [M+Na]⁺: 446.1338, found: 446.1336.

3-(4-Methoxyphenyl)-5-phenyl-1-(4-(trifluoromethyl)benzyl)-1,5-dihydro-2H pyrrol-2-one (II.5j)



MW: 423.1446 g.mol⁻¹

Molecular Formula: C₂₅H₂₀F₃NO₂

Compound **II.5j** was synthesized from the corresponding carboxylic acid **II.6f** (5 mmol, 1.0 equiv) and 4-(trifluoromethyl)benzylamine **II.21e** (8 mmol, 1.5 equiv) followed the general procedure. The α,β -unsaturated lactam **II.5j** (1.058 g, 50%) was isolated as a white solid.

Mp: 104–106 °C.

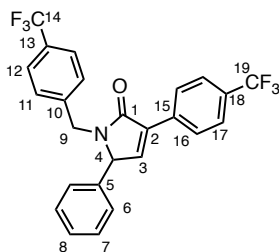
IR (neat): 1682, 1619, 1606, 1510, 1493, 1456, 1441, 1420, 1323, 1252, 1178, 1163, 1111, 1066, 1030, 1019, 940, 914 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.96 (d, J = 8.7 Hz, 2H), 7.55 (d, J = 8.0 Hz, 2H), 7.38 – 7.37 (m, 3H), 7.28 (d, J = 8.7 Hz, 2H), 7.13 – 7.08 (m, 3H), 6.96 (d, J = 8.7 Hz, 2H), 5.23 (d, J = 15.1 Hz, 1H), 4.88 (d, J = 2.1 Hz, 1H), 3.76 (s, 3H), 3.83 (d, J = 16.8 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃) δ 170.6 (s, C₁), 160.2 (s, C₁₈), 141.6 (s, C₂), 138.8 (s, C₃), 135.0 (s, C_{Ar}), 134.6 (s, C_{Ar}), 129.9 (d, J = 32.4 Hz, C₁₄), 129.4 (s, 2C, C_{Ar}), 129.0 (s, C_{Ar}),

128.7 (s, 2C, C_{Ar}), 128.6 (s, 2C, C_{Ar}), 127.8 (s, 2C, C_{Ar}), 125.8 (q, *J* = 3.8 Hz, 2C, C₁₂), 124.2 (d, *J* = 273.4 Hz, C₁₃), 124.0 (s, C₁), 114.1 (s, 2C, C₁), 63.6 (s, C₁), 55.4 (s, C₁), 43.7 (s, C₁).
HRMS (ESI) *m/z*: calculated for C₂₅H₂₀F₃NO₂Na [M+Na]⁺: 446.1338, found: 446.1338.

5-Phenyl-1-(4-(trifluoromethyl)benzyl)-3-(4-(trifluoromethyl)phenyl)-1,5-dihydro-2*H*-pyrrol-2-one (II.5k)



MW: 461.1214 g.mol⁻¹

Molecular Formula: C₂₅H₁₇F₆NO

Compound **II.5k** was synthesized from the corresponding carboxylic acid **II.6g** (5 mmol, 1.0 equiv) and 4-(trifluoromethyl)benzylamine **II.21e** (8 mmol, 1.5 equiv) followed the general procedure. The α,β -unsaturated lactam **II.5k** (1.383 g, 60%) was isolated as a green oil.

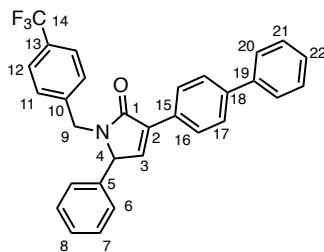
IR (neat): 1685, 1619, 1493, 1456, 1402, 1321, 1259, 1217, 1163, 1109, 1067, 1018, 940, 911 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 8.10 (d, *J* = 8.1 Hz, 2H, H_{Ar}), 7.67 (d, *J* = 8.2 Hz, 2H, H_{Ar}), 7.56 (d, *J* = 8.0 Hz, 2H, H_{Ar}), 7.40 – 7.39 (m, 3H, H₃ and H_{Ar}), 7.30 – 7.27 (m, 3H, H_{Ar}), 7.13 – 7.11 (m, 2H, H_{Ar}), 5.24 (d, *J*_{AB} = 15.1 Hz, 1H, H₉), 4.94 (d, *J* = 2.0 Hz, 1H, H₄), 3.85 (d, *J*_{AB} = 15.2 Hz, 1H, H₉).

¹³C NMR (101 MHz, CDCl₃) δ 169.7 (s, C₁), 142.8 (s, 2C, C₂ and C₃), 141.3 (s, C₂), 134.7 (s, C_{Ar}), 134.2 (s, C_{Ar}), 130.8 (d, *J* = 32.5 Hz, C₁₄ or C₁₉), 130.1 (d, *J* = 32.5 Hz, C₁₄ or C₁₉), 129.5 (s, 2C, C_{Ar}), 129.3 (s, C_{Ar}), 128.8 (s, 2C, C_{Ar}), 127.7 (s, 2C, C_{Ar}), 127.6 (s, 2C, C_{Ar}), 125.8 (q, *J* = 3.7 Hz, 2C, C₁₂ or C₁₇), 125.6 (q, *J* = 3.7 Hz, 2C, C₁₂ or C₁₇), 124.18 (d, *J* = 272.3 Hz, C₁₃ or C₁₈), 124.17 (d, *J* = 275.1 Hz, C₁₈ or C₁₃), 63.8 (s, C₄), 43.8 (s, C₉)

HRMS (ESI) *m/z*: calculated for C₂₅H₁₇F₆NOH [M+H]⁺: 462.1287, found: 462.1291.

**3-([1,1'-Biphenyl]-4-yl)-5-phenyl-1-(4-(trifluoromethyl)benzyl)-1,5-dihydro-2H
pyrrol-2-one (II.5m)**



MW: 469.1653 g.mol⁻¹

Molecular Formula: C₃₀H₂₂F₃NO

Compound **II.5m** was synthesized from the corresponding carboxylic acid **II.6i** (5 mmol, 1.0 equiv) and 4-(trifluoromethyl)benzylamine **II.21e** (8 mmol, 1.5 equiv) followed the general procedure. The α,β -unsaturated lactam **II.5m** (1.290 g, 55%) was isolated as a yellow solid.

Mp: 177–178 °C.

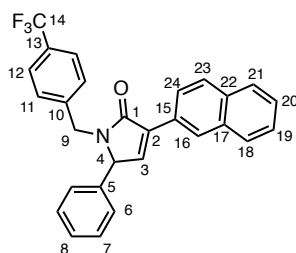
IR (neat): 3065, 3030, 1684, 1619, 1600, 1487, 1455, 1399, 1216, 1162, 1120, 1111, 1066, 1018, 1008, 969, 939 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 8.06 (d, J = 8.4 Hz, 2H, H_{Ar}), 7.67 (d, J = 8.4 Hz, 2H, H_{Ar}), 7.65 – 7.61 (m, 2H, H_{Ar}), 7.56 (d, J = 8.0 Hz, 2H, H_{Ar}), 7.46 (t, J = 7.6 Hz, 2H, H_{Ar}), 7.40 – 7.35 (m, 4H, H_{Ar}), 7.29 (d, J = 8.0 Hz, 2H, H_{Ar}), 7.23 (d, J = 2.2 Hz, 1H, H_{Ar}), 7.14 – 7.11 (m, 2H, H_{Ar} and H₃), 5.26 (d, J_{AB} = 15.2 Hz, 1H, H₉), 4.92 (d, J = 2.1 Hz, 1H, H₄), 3.84 (d, J_{AB} = 15.2 Hz, 1H, H₉).

¹³C NMR (101 MHz, CDCl₃) δ 170.3 (s, C₁), 141.7 (s, C_{Ar}), 141.6 (s, C_{Ar}), 140.8 (s, C₃), 140.7 (s, C_{Ar}), 134.9 (s, C_{Ar}), 134.8 (s, C_{Ar}), 130.3 (s, C_{Ar}), 130.0 (d, J = 32.8 Hz, C₁₄), 129.4 (s, 2C, C_{Ar}), 129.1 (s, C_{Ar}), 129.0 (s, 2C, C_{Ar}), 128.8 (s, 2C, C_{Ar}), 127.8 (s, 2C, C_{Ar}), 127.74 (s, 2C, C_{Ar}), 127.7 (s, C_{Ar}), 127.4 (s, 2C, C_{Ar}), 127.2 (s, 2C, C_{Ar}), 125.8 (q, J = 3.8 Hz, 2C, C₁₂), 124.2 (d, J = 272.2 Hz, C₁₃), 63.7 (s, C₄), 43.8 (s, C₉).

HRMS (ESI) m/z : calculated for C₃₀H₂₂F₃NOH [M+H]⁺: 470.1726, found: 470.1730.

**3-(naphthalen-2-yl)-5-phenyl-1-(4-(trifluoromethyl)benzyl)-1,5-dihydro-2H-pyrrol-
2-one (II.5n)**



MW: 443.1497 g.mol⁻¹

Molecular Formula: C₂₈H₂₀F₃NO

Compound **II.5n** was synthesized from the corresponding carboxylic acid **II.6j** (5 mmol, 1.0 equiv) and 4-(trifluoromethyl)benzylamine **II.21e** (8 mmol, 1.5 equiv.) followed the the general procedure. The α,β -unsaturated lactam **II.5n** (1.352 g, 61%) was isolated as a yellow solid.

Mp: 170–171 °C.

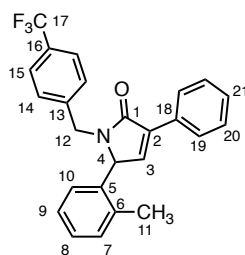
IR (neat): 3059, 2918, 1686, 1619, 1455, 1421, 1401, 1324, 1270, 1215, 1163, 1122, 1067, 1019, 1002, 967, 930 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 8.80 (s, 1H, H_{Ar}), 7.95 – 7.93 (m, 1H, H_{Ar}), 7.85 – 7.82 (m, 3H, H_{Ar}), 7.57 (d, J = 8.1 Hz, 2H, H_{Ar}), 7.53 – 7.48 (m, 2H, H_{Ar}), 7.41 – 7.38 (m, 3H, H_{Ar}), 7.32 – 7.30 (m, 3H, H_{Ar}), 7.16 – 7.14 (m, 2H, H_{Ar} and H₃), 5.28 (d, J = 15.2 Hz, 1H, H₉), 4.95 (d, J = 2.1 Hz, 1H, H₄), 3.87 (d, J = 15.2 Hz, 1H, H₉).

¹³C NMR (101 MHz, CDCl₃) δ 170.4 (s, C₁), 141.6 (s, C₂), 141.1 (s, C₃), 134.9 (s, C_{Ar}), 134.8 (s, C_{Ar}), 133.49 (s, C_{Ar}), 133.46 (s, C_{Ar}), 130.0 (d, J = 32.4 Hz, C₁₄), 129.5 (s, 2C, C_{Ar}), 129.1 (s, C_{Ar}), 129.0 (s, C_{Ar}), 128.8 (s, 2C, C_{Ar}), 128.5 (s, C_{Ar}), 128.3 (s, C_{Ar}), 127.8 (2C, C_{Ar}), 127.7 (s, C_{Ar}), 127.1 (s, C_{Ar}), 126.8 (s, C_{Ar}), 126.5 (s, C_{Ar}), 125.8 (q, J = 3.5 Hz, 2C, C₁₂), 124.5 (s, C_{Ar}), 124.2 (d, J = 273.0 Hz, C₁₃), 63.8 (s, C₄), 43.8 (s, C₉).

HRMS (ESI) m/z : calculated for C₂₈H₂₀F₃NOH [M+H]⁺: 444.1570, found: 444.1571.

1-Phenyl-5-(*o*-tolyl)-1-(4-(trifluoromethyl)benzyl)-1,5-dihydro-2*H*-pyrrol-2-one
(**II.5o**)



MW: 407.1497 g.mol⁻¹

Molecular Formula: C₂₅H₂₀F₃NO

Compound **II.5o** was synthesized from the corresponding carboxylic acid **II.6k** (5 mmol, 1.0 equiv) and 4-(trifluoromethyl)benzylamine **II.21e** (8 mmol, 1.5 equiv) followed the the general procedure. The α,β -unsaturated lactam **II.5o** (1.832 g, 90%) was isolated as yellow oil.

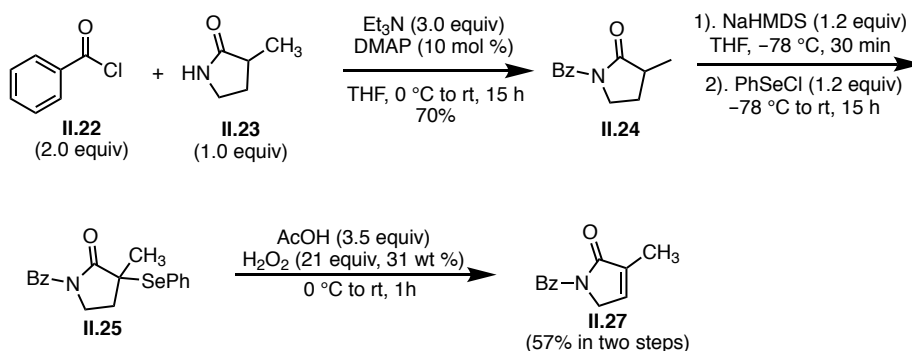
IR (neat): 1681, 1619, 1491, 1400, 1323, 1286, 1262, 1161, 1121, 1110, 1066, 1018, 939.7, 909.1 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.88 – 7.86 (m, 2H, H_{Ar}), 7.46 (d, J = 8.1 Hz, 2H, H_{Ar}), 7.35 – 7.25 (m, 3H, H_{Ar}), 7.18 – 7.09 (m, 6H, H_{Ar} and H₃), 6.87 (d, J = 7.1 Hz, 1H, H_{Ar}), 5.20 (d, J_{AB} = 15.1 Hz, 1H, H₁₂), 5.09 (s, 1H, H₄), 3.73 (d, J_{AB} = 15.1 Hz, 1H, H₁₂), 2.10 (s, 3H, H₁₁).

¹³C NMR (101 MHz, CDCl₃) δ 170.6 (s, C₁), 141.5 (s, C_{Ar}), 140.6 (s, C_{Ar}), 136.6 (s, C_{Ar}), 135.9 (d, J = 124.4 Hz, C₆), 135.3 (s, C_{Ar}), 132.3 (s, C_{Ar}), 131.45 (s, C_{Ar}), 131.40 (s, C_{Ar}), 130.0 (q, J = 32.7 Hz, C₁₇), 129.0 (s, C_{Ar}), 128.8 (s, 2C, C_{Ar}), 128.7 (s, 3C, C_{Ar}), 127.3 (s, 2C, C_{Ar}), 127.1 (s, C_{Ar}), 125.8, (q, J = 3.8 Hz, 2C, C₁₅), 124.2 (d, J = 273.3 Hz, C₁₆), 59.5 (s, C₄), 43.7 (s, C₁₂), 19.1 (s, C₁₁).

HRMS (ESI) m/z : calculated for C₂₅H₂₀F₃NOH [M+H]⁺: 408.1570, found: 408.1568.

The synthesis of II.27¹¹⁶:

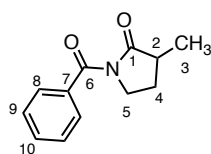


To a solution of 3-methylpyrrolidin-2-one **II.22** (0.99 g, 10 mmol, 1.0 equiv) and DMAP (0.122 g, 1 mmol, 10 mol%) in THF (30 mL), Et₃N (4.17 mL, 30 mmol, 3.0 equiv) was added at 0 °C slowly. The mixture was stirred at 0 °C for 15 min, benzoyl chloride **II.23** (3.32 mL, 20 mmol, 2.0 equiv) was added subsequently. Then, the mixture was allowed to stir at rt for further 15 h until the reaction completely finished. HCl (1.0 M) solution was added to reaction at 0 °C, and the mixture was extracted with EtOAc (3×30 mL), dried over Na₂SO₄ and concentrated under vacuum. The residue was purified by the flash column chromatography on silica gel (EtOAc/PE = 1:10) to afford the corresponding product **II.24** (1.421 g, 70%) as a white solid.

To a solution of 1-benzoyl-3-methylpyrrolidin-2-one (**II.24**) (1.218 g, 6 mmol, 1.0 equiv) in THF (20 mL) at –78 °C, NaHMDS (7.2 mL, 7.2 mmol, 1.2 equiv, 1.0 M in THF) was added dropwise through 5 min. The reaction was stirred at –78 °C for 0.5 h, phenylselenenyl chloride (1.378 g, 7.2 mmol, 1.2 equiv, in 15 mL THF) was added subsequently. The mixture was stirred at –78 °C for further 1.5 h until the reaction completely finished. Saturated NH₄Cl solution (10 mL) was added to the reaction, the mixture was extracted with EtOAc (3 × 30 mL) and washed by brine (30 mL), and dried over Na₂SO₄ and concentrated under vacuum. The crude product **II.25** was used for next step directly without further purification.

Acetic acid (3.73 mL, 21 mmol, 3.5 equiv) and H₂O₂ (12.24 mL, 126 mmol, 21 equiv, 35 wt %) were added to the crude product at 0 °C slowly, the mixture was stirred at 0 °C for 10 min which was then allowed warm to rt for 1 h. Then, saturated Na₂CO₃ solution (20 mL) was added to the mixture solution at 0 °C, the mixture was extracted with EtOAc (2 × 20 mL), and dried over Na₂SO₄ and concentrated under vacuum. The residue was purified by the flash column chromatography on silica gel (EtOAc/PE = 1:10 to 5:1) to afford the α,β-unsaturated lactam **II.27** (0.688 g, 57% in two steps) as a white solid.

1-Benzoyl-3-methylpyrrolidin-2-one (**II.24**)



MW: 203.0946 g.mol⁻¹

Molecular Formula: C₁₂H₁₃NO₂

Mp: 73–74 °C.

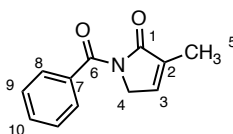
IR (neat): 2972, 2933, 2877, 1742, 1665, 1601, 1581, 1483, 1449, 1376, 1357, 1306, 1239, 1208, 1185, 1130, 1078, 1031, 979, 927, 863 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.59 – 7.56 (m, 2H, H_{Ar}), 7.53 – 7.48 (m, 1H, H_{Ar}), 7.42 – 7.38 (m, 2H, H_{Ar}), 4.02 – 3.96 (m, 1H, H₅), 3.82 – 3.75 (m, 1H, H₅), 2.72 – 2.61 (m, 1H, H₂), 2.39 – 2.31 (m, 1H, H₄), 1.81 – 1.70 (m, 1H, H₄), 1.25 (d, *J* = 7.0 Hz, 3H, H₃).

¹³C NMR (101 MHz, CDCl₃) δ 177.1 (s, C₁), 170.8 (s, C₆), 134.6 (s, C₇), 131.8 (s, C₁₀), 128.9 (s, 2C, C_{Ar}), 127.8 (s, 2C, C_{Ar}), 44.3 (s, C₅), 39.1 (s, C₂), 26.5 (s, C₄), 15.5 (s, C₃).

MS *m/z* (relative intensity): 203 (M⁺, 25), 175 (3), 105 (100), 77 (56), 70 (1), 51 (15).

1-benzoyl-3-methyl-1,5-dihydro-2*H*-pyrrol-2-one (II.27)



MW: 201.0790 g.mol⁻¹

Molecular Formula: C₁₂H₁₁NO₂

Mp: 89–91 °C.

IR (neat): 2924, 2856, 1717, 1669, 1448, 1341, 1320, 1234, 1155, 1110, 1077, 969, 928 cm⁻¹.

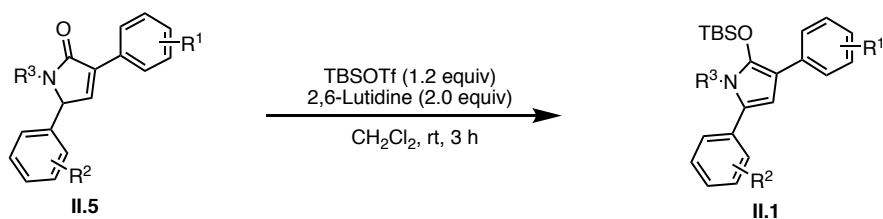
¹H NMR (400 MHz, CDCl₃) δ 7.65 – 7.62 (m, 2H, H_{Ar}), 7.55 – 7.50 (m, 1H, H_{Ar}), 7.46 – 7.40 (m, 2H, H_{Ar}), 7.00 – 6.98 (m, 1H, H₄), 4.50 (p, *J* = 2.1 Hz, 2H, H₅), 1.88 (q, *J* = 2.0 Hz, 3H, H₃).

¹³C NMR (101 MHz, CDCl₃) δ 170.2 (s, C₁), 169.6 (s, C₆), 139.8 (s, C₄), 135.3 (s, C₇), 134.4 (s, C₂), 133.8 (s, C₁₀), 128.8 (s, 2C, C_{Ar}), 127.8 (s, 2C, C_{Ar}), 49.1 (s, C₅), 11.1 (s, C₃).

MS *m/z* (relative intensity): 201 (M⁺, 35), 173 (2), 144 (2), 105 (100), 77 (66), 51 (19).

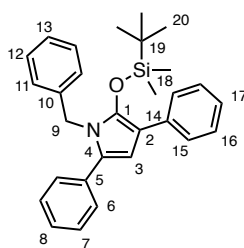
5. Synthesis of α,γ-disubstituted 2-silyloxypyrroles

General procedure for Synthesis of 2-silyloxypyrrole derivatives II.1a-m:



To a solution of **II.5a** (1.138g, 3.5 mmol, 1.0 equiv) in CH_2Cl_2 , 2,6-lutidine (0.815 mL, 7 mmol, 2.0 equiv) was added. The mixture was stirred at rt for 10 min, TBSOTf (0.965 mL, 4.2 mmol, 1.2 equiv) was added subsequently. The mixture was stirred at rt for further 3 h until the reaction completely finished. Then, the solvent was evaporated under vacuum, and the residue was purified by the flash column chromatography on silica gel (Et_2O /Petroleum ether = 1:10) to afford the corresponding 2-silyloxypyrrole **II.1a** (1.46 g, 95%) as a colourless oil.

1-benzyl-2-[(*tert*-butyldimethylsilyl)oxy]-3,5-diphenyl-1*H*-pyrrole (**II.1a**)



MW: 439.2331 $\text{g}\cdot\text{mol}^{-1}$

Molecular Formula: $\text{C}_{29}\text{H}_{33}\text{NOSi}$

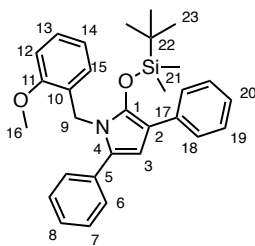
IR (neat): 2929, 2858, 2360, 2341, 1604, 1585, 1527, 1494, 1454, 1389, 1349, 1254, 1176, 1073, 1029, 1002, 953 cm^{-1} .

^1H NMR (400 MHz, CDCl_3) δ 7.63 – 7.59 (m, 2H, H_{Ar}), 7.40 – 7.32 (m, 6H, H_{Ar}), 7.29 – 7.18 (m, 5H, H_{Ar}), 6.98 – 6.96 (m, 2H, H_{Ar}), 6.38 (s, 1H, H_3), 5.16 (s, 2H, H_9), 0.98 (s, 9H, H_{20}), 0.00 (s, 6H, H_{18}).

^{13}C NMR (101 MHz, CDCl_3) δ 140.2 (s, C_{Ar}), 138.7 (s, C_{Ar}), 136.3 (s, C_{Ar}), 133.8 (s, C_{Ar}), 128.5 (s, 4C, C_{Ar}), 128.4 (s, 2C, C_{Ar}), 128.2 (s, 2C, C_{Ar}), 127.7 (s, 2C, C_{Ar}), 127.4 (s, C_{Ar}), 127.0 (s, C_{Ar}), 126.5 (s, C_{Ar}), 126.3 (s, 2C, C_{Ar}), 125.1 (s, C_{Ar}), 106.9 (s, C_3), 106.7 (s, C_2), 45.7 (s, C_9), 25.8 (s, 3C, C_{20}), 18.2 (s, C_{19}), -4.07 (s, 2C, C_{18}).

HRMS (ESI) m/z : calculated for $\text{C}_{29}\text{H}_{33}\text{NOSiNH}$ $[\text{M}+\text{H}]^+$: 440.2404, found: 440.2407.

2-[(*tert*-butyldimethylsilyl)oxy]-1-(2-methoxybenzyl)-3,5-diphenyl-1*H*-pyrrole (II.1b)



MW: 469.2437 g.mol⁻¹

Molecular Formula: C₃₀H₃₅NO₂Si

Compound **II.1b** was synthesized from the α,β -unsaturated lactam **II.5b** (0.71 g, 2 mmol, 1.0 equiv) and TBSOTf (0.55 mL, 2.4 mmol, 1.5 equiv) followed general procedure. The 2-silyloxypyrrole **II.1b** (0.9 g, 96%) was isolated as a white solid.

Mp: 114–115 °C

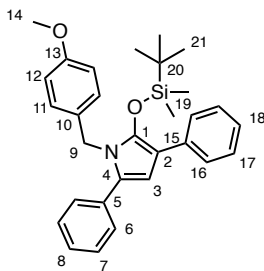
IR (neat): 2954, 2930, 2858, 1693, 1603, 1586, 1527, 1492, 1461, 1439, 1421, 1390, 1351, 1286, 1243, 1171, 1109, 1073, 1051, 1029, 1002, 980 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.55 (d, J = 7.2 Hz, 2H, H_{Ar}), 7.34 – 7.25 (m, 6H, H_{Ar}), 7.20 – 7.13 (m, 3H, H_{Ar}), 6.84 (t, J = 7.5 Hz, 1H, H₁₂), 6.79 (d, J = 8.2 Hz, 1H, H₁₄), 6.63 (d, J = 7.4 Hz, 1H, H_{Ar}), 6.35 (s, 1H, H₃), 5.11 (s, 2H, H₉), 3.77 (s, 3H, H₁₆), 0.84 (s, 9H, H₂₃), –0.10 (s, 6H, H₂₁).

¹³C NMR (101 MHz, CDCl₃) δ 155.9 (s, C₁₅), 140.3 (s, C₁), 136.4 (s, C₄), 133.8 (s, C₁₇), 128.4 (s, 2C, C_{Ar}), 128.2 (s, 2C, C_{Ar}), 128.2 (s, 3C, C_{Ar}), 127.8 (s, 3C, C_{Ar}), 127.4 (s, C₁₀), 126.9 (s, C_{Ar}), 126.3 (s, C_{Ar}), 125.0 (s, C_{Ar}), 120.9 (s, C₁₂), 109.6 (s, C₁₄), 106.6 (s, C₃), 106.5 (s, C₂), 55.2 (s, C₁₆), 41.9 (s, C₉), 25.6 (s, 3C, C₂₃), 18.2 (s, C₂₂), –4.06 (s, 2C, C₂₁).

HRMS (ESI) m/z : calculated for C₃₀H₃₅NO₂SiNa [M+Na]⁺: 492.2329, found: 492.2333.

2-[(*tert*-butyldimethylsilyl)oxy]-1-(4-methoxybenzyl)-3,5-diphenyl-1*H*-pyrrole (II.1c)



MW: 469.2437 g.mol⁻¹

Molecular Formula: C₃₀H₃₅NO₂Si

Compound **II.1c** was synthesized from the α,β -unsaturated lactam **II.5c** (0.71 g, 2 mmol, 1.0 equiv) and TBSOTf (0.55 mL, 2.4 mmol, 1.5 equiv) followed the general procedure. The 2-silyloxypyrrole **II.1c** (0.891 g, 95%) was isolated as a colourless oil.

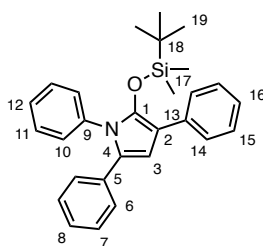
IR (neat): 2954, 2931, 2858, 2360, 1699, 1605, 1585, 1527, 1513, 1493, 1472, 1461, 1442, 1420, 1390, 1349, 1304, 1248, 1176, 1111, 1073, 1036, 1002, 957 cm^{-1} .

^1H NMR (400 MHz, CDCl_3) δ 7.61 (d, J = 8.0 Hz, 2H, H_{Ar}), 7.40 – 7.18 (m, 8H, H_{Ar}), 6.90 (d, J = 8.5 Hz, 2H, H_{12}), 6.80 (d, J = 8.7 Hz, 2H, H_{11}), 6.38 (s, 1H, H_3), 5.10 (s, 2H, H_9), 3.79 (s, 3H, H_{14}), 1.02 (s, 9H, H_{21}), 0.01 (s, 6H, H_{19}).

^{13}C NMR (101 MHz, CDCl_3) δ 158.6 (s, C_{13}), 140.2 (s, C_1), 136.3 (s, C_4), 133.8 (s, C_5), 130.8 (s, C_{Ar}), 128.5 (s, 2C, C_{Ar}), 128.4 (s, 2C, C_{Ar}), 128.2 (s, 2C, C_{Ar}), 127.7 (s, 2C, C_{Ar}), 127.6 (s, 2C, C_{Ar}), 127.4 (s, C_{Ar}), 126.5 (s, C_{Ar}), 125.0 (s, C_{Ar}), 113.9 (s, 2C, C_{Ar}), 106.9 (s, C_3), 106.7 (s, C_2), 55.3 (s, C_{14}), 46.1 (s, C_{19}), 25.9 (s, 3C, C_{21}), 18.2 (s, C_{20}), -4.1 (s, 2C, C_{19}).

HRMS (ESI) m/z : calculated for $\text{C}_{30}\text{H}_{35}\text{NO}_2\text{SiNa}$ $[\text{M}+\text{Na}]^+$: 492.2329, found: 492.2331.

2-[(*tert*-butyldimethylsilyl)oxy]-1,3,5-triphenyl-1*H*-pyrrole (**II.1d**)



MW: 425.2175 $\text{g}\cdot\text{mol}^{-1}$

Molecular Formula: $\text{C}_{28}\text{H}_{31}\text{NOSi}$

Compound **II.1d** was synthesized from the α,β -unsaturated lactam **II.5d** (0.71 g, 2 mmol, 1.0 equiv) and TBSOTf (0.55 mL, 2.4 mmol, 1.5 equiv) followed the general procedure. The 2-silyloxypyrrole **II.1d** (0.808 g, 95%) was isolated as a white solid.

Mp: 142–143 $^{\circ}\text{C}$.

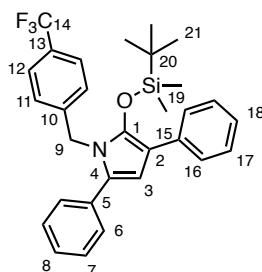
IR (neat): 1699, 1599, 1527, 1498, 1409, 1378, 1334, 1309, 1257, 1172, 1073, 1039, 948, 909 cm^{-1} .

¹H NMR (400 MHz, CDCl₃) δ 7.61 (d, *J* = 8.1 Hz, 2H, H_{Ar}), 7.38 – 7.22 (m, 7H, H_{Ar}), 7.19 – 7.07 (m, 6H, H_{Ar}), 6.43 (s, 1H, H₃), 0.81 (s, 9H, H₁₉), -0.54 (s, 6H, H₁₇).

¹³C NMR (101 MHz, CDCl₃) δ 139.9 (s, C₁), 137.3 (s, C₉), 136.1 (s, C₅ or C₁₃), 133.6 (s, C₅ or C₁₃), 128.8 (s, 2C, C_{Ar}), 128.7 (s, 2C, C_{Ar}), 128.3 (s, 2C, C_{Ar}), 128.1 (s, 2C, C_{Ar}), 127.7 (s, 4C, C_{Ar}), 127.0 (s, C_{Ar}), 126.2 (s, C₄), 125.6 (s, C_{Ar}), 125.2 (s, C_{Ar}), 108.1 (s, C₃), 107.2 (s, C₂), 25.8 (s, 3C, C₁₉), 18.1 (s, C₁₈), -4.6 (s, 2C, C₁₇).

HRMS (ESI) *m/z*: calculated for C₂₈H₃₁NOSiNa [M+Na]⁺: 448.2067, found: 448.2080.

2-[(*tert*-butyldimethylsilyl)oxy]-3,5-diphenyl-1-[4-(trifluoromethyl)benzyl]-1*H* pyrrole (II.1e)



MW: 507.2205 g.mol⁻¹

Molecular Formula: C₃₀H₃₂F₃NOSi

Compound **II.1e** was synthesized from the α,β-unsaturated lactam **II.5e** (0.786 g, 2 mmol, 1.0 equiv) and TBSOTf (0.55 mL, 2.4 mmol, 1.5 equiv) followed the general procedure. The 2-silyloxypyrrole **II.1e** (0.974 g, 96%) was isolated as a white solid.

Mp: 86–87 °C

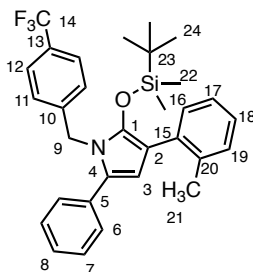
IR (neat): 2932, 2860, 1694, 1606, 1586, 1530, 1494, 1419, 1325, 1256, 1165, 1125, 1067, 1018, 980 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.60 (d, *J* = 7.2 Hz, 2H, H_{Ar}), 7.53 (d, *J* = 8.2 Hz, 2H, H_{Ar}), 7.41 – 7.27 (m, 7H, H_{Ar}), 7.22 (t, *J* = 7.4 Hz, 1H), 7.05 (d, *J* = 8.0 Hz, 2H, H_{Ar}), 6.40 (s, 1H, H₃), 5.20 (s, 2H, H₉), 0.97 (s, 9H, H₂₁), 0.00 (s, 6H, H₁₉).

¹³C NMR (101 MHz, CDCl₃) δ 142.8 (s, C₁), 140.2 (s, C₄), 136.0 (s, C₁₅), 133.5 (s, C₅), 129.3 (s, *J* = 32.4 Hz, C_{Ar}), 128.6 (s, 2C, C_{Ar}), 128.4 (s, 2C, C_{Ar}), 128.3 (s, 2C, C_{Ar}), 127.7 (s, 2C, C_{Ar}), 127.5 (s, C_{Ar}), 126.8 (s, C_{Ar}), 126.6 (s, 2C, C_{Ar}), 125.6 (q, *J* = 3.7 Hz, 2C, C₁₂), 125.3 (s, C_{Ar}), 124.1 (d, *J* = 233.9 Hz, C₁₃), 107.3 (s, C₃), 107.0 (s, C₂), 46.4 (s, C₉), 25.8 (s, 3C, C₂₁), 18.2 (s, C₂₀), -4.1 (s, 2C, C₁₉),

HRMS (ESI) m/z : calculated for $C_{30}H_{32}F_3NOSiH$ $[M+H]^+$: 508.2278, found: 508.2276.

2-[(*tert*-butyldimethylsilyl)oxy]-5-phenyl-3-(*o*-tolyl)-1-[4-(trifluoromethyl)benzyl]-1*H*-pyrrole (II.1f)



MW: 521.2362 g.mol⁻¹

Molecular Formula: C₃₁H₃₄F₃NOSi

Compound **II.1f** was synthesized from the α,β -unsaturated lactam **II.5f** (0.814 g, 2 mmol, 1.0 equiv) and TBSOTf (0.55 mL, 2.4 mmol, 1.5 equiv) followed general procedure. The 2-silyloxypyrrole **II.1f** (0.990 g, 95%) was isolated as a colourless oil.

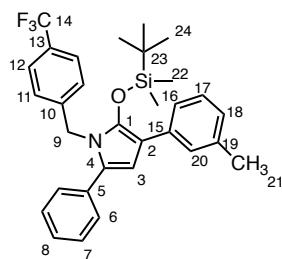
IR (neat): 2955, 2931, 2859, 1619, 1606, 1586, 1487, 1452, 1417, 1390, 1324, 1256, 1164, 1125, 1067, 1018, 980 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.52 (d, J = 7.9 Hz, 2H, H_{Ar}), 7.33 – 7.28 (m, 5H, H_{Ar}), 7.23 – 7.16 (m, 4H, H_{Ar}), 7.05 (d, J = 8.1 Hz, 2H, H_{Ar}), 6.17 (s, 1H, H₃), 5.17 (s, 2H, H₉), 2.33 (s, 3H, H₂₁), 0.78 (s, 9H, H₂₄), -0.26 (s, 6H, H₂₂).

¹³C NMR (101 MHz, CDCl₃) δ 143.3 (s, C₁), 139.9 (s, C₄), 137.3 (s, C_{Ar}), 135.6 (s, C_{Ar}), 133.6 (s, C_{Ar}), 131.3 (s, C_{Ar}), 130.1 (s, C_{Ar}), 129.4 (d, J = 32.5 Hz, C₁₄), 128.6 (s, 2C, C_{Ar}), 128.1 (s, 2C, C_{Ar}), 126.59 (s, C_{Ar}), 126.57 (s, C_{Ar}), 126.51 (s, 2C, C_{Ar}), 126.46 (s, C_{Ar}), 125.56, 125.5 (q, J = 3.8 Hz, 2C, H₁₂), 124.3 (d, J = 273.1 Hz, C₁₃), 109.1 (s, C₃), 106.3 (s, C₂), 46.2 (s, C₉), 25.7 (s, 3C, C₂₄), 20.6 (s, C₂₁), 18.15 (s, C₂₃), -4.8 (s, 2C, C₂₂).

HRMS (ESI) m/z : calculated for $C_{31}H_{34}F_3NO_2SiH$ $[M+H]^+$: 522.2435, found: 522.2451.

2[(*tert*-butyldimethylsilyl)oxy]-5-phenyl-3-(*m*-tolyl)-1-[4-(trifluoromethyl)benzyl]-1*H*-pyrrole (II.1g)



MW: 521.2362 g.mol⁻¹

Molecular Formula: C₃₁H₃₄F₃NOSi

Compound **II.1g** was synthesized from the α,β -unsaturated lactam **II.5g** (0.814 g, 2 mmol, 1.0 equiv) and TBSOTf (0.55 mL, 2.4 mmol, 1.5 equiv) followed the general procedure. The 2-silyloxypyrrole **II.1g** (1.0 g, 96%) was isolated as a white solid.

Mp: 99–100 °C.

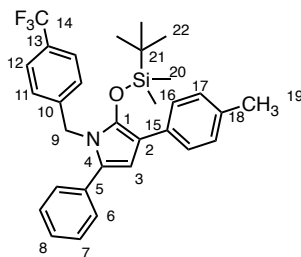
IR (neat): 2953, 2931, 2859, 1607, 1590, 1527, 1483, 1463, 1419, 1323, 1278, 1255, 1211, 1124, 1067, 1018, 943 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.52 (d, J = 8.1 Hz, 2H, H_{Ar}), 7.44 (s, 1H, H₂₀), 7.39 – 7.25 (m, 7H, H_{Ar}), 7.05 – 7.03 (m, 3H, H_{Ar}), 6.39 (s, 1H, H₃), 5.19 (s, 2H, H₉), 2.41 (s, 3H, H₂₁), 0.97 (s, 9H, H₂₄), 0.00 (s, 6H, H₂₂).

¹³C NMR (101 MHz, CDCl₃) δ 142.9 (s, C₁), 140.2 (s, C₄), 137.6 (s, C_{Ar}), 135.8 (s, C_{Ar}), 133.5 (s, C_{Ar}), 129.4 (d, J = 32.6 Hz, C₁₄), 128.6 (s, 2C, C_{Ar}), 128.5 (s, C_{Ar}), 128.4 (s, 2C, C_{Ar}), 128.3 (s, C_{Ar}), 127.4 (s, C_{Ar}), 126.7 (s, C_{Ar}), 126.6 (s, 2C, C_{Ar}), 126.0 (s, C_{Ar}), 125.55 (q, J = 3.8 Hz, 2C, C₁₂), 124.7 (s, C_{Ar}), 123.8 (d, J = 270.4 Hz, C₁₃), 107.4 (s, C₃), 107.1 (s, C₂), 46.4 (s, C₉), 25.8 (s, 3C, C₂₄), 21.6 (s, C₂₁), 18.2 (s, C₂₃), -4.1 (s, 2C, C₂₂).

HRMS (ESI) m/z : calculated for C₃₁H₃₄F₃NO₂SiH [M+H]⁺: 522.2435, found: 522.2430.

2-[(*tert*-butyldimethylsilyl)oxy]-5-phenyl-3-(*p*-tolyl)-1-[4-(trifluoromethyl)benzyl]-1*H*-pyrrole (II.1h)



MW: 521.2362 g.mol⁻¹

Molecular Formula: C₃₁H₃₄F₃NOSi

Compound **II.1h** was synthesized from the α,β -unsaturated lactam **II.5h** (0.814 g, 2 mmol, 1.0 equiv) and TBSOTf (0.55 mL, 2.4 mmol, 1.5 equiv) followed the general procedure. The 2-silyloxypyrrole **II.1h** (0.99 g, 96%) was isolated as a white solid.

Mp: 77–78 °C.

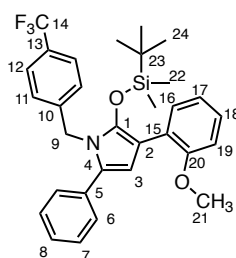
IR (neat): 2955, 2931, 2859, 1700, 1618, 1605, 1587, 1533, 1507, 1473, 1455, 1420, 1404, 1324, 1255, 1164, 1124, 1112, 1067, 1018, 980, 961, 909 cm^{-1} .

^1H NMR (400 MHz, CDCl_3) δ 7.53 – 7.46 (m, 4H, H_{Ar}), 7.37 – 7.24 (m, 5H, H_{Ar}), 7.19 (d, J = 8.1 Hz, 2H, H_{Ar}), 7.04 (d, J = 8.2 Hz, 2H, H_{Ar}), 6.37 (s, 1H, H_3), 5.19 (s, 2H, H_9), 2.40 (s, 3H, H_{19}), 0.97 (s, 9H, H_{22}), -0.00 (s, 6H, H_{20}).

^{13}C NMR (101 MHz, CDCl_3) δ 142.9 (s, C_1), 140.0 (s, C_4), 134.7 (s, C_{Ar}), 133.5 (s, C_{Ar}), 133.0 (s, C_{Ar}), 129.3 (d, J = 32.3 Hz, C_{14}), 129.0 (s, 2C, C_{Ar}), 128.6 (s, 2C, C_{Ar}), 128.4 (s, 2C, C_{Ar}), 127.6 (s, 2C, C_{Ar}), 127.3 (s, C_{Ar}), 126.7 (s, C_{Ar}), 126.6 (s, 2C, C_{Ar}), 125.5 (q, J = 3.6 Hz, 2C, C_{12}), 124.3 (d, J = 273.0 Hz, C_{13}), 107.4 (s, C_3), 107.0 (s, C_2), 46.4 (s, C_9), 25.8 (s, 3C, C_{22}), 21.3 (s, C_{19}), 18.2 (s, C_{21}), -4.1 (s, 2C, C_{20}).

HRMS (ESI) m/z : calculated for $\text{C}_{31}\text{H}_{34}\text{F}_3\text{NO}_2\text{SiH}$ $[\text{M}+\text{H}]^+$: 522.2435, found: 522.2432.

2-[(*tert*-butyldimethylsilyl)oxy]-3-(2-methoxyphenyl)-5-phenyl-1-[4-(trifluoromethyl)benzyl]-1*H*-pyrrole (II.1i**)**



MW: 537.2311 $\text{g}\cdot\text{mol}^{-1}$

Molecular Formula: $\text{C}_{31}\text{H}_{34}\text{F}_3\text{NO}_2\text{Si}$

Compound **II.1i** was synthesized from the α,β -unsaturated lactam **II.5i** (0.846 g, 2 mmol, 1.0 equiv) and TBSOTf (0.55 mL, 2.4 mmol, 1.5 equiv) followed the general procedure. The 2-silyloxypyrrole **II.1i** (1.021 g, 95%) was isolated as a colourless oil.

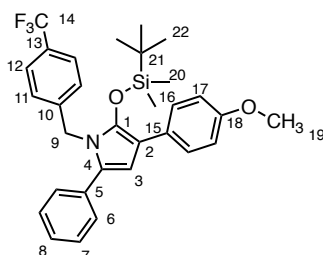
IR (neat): 2932, 2859, 1604, 1586, 1527, 1489, 1463, 1418, 1390, 1324, 1246, 1164, 1123, 1067, 1049, 1018, 981, 939 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.68 (d, *J* = 8.1 Hz, 2H, H_{Ar}), 7.60 (dd, *J* = 7.5, 1.8 Hz, 1H, H_{Ar}), 7.46 (d, *J* = 4.4 Hz, 4H, H_{Ar}), 7.42 – 7.36 (m, 2H, H_{Ar}), 7.25 (d, *J* = 8.0 Hz, 2H, H_{Ar}), 7.15 – 7.06 (m, 2H, H_{Ar}), 6.56 (s, 1H, H₃), 5.32 (s, 2H, H₉), 4.01 (s, 3H, H₂₁), 0.99 (s, 9H, H₂₄), 0.00 (s, 6H, H₂₂).

¹³C NMR (101 MHz, CDCl₃) δ 157.1 (s, C₁), 143.2 (s, C₄), 140.7 (s, C_{Ar}), 133.7 (s, C_{Ar}), 131.8 (s, C_{Ar}), 129.3 (d, *J* = 32.7 Hz, C₁₄), 128.5 (s, 2C, C_{Ar}), 128.3 (s, 2C, C_{Ar}), 127.3 (s, C_{Ar}), 126.6 (s, 2C, C_{Ar}), 126.5 (s, C_{Ar}), 126.4 (s, C_{Ar}), 125.5 (q, *J* = 3.7 Hz, 2C, C₁₂), 124.9 (s, C_{Ar}), 124.3 (d, *J* = 273.0 Hz, C₁₃), 120.4 (s, C_{Ar}), 110.8 (s, C_{Ar}), 109.3 (s, C₃), 102.6 (s, C₂), 55.5 (s, C₂₁), 46.3 (s, C₉), 25.67 (s, 3C, C₂₄), 18.1 (s, C₂₃), -4.5 (s, 2C, C₂₂)

HRMS (ESI) *m/z*: calculated for C₃₁H₃₄F₃NO₃SiH [M+H]⁺: 538.2384, found: 538.2380.

2-[(*tert*-butyldimethylsilyl)oxy]-3-(4-methoxyphenyl)-5-phenyl-1-[4-(trifluoromethyl)benzyl]-1*H*-pyrrole (II.1j)



MW: 537.2311 g.mol⁻¹

Molecular Formula: C₃₁H₃₄F₃NO₂Si

Compound **II.1j** was synthesized from the α,β-unsaturated lactam **II.5j** (0.846 g, 2 mmol, 1.0 equiv) and TBSOTf (0.55 mL, 2.4 mmol, 1.5 equiv) followed the general procedure. The 2-silyloxypyrrole **II.1j** (1.031 g, 96%) was isolated as a yellow solid.

Mp: 98–99 °C.

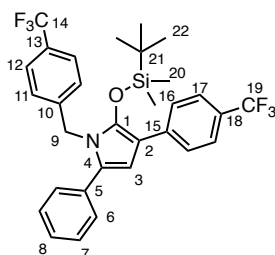
IR (neat): 2953, 2932, 2859, 1618, 1604, 1587, 1572, 1530, 1506, 1472, 1464, 1442, 1420, 1408, 1390, 1323, 1288, 1244, 1163, 1122, 1112, 1066, 1036, 1018, 980, 961, 939, 912 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.57 – 7.45 (m, 4H, H_{Ar}), 7.40 – 7.25 (m, 5H, H_{Ar}), 7.09 – 6.91 (m, 4H, H_{Ar}), 6.35 (s, 1H, H₃), 5.19 (s, 2H, H₉), 3.88 (s, 3H, H₁₉), 0.97 (s, 9H, H₂₃), 0.00 (s, 6H, H₂₀).

¹³C NMR (101 MHz, CDCl₃) δ 157.6 (s, C₁), 142.9 (s, C₄), 139.8 (s, C_{Ar}), 133.5 (s, C_{Ar}), 129.4 (d, *J* = 32.0 Hz, C₁₄), 128.9 (s, 2C, C_{Ar}), 128.7 (s, C_{Ar}), 128.6 (s, 2C, C_{Ar}), 128.3 (s, 2C, C_{Ar}), 127.2 (s, C_{Ar}), 126.7 (s, C_{Ar}), 126.6 (s, 2C, C_{Ar}), 125.5 (q, *J* = 3.9 Hz, 2C, C₁₂), 124.3 (d, *J* = 274.1 Hz, C₁₃), 113.8 (s, 2C, C_{Ar}), 107.4 (s, C₃), 106.6 (s, C₂), 55.4 (s, C₁₉), 46.4 (s, C₉), 25.8 (s, 3C, C₂₂), 18.2 (s, C₂₁), –4.1 (s, 2C, C₂₀).

HRMS (ESI) *m/z*: calculated for C₃₁H₃₄F₃NO₂SiNa [M+Na]⁺: 560.2203, found: 560.2210.

2-[(*tert*-butyldimethylsilyl)oxy]-5-phenyl-1-[4-(trifluoromethyl)benzyl]-3-[4-(trifluoromethyl)phenyl]-1*H*-pyrrole (II.1k)



MW: 575.2079 g.mol⁻¹

Molecular Formula: C₃₁H₃₁F₆NO₂Si

Compound **II.1k** was synthesized from the α,β-unsaturated lactam **II.5j** (0.922 g, 2 mmol, 1.0 equiv) and TBSOTf (0.55 mL, 2.4 mmol, 1.5 equiv) followed the general procedure. The 2-silyloxypyrrole **II.1k** (1.093 g, 95%) was isolated as a colourless oil.

IR (neat): 2933, 2860, 1705, 1617, 1586, 1536, 1510, 1462, 1406, 1323, 1254, 1163, 1121, 1067, 1036, 1018, 965, 940, 865 cm⁻¹.

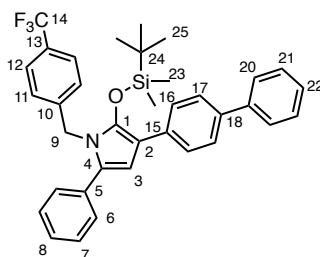
¹H NMR (400 MHz, CDCl₃) δ 7.67 (d, *J* = 8.2 Hz, 2H, H_{Ar}), 7.60 (d, *J* = 8.2 Hz, 2H, H_{Ar}), 7.50 (d, *J* = 8.1 Hz, 2H, H_{Ar}), 7.37 – 7.33 (m, 2H, H_{Ar}), 7.30 – 7.28 (m, 4H, H_{Ar}), 7.00 (d, *J* = 8.0 Hz, 1H, H_{Ar}), 6.37 (s, 1H, H₃), 5.16 (s, 2H, H₉), 0.96 (s, 9H, H₂₂), 0.00 (s, 6H, H₂₀).

¹³C NMR (101 MHz, CDCl₃) δ 142.3 (s, C₁), 140.7 (s, C₄), 139.5 (s, C_{Ar}), 140.0 (s, C_{Ar}), 129.4 (d, *J* = 32.1 Hz, C₁₄), 128.6 (s, 3C, C_{Ar}), 128.4 (s, 3C, C_{Ar}), 127.9 (s, C_{Ar}), 127.1 (s, 2C, C_{Ar}), 127.0 (s, C_{Ar}), 126.8 (d, *J* = 32.5 Hz, C₁₈), 126.4 (s, 2C, C_{Ar}), 125.5 (q, *J* = 3.9 Hz,

2C, C₁₄ or C₁₉), 125.1 (q, *J* = 3.8 Hz, 2C, C₁₄ or C₁₉), 106.7 (s, C₃), 105.7 (s, C₂), 46.3 (s, C₉), 25.6 (s, 3C, C₂₂), 18.1 (s, C₂₁), -4.1 (s, 2C, C₂₀).

HRMS (ESI) *m/z*: calculated for C₃₁H₃₁F₆NO₂SiH [M+H]⁺: 576.2152, found: 576.2146.

3-[(1,1'-biphenyl)-4-yl]-2-[(*tert*-butyldimethylsilyl)oxy]-5-phenyl-1-[4-(trifluoromethyl)benzyl]-1*H*-pyrrole (II.1I)



MW: 583.2518 g.mol⁻¹

Molecular Formula: C₃₆H₃₆F₃NOSi

Compound **II.1I** was synthesized from the α,β -unsaturated lactam **II.5m** (0.938 g, 2 mmol, 1.0 equiv) and TBSOTf (0.55 mL, 2.4 mmol, 1.5 equiv) followed the general procedure. The 2-silyloxypyrrole lactam **II.5I** (1.131 g, 97%) was isolated as a yellow solid.

Mp: 55–56°C.

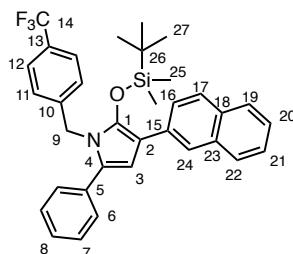
IR (neat): 3031, 2954, 2931, 2886, 2859, 1605, 1585, 1536, 1513, 1486, 1473, 1461, 1420, 1404, 1324, 1281, 1257, 1164, 1124, 1067, 1030, 1018, 1008, 980, 961, 939, 912 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.68 – 7.59 (m, 6H, H_{Ar}), 7.47 (dd, *J* = 17.4, 8.1 Hz, 4H, H_{Ar}), 7.36 – 7.23 (m, 6H, H_{Ar}), 7.01 (d, *J* = 7.9 Hz, 2H, H₁₁), 6.39 (s, 1H, H₃), 5.16 (s, 2H, H₉), 0.95 (s, 9H, H₂₅), 0.00 (s, 6H, H₂₃).

¹³C NMR (101 MHz, CDCl₃) δ 142.7 (s, C₁), 141.3 (s, C₄), 140.4 (s, C_{Ar}), 137.8 (s, C_{Ar}), 135.1 (s, C_{Ar}), 133.4 (s, C_{Ar}), 129.4 (d, *J* = 32.3 Hz, C₁₄), 128.9 (s, 2C, C_{Ar}), 128.7 (s, 2C, C_{Ar}), 128.4 (s, 2C, C_{Ar}), 127.9 (s, 2C, C_{Ar}), 127.6 (s, C_{Ar}), 127.0 (s, C_{Ar}), 126.9 (s, 4C, C_{Ar}), 126.8 (s, C_{Ar}), 126.6 (s, 2C, C_{Ar}), 125.6 (q, *J* = 3.7 Hz, 2C, C₁₂), 124.2 (d, *J* = 273.2 Hz, C₁₃), 107.2 (s, C₃), 106.6 (s, C₂), 46.4 (s, C₉), 25.8 (s, 3C, C₂₅), 18.2 (s, C₂₄), -4.0 (s, 2C, C₂₃).

HRMS (ESI) *m/z*: calculated for C₃₆H₃₆F₃NOSiH [M+H]⁺: 584.2591, found: 584.2596.

2-[(*tert*-butyldimethylsilyl)oxy]-3-(naphthalen-2-yl)-5-phenyl-1-[4-(trifluoromethyl)benzyl]-1*H*-pyrrole (II.1m)



MW: 557.2362 g.mol⁻¹

Molecular Formula: C₃₄H₃₄F₃NOSi

Compound **II.1m** was synthesized from the α,β -unsaturated lactam **II.5n** (0.886 g, 2 mmol, 1.0 equiv) and TBSOTf (0.55 mL, 2.4 mmol, 1.5 equiv) followed the general procedure. The silyl dienol ether **II.1m** (1.058 g, 95%) was isolated as a colourless oil.

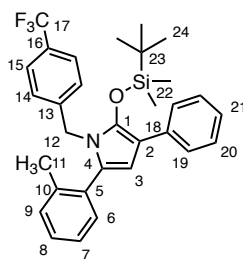
IR (neat): 2953, 2931, 2859, 1629, 1619, 1604, 1582, 1527, 1506, 1473, 1454, 1418, 1390, 1323, 1289, 1255, 1233, 1198, 1164, 1122, 1067, 1031, 1018, 1002, 986, 967, 948, 935 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.98 (s, 1H, H₂₄), 7.80 (t, J = 9.1 Hz, 3H, H_{Ar}), 7.73 (d, J = 8.5 Hz, 1H, H_{Ar}), 7.50 (d, J = 8.2 Hz, 2H, H_{Ar}), 7.47 – 7.39 (m, 2H, H_{Ar}), 7.35 – 7.23 (m, 5H, H_{Ar}), 7.03 (d, J = 8.1 Hz, 2H, H_{Ar}), 6.47 (s, 1H, H₃), 5.17 (s, 2H, H₉), 0.94 (s, 9H, H₂₇), -0.06 (s, 6H, H₂₅).

¹³C NMR (101 MHz, CDCl₃) δ 142.7 (s, C₁), 140.5 (s, C₄), 133.9 (s, C_{Ar}), 133.5 (s, C_{Ar}), 133.4 (s, C_{Ar}), 131.7 (s, C_{Ar}), 129.4 (d, J = 32.5 Hz, C₁₄), 128.7 (s, 2C, C_{Ar}), 128.4 (s, 2C, C_{Ar}), 127.79 (s, C_{Ar}), 127.77 (s, C_{Ar}), 127.7 (s, C_{Ar}), 127.6 (s, C_{Ar}), 126.9 (s, C_{Ar}), 126.8 (s, C_{Ar}), 126.6 (s, 2C, C_{Ar}), 126.0 (s, C_{Ar}), 125.6 (q, J = 3.9 Hz, 2C, C₁₂), 125.2 (s, C_{Ar}), 124.9 (s, C_{Ar}), 124.3 (d, J = 273.2 Hz, C₁₃), 107.3 (s, C₃), 106.9 (s, C₂), 46.4 (s, C₉), 25.8 (s, 3C, C₂₇), 18.2 (s, C₂₆), -4.0 (s, 2C, C₂₅).

HRMS (ESI) m/z : calculated for C₃₄H₃₄F₃NO₂SiH [M+H]⁺: 558.2435, found: 558.2439.

2-[(*tert*-butyldimethylsilyl)oxy]-3-phenyl-5-(*o*-tolyl)-1-[4-(trifluoromethyl)benzyl]-1*H*-pyrrole (II.1n)



MW: 521.2362 g.mol⁻¹

Molecular Formula: C₃₁H₃₄F₃NOSi

Compound **II.1n** was synthesized from the α,β -unsaturated lactam **II.5o** (0.814 g, 2 mmol, 1.0 equiv) and TBSOTf (0.55 mL, 2.4 mmol, 1.2 equiv) followed the general procedure. The silyl dienol ether **II.1n** (0.990 g, 95%) was isolated as a yellow solid.

Mp: 80–82 °C.

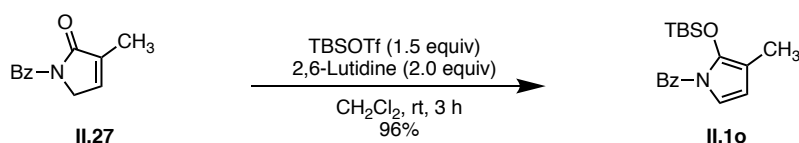
IR (neat): 2954, 2931, 2859, 1605, 1588, 1536, 1495, 1472, 1415, 1380, 1350, 1323, 1255, 1164, 1124, 1067, 1018, 980, 939 cm⁻¹.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.57 (d, *J* = 8.2 Hz, 2H, H_{Ar}), 7.51 (dd, *J* = 8.3, 1.3 Hz, 2H, H_{Ar}), 7.31 (t, *J* = 7.7 Hz, 2H, H_{Ar}), 7.23 – 7.21 (m, 2H, H_{Ar}), 7.15 – 7.08 (m, 3H, H_{Ar}), 6.93 (d, *J* = 8.1 Hz, 2H, H_{Ar}), 6.24 (s, 1H, H₃), 4.88 (s, 2H, H₁₂), 2.13 (s, 3H, H₁₁), 0.89 (s, 9H, H₂₄), -0.03 (s, 6H, H₂₂).

¹³C NMR (101 MHz, DMSO-*d*₆) δ 143.2 (s, C₁), 138.6 (s, C_{Ar}), 137.1 (s, C_{Ar}), 135.5 (s, C_{Ar}), 132.1 (s, C_{Ar}), 130.9 (s, C_{Ar}), 130.1 (s, C_{Ar}), 128.1 (s, C_{Ar}), 127.9 (s, C_{Ar}), 127.6 (d, *J* = 32.0 Hz, C₁₇), 126.7 (s, 2C, C_{Ar}), 126.5 (s, 2C, C_{Ar}), 125.6 (s, 2C, C_{Ar}), 125.4 (s, C_{Ar}), 125.2 (q, *J* = 3.8 Hz, 2C, C₁₅), 124.8 (s, C_{Ar}), 124.2 (d, *J* = 272.8 Hz, C₁₆), 106.3 (s, C₃), 105.5 (s, C_{Ar}), 45.6 (s, C₁₂), 25.4 (s, 3C, C₂₄), 19.6 (s, C₂₃), 17.7 (s, C₁₁), -4.4 (s, 2C, C₂₂).

HRMS (ESI) *m/z*: calculated for C₃₁H₃₄F₃NOSiH: 522.2435, found: 522.2430.

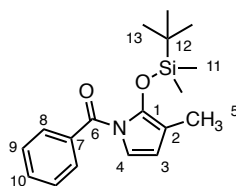
Synthesis of 2-silyloxypyrrole derivative **II.1o**



To a solution of **II.27** (0.603 g, 3.0 mmol, 1.0 equiv) in CH₂Cl₂, 2,6-Lutidine (0.699 mL, 6 mmol, 2.0 equiv) was added. The mixtures were stirred at rt for 10 min, TBSOTf

(0.827 mL, 3.6 mmol, 1.2 equiv) was added subsequently. The mixtures were stirred at rt for further 3 h until the reaction completely finished. Then, the solvent was evaporated under vacuum, and the residue was purified by the flash column chromatography on silica gel (Et₂O/Petroleum ether = 1:10) to afford the corresponding silyl dienol ether **II.1o** (0.907 g, 96%) as a green oil.

{2-[(*tert*-butyldimethylsilyl)oxy]-3-methyl-1*H*-pyrrol-1-yl}(phenyl)methanone (II.1o)



MW: 315.1655 g.mol⁻¹

Molecular Formula: C₁₈H₂₅NO₂Si

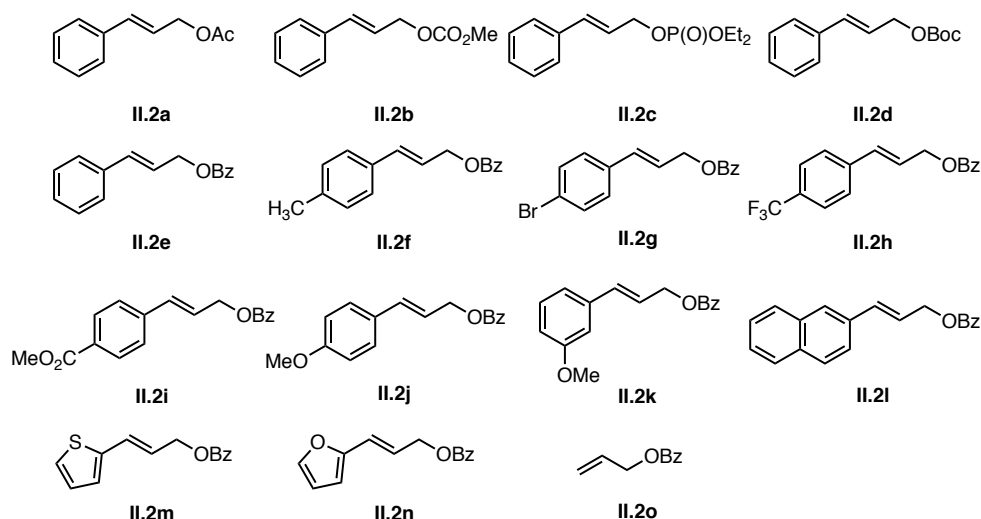
IR (neat): 2929, 2859, 1703, 1615, 1509, 1472, 1415, 1381, 1326, 1299, 1252, 1197, 1176, 1070, 1026, 912, 874 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.76 – 7.73 (m, 2H, H₈), 7.57 – 7.53 (m, 1H, H₁₀), 7.46 – 7.42 (m, 2H, H₉), 6.47 (d, *J* = 3.8 Hz, 1H, H₄), 5.92 (d, *J* = 3.8 Hz, 1H, H₃), 1.93 (s, 3H, H₅), 0.86 (s, 9H, H₁₃), 0.05 (s, 6H, H₁₁).

¹³C NMR (101 MHz, CDCl₃) δ 168.1 (s, C₆), 139.3 (s, C₁), 134.3 (s, C₇), 132.5 (s, C₁₀), 130.4 (s, 2C, C₈), 128.3 (s, 2C, C₉), 114.5 (s, C₄), 112.1 (s, C₃), 103.5 (s, C₂), 25.7 (s, 3C, C₁₃), 18.1 (s, C₁₂), 10.4 (s, C₅), -4.3 (s, 2C, C₁₁).

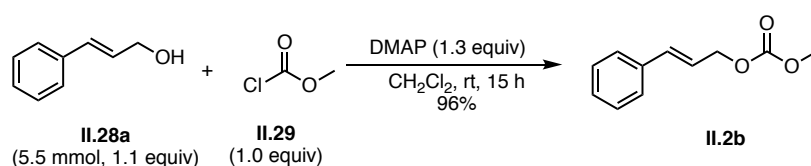
HRMS (ESI) *m/z*: calculated for C₁₈H₂₅NO₂SiNa [M+Na]⁺: 338.1547, found: 338.1543.

6. Synthesis of β-substituted allyl donor reagents

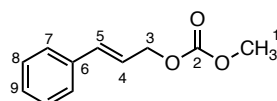


The allylic reagents **II.2a** and **II.2o** were commercially available and used directly as received, **II.2b-n** were synthesized according to the previous reports from the corresponding allyl alcohol.¹¹⁸

The synthesis of cinnamyl methyl carbonate (**II.2b**)¹²⁸



To a solution of cinnamyl alcohol **II.28a** (0.738 g, 5.5 mmol, 1.1 equiv) and DMAP (0.794 g, 1.3 equiv) in CH_2Cl_2 (20 ml) at rt, methyl chloroformate **II.29** (0.473 g, 5 mmol, 1.0 equiv) was added. The reaction mixture was stirred at rt for 15 h. After the reaction was completely finished, the mixture was washed with HCl (10 mL) (1M) solution and extracted with CH_2Cl_2 (2×15 mL), dried over Na_2SO_4 , and concentrated under vacuo. The residue was purified by the flash column chromatography over silica gel (PE/Et₂O = 10:1) to give the pure cinnamyl methyl carbonate **II.2b** (0.922 g, 96%) as a colourless oil.



MW: 192.0786 g.mol⁻¹

Molecular Formula: C₁₁H₁₂O₃

¹²⁸ Tomita, R.; Mantani, K.; Hamasaki, A.; Ishida, T.; Tokunaga, M. *Chem. Eur. J.* **2014**, *20*, 9914-9917.

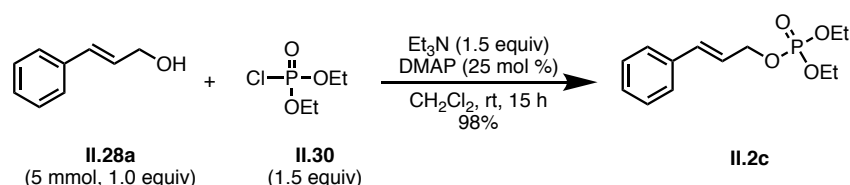
IR (neat): 1743, 1497, 1441, 1379, 1298, 1254, 1118, 944, 905.2 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.41 – 7.39 (m, 2H, H_{Ar}), 7.35 – 7.31 (m, 2H, H_{Ar}), 7.29 – 7.25 (m, 1H, H₉), 6.70 (dd, *J* = 15.9, 1.5 Hz, 1H, H₅), 6.30 (dt, *J* = 15.8, 6.3 Hz, 1H, H₄), 4.80 (dd, *J* = 6.3, 1.3 Hz, 2H, H₃), 3.81 (s, 3H, H₁).

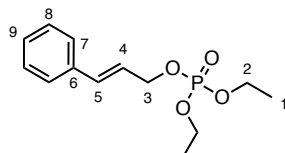
¹³C NMR (101 MHz, CDCl₃) δ 155.8 (s, C₂), 136.2 (s, C₆), 134.9 (s, C₅), 128.7 (s, 2C, C_{Ar}), 128.3 (s, C₉), 126.8 (s, 2C, C_{Ar}), 122.6 (s, C₄), 68.5 (s, C₃), 55.0 (s, C₁).

MS *m/z* (relative intensity): 192 (M⁺, 36), 174 (2), 163 (4), 147 (6), 133 (29), 131 (5), 117 (64), 115 (100), 105 (29), 91 (22), 77 (19), 65 (6), 59 (15), 51 (12).

The synthesis of cinnamyl diethyl phosphate (II.2c)¹²⁹



To a solution of cinnamyl alcohol **II.28a** (0.738 g, 5 mmol, 1.1 equiv) and DMAP (0.153 g, 25 mol %) in CH₂Cl₂ (20 mL), Et₃N (7.5 mmol, 1.5 equiv) and diethyl chlorophosphate **II.30** (1.084 mL, 7.5 mmol, 1.5 equiv) was added at 0 °C. The reaction mixture was stirred at rt for 15 h. After the reaction was completely finished, the mixture was washed with HCl (10 mL) (1M) solution and extracted with CH₂Cl₂ (2×15 mL), dried over Na₂SO₄, and concentrated under vacuo. The residue was purified by the flash column chromatography over silica gel (PE/Et₂O = 10:1) to give the pure cinnamyl diethyl phosphate **II.2c** (1.323 g, 98%) as a colourless oil.



MW: 270.1021 g.mol⁻¹

Molecular Formula: C₁₃H₁₉O₄P

IR (neat): 2984, 1496, 1450, 1393, 1264, 1166, 1101, 1027, 968 cm⁻¹.

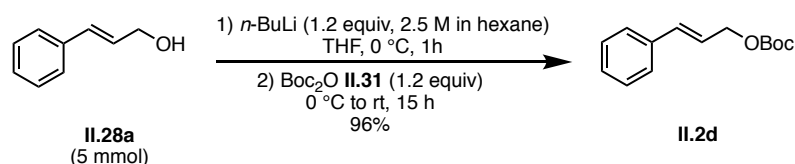
¹²⁹ B. Delves, L.; J. Vyas, D.; Oestreich, M. *Angew. Chem. Int. Ed.* **2013**, 52, 4650-4653.

¹H NMR (400 MHz, CDCl₃) δ 7.41 – 7.38 (m, 2H, H_{Ar}), 7.35 – 7.30 (m, 2H, H_{Ar}), 7.29 – 7.24 (m, 1H, H₉), 6.68 (d, *J* = 15.5 Hz, 1H, H₅), 6.35 – 6.27 (m, 1H, H₄), 4.72 – 4.68 (m, 2H, H₃), 4.18 – 4.10 (m, 4H, H₂), 1.37 – 1.32 (m, 6H, H₁).

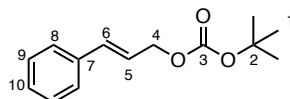
¹³C NMR (101 MHz, CDCl₃) δ 136.1 (s, C₆), 134.0 (s, C₅), 128.7 (s, 2C, C_{Ar}), 128.3 (s, C₉), 126.8 (s, 2C, C_{Ar}), 123.7 (d, *J* = 6.6 Hz, C₄), 68.0 (d, *J* = 5.5 Hz, C₃), 63.9 (d, *J* = 5.8 Hz, 2C, C₂), 16.26 (d, *J* = 7.0 Hz, 2C, C₁)

MS *m/z* (relative intensity): 270 (M⁺, 20), 242 (1), 155 (19), 127 (19), 115 (100), 99 (22), 91 (9), 81 (4), 65 (4), 51 (3).

The synthesis of *tert*-butyl cinnamyl carbonate (**II.2d**)¹³⁰



To a solution of cinnamyl alcohol **II.28a** (5 mmol) in THF (20 mL) under an argon atmosphere, *n*-BuLi (6 mmol, 1.2 equiv, 2.5 M in hexane) was added slowly at 0 °C. The mixture was stirred at 0 °C for 1 h. Boc₂O **II.31** (6 mmol, 1.2 equiv) in THF (5 mL) was added subsequently, the reaction mixture was allowed to stir at rt overnight. When the reaction was completely finished, it was quenched by saturated NH₄Cl solution at 0 °C. The mixture was extracted with EtOAc (3 × 25 mL), washed by brine (30 mL), dried over Na₂SO₄ and concentrated under vacuo. The crude residue was purified by the flash chromatography column on silica gel (PE/Et₂O = 15:1) to give compound **II.2d** (1.124 g, 96%) as a colourless oil.¹³¹



MW: 234.1256 g.mol⁻¹

Molecular Formula: C₁₄H₁₈O₃

¹³⁰ Li, C.; Xing, J.; Zhao, J.; Huynh, P.; Zhang, W.; Jiang, P.; Zhang, Y.-J. *Org. Lett.*, **2012**, *14*, 390-393.

¹³¹ Yuan, Q. J.; Yao, K.; Liu, D. L.; Zhang, W. B. *Chem. Commun.*, **2015**, *51*, 11834-11836.

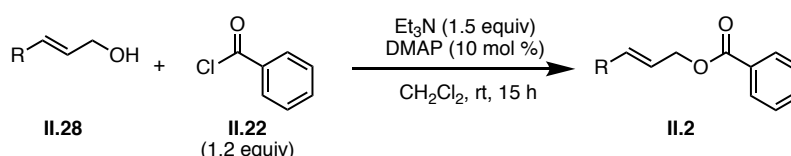
IR (neat): 2980, 1738, 1497, 1450, 1369, 1274, 1254, 1161, 1117, 1086, 1035, 967, 929 cm^{-1} .

^1H NMR (400 MHz, CDCl_3) δ 7.43 – 7.40 (m, 2H, H_{Ar}), 7.37 – 7.32 (m, 2H, H_{Ar}), 7.30 – 7.26 (m, 1H, H_{10}), 6.70 (d, $J = 15.9$ Hz, 1H, H_6), 6.32 (dt, $J = 15.9, 6.4$ Hz, 1H, H_5), 4.75 (dd, $J = 6.5, 1.4$ Hz, 2H, H_4), 1.53 (s, 9H, H_1).

^{13}C NMR (101 MHz, CDCl_3) δ 153.5 (s, C_3), 136.3 (s, C_7), 134.5 (s, C_6), 128.7 (s, 2C, C_{Ar}), 128.2 (s, C_{10}), 126.8 (s, 2C, C_{Ar}), 123.0 (s, C_5), 82.3 (s, C_2), 67.6 (s, C_4), 27.9 (s, 3C, C_1).

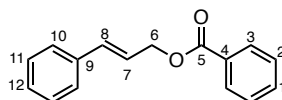
MS m/z (relative intensity): 234 (M^+ , 0.9), 178 (88), 172 (3), 149 (4), 133 (38), 117 (100), 105 (15), 92 (69), 78 (20), 57 (77).

General procedure of synthesis II.2e-n:



To a solution of cinnamyl alcohol **II.28a** (5 mmol, 1.0 equiv) and DMAP (61 mg, 0.5 mmol, 10 mol %) in CH_2Cl_2 (25 mL) at 0 °C, triethylamine (1.04 mL, 7.5 mmol, 1.5 equiv) was added. The mixtures were stirred at 0 °C for 10 min, benzoyl chloride **II.22** (0.696 mL, 6 mmol, 1.2 equiv) was added subsequently. The mixture was stirred at rt for further 15 h until completely finished. Then, HCl (1.0 M) solution was added to the mixture at 0 °C until pH to 7. The mixture solution was extracted with CH_2Cl_2 (2×25 mL), dried over Na_2SO_4 , and concentrated under vacuo. The residue was purified by the flash column chromatography over silica gel to give the pure cinnamyl benzoate **II.2e** (1.19 g, 99%) as a white solid.

Cinnamyl benzoate (**II.2e**)¹³²



MW: 238.0994 $\text{g}\cdot\text{mol}^{-1}$

Molecular Formula: $\text{C}_{16}\text{H}_{14}\text{O}_2$

¹³² Chun, S.; Chung, Y. K. *Org. Lett.*, **2017**, 19, 3787-3790.

Mp: 38–39 °C

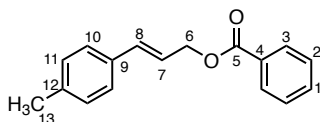
IR (neat): 1716, 1601, 1584, 1495, 1450, 1376, 1314, 1296, 1266, 1176, 1109, 1069, 1026, 965 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 8.06 – 8.03 (m, 2H, H_{Ar}), 7.54 – 7.50 (m, 1H, H_{Ar}), 7.42 – 7.37 (m, 4H, H_{Ar}), 7.31 – 7.20 (m, 3H, H_{Ar}), 6.70 (d, *J* = 15.9 Hz, 1H, H₈), 6.37 (dt, *J* = 15.9, 6.4 Hz, 1H, H₇), 4.94 (dd, *J* = 6.3, 1.4 Hz, 2H, H₆).

¹³C NMR (101 MHz, CDCl₃) δ 166.5 (s, C₅), 136.4 (s, C₉), 134.4 (s, C₈), 133.1 (s, C₁), 130.3 (s, C₉), 129.8 (s, 2C, C_{Ar}), 128.8 (s, 2C, C_{Ar}), 128.5 (s, 2C, C_{Ar}), 128.2 (s, C₁₂), 126.8 (s, 2C, C_{Ar}), 123.4 (s, C₇), 65.7 (s, C₆).

MS *m/z* (relative intensity): 238 (M⁺, 7), 209 (3), 115 (29), 105 (100), 91 (5), 77 (24), 65 (2), 51 (7).

(*E*)-3-(*p*-tolyl)allyl benzoate (II.2f)¹³³



MW: 252.1150 g.mol⁻¹

Molecular Formula: C₁₇H₁₆O₂

Prepared according to the general procedure from (*E*)-3-(*p*-tolyl)prop-2-en-1-ol **II.28b** (0.740 g, 5 mmol). Compound **II.2f** (1.25 g, >99%) was isolated as a white solid

Mp: 37–38 °C.

IR (neat): 1715, 1601, 1584, 1487, 1451, 1376, 1314, 1264, 1176, 1106, 1069, 1026, 964 cm⁻¹.

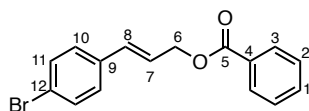
¹H NMR (400 MHz, CDCl₃) δ 8.11 – 8.09 (m, 2H, H₃), 7.60 – 7.55 (m, 1H, H_{Ar}), 7.50 – 7.44 (m, 3H, H_{Ar}), 7.20 – 7.16 (m, 3H, H_{Ar}), 7.0 (d, *J* = 15.8 Hz, 1H, H₈), 6.34 -6.27 (m, 1H, H₇), 5.01 (d, *J* = 6.4 Hz, 2H, H₆), 2.38 (s, 3H, H₁₃).

¹³C NMR (101 MHz, CDCl₃) δ 166.5 (s, C₅), 135.8 (s, C₁₂), 135.5 (s, C₉), 133.1 (s, C₁), 132.3 (s, C₈), 130.5 (s, C_{Ar}), 130.4 (s, C₄), 129.8 (s, 2C, C_{Ar}), 128.5 (s, 2C, C_{Ar}), 128.1 (s, C_{Ar}), 126.3 (s, C_{Ar}), 126.0 (s, C_{Ar}), 124.7 (s, C₇), 65.9 (s, C₆), 19.9 (s, C₁₃).

¹³³ Niwa, T.; Nakada, M. *J. Am. Chem. Soc.*, **2012**, *134*, 13538-13541.

MS m/z (relative intensity): 257 (M^+ , 5), 223 (2), 147 (9), 130 (29), 115 (19), 105 (100), 91 (9), 77 (24), 65 (2), 51 (6).

(E)-3-(4-bromophenyl)allyl benzoate (II.2g)¹¹⁸



MW: 316.0099 g.mol⁻¹

Molecular Formula: C₁₆H₁₃BrO₂

Prepared according to the general procedure from (E)-3-(4-bromophenyl)prop-2-en-1-ol **II.28c** (1.055 g, 5 mmol). Compound **II.2g** (1.580 g, >99%) was isolated as a white solid.

Mp: 50–52 °C

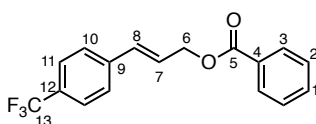
IR (neat): 1716, 1602, 1587, 1487, 1451, 1402, 1374, 1314, 1293, 1267, 1176, 1158, 1110, 1070, 1026, 1009, 966 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 8.10 – 8.09 (m, 2H, H₃), 7.60 – 7.56 (m, 1H), 7.48 – 7.44 (m, 4H, H_{Ar}), 7.31 – 7.21 (m, 2H, H_{Ar}), 6.68 (d, J = 15.9 Hz, 1H, H₈), 6.40 (dt, J = 15.9, 6.3 Hz, 1H, H₇), 4.98 (dd, J = 6.3, 1.3 Hz, 2H, H₆).

¹³C NMR (101 MHz, CDCl₃) δ 166.5 (s, C₅), 135.3 (s, C₉), 133.2 (s, C₈), 133.0 (s, C₁), 131.9 (s, 2C, C_{Ar}), 130.2 (s, C₄), 129.8 (s, 2C, C_{Ar}), 128.5 (s, 2C, C_{Ar}), 128.3 (s, 2C, C_{Ar}), 125.3 (s, C₇), 122.1 (s, C₁₂), 65.4 (s, C₆).

MS m/z (relative intensity): 318 (M^+ , 4), 316 (4), 287 (0.7), 237 (1), 211 (2), 195 (1), 132 (1), 115 (26), 105 (100), 89 (3), 77 (23), 63 (2), 51 (6).

(E)-3-(4-(trifluoromethyl)phenyl)allyl benzoate (II.2h)¹³⁴



MW: 306.0868 g.mol⁻¹

Molecular Formula: C₁₇H₁₃F₃O₂

¹³⁴ Stanely, L. M.; Bai, C.; Ueda, M.; Hartwig, J. F. *J. Am. Chem. Soc.*, **2010**, 132, 8918-8920.

Prepared according to the general procedure from (*E*)-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-ol **II.28d** (1.010 g, 5 mmol). Compound **II.2h** (1.530 g, >99%) was isolated as a white solid.

Mp: 37–38 °C

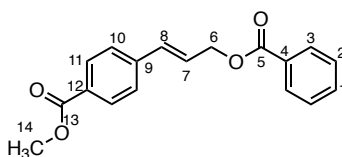
IR (neat): 1718, 1615, 1452, 1415, 1376, 1324, 1266, 1164, 1109, 1066, 1026, 1016, 967, 952 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 8.10 (dd, *J* = 8.1, 1.3 Hz, 2H, H_{Ar}), 7.60 – 7.56 (m, 3H, H_{Ar}), 7.52 – 7.45 (m, 4H, H_{Ar}), 6.77 (d, *J* = 15.9 Hz, 1H, H₈), 6.50 (dt, *J* = 15.9, 6.1 Hz, 1H, H₇), 5.02 (dd, *J* = 6.1, 1.4 Hz, 2H, H₆).

¹³C NMR (101 MHz, CDCl₃) δ 166.4 (s, C₅), 139.8 (s, C₉), 133.3 (s, C₁), 132.5 (s, C₈), 130.1 (s, C₄), 129.8 (s, 2C, C_{Ar}), 129.7 (d, *J* = 44.8 Hz, C₁₃), 128.6 (s, 2C, C_{Ar}), 126.9 (s, 2C, C_{Ar}), 126.2 (s, C₇), 125.7 (q, *J* = 3.7 Hz, 2C, C₁₁), 124.2 (q, *J* = 271.8 Hz, C₁₂), 65.1 (s, C₆).

MS *m/z* (relative intensity): 306 (M⁺, 4), 277 (0.5), 185 (4), 165 (5), 145 (2), 133 (1), 105 (100), 89 (0.5), 77 (21), 63 (0.7), 51 (5).

Methyl (*E*)-4-(3-(benzoyloxy)prop-1-en-1-yl)benzoate (II.2i**)**



MW: 296.1049 g.mol⁻¹

Molecular Formula: C₁₈H₁₆O₄

Prepared according to the general procedure from methyl (*E*)-4-(3-hydroxyprop-1-en-1-yl)benzoate **II.28e** (0.960 g, 5 mmol). Compound **II.2i** (1.480 g, >99%) was isolated as a white solid.

Mp: 69–70 °C.

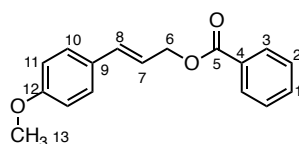
IR (neat): 1714, 1605, 1451, 1435, 1413, 1376, 1313, 1263, 1177, 1106, 1070, 1026, 1018, 958 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 8.11–8.08 (m, 2H, H_{Ar}), 8.02–8.00 (m, 2H, H_{Ar}), 7.60–7.55 (m, 1H, H₁), 7.49–7.43 (m, 4H, H_{Ar}), 6.77 (d, *J* = 16.1 Hz, 1H, H₈), 6.52 (dt, *J* = 16.0, 6.2 Hz, 1H, H₇), 5.01 (dd, *J* = 6.2, 1.4 Hz, 2H, H₆), 3.91 (s, 3H, H₁₄).

¹³C NMR (101 MHz, CDCl₃) δ 166.9 (s, C₅ or C₁₂), 166.5 (s, C₅ or C₁₂), 140.8 (s, C₉), 133.3 (s, C₈), 133.0 (s, C₁), 130.2 (s, C₁₁ or C₄), 130.1 (s, 2C, C_{Ar}), 129.8 (s, 2C, C_{Ar}), 129.6 (s, C₁₁ or C₄), 128.6 (s, 2C, C_{Ar}), 126.7 (s, 2C, C_{Ar}), 126.2 (s, C₇), 65.2 (s, C₆), 52.3 (s, C₁₄).

HRMS (ESI) *m/z*: calculated for C₁₈H₁₆O₄Na [M+Na]⁺: 319.0941, found: 319.0937.

(*E*)-3-(4-methoxyphenyl)allyl benzoate (II.2j)¹³⁵



MW: 268.1099 g.mol⁻¹

Molecular Formula: C₁₇H₁₆O₃

Prepared according to the general procedure from methyl (*E*)-3-(4-methoxyphenyl)prop-2-en-1-ol **II.28f** (0.805 g, 5 mmol). Compound **II.2j** (1.340 g, >99%) was isolated as a white solid.

Mp: 54–56 °C.

IR (neat): 1787, 1714, 1606, 1578, 1511, 1452, 1421, 1377, 1325, 1314, 1267, 1246, 1174, 1108, 1067, 1026, 967 cm⁻¹.

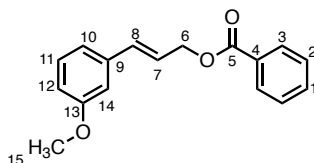
¹H NMR (400 MHz, CDCl₃) δ 8.09 (d, *J* = 8.0 Hz, 2H, H_{Ar}), 7.56 (t, *J* = 7.7 Hz, 1H, H₁), 7.45 (t, *J* = 7.8 Hz, 2H, H_{Ar}), 7.36 (d, *J* = 8.7 Hz, 2H, H_{Ar}), 6.87 (d, *J* = 8.5 Hz, 2H, H_{Ar}), 6.70 (d, *J* = 15.8 Hz, 1H, H₈), 6.28 (dt, *J* = 15.8, 7.2 Hz, 1H, H₇), 4.97 (d, *J* = 6.6 Hz, 2H, H₆), 3.81 (s, 3H, H₁₃).

¹³C NMR (101 MHz, CDCl₃) δ 166.6 (s, C₅), 159.7 (s, C₁₂), 134.2 (s, C₈), 133.1 (s, C₁), 130.4 (s, C₄ or C₉), 129.8 (s, 2C, C_{Ar}), 129.1 (s, C₄ or C₉), 128.5 (s, 2C, C_{Ar}), 128.0 (s, 2C, C_{Ar}), 121.1 (s, C₇), 114.1 (s, 2C, C_{Ar}), 66.0 (s, C₆), 55.4 (s, C₁₃).

MS *m/z* (relative intensity): 268 (M⁺, 16), 239 (0.5), 163 (35), 147 (14), 131 (11), 117 (3), 105 (100), 103 (11), 91 (10), 77 (24), 65 (2), 51 (6).

¹³⁵ Lim, S.; Ji, M.; Wang, X.; Lee, C.; Jang, H.-Y. *Eur. J. Org. Chem.* **2015**, 3, 591-595.

(E)-3-(3-methoxyphenyl)allyl benzoate (II.2k)



MW: 268.1099 g.mol⁻¹

Molecular Formula: C₁₇H₁₆O₃

Prepared according to the general procedure from methyl (E)-3-(2-methoxyphenyl)prop-2-en-1-ol **II.28g** (0.805 g, 5 mmol). Compound **II.2k** (1.340 g, >99%) was isolated as a colourless oil.

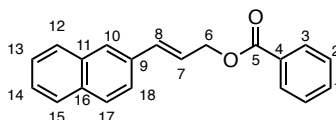
IR (neat): 1714, 1599, 1580, 1489, 1451, 1435, 1375, 1314, 1264, 1174, 1157, 1109, 1069, 1047, 1026, 965 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 8.11 – 8.08 (m, 2H, H₃), 7.59 – 7.55 (m, 1H, H₁), 7.48 – 7.44 (m, 2H, H₂), 7.25 (t, *J* = 7.6 Hz, 1H, H₁₁), 7.02 (d, *J* = 7.7 Hz, 1H, H₁₀), 6.96 (s, 1H, H₁₄), 6.83 (dd, *J* = 8.2, 2.6 Hz, 1H, H₁₂), 6.73 (d, *J* = 15.9 Hz, 1H, H₈), 6.41 (dt, *J* = 15.9, 6.3 Hz, 1H, H₇), 4.99 (dd, *J* = 6.4, 1.4 Hz, 2H, H₆), 3.82 (s, 3H, H₁₅).

¹³C NMR (101 MHz, CDCl₃) δ 166.5 (s, C₅), 159.9 (s, C₁₃), 137.8 (s, C₉), 134.3 (s, C₈), 133.1 (s, C₁), 130.3 (s, C₄), 129.8 (s, 2C, C₃), 129.7 (s, C₁₁), 128.5 (s, 2C, C₂), 123.7 (s, C₇), 119.5 (s, C₁₀), 114.0 (s, C₁₂), 111.9 (s, C₁₄), 65.6 (s, C₆), 55.4 (s, C₁₅).

MS *m/z* (relative intensity): 268 (M⁺, 14), 239 (0.8), 163 (20), 147 (3), 131 (5), 117 (2), 105 (100), 103 (8), 91 (7), 77 (23), 65 (2), 51 (5).

(E)-3-(naphthalen-2-yl)allyl benzoate (II.2l)¹³⁶



MW: 288.1150 g.mol⁻¹

Molecular Formula: C₂₀H₁₆O₂

¹³⁶ Seo, H.; Hirsch-Weil, D.; Abboud, K. A.; Hong, S. J. *Org. Chem.*, **2008**, *73*, 1983-1986.

Prepared according to the general procedure from methyl (*E*)-3-(naphthalen-2-yl)prop-2-en-1-ol **II.28h** (0.920 g, 5 mmol). Compound **II.2i** (1.440 g, >99%) was isolated as a white solid.

Mp: 99–100 °C.

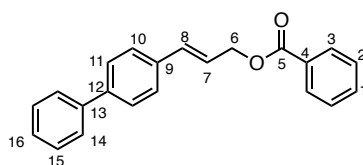
IR (neat): 1714, 1598, 1508, 1450, 1373, 1353, 1314, 1298, 1266, 1175, 1113, 1091, 1069, 1024, 975, 939, 904 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 8.14 – 8.12 (m, 2H, H_{Ar}), 7.83 – 7.79 (m, 4H, H_{Ar}), 7.65 – 7.56 (m, 2H, H_{Ar}), 7.50 – 7.45 (m, 4H, H_{Ar}), 6.91 (d, *J* = 15.9 Hz, 1H, H₈), 6.55 (dt, *J* = 15.8, 6.4 Hz, 1H, H₇), 5.06 (dd, *J* = 6.4, 1.4 Hz, 2H, H₆).

¹³C NMR (101 MHz, CDCl₃) δ 166.6 (s, C₅), 134.4 (s, C₈), 133.8 (s, C_{Ar}), 133.6 (s, C_{Ar}), 133.3 (s, C_{Ar}), 133.2 (s, C₁), 130.3 (s, C_{Ar}), 129.8 (s, 2C, C_{Ar}), 128.5 (s, 2C, C_{Ar}), 128.4 (s, C_{Ar}), 128.2 (s, C_{Ar}), 127.8 (s, C_{Ar}), 127.0 (s, C_{Ar}), 126.5 (s, C_{Ar}), 126.2 (s, C_{Ar}), 123.7 (s, C_{Ar}), 123.6 (s, C₇), 65.7 (s, C₆).

MS *m/z* (relative intensity): 288 (M⁺, 13), 183 (18), 165 (24), 152 (9), 139 (1), 128 (2), 115 (2), 105 (100), 89 (0.5), 77 (17), 63 (0.8), 51 (3).

(*E*)-3-([1,1'-biphenyl]-4-yl)allyl benzoate (II.2m**)¹¹⁸**



MW: 314.1307 g.mol⁻¹

Molecular Formula: C₂₂H₁₈O₂

Prepared according to the general procedure from methyl (*E*)-3-([1,1'-biphenyl]-4-yl)prop-2-en-1-ol **II.28i** (1.05 g, 5 mmol). Compound **II.2m** (1.340 g, >99%) was isolated as a colourless oil.

Mp: 76–78 °C

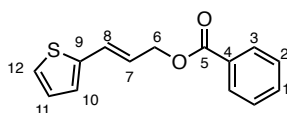
IR (neat): 1715, 1601, 1487, 1376, 1314, 1267, 1213, 1175, 1109, 1070, 1026, 1007, 968, 949, 907 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 8.14 – 8.11 (m, 2H), 7.63 – 7.44 (m, 11H), 7.39 – 7.34 (m, 1H), 6.80 (d, *J* = 15.9 Hz, 1H), 6.47 (dt, *J* = 15.9, 6.4 Hz, 1H), 5.03 (dd, *J* = 6.4, 1.3 Hz, 2H).

¹³C NMR (101 MHz, CDCl₃) δ 166.5 (s, C₅), 140.9 (s, C₁₂ or C₁₃), 140.7 (s, C₁₂ or C₁₃), 135.4 (s, C₉), 133.9 (s, C₈), 133.1 (s, C₁), 130.3 (s, C₄), 129.8 (s, 2C, C_{Ar}), 128.9 (s, 2C, C_{Ar}), 128.5 (s, 2C, C_{Ar}), 127.5 (s, C₁₆), 127.4 (s, 2C, C_{Ar}), 127.2 (s, 2C, C_{Ar}), 127.1 (s, 2C, C_{Ar}), 123.4 (s, C₇), 65.7 (s, C₆).

HRMS (ESI) *m/z*: calculated for C₂₂H₁₈O₂Na [M+Na]⁺: 337.1199, found: 337.1199.

(*E*)-3-(thiophen-2-yl)allyl benzoate (II.2n)¹³⁷



MW: 244.0558 g.mol⁻¹

Molecular Formula: C₁₄H₁₂O₂S

Prepared according to the general procedure from methyl (*E*)-3-(thiophen-2-yl)prop-2-en-1-ol **II.28j** (0.700 g, 5 mmol). Compound **II.2n** (1.220 g, >99%) was isolated as a colourless oil

IR (neat): 1714, 1650, 1601, 1450, 1378, 1314, 1263, 1206, 1175, 1110, 1069, 1042, 1026, 952 cm⁻¹.

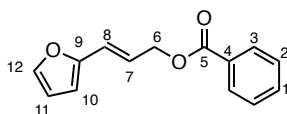
¹H NMR (400 MHz, CDCl₃) δ 8.09 (dd, *J* = 8.3, 1.6 Hz, 2H, H₃), 7.57 (t, *J* = 7.4 Hz, 1H, H₁), 7.47 – 7.43 (m, 2H, H₂), 7.20 (d, *J* = 5.1 Hz, 1H, H₁₂), 7.02 – 6.96 (m, 2H, H₁₀ and H₁₁), 6.88 (d, *J* = 15.6 Hz, 1H, H₈), 6.24 (dt, *J* = 15.3, 6.5 Hz, 1H, H₇), 4.95 (d, *J* = 6.5 Hz, 2H, H₆).

¹³C NMR (101 MHz, CDCl₃) δ 166.5 (s, C₅), 141.3 (s, C₉), 133.2 (s, C₁), 130.3 (s, C₄), 129.8 (s, 2C, C₃), 128.5 (s, 2C, C₂), 127.60 (s, C₈), 127.56 (s, C₁₁), 126.7 (s, C₁₀), 125.1 (s, C₁₂), 122.8 (s, C₇), 65.3 (s, C₆).

MS *m/z* (relative intensity): 244 (M⁺, 14), 215 (2), 139 (20), 121 (12), 105 (100), 96 (3), 79 (7), 77 (32), 65 (2), 51 (8).

¹³⁷ Zhang, Y.; Li, Z.; Liu, Z.-Q. *Org. Lett.*, **2012**, 14, 226-229

(*E*)-3-(furan-2-yl)allyl benzoate (II.2o)¹³⁸



MW: 228.0786 g.mol⁻¹

Molecular Formula: C₁₄H₁₂O₃

Prepared according to the general procedure from methyl (*E*)-3-(furan-2-yl)prop-2-en-1-ol **II.28k** (0.620 g, 5 mmol). Compound **II.2o** (1.140 g, >99%) was isolated as a colourless oil

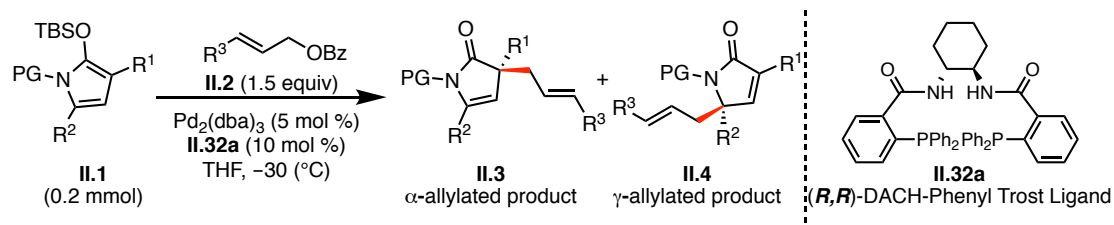
IR (neat): 1714, 1602, 1584, 1489, 1451, 1371, 1314, 1265, 1176, 1152, 1111, 1069, 1026, 1014, 957 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 8.10 – 8.08 (m, 2H, H₃), 7.56 – 7.55 (m, 1H, H₁), 7.47 – 7.43 (m, 2H, H₂), 7.37 (d, *J* = 1.8 Hz, 1H, H₁₂), 6.56 (d, *J* = 15.8 Hz, 1H, H₈), 6.39 – 6.30 (m, 3H, H₇, H₁₀ and H₁₁), 4.96 (dd, *J* = 6.3, 1.4 Hz, 2H, H₆).

¹³C NMR (101 MHz, CDCl₃) δ 166.4 (s, C₅), 152.0 (s, C₉), 142.5 (s, C₁₂), 133.1 (s, C₁), 130.3 (s, C₄), 129.8 (s, 2C, C₃), 128.5 (s, 2C, C₂), 122.3 (s, C₈), 121.9 (s, C₇), 111.5 (s, C₁₁), 109 (s, C₁₀), 65.2 (s, C₆).

MS *m/z* (relative intensity): 228 (M⁺, 17), 199 (1), 123 (11), 105 (100), 95 (1), 77 (42), 65 (2), 55 (1), 51 (11).

7. Substrate scope and limitation



General procedure for the chiral allylic alkylation:

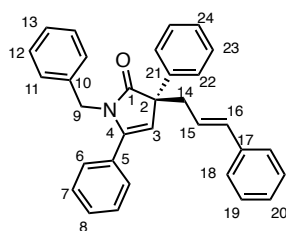
¹³⁸ Mahajan, P. S.; Gonnade, R. G.; Mhaske, S. B. *Eur. J. Org. Chem.* **2014**, 36, 8049-8054.

To a solution of $\text{Pd}_2(\text{dba})_3$ (9 mg, 0.01 mmol, 0.05 equiv) in THF (1.5 mL) at rt was added the (*R,R*)-DACH phenyl Trost ligand **II.32a** (14 mg, 0.02 mmol, 0.1 equiv) and the mixture was stirred at rt for 1 h. In parallel, a solution of the dienol silyl ether substrate **II.1a** (87.8 mg, 0.2 mmol, 1.0 equiv) and cinnamyl benzoate **II.2e** (71.4 mg, 0.3 mmol, 1.5 equiv) in THF (0.5 mL) at rt was prepared. Both mixtures were cooled to $-30\text{ }^\circ\text{C}$ and the solution containing the catalyst was transferred to substrate solution *via* cannula. The reaction was stirred at $-30\text{ }^\circ\text{C}$ until complete consumption of the starting material (reaction monitored by TLC). Once completed, a saturated aqueous solution of NH_4Cl (2 mL) was added and the aqueous phase was extracted with EtOAc ($3 \times 5\text{ mL}$). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4 , filtered and evaporated under reduced pressure to afford a crude residue, which was purified by flash column chromatography over silica gel (PE/EtOAc = 15:1) to afford the corresponding major allylated product **II.3a** (78.0 mg, 89%) as a white solid.

General procedure for the racemic allylic alkylation:

To a solution of the enol silyl ether **II.1a** (0.2 mmol, 1.0 equiv) and $\text{Pd}(\text{PPh}_3)_4$ (12 mg, 0.01 mmol, 0.05 equiv) in THF (1 mL) was added cinnamyl benzoate **II.2e** (0.3 mmol, 1.5 equiv), the reaction mixture was stirred at rt for 15 h until complete consumption of the starting material (reaction monitored by TLC). The reaction mixture was then filtered through Celite[®] and washed by CH_2Cl_2 to remove the Pd salts and evaporated under reduced pressure to afford a crude residue, which was purified by flash column chromatography over silica gel to afford the corresponding racemic α -allylated product **II.3a**.

(*S*)-1-Benzyl-3-cinnamyl-3,5-diphenyl-1,3-dihydro-2*H*-pyrrol-2-one (**II.3a**)



MW: 441.2093 g.mol⁻¹

Molecular Formula: C₃₂H₂₇NO

Mp: 121–122 °C

[α] $^{20}_{\text{D}}$ = –49.1 (c = 1.25, CHCl₃), ee = –84% (determined by SFC) from (*S,S*)-**II.32a**.

SFC: AD-H column, pressure = 100 bar, eluent = CO₂/MeOH (80:20), flow rate = 5.0 mL/min, detection wavelength = 220 nm, t_{R1} = 9.05 (major), t_{R2} = 50.98 (minor).

IR (neat): 3028, 1702, 1598, 1494, 1446, 1374, 1353, 1217, 1187, 1140, 1076, 1030, 966, 910 cm^{–1}.

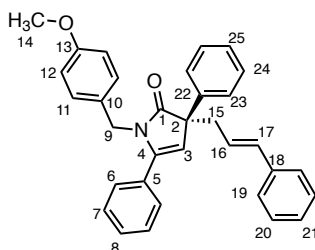
^1H NMR (400 MHz, CDCl₃) δ 7.67 – 7.64 (m, 2H, H_{Ar}), 7.43 – 7.17 (m, 13H, H_{Ar}), 7.12 – 7.07 (m, 1H, H_{Ar}), 7.00 – 6.96 (m, 2H, H_{Ar}), 6.90 (dd, J = 8.0, 1.1 Hz, 2H, H_{Ar}), 6.55 (d, J = 15.7 Hz, 1H, H₂₀), 6.15 – 6.07 (m, 1H, H₁₉), 5.70 (s, 1H, H₃), 4.81 (d, J_{AB} = 15.6 Hz, 1H, H₉), 4.50 (d, J_{AB} = 15.7 Hz, 1H, H₉), 3.12 (ddd, J = 13.3, 8.0, 1.2 Hz, 1H, H₁₈), 3.03 (ddd, J = 13.4, 6.8, 1.4 Hz, 1H, H₁₈).

^{13}C NMR (101 MHz, CDCl₃) δ 180.5 (s, C₁), 145.0 (s, C_{Ar}), 140.1 (s, C_{Ar}), 137.5 (s, C_{Ar}), 137.3 (s, C_{Ar}), 133.8 (s, C₁₆), 131.5 (s, C_{Ar}), 129.1 (s, C_{Ar}), 128.8 (s, 2C, C_{Ar}), 128.6 (s, 2C, C_{Ar}), 128.6 (s, 2C, C_{Ar}), 128.5 (s, 2C, C_{Ar}), 128.4 (s, 2C, C_{Ar}), 127.40 (s, C_{Ar}), 127.38 (s, 3C, C_{Ar}), 127.1 (s, C_{Ar}), 127.0 (s, 2C, C_{Ar}), 126.4 (s, 2C, C_{Ar}), 124.9 (s, C₁₅), 111.4 (s, C₃), 57.7 (s, C₂), 44.6 (s, C₉), 42.5 (s, C₁₄).

HRMS (ESI) m/z : calculated for C₃₂H₂₇NONa [$M+\text{Na}$]⁺: 464.1985, found: 464.1984.

(*R*)-3-Cinnamyl-1-(4-methoxybenzyl)-3,5-diphenyl-1,3-dihydro-2H-pyrrol-2-one

(II.3b)



MW: 471.2198 g.mol^{–1}

Molecular Formula: C₃₃H₂₉NO₂

Compound **II.3b** was synthesized according to the general method from 2-[(*tert*-butyldimethylsilyl)oxy]-1-(4-methoxybenzyl)-3,5-diphenyl-1*H*-pyrrole **II.1b** (93.8 mg, 0.2 mmol) and cinnamyl benzoate **II.2e** (71.4 mg, 0.3 mmol, 1.5 equiv). Compound **II.3b** was isolated as a white solid (65.0 mg, 69%) after purification by flash column chromatography over silica gel (PE/EtOAc = 10:1).

Mp: 137–139 °C.

$[\alpha]_D^{20}$ = 43.7 (c = 1.77, CHCl₃), ee = 81% (determined by SFC).

SFC: AD-H column, pressure = 100 bar, eluent = CO₂/MeOH (85:15), flow rate = 5.0 mL/min, detection wavelength = 220 nm, t_{R1} = 13.02 (minor), t_{R2} = 49.93 (major).

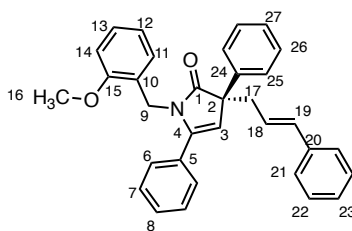
IR (neat): 1844, 1801, 1771, 1750, 1702, 1647, 1611, 1600, 1513, 1493, 1462, 1446, 1374, 1352, 1292, 1246, 1141, 1110, 1074, 1032, 967, 917 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.65 (d, J = 7.2 Hz, 2H, H_{Ar}), 7.42 – 7.19 (m, 13H, H_{Ar}), 6.79 (d, J = 8.5 Hz, 2H, H₁₁), 6.55 (d, J = 15.8 Hz, 1H, H₁₇), 6.47 (d, J = 8.5 Hz, 2H, H₁₂), 6.09 (dt, J = 15.2, 7.4 Hz, 1H, H₁₆), 5.68 (s, 1H, H₃), 4.80 (d, J = 15.3 Hz, 1H, H₉), 4.39 (d, J = 15.4 Hz, 1H, H₉), 3.67 (s, 3H, H₁₄), 3.13 (dd, J = 13.3, 8.0 Hz, 1H, H₁₅), 3.00 (dd, J = 13.4, 6.8 Hz, 1H, H₁₅).

¹³C NMR (101 MHz, CDCl₃) δ 180.4 (s, C₁), 158.6 (s, C₁₃), 145.0 (s, C_{Ar}), 140.1 (s, C_{Ar}), 137.4 (s, C_{Ar}), 133.8 (s, C₁₇), 131.6 (s, C_{Ar}), 129.6 (s, C_{Ar}), 129.1 (s, C_{Ar}), 128.8 (s, 2C, C₁₁), 128.7 (s, 2C, C_{Ar}), 128.60 (s, 2C, C_{Ar}), 128.58 (s, 2C, C_{Ar}), 128.5 (s, 2C, C_{Ar}), 127.4 (s, C_{Ar}), 127.3 (s, C_{Ar}), 126.9 (s, 2C, C_{Ar}), 126.4 (s, 2C, C_{Ar}), 125.0 (s, C₁₆), 113.7 (s, 2C, C₁₂), 111.4 (s, C₃), 57.7 (s, C₂), 55.2 (s, C₁₄), 44.0 (s, C₉), 42.5 (s, C₁₅).

HRMS (ESI) m/z : calculated for C₃₃H₂₉NO₂Na [M+Na]⁺: 494.2091, found: 494.2091.

(*R*)-3-Cinnamyl-1-(2-methoxybenzyl)-3,5-diphenyl-1,3-dihydro-2*H*-pyrrol-2-one
(II.3c)



MW: 471.2198 g.mol⁻¹

Molecular Formula: C₃₃H₂₉NO₂

Compound **II.3c** was synthesized according to the general method from 2-[(*tert*-butyldimethylsilyl)oxy]-1-(2-methoxybenzyl)-3,5-diphenyl-1*H*-pyrrole **II.1c** (93.8 mg, 0.2 mmol) and cinnamyl benzoate **II.2e** (71.4 mg, 0.3 mmol, 1.5 equiv). Compound

II.3c was isolated as a colourless oil (56.0 mg, 60%) after purification by flash column chromatography over silica gel (PE/EtOAc = 10:1).

$[\alpha]_D^{20} = 38.0$ ($c = 1.2$, CHCl_3), $ee = 80\%$ (determined by SFC).

SFC: AD-H column, pressure = 100 bar, eluent = CO_2/MeOH (85:15), flow rate = 5.0 mL/min, detection wavelength = 220 nm, $t_{R1} = 19.37$ (minor), $t_{R2} = 33.53$ (major).

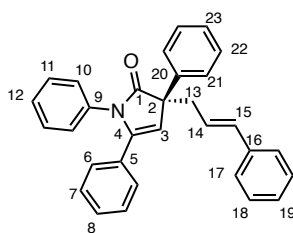
IR (neat): 1703, 1600, 1492, 1462, 1446, 1350, 1288, 1243, 1173, 1110, 1050, 1029, 967, 912 cm^{-1} .

^1H NMR (400 MHz, CDCl_3) δ 7.70 (d, $J = 7.6$ Hz, 2H, H_{Ar}), 7.42 (t, $J = 7.6$ Hz, 2H, H_{Ar}), 7.35 – 7.21 (m, 11H, H_{Ar}), 7.09 (t, $J = 7.2$ Hz, 1H, H_{12}), 6.93 (d, $J = 7.0$ Hz, 1H, H_{11}), 6.67 (d, $J = 8.2$ Hz, 1H, H_{14}), 6.57 (d, $J = 15.8$ Hz, 1H, H_{19}), 6.47 (t, $J = 7.5$ Hz, 1H, H_{13}), 6.18 (dt, $J = 15.3, 7.4$ Hz, 1H, H_{18}), 5.75 (s, 1H, H_3), 4.71 (s, 2H, H_9), 3.53 (s, 3H, H_{16}), 3.14 – 3.03 (m, 2H, H_{17}).

^{13}C NMR (101 MHz, CDCl_3) δ 180.5 (s, C_1), 156.5 (s, C_{15}), 145.4 (s, C_{Ar}), 140.3 (s, C_{Ar}), 137.4 (s, C_{Ar}), 133.8 (s, C_{17}), 131.6 (s, C_{Ar}), 128.9 (s, C_{Ar}), 128.7 (s, 2C, C_{Ar}), 128.6 (s, 2C, C_{Ar}), 128.4 (s, 2C, C_{Ar}), 128.1 (s, 2C, C_{Ar}), 128.0 (s, C_{12}), 127.9 (s, C_{11}), 127.4 (s, C_{Ar}), 127.3 (s, C_{Ar}), 127.1 (s, 2C, C_{Ar}), 126.4 (s, 2C, C_{Ar}), 125.4 (s, C_{Ar}), 125.1 (s, C_{18}), 120.4 (s, C_{13}), 111.1 (s, C_3), 110.0 (s, C_{14}), 57.7 (s, C_2), 55.0 (s, C_{16}), 42.6 (s, C_{17}), 39.8 (s, C_9).

HRMS (ESI) m/z : calculated for $\text{C}_{33}\text{H}_{29}\text{NO}_2\text{Na}$ $[\text{M}+\text{Na}]^+$: 494.2091, found: 494.2090.

(*R*)-3-Cinnamyl-1,3,5-triphenyl-1,3-dihydro-2*H*-pyrrol-2-one (**II.3d**)



MW: 427.1936 $\text{g}\cdot\text{mol}^{-1}$

Molecular Formula: $\text{C}_{31}\text{H}_{25}\text{NO}$

Compound **II.3d** was synthesized according to the general method from 2-[(*tert*-butyldimethylsilyl)oxy]-1,3,5-triphenyl-1*H*-pyrrole **II.1d** (85.0 mg, 0.2 mmol) and cinnamyl benzoate **II.2e** (71.4 mg, 0.3 mmol, 1.5 equiv). Compound **II.3d** was isolated

as a white solid (17.0 mg, 20%) after purification by flash column chromatography over silica gel (PE/Et₂O = 10:1).

Mp: 106–108 °C.

[α]²⁰_D = 73.5 (*c* = 1.0, CHCl₃), *ee* = 80% (determined by SFC).

SFC: AD-H column, pressure = 100 bar, eluent = CO₂/MeOH (85:15), flow rate = 5.0 mL/min, detection wavelength = 220 nm, *t*_{R1} = 9.16 (minor), *t*_{R2} = 12.23 (major).

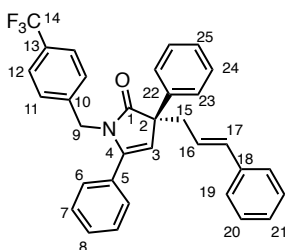
IR (neat): 1717, 1597, 1493, 1447, 1362, 1316, 1295, 1168, 1074, 1030, 967, 916 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.71 (d, *J* = 7.4 Hz, 2H, H_{Ar}), 7.42 (t, *J* = 7.6 Hz, 2H, H_{Ar}), 7.35–7.15 (m, 14H, H_{Ar}), 6.98 (d, *J* = 7.0 Hz, 2H, H_{Ar}), 6.57 (d, *J* = 15.8 Hz, 1H, H₁₅), 6.19 (dt, *J* = 15.4, 7.4 Hz, 1H, H₁₄), 5.95 (s, 1H, H₃), 3.16–3.07 (m, 2H, H₁₃).

¹³C NMR (101 MHz, CDCl₃) δ 179.5 (s, C₁), 144.5 (s, C_{Ar}), 139.7 (s, C_{Ar}), 137.3 (s, C_{Ar}), 135.6 (s, C_{Ar}), 134.0 (s, C₁₅), 131.2 (s, C_{Ar}), 128.77 (s, 2C, C_{Ar}), 128.76 (s, C_{Ar}), 128.70 (s, 2C, C_{Ar}), 128.6 (s, 2C, C_{Ar}), 128.3 (s, 2C, C_{Ar}), 127.8 (s, 2C, C_{Ar}), 127.5 (s, C_{Ar}), 127.4 (s, C_{Ar}), 127.1 (s, 4C, C_{Ar}), 126.9 (s, C_{Ar}), 126.3 (s, 2C, C_{Ar}), 124.6 (s, C₁₄), 112.1 (s, C₃), 58.1 (s, C₂), 42.9 (s, C₁₃).

HRMS (ESI) *m/z*: calculated for C₃₁H₂₅NONa [M+Na]⁺: 450.1828, found: 450.1830.

(*R*)-3-Cinnamyl-3,5-diphenyl-1-[4-(trifluoromethyl)benzyl]-1,3-dihydro-2*H*-pyrrol-2-one (II.3e)



MW: 509.1966 g.mol⁻¹

Molecular Formula: C₃₃H₂₆F₃NO

Compound **II.3e** was synthesized according to the general method from 3,5-diphenyl-1-[4-(trifluoromethyl)benzyl]-1,3-dihydro-2*H*-pyrrol-2-one **II.1e** (101.4 mg, 0.2 mmol) and cinnamyl benzoate **II.2e** (71.4 mg, 0.3 mmol, 1.5 equiv). Compound **II.3e** was isolated as yellow solid (95.0 mg, 93%) after purification by flash column chromatography over silica gel (PE/Et₂O = 12:1).

Mp: 92–94 °C.

[α]²⁰_D = 27.2 (*c* = 5.1, CHCl₃), ee = 89% (determined by SFC).

SFC: AD-H column, pressure = 100 bar, eluent = CO₂/MeOH (85:15), flow rate = 5.0 mL/min, detection wavelength = 220 nm, *t*_{R1} = 5.26 (major), *t*_{R2} = 7.96 (minor).

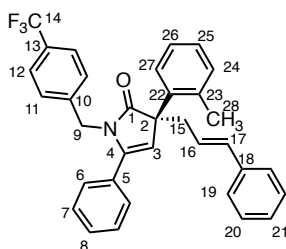
IR (neat): 1704, 1688, 1620, 1599, 1511, 1493, 1446, 1421, 1394, 1352, 1324, 1253, 1164, 1122, 1067, 1030, 1019, 967, 942, 911 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.63 (d, *J* = 7.7 Hz, 2H, H_{Ar}), 7.41 – 7.25 (m, 11H, H_{Ar}), 7.14 (d, *J* = 7.5 Hz, 2H, H_{Ar}), 7.08 (d, *J* = 7.9 Hz, 2H, H_{Ar}), 6.95 (d, *J* = 8.0 Hz, 2H, H_{Ar}), 6.57 (d, *J* = 15.8 Hz, 1H, H₁₇), 6.16 – 6.08 (m, 1H, H₁₆), 5.72 (s, 1H, H₃), 4.86 (d, *J*_{AB} = 15.9 Hz, 1H, H₉), 4.45 (d, *J*_{AB} = 15.9 Hz, 1H, H₉), 3.12 (dd, *J* = 13.4, 8.5 Hz, 1H, H₁₅), 3.00 (dd, *J* = 13.4, 6.4 Hz, 1H, H₁₅).

¹³C NMR (101 MHz, CDCl₃) δ 180.4 (s, C₁), 144.7 (s, C_{Ar}), 141.4 (s, C_{Ar}), 139.9 (s, C_{Ar}), 137.2 (s, C_{Ar}), 134.2 (s, C_{Ar}), 131.2 (s, C_{Ar}), 129.4 (s, C_{Ar}), 129.3 (d, *J* = 32.2 Hz, C₁₄), 128.9 (s, 2C, C_{Ar}), 128.8 (s, 2C, C_{Ar}), 128.7 (s, 2C, C_{Ar}), 128.5 (s, 2C, C_{Ar}), 127.7 (s, C_{Ar}), 127.6 (s, C_{Ar}), 127.5 (s, 2C, C_{Ar}), 126.9 (s, 2C, C_{Ar}), 126.3 (s, 2C, C_{Ar}), 125.4 (q, *J* = 3.6 Hz, 2C, C₁₂), 124.7 (s, C₁₆), 124.1 (d, *J* = 273.0 Hz, C₁₃), 111.5 (s, C₃), 57.9 (s, C₂), 44.2 (s, C₉), 42.5 (s, C₁₅).

HRMS (ESI) *m/z*: calculated for C₃₃H₂₆F₃NONa [M+Na]⁺: 532.1859, found: 532.1857.

(*R*)-3-Cinnamyl-5-phenyl-3-(*o*-tolyl)-1-(4-(trifluoromethyl)benzyl)-1,3-dihydro-2*H*-pyrrol-2-one (II.3f)



MW: 523.2123 g.mol⁻¹

Molecular Formula: C₃₄H₂₈F₃NO

Compound **II.3f** was synthesized according to the general method from 2-[(*tert*-butyldimethylsilyl)oxy]-5-phenyl-3-(*o*-tolyl)-1-[4-(trifluoromethyl)benzyl]-1*H*-pyrrole **II.1f** (104.2 mg, 0.2 mmol) and cinnamyl benzoate **II.2e** (71.4 mg, 0.3 mmol, 1.5 equiv).

Compound **II.3f** was isolated as a colourless oil (47.0 mg, 45%) after purification by flash column chromatography over silica gel (PE/Et₂O = 1:10).

[α]_D²⁰ = −12.5 (*c* = 1.0, CHCl₃), ee = 95% (determined by SFC).

SFC: AD-H column, pressure = 100 bar, eluent = CO₂/MeOH (85:15), flow rate = 4.0 mL/min, detection wavelength = 220 nm, *t*_{R1} = 7.74 (major), *t*_{R2} = 11.44 (minor).

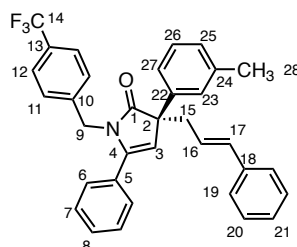
IR (neat): 1708, 1620, 1598, 1492, 1447, 1421, 1352, 1324, 1259, 1164, 1122, 1067, 1019, 967 cm^{−1}.

¹H NMR (400 MHz, CDCl₃) δ 7.62 (d, *J* = 7.6 Hz, 1H, H_{Ar}), 7.40 – 7.18 (m, 11H, H_{Ar}), 7.12 – 7.05 (m, 6H, H_{Ar}), 6.61 (d, *J* = 15.7 Hz, 1H, H₁₇), 6.20 (ddd, *J* = 15.2, 8.3, 6.4 Hz, 1H, H₁₆), 5.50 (s, 1H, H₃), 4.93 (d, *J*_{AB} = 15.6 Hz, 1H, H₉), 4.44 (d, *J*_{AB} = 15.7 Hz, 1H, H₉), 3.27 (dd, *J* = 13.0, 6.4 Hz, 1H, H₁₅), 3.17 (dd, *J* = 12.9, 8.4 Hz, 1H, H₁₅), 2.31 (s, 3H, H₂₈).

¹³C NMR (101 MHz, CDCl₃) δ 181.1 (s, C₁), 144.8 (s, C_{Ar}), 141.3 (s, C_{Ar}), 137.4 (s, C_{Ar}), 137.18 (s, C_{Ar}), 137.16 (s, C_{Ar}), 134.4 (s, C₁₇), 132.4 (s, C_{Ar}), 131.2 (s, C_{Ar}), 129.4 (s, C_{Ar}), 129.37 (d, *J* = 32.3 Hz, C₁₄), 128.8 (s, 2C, C_{Ar}), 128.7 (s, 2C, C_{Ar}), 128.4 (s, 2C, C_{Ar}), 128.0 (s, 2C, C_{Ar}), 127.7 (s, C_{Ar}), 127.6 (s, C_{Ar}), 127.2 (s, C_{Ar}), 126.5 (s, C_{Ar}), 126.3 (s, 2C, C_{Ar}), 125.4 (q, *J* = 3.8 Hz, 2C, C₁₂), 124.11 (s, C_{Ar}), 124.08 (d, *J* = 257.3 Hz, C₁₃), 111.0 (s, C₃), 58.4 (s, C₂), 44.7 (s, C₉), 40.4 (s, C₁₅), 20.6 (s, C₂₈).

HRMS (ESI) *m/z*: calculated for C₃₄H₂₈F₃NOH [M+H]⁺: 524.2196, found: 524.2194.

(*R*)-3-Cinnamyl-5-phenyl-3-(*m*-tolyl)-1-[4-(trifluoromethyl)benzyl]-1,3-dihydro-2H-pyrrol-2-one (II.3g)



MW: 523.2123 g.mol^{−1}

Molecular Formula: C₃₄H₂₈F₃NO

Compound **II.3g** was synthesized according to the general method from 2-[(*tert*-butyldimethylsilyl)oxy]-5-phenyl-3-(*m*-tolyl)-1-[4-(trifluoromethyl)benzyl]-1H pyrrole **II.1g** (104.2 mg, 0.2 mmol) and cinnamyl benzoate **II.2e** (71.4 mg, 0.3 mmol, 1.5 equiv).

Compound **II.3g** was isolated as a white solid (81.0 mg, 78%) after purification by flash column chromatography over silica gel (PE/Et₂O = 10:1).

Mp: 124–126 °C.

[α]²⁰_D = 16.0 (*c* = 1.73, CHCl₃), ee = 81% (determined by SFC).

SFC: OD-H column, pressure = 100 bar, eluent = CO₂/MeOH (85:15), flow rate = 4.0 mL/min, detection wavelength = 220 nm, *t*_{R1} = 4.26 (minor), *t*_{R2} = 7.22 (major).

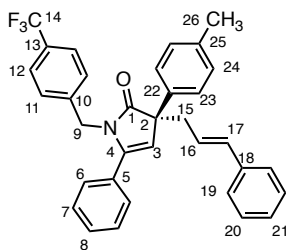
IR (neat): 1703, 1619, 1601, 1492, 1447, 1421, 1323, 1163, 1121, 1066, 1018, 966, 942, 908 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.42 – 7.22 (m, 11H, H_{Ar}), 7.12 – 7.09 (m, 3H, H_{Ar}), 7.05 (d, *J* = 8.1 Hz, 2H, H_{Ar}), 6.93 (d, *J* = 8.0 Hz, 2H, H_{Ar}), 6.55 (d, *J* = 16.0 Hz, 1H, H₁₇), 6.10 (ddd, *J* = 15.4, 8.5, 6.3 Hz, 1H, H₁₆), 5.68 (s, 1H, H₃), 4.84 (d, *J*_{AB} = 15.9 Hz, 1H, H₉), 4.41 (d, *J*_{AB} = 15.9 Hz, 1H, H₉), 3.10 (dd, *J* = 13.8, 8.5 Hz, 1H, H₁₅), 2.96 (ddd, *J* = 13.3, 6.3, 1.5 Hz, 1H, H₁₅), 2.36 (s, 3H, H₂₈).

¹³C NMR (101 MHz, CDCl₃) δ 180.4 (s, C₁), 144.5 (s, C_{Ar}), 141.4 (s, C_{Ar}), 139.9 (s, C_{Ar}), 138.5 (s, C_{Ar}), 137.2 (s, C_{Ar}), 131.3 (s, C_{Ar}), 129.3 (s, C_{Ar}), 129.28 (d, *J* = 32.7 Hz, C₁₄), 128.8 (s, 2C, C_{Ar}), 128.69 (s, C_{Ar}), 128.67 (s, 2C, C_{Ar}), 128.5 (s, 2C, C_{Ar}), 128.3 (s, C_{Ar}), 127.6 (s, 2C, C_{Ar}), 127.56 (s, C_{Ar}), 127.5 (s, C_{Ar}), 126.3 (s, 2C, C_{Ar}), 124.8 (s, C_{Ar}), 125.4 (q, *J* = 3.8 Hz, 2C, C₁₂), 124.8 (s, C_{Ar}), 124.1 (d, *J* = 272.9 Hz, C₁₃), 122.9 (s, C_{Ar}), 111.6 (s, C₃), 57.9 (s, C₂), 44.2 (s, C₉), 42.5 (s, C₂₅), 21.8 (s, C₂₈).

HRMS (ESI) *m/z*: calculated for C₃₄H₂₈F₃NOH [M+H]⁺: 524.2196, found: 524.2206.

(*R*)-3-Cinnamyl-5-phenyl-3-(*p*-tolyl)-1-[4-(trifluoromethyl)benzyl]-1,3-dihydro-2*H* pyrr-ol-2-one (II.3h**)**



MW: 523.2123 g.mol⁻¹

Molecular Formula: C₃₄H₂₈F₃NO

Compound **II.3h** was synthesized according to the general method from 2-[(*tert*-butyldimethylsilyl)oxy]-5-phenyl-3-(*o*-tolyl)-1-[4-(trifluoromethyl)benz-yl]-1*H*-pyrrole **II.1h** (104.2 mg, 0.2 mmol) and cinnamyl benzoate **II.2e** (71.4 mg, 0.3 mmol, 1.5 equiv). Compound **II.3h** was isolated as a yellow solid (76.0 mg, 73%) after purification by flash column chromatography over silica gel (PE/Et₂O = 10:1).

Mp: 117–119 °C.

[α]²⁰_D = 24.7 (*c* = 0.65, CHCl₃), ee = 67% (determined by SFC).

SFC: AD-H column, pressure = 100 bar, eluent = CO₂/MeOH (85:15), flow rate = 4.0 mL/min, detection wavelength = 220 nm, *t*_{R1} = 8.76 (major), *t*_{R2} = 11.5 (minor).

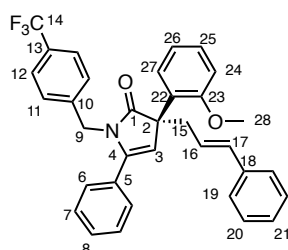
IR (neat): 3027, 2922, 1705, 1650, 1619, 1511, 1494, 1421, 1373, 1350, 1324, 1261, 1216, 1190, 1164, 1122, 1067, 1019, 967, 943, 920 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.52 (d, *J* = 8.2 Hz, 2H, H_{Ar}), 7.36 – 7.25 (m, 8H, H_{Ar}), 7.20 (d, *J* = 7.9 Hz, 2H, H_{Ar}), 7.15 – 7.12 (m, 2H, H_{Ar}), 7.08 (d, *J* = 8.3 Hz, 2H, H_{Ar}), 6.95 (d, *J* = 7.9 Hz, 2H, H_{Ar}), 6.57 (d, *J* = 15.8 Hz, 1H, H₁₇), 6.13 (ddd, *J* = 15.3, 8.5, 6.3 Hz, 1H, H₁₆), 5.71 (s, 1H), 4.85 (d, *J*_{AB} = 16.0 Hz, 1H, H₉), 4.44 (d, *J*_{AB} = 16.0 Hz, 1H, H₉), 3.11 (dd, *J* = 13.3, 8.6 Hz, 1H, H₁₅), 2.98 (ddd, *J* = 13.2, 6.3, 1.5 Hz, 1H, H₁₅), 2.36 (s, 3H, H₂₆).

¹³C NMR (101 MHz, CDCl₃) δ 180.5 (s, C₁), 144.5 (s, C_{Ar}), 141.4 (s, C_{Ar}), 137.3 (s, C_{Ar}), 137.2 (s, C_{Ar}), 136.9 (s, C_{Ar}), 134.1 (s, C_{Ar}), 131.3 (s, C_{Ar}), 129.6 (s, 2C, C_{Ar}), 129.34 (s, C_{Ar}), 129.29 (d, *J* = 32.7 Hz, C₁₄), 128.8 (s, 2C, C_{Ar}), 128.7 (s, 2C, C_{Ar}), 128.5 (s, 2C, C_{Ar}), 127.6 (s, C_{Ar}), 127.5 (s, 2C, C_{Ar}), 126.7 (s, 2C, C_{Ar}), 126.3 (s, 2C, C_{Ar}), 125.4 (q, *J* = 3.7 Hz, 2C, C₁₂), 124.8 (s, C_{Ar}), 124.1 (d, *J* = 273.5 Hz, C₁₃), 11.6 (s, C₃), 57.6 (s, C₂), 44.2 (s, C₉), 42.4 (s, C₁₅), 21.2 (s, C₂₆).

HRMS (ESI) *m/z*: calculated for C₃₁H₂₅NOH [M+H]⁺: 524.2196, found: 524.2207.

(*R*)-3-Cinnamyl-3-(2-methoxyphenyl)-5-phenyl-1-[4-(trifluoromethyl)benzyl]1,3-dihydro-2*H*-pyrrol-2-one (II.3i)



MW: 539.2072 g.mol⁻¹

Molecular Formula: C₃₄H₂₈F₃NO₂

Compound **II.3i** was synthesized according to the general method from 2-[(*tert*-butyldimethylsilyl)oxy]-3-(2-methoxyphenyl)-5-phenyl-1-[4-(trifluoro-methyl)benzyl]-1*H*-pyrrole **II.1i** (107.4 mg, 0.2 mmol) and cinnamyl benzoate **II.2e** (71.4 mg, 0.3 mmol, 1.5 equiv). Compound **II.1i** was isolated as a colourless oil (45.0 mg, 42%) after purification by flash column chromatography over silica gel (PE/Et₂O = 10:1).

[α]_D²⁰ = -15 (*c* = 0.6, CHCl₃), ee = 78% (determined by SFC).

SFC: AD-H column, pressure = 100 bar, eluent = CO₂/MeOH (85:15), flow rate = 5.0 mL/min, detection wavelength = 220 nm, *t*_{R1} = 5.65 (major), *t*_{R2} = 11.23 (minor).

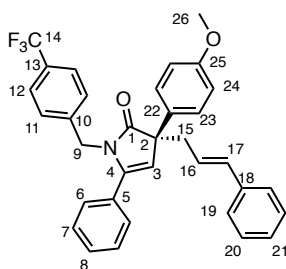
IR (neat): 1702, 1619, 1597, 1492, 1463, 1448, 1436, 1421, 1355, 1324, 1249, 1164, 1123, 1067, 1020, 968, 909 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.57 (dd, *J* = 7.8, 1.6 Hz, 1H, H_{Ar}), 7.33 – 7.21 (m, 9H, H_{Ar}), 7.09 – 7.00 (m, 7H, H_{Ar}), 6.93 (dd, *J* = 8.2, 1.2 Hz, 1H, H₂₄), 6.59 (d, *J* = 15.9 Hz, 1H, H₁₇), 6.25 – 6.17 (m, 1H, H₁₆), 5.70 (s, 1H, H₃), 4.92 (d, *J*_{AB} = 15.9 Hz, 1H, H₉), 4.48 (d, *J*_{AB} = 15.9 Hz, 1H, H₉), 3.79 (s, 3H, H₂₈), 3.35 (ddd, *J* = 13.0, 6.3, 1.6 Hz, 1H, H₁₅), 2.98 (dd, *J* = 13.2, 8.8 Hz, 1H, H₁₅).

¹³C NMR (101 MHz, CDCl₃) δ 180.9 (s, C₁), 157.8 (s, C₂₃), 144.2 (s, C_{Ar}), 141.8 (s, C_{Ar}), 137.4 (s, C_{Ar}), 133.9 (s, C₁₇), 131.7 (s, C_{Ar}), 129.9 (s, C_{Ar}), 129.2 (d, *J* = 32.5 Hz, C₁₃), 129.1 (s, C_{Ar}), 128.8 (s, 2C, C_{Ar}), 128.58 (s, C_{Ar}), 128.56 (s, 2C, C_{Ar}), 128.5 (s, 2C, C_{Ar}), 127.9 (s, C_{Ar}), 127.8 (s, 2C, C_{Ar}), 127.5 (s, C_{Ar}), 127.4 (s, C_{Ar}), 126.3 (s, C_{Ar}), 125.3 (q, *J* = 3.7 Hz, 2C, C₁₂), 124.9 (s, C₁₆), 124.2 (d, *J* = 273.1 Hz, C₁₄), 121.1 (s, C_{Ar}), 111.7 (s, C₂₄), 111.2 (s, C₃), 57.0 (s, C₂), 55.5 (s, C₂₈), 44.3 (s, C₉), 39.0 (s, C₁₅)

HRMS (ESI) *m/z*: calculated for C₃₄H₂₈F₃NO₂H [M+H]⁺: 540.2145, found: 540.2143.

(*R*)-3-Cinnamyl-3-(4-methoxyphenyl)-5-phenyl-1-[4-(trifluoromethyl)benzyl]-1,3-dihydro-2*H*-pyrrol-2-one (II.3j)



MW: 539.2072 g.mol⁻¹

Molecular Formula: C₃₄H₂₈F₃NO₂

Compound **II.3j** was synthesized according to the general method from 2-[(*tert*-butyldimethylsilyl)oxy]-3-(4-methoxyphenyl)-5-phenyl-1-[4-(trifluoro-methyl)benzyl]-1*H*-pyrrole **II.1j** (107.4 mg, 0.2 mmol) and cinnamyl benzoate **II.2e** (71.4 mg, 0.3 mmol, 1.5 equiv). Compound **II.3j** and **II.4j** were isolated as a mixture (96.0 mg, 90%) in a ratio of 5.5:1 in favor of **II.3j** after purification by flash column chromatography over silica gel (PE/Et₂O = 10:1).

[α]²⁰_D = 25.7 (*c* = 4.75, CHCl₃), ee = 79% (determined by SFC).

SFC: AD-H column, pressure = 100 bar, eluent = CO₂/MeOH (95:5), flow rate = 5.0 mL/min, detection wavelength = 220 nm, *t*_{R1} = 33.18 (major), *t*_{R2} = 37.27 (minor).

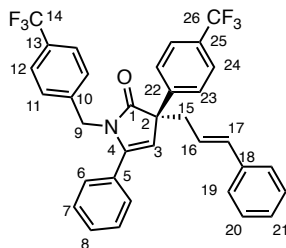
IR (neat): 2933, 2837, 1701, 1608, 1578, 1494, 1464, 1446, 1421, 1373, 1352, 1323, 1250, 1180, 1164, 1121, 1066, 1033, 1018, 966, 943, 908 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.57 (d, *J* = 8.8 Hz, 1H, H_{Ar}), 7.38 – 7.28 (m, 8H, H_{Ar}), 7.15 (d, *J* = 6.9 Hz, 2H, H_{Ar}), 7.10 (d, *J* = 8.1 Hz, 2H, H_{Ar}), 6.98 – 6.93 (m, 4H, H_{Ar}), 6.58 (d, *J* = 15.4 Hz, 1H, H₁₇), 6.14 (dt, *J* = 14.9, 7.5 Hz, 1H, H₁₆), 5.72 (s, 1H, H₃), 4.86 (d, *J*_{AB} = 16.0 Hz, 2H, H₉), 4.46 (d, *J*_{AB} = 15.9 Hz, 1H, H₉), 3.83 (s, 3H, H₂₆), 3.11 (dd, *J* = 13.3, 8.5 Hz, 1H, H₁₅), 2.98 (dd, *J* = 13.4, 6.3 Hz, 1H, H₁₅).

¹³C NMR (101 MHz, CDCl₃) δ 180.6 (s, C₁), 159.0 (s, C₂₅), 144.5 (s, C_{Ar}), 141.4 (s, C_{Ar}), 137.2 (s, C_{Ar}), 134.0 (s, C₁₇), 131.9 (s, C_{Ar}), 131.3 (s, C_{Ar}), 129.4 (s, C_{Ar}), 129.3 (d, *J* = 32.5 Hz, C₁₃), 128.74 (s, 2C, C_{Ar}), 128.65 (s, 2C, C_{Ar}), 128.4 (s, 2C, C_{Ar}), 128.0 (s, 2C, C_{Ar}), 127.6 (s, C_{Ar}), 127.5 (s, 2C, C_{Ar}), 126.3 (s, 2C, C_{Ar}), 125.4 (q, *J* = Hz, 2C, C₁₂), 124.8 (s, C₁₆), 124.1 (d, *J* = 273.1 Hz, C₁₄), 114.2 (s, 2C, C_{Ar}), 111.6 (s, C₃), 57.2 (s, C₂), 55.4 (s, C₂₆), 44.2 (s, C₉), 42.5 (s, C₁₅)

HRMS (ESI) *m/z*: calculated for C₃₄H₂₈F₃NO₂H [M+H]⁺: 540.2145, found: 540.2161

(R)-3-Cinnamyl-5-phenyl-1-[4-(trifluoromethyl)benzyl]-3-[4-(trifluoromethyl)phenyl]-1,3-dihydro-2H-pyrrol-2-one (II.3k)



MW: 577.1840 g.mol⁻¹

Molecular Formula: C₃₄H₂₅F₆NO

Compound **II.3k** was synthesized according to the general method from 5-phenyl-1-(4-(trifluoromethyl)benzyl)-3-(4-(trifluoromethyl)phenyl)-1,5-dihydro-2H-pyrrol-2-one **II.1k** (115.0 mg, 0.2 mmol) and cinnamyl benzoate **II.2e** (71.4 mg, 0.3 mmol, 1.5 equiv). Compound **II.3k** was isolated as a white solid (100.0 mg, 87%) after purification by flash column chromatography over silica gel (PE/Et₂O = 10:1).

Mp: 164–165 °C.

[α]²⁰_D = 33.9 (*c* = 2.27, CHCl₃), ee = 70% (determined by SFC).

SFC: OD-H column, pressure = 100 bar, eluent = CO₂/MeOH (85:15), flow rate = 4.0 mL/min, detection wavelength = 220 nm, *t*_{R1} = 3.04 (major), *t*_{R2} = 89.51 (minor).

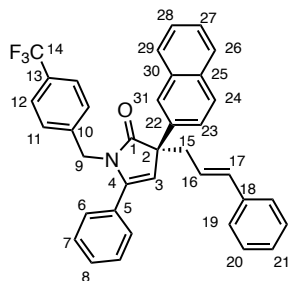
IR (neat): 1706, 1619, 1599, 1494, 1447, 1421, 1324, 1165, 1121, 1068, 1018, 967, 943 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.79 (d, *J* = 8.1 Hz, 2H, H_{Ar}), 7.66 (d, *J* = 8.4 Hz, 2H, H_{Ar}), 7.47 – 7.24 (m, 8H, H_{Ar}), 7.18 – 7.07 (m, 4H, H_{Ar}), 6.96 (d, *J* = 8.0 Hz, 2H, H_{Ar}), 6.59 (d, *J* = 15.7 Hz, 1H, H₁₇), 6.11 (dt, *J* = 15.3, 7.1 Hz, 1H, H₁₆), 5.74 (s, 1H, H₃), 4.87 (d, *J*_{AB} = 15.9 Hz, 1H, H₉), 4.47 (d, *J*_{AB} = 15.9 Hz, 1H, H₉), 3.13 (dd, *J* = 13.4, 8.4 Hz, 1H, H₁₅), 3.01 (dd, *J* = 13.4, 6.0 Hz, 1H, H₁₅).

¹³C NMR (101 MHz, CDCl₃) δ 179.7 (s, C₁), 145.4 (s, C_{Ar}), 143.9 (s, C_{Ar}), 141.1 (s, C_{Ar}), 136.9 (s, C_{Ar}), 134.7 (s, C₁₇), 130.9 (s, C_{Ar}), 129.8 (d, *J* = 34.2 Hz, C₁₄ or C₂₆), 129.6 (s, C_{Ar}), 129.1 (d, *J* = 38.7 Hz, C₁₄ or C₂₆, C_{Ar}), 128.82 (s, 2C, C_{Ar}), 128.79 (s, 2C, C_{Ar}), 128.5 (s, 2C, C_{Ar}), 127.9 (s, C_{Ar}), 127.5 (s, 2C, C_{Ar}), 127.4 (s, 2C, C_{Ar}), 126.4 (s, 2C, C_{Ar}), 125.8 (q, *J* = 3.8 Hz, 2C, C₁₂ or C₂₄, C_{Ar}), 125.5 (q, *J* = 3.8 Hz, 2C, C₁₄ or C₂₆, C_{Ar}), 124.3 (d, *J* = 272.9 Hz, C₁₃ or C₂₅, C_{Ar}), 124.1 (d, *J* = 272.9 Hz, C₁₃ or C₂₅, C_{Ar}), 123.9 (s, C₁₆), 110.5 (s, C₃), 57.8 (s, C₂), 44.3 (s, C₉), 42.7 (s, C₁₅).

HRMS (ESI) m/z : calculated for $C_{34}H_{25}F_6NOH$ $[M+H]^+$: 578.1913, found: 578.1918.

(*R*)-3-Cinnamyl-3-(naphthalen-2-yl)-5-phenyl-1-[4-(trifluoromethyl)benzyl]-1,3-dihydro-2*H*-pyrrol-2-one (II.3I)



MW: 559.2123 g.mol⁻¹

Molecular Formula: C₃₇H₂₈F₃NO

Compound **II.3I** was synthesized according to the general method from 2-[(*tert*-butyldimethylsilyl)oxy]-3-(naphthalen-2-yl)-5-phenyl-1-[4-(trifluoro-methyl)benzyl]-1*H*-pyrrole **II.1I** (111.4 mg, 0.2 mmol) and cinnamyl benzoate **II.2e** (71.4 mg, 0.3 mmol, 1.5 equiv). Compound **II.3I** was isolated as a white solid (90.0 mg, 77%) after purification by flash column chromatography over silica gel (PE/Et₂O = 10:1).

Mp: 122–124 °C.

[α]_D²⁰ = 7.7 (c = 1.4, CHCl₃), ee = 81% (determined by SFC).

SFC: OD-H column, pressure = 100 bar, eluent = CO₂/MeOH (85:15), flow rate = 5.0 mL/min, detection wavelength = 220 nm, t_{R1} = 13.7 (minor), t_{R2} = 24.6 (major).

IR (neat): 1702, 1619, 1598, 1494, 1447, 1421, 1323, 1163, 1120, 1066, 1018, 965, 943, 907 cm⁻¹.

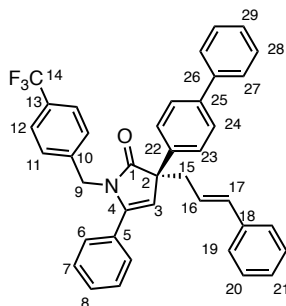
¹H NMR (400 MHz, CDCl₃) δ 8.04 (s, 1H, H₃₁), 7.90 – 7.78 (m, 4H, H_{Ar}), 7.52 – 7.47 (m, 2H, H_{Ar}), 7.40 – 7.23 (m, 8H, H_{Ar}), 7.19 – 7.17 (m, 2H, H_{Ar}), 7.10 (d, J = 8.0 Hz, 2H, H_{Ar}), 6.98 (d, J = 8.0 Hz, 2H, H_{Ar}), 6.61 (d, J = 15.6 Hz, 1H, H₁₇), 6.16 (ddd, J = 15.3, 8.5, 6.4 Hz, 1H, H₁₆), 5.84 (s, 1H, H₃), 4.89 (d, J_{AB} = 15.9 Hz, 1H, H₉), 4.50 (d, J_{AB} = 15.9 Hz, 1H, H₉), 3.22 (dd, J = 13.4, 8.5 Hz, 1H, H₁₅), 3.12 (dd, J = 13.4, 6.4 Hz, 1H, H₁₅).

¹³C NMR (101 MHz, CDCl₃) δ 180.3 (s, C₁), 144.8 (s, C_{Ar}), 141.4 (s, C_{Ar}), 137.3 (s, C_{Ar}), 137.2 (s, C_{Ar}), 134.2 (s, C_{Ar}), 133.5 (s, C_{Ar}), 132.8 (s, C_{Ar}), 131.2 (s, C_{Ar}), 129.4 (s, C_{Ar}), 129.3 (d, J = 32.2 Hz, C₁₄), 128.8 (s, 2C, C_{Ar}), 128.7 (s, 2C, C_{Ar}), 128.6 (s, C_{Ar}), 128.5 (s, 2C, C_{Ar}), 128.3 (s, C_{Ar}), 127.7 (s, 2C, C_{Ar}), 127.6 (s, 2C, C_{Ar}), 126.4 (s, 2C, C_{Ar}), 126.3 (s,

C_{Ar}), 126.2 (s, C_{Ar}), 125.6 (s, C_{Ar}), 125.4 (q, *J* = 3.8 Hz, 2C, C₁₂), 125.1 (s, C_{Ar}), 124.6 (s, 16), 124.2 (d, *J* = 279.7 Hz, C₁₃), 111.5 (s, C₃), 58.0 (s, C₂), 44.3 (s, C₉), 42.5 (s, C₅).

HRMS (ESI) *m/z*: calculated for C₃₇H₂₈F₃NONa [M+Na]⁺: 582.2015, found: 582.2007.

(*R*)-3-([1,1'-Biphenyl]-4-yl)-3-cinnamyl-5-phenyl-1-(4-(trifluoromethyl)benzyl)-1,3-dihydro-2*H*-pyrrol-2-one (II.3m)



MW: 585.2279 g.mol⁻¹

Molecular Formula: C₃₉H₃₀F₃NO

Compound **II.3m** was synthesized according to the general method from 3-[(1,1'-biphenyl)-4-yl]-2-[(*tert*-butyldimethylsilyl)oxy]-5-phenyl-1-[4-(trifluoro-methyl)benzyl]-1*H*-pyrrole **II.1m** (117.0 mg, 0.2 mmol) and cinnamyl benzoate **II.2e** (71.4 mg, 0.3 mmol, 1.5 equiv). Compound **II.3m** was isolated as a white solid (99.0 mg, 85%) after purification by flash column chromatography over silica gel (PE/Et₂O = 10:1).

Mp: 153–155 °C.

[α]²⁰_D = 13.3 (*c* = 1.5, CHCl₃), ee = 80% (determined by SFC).

SFC: AD-H column, pressure = 100 bar, eluent = CO₂/MeOH (85:15), flow rate = 5.0 mL/min, detection wavelength = 220 nm, *t*_{R1} = 23.64 (major), *t*_{R2} = 25.82 (minor).

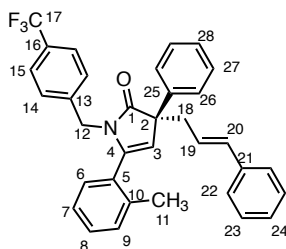
IR (neat): 1703, 1620, 1487, 1447, 1421, 1323, 1164, 1121, 1067, 1018, 1008, 967, 909 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.75 – 7.74 (m, 2H, H_{Ar}), 7.66 – 7.62 (m, 4H, H_{Ar}), 7.49 – 7.45 (m, 2H, H_{Ar}), 7.39 – 7.26 (m, 9H, H_{Ar}), 7.19 – 7.16 (m, 2H, H_{Ar}), 7.11 (d, *J* = 8.0 Hz, 2H, H_{Ar}), 6.99 (d, *J* = 8.0 Hz, 2H, H_{Ar}), 6.62 (d, *J* = 15.7 Hz, 1H, H₇), 6.17 (ddd, *J* = 15.3, 8.5, 6.4 Hz, 1H, H₁₆), 5.78 (s, 1H, H₃), 4.90 (d, *J*_{AB} = 15.9 Hz, 1H, H₉), 4.48 (d, *J*_{AB} = 16.0 Hz, 1H, H₉), 3.19 (dd, *J* = 13.4, 8.5 Hz, 1H, H₁₅), 3.06 (ddd, *J* = 13.4, 6.4, 1.5 Hz, 1H, H₁₅).

¹³C NMR (101 MHz, CDCl₃) δ 180.4 (s, C₁), 144.8 (s, C_{Ar}), 141.4 (s, C_{Ar}), 140.8 (s, C_{Ar}), 140.5 (s, C_{Ar}), 139.0 (s, C_{Ar}), 137.2 (s, C_{Ar}), 134.3 (s, C₁₇), 131.2 (s, C_{Ar}), 129.4 (s, C_{Ar}), 129.3 (d, *J* = 31.9 Hz, C₁₄), 128.9 (s, 2C, C_{Ar}), 128.8 (s, 2C, C_{Ar}), 128.7 (s, 2C, C_{Ar}), 128.5 (s, 2C, C_{Ar}), 127.7 (s, C_{Ar}), 127.6 (s, 2C, C_{Ar}), 127.54 (s, 2C, C_{Ar}), 127.48 (s, C_{Ar}), 127.3 (s, 2C, C_{Ar}), 127.2 (s, 2C, C_{Ar}), 126.4 (s, 2C, C_{Ar}), 125.4 (q, *J* = 3.9 Hz, 2C, C₁₄), 124.6 (s, C₁₆), 124.1 (d, *J* = 270.6 Hz, C₁₃), 111.4 (s, C₃), 57.7 (s, C₂), 44.3 (s, C₉), 42.5 (s, C₁₅).

HRMS (ESI) *m/z*: calculated for C₃₉H₃₀F₃NONa [M+Na]⁺: 608.2172, found: 608.2170.

(*R*)-3-Cinnamyl-3-phenyl-5-(*o*-tolyl)-1-(4-(trifluoromethyl)benzyl)-1,3-dihydro-2*H*-pyrrol-2-one (II.3n)



MW: 523.2123 g.mol⁻¹

Molecular Formula: C₃₄H₂₈F₃NO

Compound **II.3n** was synthesized according to the general method from 2-[(*tert*-butyldimethylsilyl)oxy]-3-phenyl-5-(*o*-tolyl)-1-[4-(trifluoromethyl)benzyl]-1*H* pyrrole **II.1n** (104.2 mg, 0.2 mmol) and cinnamyl benzoate **II.2e** (71.4 mg, 0.3 mmol, 1.5 equiv). Compound **II.3n** was isolated as a white solid (87.0 mg, 83%) after purification by flash column chromatography over silica gel (PE/Et₂O = 10:1).

Mp: 88–89 °C.

[α]_D²⁰ = 3.5 (*c* = 3.15, CHCl₃), ee = 68% (determined by SFC).

SFC: OD-H column, pressure = 100 bar, eluent = CO₂/MeOH (85:15), flow rate = 4.0 mL/min, detection wavelength = 220 nm, *t*_{R1} = 4.40 (minor), *t*_{R2} = 6.96 (major).

IR (neat): 1704, 1649, 1620, 1598, 1494, 1447, 1422, 1324, 1165, 1124, 1067, 1019, 967, 941 cm⁻¹.

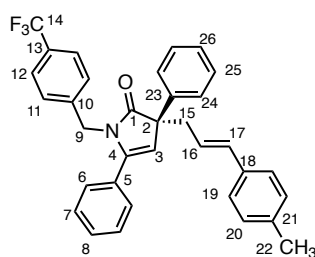
¹H NMR (400 MHz, CDCl₃) δ 7.56 – 7.54 (m, 2H, H_{Ar}), 7.34 – 7.29 (m, 2H, H_{Ar}), 7.26 – 7.17 (m, 7H, H_{Ar}), 7.02 (dd, *J* = 17.5, 7.3 Hz, 2H, H_{Ar}), 6.94 (d, *J* = 8.1 Hz, 2H, H_{Ar}), 6.84 (d, *J* = 6.5 Hz, 1H, H₉), 6.69 (d, *J* = 8.0 Hz, 2H, H_{Ar}), 6.49 (d, *J* = 15.8 Hz, 1H, H₂₀), 6.09 –

6.02 (m, 1H, H₁₉), 5.52 (s, 1H, H₃), 4.66 (d, J_{AB} = 15.2 Hz, 1H, H₁₂), 4.07 (d, J_{AB} = 15.2 Hz, 1H, H₁₂), 3.12 (dd, J = 13.3, 8.2 Hz, 1H, H₁₈), 2.90 (ddd, J = 13.3, 6.7, 1.3 Hz, 1H, H₁₈), 1.86 (s, 3H, H₁₁).

¹³C NMR (101 MHz, CDCl₃) δ 179.9 (s, C₁), 143.0 (s, C_{Ar}), 141.3 (s, C_{Ar}), 140.2 (s, C_{Ar}), 137.4 (s, C_{Ar}), 137.1 (s, C_{Ar}), 134.1 (s, C₂₀), 130.7 (s, C_{Ar}), 130.3 (s, C_{Ar}), 130.2 (s, C_{Ar}), 129.5 (s, C_{Ar}), 129.4 (d, J = 31.9 Hz, C₁₇), 128.9 (s, 2C, C_{Ar}), 128.7 (s, 2C, C_{Ar}), 128.2 (s, 2C, C_{Ar}), 127.7 (s, C_{Ar}), 127.5 (s, C_{Ar}), 126.8 (s, 2C, C_{Ar}), 126.3 (s, 2C, C_{Ar}), 125.7 (s, C_{Ar}), 125.1 (q, J = 3.8 Hz, 2C, C₁₅), 124.8 (s, C₁₉), 124.1 (d, J = 273.2 Hz, C₁₆), 111.7 (s, C₃), 58.0 (s, C₂), 43.9 (s, C₁₂), 42.4 (s, C₁₈), 19.7 (s, C₁₁).

HRMS (ESI) m/z : calculated for C₃₄H₂₈F₃NOH [M+H]⁺: 524.2196, found: 524.2192.

(*R*)-(*E*)-3,5-Diphenyl-3-(3-(*p*-tolyl)allyl)-1-[4-(trifluoromethyl)benzyl]-1,3-dihydro-2*H*-pyrrol-2-one (II.3o)



MW: 523.2123 g.mol⁻¹

Molecular Formula: C₃₄H₂₈F₃NO

Compound **II.3o** was synthesized according to the general method from 3,5-diphenyl-1-[4-(trifluoromethyl)benzyl]-1,5-dihydro-2*H*-pyrrol-2-one **II.1e** (101.4 mg, 0.2 mmol) and (*E*)-3-(*p*-tolyl)allyl benzoate **II.2f** (75.6 mg, 0.3 mmol, 1.5 equiv). Compound **II.3o** was isolated as a colourless oil (56.0 mg, 54%) after purification by flash column chromatography over silica gel (PE/Et₂O = 12:1).

[α]_D²⁰ = 8.7 (c = 0.75, CHCl₃), ee = 61% (determined by SFC).

SFC: OD-H column, pressure = 100 bar, eluent = CO₂/MeOH (85:15), flow rate = 4.0 mL/min, detection wavelength = 220 nm, t_{R1} = 4.74 (minor), t_{R2} = 7.85 (major).

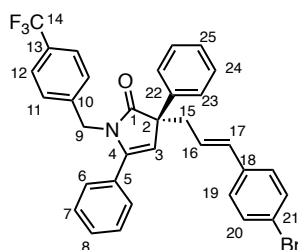
IR (neat): 1704, 1619, 1599, 1493, 1446, 1421, 1373, 1323, 1217, 1164, 1121, 1066, 1032, 1018, 967, 942, 909 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.56 – 7.52 (m, 2H, H_{Ar}), 7.31 – 7.12 (m, 8H, H_{Ar}), 7.07 – 7.00 (m, 7H, H_{Ar}), 6.85 (d, *J* = 8.0 Hz, 2H, H_{Ar}), 6.65 (d, *J* = 15.7 Hz, 1H, H₁₇), 5.90 (ddd, *J* = 15.3, 8.2, 6.7 Hz, 1H, H₁₆), 5.64 (s, 1H, C₃), 4.74 (d, *J* = 15.9 Hz, 1H, H₉), 4.39 (d, *J* = 16.0 Hz, 1H, H₉), 3.03 (ddd, *J* = 13.3, 8.2, 1.1 Hz, 1H, H₁₅), 2.93 (ddd, *J* = 13.4, 6.7, 1.5 Hz, 1H, H₁₅), 2.17 (s, 3H, H₂₂).

¹³C NMR (101 MHz, CDCl₃) δ 180.4 (s, C₁), 144.6 (s, C_{Ar}), 141.4 (s, C_{Ar}), 139.9 (s, C_{Ar}), 136.3 (s, C_{Ar}), 135.4 (s, C_{Ar}), 132.2 (s, C_{Ar}), 131.2 (s, C_{Ar}), 130.5 (s, C_{Ar}), 129.4 (s, C_{Ar}), 129.3 (d, *J* = 32.9 Hz, C₁₄), 128.8 (s, 2C, C_{Ar}), 128.7 (s, 2C, C_{Ar}), 128.4 (s, 2C, C_{Ar}), 127.56 (s, C_{Ar}), 127.53 (s, C_{Ar}), 127.48 (s, 2C, C_{Ar}), 126.9 (s, 2C, C_{Ar}), 126.2 (s, C_{Ar}), 126.1 (s, C_{Ar}), 125.6 (s, C_{Ar}), 125.4 (q, *J* = 3.6 Hz, 2C, C₁₂), 124.1 (d, *J* = 288 Hz, C₁₃), 111.5 (s, C₃), 58.0 (s, C₂), 44.2 (s, C₉), 42.8 (s, C₁₅), 19.9 (s, C₂₂).

HRMS (ESI) *m/z*: calculated for C₃₄H₂₈F₃NOH [M+H]⁺: 524.2196, found: 524.2204.

(*R*)-(*E*)-3-[3-(4-Bromophenyl)allyl]-3,5-diphenyl-1-[4-(trifluoromethyl)benzyl]-1,3-dihydro-2*H*-pyrrol-2-one (II.3p)



MW: 587.1072 g.mol⁻¹

Molecular Formula: C₃₃H₂₅BrF₃NO

Compound **II.3p** was synthesized according to the general method from 3,5-diphenyl-1-[4-(trifluoromethyl)benzyl]-1,5-dihydro-2*H*-pyrrol-2-one **II.1e** (101.4 mg, 0.2 mmol) and (*E*)-3-(4-bromophenyl)allyl benzoate **II.2g** (94.8 mg, 0.3 mmol, 1.5 equiv). Compound **II.3p** was isolated as a white solid (94.0 mg, 80%) after purification by flash column chromatography over silica gel (PE/Et₂O = 12:1).

Mp: 124–126 °C.

[α]_D²⁰ = 36.1 (*c* = 0.75, CHCl₃), ee = 72% (determined by SFC).

SFC: OD-H column, pressure = 100 bar, eluent = CO₂/MeOH (85:15), flow rate = 4.0 mL/min, detection wavelength = 220 nm, *t*_{R1} = 7.74 (minor), *t*_{R2} = 10.18 (major).

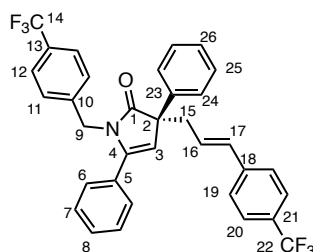
IR (neat): 1704, 1620, 1488, 1446, 1421, 1323, 1164, 1122, 1067, 1018, 1009, 968, 909 cm^{-1} .

^1H NMR (400 MHz, CDCl_3) δ 7.65 – 7.59 (m, 2H, H_{Ar}), 7.45 – 7.29 (m, 8H, H_{Ar}), 7.19 – 7.09 (m, 6H, H_{Ar}), 6.96 (d, $J = 8.0$ Hz, 2H, H_{Ar}), 6.48 (d, $J = 15.7$ Hz, 1H, H_{17}), 6.13 – 6.06 (m, 1H, H_{16}), 5.71 (s, 1H, H_3), 4.81 (d, $J_{\text{AB}} = 15.9$ Hz, 1H, H_9), 4.50 (d, $J_{\text{AB}} = 15.8$ Hz, 1H, H_9), 3.10 (dd, $J = 13.4, 8.4$ Hz, 1H, H_{15}), 2.99 (ddd, $J = 13.4, 6.6, 1.5$ Hz, 1H, H_{15}).

^{13}C NMR (101 MHz, CDCl_3) δ 180.3 (s, C_1), 144.7 (s, C_{Ar}), 141.4 (s, C_{Ar}), 139.7 (s, C_{Ar}), 136.1 (s, C_{Ar}), 132.9 (s, C_{17}), 131.9 (s, 2C, C_{Ar}), 131.2 (s, C_{Ar}), 129.5 (d, $J = 32.6$ Hz, C_{14}), 129.5 (s, C_{Ar}), 128.9 (s, 2C, C_{Ar}), 128.8 (s, 2C, C_{Ar}), 128.4 (s, 2C, C_{Ar}), 127.8 (s, 2C, C_{Ar}), 127.6 (s, 3C, C_{Ar}), 126.9 (s, 2C, C_{Ar}), 125.6 (s, C_{Ar}), 125.4 (q, $J = 3.6$ Hz, 2C, C_{12}), 124.1 (d, $J = 273.8$ Hz, C_{13}), 121.4 (s, C_{Ar}), 111.4 (s, C_3), 57.7 (s, C_2), 44.2 (s, C_9), 42.4 (s, C_{15}).

HRMS (ESI) m/z : calculated for $\text{C}_{33}\text{H}_{25}\text{BrF}_3\text{NOH}$ $[\text{M}+\text{H}]^+$: 588.1144 and 590.1124, found: 588.1143 and 588.1121.

(*R*)-(E)-3,5-Diphenyl-1-[4-(trifluoromethyl)benzyl]-3-[3-(4-(trifluoromethyl)phenyl)allyl]-1,3-dihydro-2*H*-pyrrol-2-one (II.3q)



MW: 577.1840 $\text{g}\cdot\text{mol}^{-1}$

Molecular Formula: $\text{C}_{34}\text{H}_{25}\text{F}_6\text{NO}$

Compound **II.3q** was synthesized according to the general method from 3,5-diphenyl-1-[4-(trifluoromethyl)benzyl]-1,5-dihydro-2*H*-pyrrol-2-one **II.1e** (101.4 mg, 0.2 mmol) and (*E*)-3-(4-(trifluoromethyl)phenyl)allyl benzoate **II.2h** (91.8 mg, 0.3 mmol, 1.5 equiv). Compound **II.3q** and **II.4q** were isolated as a mixture (84.0 mg, 73%) in a ratio of 4.3:1 in favor of **II.3q** after purification by flash column chromatography over silica gel (PE/Et₂O = 12:1).

$[\alpha]_{\text{D}}^{20} = -15.0$ ($c = 0.6$, CHCl_3), ee = 56% (determined by SFC).

SFC: OD-H column, pressure = 100 bar, eluent = CO₂/MeOH (85:15), flow rate = 4.0 mL/min, detection wavelength = 220 nm, *t*_{R1} = 3.65 (minor), *t*_{R2} = 4.29 (major).

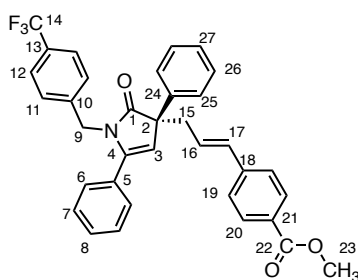
IR (neat): 1705, 1617, 1493, 1447, 1420, 1325, 1165, 1121, 1325, 1165, 1121, 1068, 1018, 970 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.64 – 7.61 (m, 2H, H_{Ar}), 7.54 (d, *J* = 8.0 Hz, 2H, H_{Ar}), 7.42 – 7.30 (m, 8H, H_{Ar}), 7.15 – 7.11 (m, 4H, H_{Ar}), 6.95 (d, *J* = 8.0 Hz, 2H, H_{Ar}), 6.58 (d, *J* = 15.8 Hz, 1H, H₁₇), 6.24 – 6.17 (m, 1H, H₁₆), 5.72 (s, 1H, H₃), 4.83 (d, *J* = 15.9 Hz, 1H, H₉), 4.49 (d, *J* = 15.8 Hz, 1H, H₉), 3.14 (dd, *J* = 13.5, 8.5 Hz, 1H, H₁₅), 3.03 (ddd, *J* = 13.4, 6.4, 1.2 Hz, 1H, H₁₅).

¹³C NMR (101 MHz, CDCl₃) δ 180.3 (s, C₁), 144.8 (s, C_{Ar}), 141.4 (s, C_{Ar}), 140.6 (s, C_{Ar}), 139.7 (s, C_{Ar}), 132.8 (s, C₁₇), 131.1 (s, C_{Ar}), 129.7 (s, C_{Ar}), 129.54 (s, C_{Ar}), 129.4 (s, C_{Ar}), 128.9 (s, 2C, C_{Ar}), 128.8 (s, 2C, C_{Ar}), 128.4 (s, 2C, C_{Ar}), 127.69 (s, C_{Ar}), 127.67 (s, C₁₆), 127.6 (s, 2C, C_{Ar}), 126.9 (s, 2C, C_{Ar}), 126.4 (s, 2C, C_{Ar}), 125.7 (q, *J* = 3.8 Hz, 2C, C₁₂), 125.4 (q, *J* = 3.7 Hz, 2C, C₂₀), 124.3 (d, *J* = 272.9 Hz, C₁₃), 124.0 (d, *J* = 266.9 Hz, C₂₁), 111.3 (s, C₃), 57.7 (s, C₂), 44.2 (s, C₉), 42.4 (s, C₁₅).

HRMS (ESI) *m/z*: calculated for C₃₄H₂₅F₆NOH [M+H]⁺: 578.1913, found: 578.1913.

(*R*)-Methyl (E)-4-(3-(2-oxo-3,5-diphenyl-1-[4-(trifluoromethyl)benzyl]-2,3-dihydro-1*H*-pyrrol-3-yl)prop-1-en-1-yl)benzoate (II.3r)



MW: 567.2021 g.mol⁻¹

Molecular Formula: C₃₅H₂₈F₃NO₃

Compound **II.3r** was synthesized according to the general method from 3,5-diphenyl-1-[4-(trifluoromethyl)benzyl]-1,5-dihydro-2*H*-pyrrol-2-one **II.1e** (101.4 mg, 0.2 mmol) and methyl (*E*)-4-(3-(benzoyloxy)prop-1-en-1-yl)benzoate **II.2i** (88.8 mg, 0.3 mmol, 1.5 equiv). Compound **II.3r** was isolated as a yellow solid (96.0 mg, 85%) after purification by flash column chromatography over silica gel (PE/Et₂O = 12:1).

Mp: 159–160 °C.

[α] $^{20}_{\text{D}}$ = 43.0 (c = 2.1, CHCl_3), ee = 73% (determined by SFC).

SFC: OD-H column, pressure = 100 bar, eluent = CO_2/MeOH (85:15), flow rate = 4.0 mL/min, detection wavelength = 220 nm, $t_{\text{R}1}$ = 6.93 (minor), $t_{\text{R}2}$ = 9.42 (major).

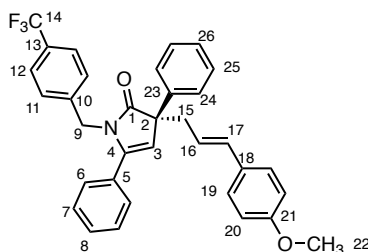
IR (neat): 1710, 1606, 1493, 1435, 1323, 1277, 1164, 1110, 1067, 1018, 970, 910 cm^{-1} .

^1H NMR (400 MHz, CDCl_3) δ 7.97 (d, J = 8.4 Hz, 2H, H_{Ar}), 7.63 (d, J = 8.2 Hz, 2H, H_{Ar}), 7.40 (q, J = 7.1 Hz, 3H, H_{Ar}), 7.32 (t, J = 7.7 Hz, 5H, H_{Ar}), 7.13 (t, J = 7.6 Hz, 4H, H_{Ar}), 6.95 (d, J = 8.0 Hz, 2H, H_{Ar}), 6.59 (d, J = 15.6 Hz, 1H, H_{17}), 6.24 (dt, J = 15.5, 7.4 Hz, 1H, H_{16}), 5.72 (s, 1H, H_3), 4.81 (d, J_{AB} = 15.7 Hz, 1H, H_9), 4.50 (d, J_{AB} = 15.8 Hz, 1H, H_9), 3.92 (s, 3H, H_{23}), 3.14 (dd, J = 13.3, 8.4 Hz, 1H, H_{15}), 3.03 (dd, J = 13.4, 6.5 Hz, 1H, H_{15}).

^{13}C NMR (101 MHz, CDCl_3) δ 180.3 (s, C_1), 166.9 (s, C_{22}), 144.8 (s, C_{Ar}), 141.6 (s, C_{Ar}), 141.3 (s, C_{Ar}), 139.6 (s, C_{Ar}), 133.2 (s, C_{17}), 131.1 (s, C_{Ar}), 130.1 (s, 2C, C_{Ar}), 129.5 (s, C_{Ar}), 129.4 (d, J = 32.2 Hz, C_{14}), 129.1 (s, C_{Ar}), 128.9 (s, 2C, C_{Ar}), 128.7 (s, 2C, C_{Ar}), 128.4 (s, 2C, C_{Ar}), 127.7 (s, C_{Ar}), 127.65 (s, C_{16}), 127.6 (s, 2C, C_{Ar}), 126.9 (s, 2C, C_{Ar}), 126.1 (s, 2C, C_{Ar}), 125.4 (q, J = 3.6 Hz, 2C, C_{12}), 124.1 (d, J = 273.7 Hz, C_{13}), 111.3 (s, C_3), 57.7 (s, C_2), 52.2 (s, C_{23}), 44.2 (s, C_9), 42.4 (s, C_{15}).

HRMS (ESI) m/z : calculated for $\text{C}_{35}\text{H}_{28}\text{F}_3\text{NO}_3\text{H}$ [$\text{M}+\text{H}$] $^+$: 568.2094, found: 568.2107.

(*R*)-(E)-3-[3-(4-Methoxyphenyl)allyl]-3,5-diphenyl-1-[4-(trifluoromethyl)benzyl]-1,3-dihydro-2*H*-pyrrol-2-one (II.3s)



MW: 539.2072 $\text{g}\cdot\text{mol}^{-1}$

Molecular Formula: $\text{C}_{34}\text{H}_{28}\text{F}_3\text{NO}_2$

Compound **II.3s** was synthesized according to the general method from 3,5-diphenyl-1-[4-(trifluoromethyl)benzyl]-1,5-dihydro-2*H*-pyrrol-2-one **II.1e** (101.4 mg, 0.2 mmol) and (*E*)-3-(4-methoxyphenyl)allyl benzoate **II.2j** (80.4 mg, 0.3 mmol, 1.5 equiv). Compound **II.3s** was isolated as a white solid (82.0 mg, 76%) after purification by flash column chromatography over silica gel ($\text{PE}/\text{Et}_2\text{O}$ = 12:1).

Mp: 118–120 °C.

[α]²⁰_D = –51.2 (*c* = 1.25, CHCl₃), *ee* = 85% (determined by SFC).

SFC: OD-H column, pressure = 100 bar, eluent = CO₂/MeOH (85:15), flow rate = 4.0 mL/min, detection wavelength = 220 nm, *t*_{R1} = 6.12 (minor), *t*_{R2} = 8.96 (major).

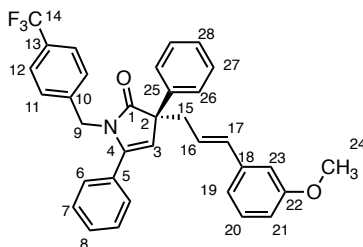
IR (neat): 1703, 1607, 1510, 1493, 1446, 1420, 1323, 1249, 1163, 1120, 1066, 1032, 1018, 967, 909 cm^{–1}.

¹H NMR (400 MHz, CDCl₃) δ 7.65 – 7.63 (m, 2H, H_{Ar}), 7.43 – 7.28 (m, 7H, H_{Ar}), 7.24 – 7.12 (m, 2H, H_{Ar}), 7.09 (d, *J* = 8.1 Hz, 2H, H_{Ar}), 6.97 (d, *J* = 8.0 Hz, 2H, H_{Ar}), 6.88 – 6.82 (m, 2H, H_{Ar}), 6.53 (d, *J* = 15.7 Hz, 1H, H₁₇), 6.04 – 5.92 (m, 1H, H₁₆), 5.72 (s, 1H, H₃), 4.89 (d, *J*_{AB} = 15.8 Hz, 1H, H₉), 4.42 (d, *J*_{AB} = 16.0 Hz, 1H, H₉), 3.82 (s, 3H, H₂₂), 3.12 (ddd, *J* = 13.3, 8.6, 1.1 Hz, 1H, H₁₅), 2.98 (ddd, *J* = 13.3, 6.3, 1.6 Hz, 1H, H₁₅).

¹³C NMR (101 MHz, CDCl₃) δ 180.4 (s, C₁), 159.4 (s, C₂₁), 144.6 (s, C_{Ar}), 141.4 (s, C_{Ar}), 140.1 (s, C_{Ar}), 133.6 (s, C_{Ar}), 131.3 (s, C_{Ar}), 130.0 (s, C_{Ar}), 129.3 (s, C_{Ar}), 129.2 (d, *J* = 32.3 Hz, C₁₄), 128.8 (s, 2C, C_{Ar}), 128.7 (s, 2C, C_{Ar}), 128.5 (s, 2C, C_{Ar}), 127.55 (s, 2C, C_{Ar}), 127.51 (s, 3C, C_{Ar}), 126.9 (s, 2C, C_{Ar}), 125.4 (q, *J* = 3.8 Hz, 2C, C₁₂), 124.2 (d, *J* = 273.0 Hz, C₁₃), 122.3 (s, C₁₆), 114.1 (s, 2C, C₂₀), 111.5 (s, C₃), 58.0 (s, C₂), 55.4 (s, C₂₂), 44.2 (s, C₉), 42.6 (s, C₁₅).

HRMS (ESI) *m/z*: calculated for C₃₄H₂₈F₃NO₂H [M+H]⁺: 540.2145, found: 540.2153.

(*R*)-(E)-3-[3-(3-Methoxyphenyl)allyl]-3,5-diphenyl-1-(4-(trifluoromethyl)benzyl)-1,3-dihydro-2*H*-pyrrol-2-one (II.3t)



MW: 539.2072 g.mol^{–1}

Molecular Formula: C₃₄H₂₈F₃NO₂

Compound **II.3t** was synthesized according to the general method from 3,5-diphenyl-1-[4-(trifluoromethyl)benzyl]-1,5-dihydro-2*H*-pyrrol-2-one **II.1e** (101.4 mg, 0.2 mmol) and (*E*)-3-(3-methoxyphenyl)allyl benzoate **II.2k** (80.4 mg, 0.3 mmol, 1.5 equiv).

Compound **II.3t** was isolated as a colourless oil (84.0 mg, 78%) after purification by flash column chromatography over silica gel (PE/Et₂O = 12:1).

$[\alpha]_D^{20} = 30.8$ ($c = 2.25$, CHCl₃), ee = 76% (determined by SFC).

SFC: OD-H column, pressure = 100 bar, eluent = CO₂/MeOH (85:15), flow rate = 4.0 mL/min, detection wavelength = 220 nm, $t_{R1} = 5.80$ (minor), $t_{R2} = 8.25$ (major).

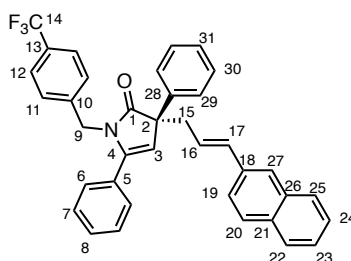
IR (neat): 1704, 1619, 1598, 1579, 1492, 1324, 1290, 1266, 1158, 1121, 1067, 1048, 1018, 969, 911 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.65 – 7.62 (m, 2H, H_{Ar}), 7.42 – 7.28 (m, 6H, H_{Ar}), 7.23 (t, $J = 7.9$ Hz, 1H, H_{Ar}), 7.16 – 7.13 (m, 2H, H_{Ar}), 7.11 (d, $J = 8.0$ Hz, 2H, H_{Ar}), 6.96 (d, $J = 8.4$ Hz, 2H, H_{Ar}), 6.90 (d, $J = 7.6$ Hz, 1H, H_{Ar}), 6.86 – 6.81 (m, 2H, H_{Ar}), 6.56 (d, $J = 15.7$ Hz, 1H, H₁₇), 6.19 – 6.11 (m, 1H, H₁₆), 5.73 (s, 1H, H₃), 4.87 (d, $J_{AB} = 15.9$ Hz, 1H, H₉), 4.45 (d, $J_{AB} = 16.0$ Hz, 1H, H₉), 3.79 (s, 3H, H₂₄), 3.13 (ddd, $J = 13.3, 8.6, 1.0$ Hz, 1H, H₁₅), 3.01 (ddd, $J = 13.3, 6.3, 1.5$ Hz, 1H, H₁₅).

¹³C NMR (101 MHz, CDCl₃) δ 180.3 (s, C₁), 160.0 (s, C₂₂), 144.7 (s, C_{Ar}), 141.4 (s, C_{Ar}), 139.9 (s, C_{Ar}), 138.6 (s, C_{Ar}), 134.1 (s, C₁₇), 131.2 (s, C_{Ar}), 129.7 (s, C_{Ar}), 129.4 (s, C_{Ar}), 129.3 (d, $J = 32.7$ Hz, C₁₄), 128.9 (s, 2C, C_{Ar}), 128.7 (s, 2C, C_{Ar}), 128.4 (s, 2C, C_{Ar}), 127.6 (s, C_{Ar}), 127.5 (s, 2C, C_{Ar}), 126.9 (s, 2C, C_{Ar}), 125.4 (q, $J = 3.9$ Hz, 2C, C₁₂), 125.1 (s, C₁₆), 124.2 (d, $J = 272.8$ Hz, C₁₃), 119.0 (s, C_{Ar}), 112.9 (s, C_{Ar}), 112.1 (s, C_{Ar}), 111.4 (s, C₃), 57.9 (s, C₂), 55.3 (s, C₁₄), 44.2 (s, C₉), 42.4 (s, C₁₅).

HRMS (ESI) m/z : calculated for C₃₄H₂₈F₃NO₂H [M+H]⁺: 540.2145, found: 540.2142.

(*R*)-(E)-3-[3-(Naphthalen-2-yl)allyl]-3,5-diphenyl-1-(4-(trifluoromethyl)benzyl)-1,3-dihydro-2*H*-pyrrol-2-one (II.3u)



MW: 559.2123 g.mol⁻¹

Molecular Formula: C₃₇H₂₈F₃NO

Compound **II.3u** was synthesized according to the general method from 3,5-diphenyl-1-[4-(trifluoromethyl)benzyl]-1,5-dihydro-2*H*-pyrrol-2-one **II.1e** (101.4 mg, 0.2 mmol) and (*E*)-3-(naphthalen-2-yl)allyl benzoate **II.2l** (86.4 mg, 0.3 mmol, 1.5 equiv). Compound **II.3u** was isolated as a white solid (92.4 mg, 79%) after purification by flash column chromatography over silica gel (PE/Et₂O = 12:1).

$[\alpha]_D^{20} = 13.5$ ($c = 2.67$, CHCl₃), ee = 84% (determined by SFC).

SFC: OD-H column, pressure = 100 bar, eluent = CO₂/MeOH (80:20), flow rate = 4.0 mL/min, detection wavelength = 220 nm, $t_{R1} = 10.12$ (minor), $t_{R2} = 13.89$ (major).

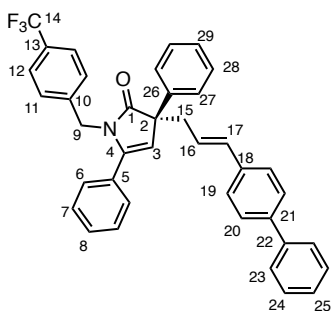
IR (neat): 1705, 1620, 1598, 1493, 1446, 1421, 1352, 1324, 1165, 1122, 1067, 1018, 964, 943, 909 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.83 – 7.75 (m, 3H, H_{Ar}), 7.68 – 7.65 (m, 3H, H_{Ar}), 7.50 – 7.24 (m, 9H, H_{Ar}), 7.17 – 7.15 (m, 2H, H_{Ar}), 7.08 (d, $J = 8.1$ Hz, 2H, H_{Ar}), 6.97 (d, $J = 8.1$ Hz, 2H, H_{Ar}), 6.74 (d, $J = 15.7$ Hz, 1H, H₁₇), 6.26 (ddd, $J = 15.4, 8.4, 6.5$ Hz, 1H, H₁₆), 5.76 (s, 1H, H₃), 4.83 (d, $J = 15.9$ Hz, 1H, H₉), 4.50 (d, $J = 15.9$ Hz, 1H, H₉), 3.19 (dd, $J = 13.3, 8.4$ Hz, 1H, H₁₅), 3.07 (ddd, $J = 13.3, 6.6, 1.5$ Hz, 1H, H₁₅).

¹³C NMR (101 MHz, CDCl₃) δ 180.4 (s, C₁), 144.7 (s, C_{Ar}), 141.4 (s, C_{Ar}), 139.9 (s, C_{Ar}), 134.6 (s, C_{Ar}), 134.2 (s, C₁₇), 133.7 (s, C_{Ar}), 133.1 (s, C_{Ar}), 131.2 (s, C_{Ar}), 129.4 (s, C_{Ar}), 129.3 (d, $J = 32.2$ Hz, C₁₄), 128.9 (s, 2C, C_{Ar}), 128.7 (s, 2C, C_{Ar}), 128.5 (s, 2C, C_{Ar}), 128.4 (s, C_{Ar}), 128.0 (s, C_{Ar}), 127.8 (s, C_{Ar}), 127.6 (s, C_{Ar}), 127.5 (s, 2C, C_{Ar}), 126.9 (s, 2C, C_{Ar}), 126.5 (s, C_{Ar}), 126.3 (s, C_{Ar}), 126.0 (s, C_{Ar}), 125.4 (q, $J = 3.7$ Hz, 2C, C₁₂), 125.1 (s, C_{Ar}), 124.0 (d, $J = 273.4$ Hz, C₁₃), 123.4 (s, C₁₆), 111.5 (s, C₃), 58.0 (s, C₂), 44.2 (s, C₉), 42.6 (s, C₁₅).

HRMS (ESI) m/z : calculated for C₃₇H₂₈F₃NOH [M+H]⁺:560.2196, found: 560.2194.

(*R*)-(*E*)-3-(3-([1,1'-Biphenyl]-4-yl)allyl)-3,5-diphenyl-1-(4-(trifluoromethyl)benzyl)-1,3-dihydro-2*H*-pyrrol-2-one (II.3v)



MW: 585.2279 g.mol⁻¹

Molecular Formula: C₃₉H₃₀F₃NO

Compound **II.3v** was synthesized according to the general method from 3,5-diphenyl-1-[4-(trifluoromethyl)benzyl]-1,5-dihydro-2*H*-pyrrol-2-one **II.1e** (101.4 mg, 0.2 mmol) and (*E*)-3-([1,1'-biphenyl]-4-yl)allyl benzoate **II.2m** (94.2 mg, 0.3 mmol, 1.5 equiv). Compound **II.3v** and **II.4v** were isolated as a mixture (91.0 mg, 78%) in a ratio of 4:1 in favor of **3v** after purification by flash column chromatography over silica gel (PE/Et₂O = 1:12).

[α]_D²⁰ = 3.1 (*c* = 0.8, CHCl₃), ee = 81% (determined by SFC).

SFC: OD-H column, pressure = 100 bar, eluent = CO₂/MeOH (77:23), flow rate = 4.0 mL/min, detection wavelength = 220 nm, *t*_{R1} = 9.54 (minor), *t*_{R2} = 38.38 (major).

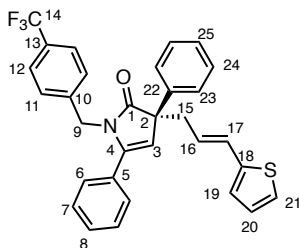
IR (neat): 1705, 1619, 1598, 1489, 1421, 1324, 1164, 1122, 1067, 1018, 969, 909 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.66 – 7.60 (m, 4H, H_{Ar}), 7.55 (d, *J* = 8.3 Hz, 2H, H_{Ar}), 7.47 – 7.29 (m, 11H, H_{Ar}), 7.17 – 7.14 (m, 4H, H_{Ar}), 6.99 (d, *J* = 8.0 Hz, 2H, H_{Ar}), 6.60 (d, *J* = 15.7 Hz, 1H, H₁₇), 6.21 – 6.13 (m, 1H, H₁₆), 5.74 (s, 1H, H₃), 4.86 (d, *J*_{AB} = 15.9 Hz, 1H, H_{Ar}), 4.48 (d, *J*_{AB} = 15.9 Hz, 1H, H₉), 3.15 (dd, *J* = 13.4, 8.5 Hz, 1H, H₁₅), 3.03 (ddd, *J* = 13.6, 6.4, 1.2 Hz, 1H, H₁₅).

¹³C NMR (101 MHz, CDCl₃) δ 180.4 (s, C₁), 144.7 (s, C_{Ar}), 141.4 (s, C_{Ar}), 140.8 (s, C_{Ar}), 140.5 (s, C_{Ar}), 139.9 (s, C_{Ar}), 136.2 (s, C_{Ar}), 133.7 (s, C₁₇), 131.2 (s, C_{Ar}), 129.4 (s, C_{Ar}), 129.37 (d, *J* = 32.4 Hz, C₁₄), 128.90 (s, 2C, C_{Ar}), 128.89 (s, 2C, C_{Ar}), 128.7 (s, 2C, C_{Ar}), 128.5 (s, 2C, C_{Ar}), 127.6 (s, 3C, C_{Ar}), 127.5 (s, 2C, C_{Ar}), 127.4 (s, C_{Ar}), 127.1 (s, 2C, C_{Ar}), 126.9 (s, 2C, C_{Ar}), 126.8 (s, 2C, C_{Ar}), 125.4 (q, *J* = 3.7 Hz, 2C, C₁₂), 124.8 (s, C₁₆), 124.1 (d, *J* = 274.3 Hz, C₁₃), 111.5 (s, C₃), 57.9 (s, C₂), 42.3 (s, C₉), 42.6 (s, C₁₅).

HRMS (ESI) *m/z*: calculated for C₃₉H₃₀F₃NOH [M+H]⁺: 586.2352, found: 586.2350.

(R)-(E)-3,5-Diphenyl-3-[3-(thiophen-2-yl)allyl]-1-[4-(trifluoromethyl)benzyl]-1,3-dihydro-2H-pyrrol-2-one (II.3w)



MW: 515.1531 g.mol⁻¹

Molecular Formula: C₃₁H₂₄F₃NOS

Compound **II.3w** was synthesized according to the general method from 3,5-diphenyl-1-[4-(trifluoromethyl)benzyl]-1,5-dihydro-2H-pyrrol-2-one **II.1e** (101.4 mg, 0.2 mmol) and (E)-3-(thiophen-2-yl)allyl benzoate **II.2n** (73.2 mg, 0.3 mmol, 1.5 equiv). Compound **II.3w** was isolated as a green oil (69.0 mg, 67%) after purification by flash column chromatography over silica gel (PE/Et₂O = 12:1).

[α]_D²⁰ = 51.6 (*c* = 0.5, CHCl₃), ee = 87% (determined by SFC).

SFC: OD-H column, pressure = 100 bar, eluent = CO₂/MeOH (80:20), flow rate = 4.0 mL/min, detection wavelength = 220 nm, *t*_{R1} = 5.05 (minor), *t*_{R2} = 8.15 (major).

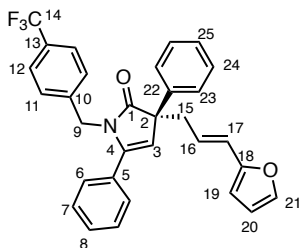
IR (neat): 1705, 1620, 1493, 1446, 1421, 1324, 1164, 1122, 1067, 1018, 958 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.64 – 7.61 (m, 2H, H_{Ar}), 7.41 – 7.29 (m, 6H, H_{Ar}), 7.18 – 7.13 (m, 5H, H_{Ar}), 6.99 – 6.96 (m, 3H, H_{Ar}), 6.89 (d, *J* = 3.4 Hz, 1H, H_{Ar}), 6.70 (d, *J* = 15.5 Hz, 1H, H₁₇), 6.00 – 5.93 (m, 1H, H₁₆), 5.70 (s, 1H, H₃), 4.85 (d, *J*_{AB} = 15.9 Hz, 1H, H₉), 4.44 (d, *J*_{AB} = 15.9 Hz, 1H, H₉), 3.11 (dd, *J* = 13.5, 8.8 Hz, 1H, H₁₅), 2.95 (ddd, *J* = 13.4, 6.3, 1.6 Hz, 1H, H₁₅).

¹³C NMR (101 MHz, CDCl₃) δ 180.3 (s, C₁), 144.8 (s, C_{Ar}), 142.4 (s, C_{Ar}), 141.3 (s, C_{Ar}), 139.9 (s, C_{Ar}), 131.2 (s, C_{Ar}), 129.4 (s, C_{Ar}), 129.3 (d, *J* = 32.2 Hz, C₁₄), 128.9 (s, 2C, C_{Ar}), 128.7 (s, 2C, C_{Ar}), 128.6 (s, 2C, C_{Ar}), 127.6 (s, C_{Ar}), 127.56 (s, 2C, C_{Ar}), 127.54 (s, C_{Ar}), 127.3 (s, C₁₇), 126.8 (s, 2C, C_{Ar}), 125.6 (s, C_{Ar}), 125.3 (q, *J* = 3.8 Hz, 2C, C₁₂), 124.5 (s, C₁₆), 124.1 (d, *J* = 273.3 Hz, C₁₃), 124.0 (s, C_{Ar}), 111.2 (s, C₃), 57.9 (s, C₂), 44.3 (s, C₉), 42.3 (s, C₁₅).

HRMS (ESI) *m/z*: calculated for C₃₁H₂₄F₃NOSH [M+H]⁺: 516.1603, found: 516.1601.

(R)-(E)-3-[3-(Furan-2-yl)allyl]-3,5-diphenyl-1-[4-(trifluoromethyl)benzyl]-1,3-dihydro-2H-pyrrol-2-one (II.3x)



MW: 499.1759 g.mol⁻¹

Molecular Formula: C₃₁H₂₄F₃NO₂

Compound **II.3x** was synthesized according to the general method from 3,5-diphenyl-1-[4-(trifluoromethyl)benzyl]-1,5-dihydro-2H-pyrrol-2-one **II.1e** (101.4 mg, 0.2 mmol) and (*E*)-3-(furan-2-yl)allyl benzoate **II.2o** (68.4 mg, 0.3 mmol, 1.5 equiv). Compound **II.3x** was isolated as a green oil (68.0 mg, 68%) after purification by flash column chromatography over silica gel (PE/Et₂O= 12:1).

[α]²⁰_D = 40.7 (*c* = 2.27, CHCl₃), ee = 94% (determined by SFC).

SFC: OD-H column, pressure = 100 bar, eluent = CO₂/MeOH (88:12), flow rate = 4.0 mL/min, detection wavelength = 220 nm, *t*_{R1} = 4.31 (minor), *t*_{R2} = 6.56 (major).

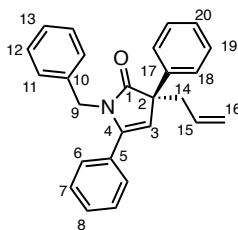
IR (neat): 1702, 1620, 1492, 1446, 1421, 1323, 1164, 1121, 1066, 1017, 963, 908 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.64 – 7.62 (m, 2H, H_{Ar}), 7.41 – 7.29 (m, 7H, H_{Ar} and H₂₁), 7.21 (d, *J* = 8.1 Hz, 2H, H_{Ar}), 7.18 – 7.16 (m, 2H, H_{Ar}), 7.00 (d, *J* = 8.0 Hz, 2H, H_{Ar}), 6.41 – 6.37 (m, 2H, H₂₀ and H₁₇), 6.17 (d, *J* = 3.3 Hz, 1H, H₁₉), 6.12 – 6.04 (m, 1H, H₁₆), 5.72 (s, 1H, H₃), 4.88 (d, *J* = 15.9 Hz, 1H, H₉), 4.46 (d, *J* = 15.9 Hz, 1H, H₉), 3.08 (dd, *J* = 13.5, 8.8 Hz, 1H, H₁₅), 2.99 (ddd, *J* = 13.5, 6.4, 1.6 Hz, 1H, H₁₅).

¹³C NMR (101 MHz, CDCl₃) δ 180.3 (s, C₁), 152.7 (s, C_{Ar}), 144.8 (s, C_{Ar}), 141.9 (s, C₂₁), 141.4 (s, C_{Ar}), 139.9 (s, C_{Ar}), 131.3 (s, C_{Ar}), 129.4 (s, C_{Ar}), 129.3 (d, *J* = 32.3 Hz, C₁₄), 128.8 (s, 2C, C_{Ar}), 128.7 (s, 2C, C_{Ar}), 128.5 (s, 2C, C_{Ar}), 127.5 (s, 3C, C_{Ar}), 126.9 (s, 2C, C_{Ar}), 125.3 (q, *J* = 3.7 Hz, 2C, C₁₂), 124.2 (d, *J* = 272.9 Hz, C₁₃), 123.6 (s, C₁₆), 122.5 (s, C₁₇), 111.4 (s, C₃), 111.3 (s, C₂₀), 107.7 (s, C₉), 57.9 (s, C₂), 44.2 (s, C₉), 42.4 (s, C₁₅).

HRMS (ESI) *m/z*: calculated for C₃₁H₂₄F₃NO₂H [M+H]⁺: 500.1832, found: 500.1827.

(R)-3-Allyl-1-benzyl-3,5-diphenyl-1,3-dihydro-2H-pyrrol-2-one (II.3y)



MW: 365.1780 g.mol⁻¹

Molecular Formula: C₂₆H₂₃NO

Compound **II.3y** was synthesized according to the general method from 1-benzyl-2-[(*tert*-butyldimethylsilyl)oxy]-3,5-diphenyl-1*H*-pyrrole **II.1e** (87.8 mg, 0.2 mmol) and allyl benzoate **II.2p** (48.6 mg, 0.3 mmol, 1.5 equiv). Compound **II.3y** was isolated as a colourless solid (72.3 mg, 99%) after purification by flash column chromatography over silica gel (PE/Et₂O = 10:1).

[α]²⁰_D = −25.4 (*c* = 2.0, CHCl₃), ee = 64% (determined by SFC).

SFC: AD-H column, pressure = 100 bar, eluent = CO₂/MeOH (97:3), flow rate = 5.0 mL/min, detection wavelength = 220 nm, *t*_{R1} = 19.52 (minor), *t*_{R2} = 27.17 (major).

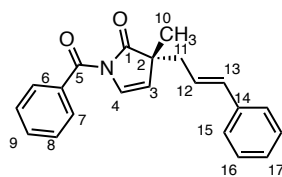
IR (neat): 3060, 1704, 1640, 1598, 1494, 1446, 1342, 1223, 1188, 1139, 1077, 1031, 994, 920 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.52 – 7.49 (m, 2H, H_{Ar}), 7.31– 7.13 (m, 8H, H_{Ar}), 7.09 – 7.06 (m, 3H, H_{Ar}), 6.86 – 6.84 (m, 2H, H_{Ar}), 5.63 – 5.52 (m, 2H, H₃ and H₁₅), 5.09 – 5.03 (m, 1H, H₂₀), 4.97 – 4.93 (m, 1H, H₂₀), 4.61 (d, *J*_{AB} = 15.5 Hz, 1H, H₉), 4.53 (d, *J*_{AB} = 15.6 Hz, 1H, H₉), 2.85 – 2.72 (m, 2H, H₁₄).

¹³C NMR (101 MHz, CDCl₃) δ 180.6 (s, C₁), 144.9 (s, C_{Ar}), 139.8 (s, C_{Ar}), 137.6 (s, C_{Ar}), 133.3 (s, C₁₅), 131.6 (s, C_{Ar}), 129.2 (s, C_{Ar}), 128.7 (s, 2C, C_{Ar}), 128.5 (s, 4C, C_{Ar}), 128.4 (s, 2C, C_{Ar}), 127.5 (s, 2C, C_{Ar}), 127.3 (s, C_{Ar}), 127.2 (s, C_{Ar}), 127.0 (s, 2C, C_{Ar}), 118.7 (s, C₁₆), 111.5 (s, C₃), 57.2 (s, C₂), 44.6 (s, C₉), 43.1 (s, C₁₄).

HRMS (ESI) *m/z*: calculated for C₂₆H₂₃NONa [M+Na]⁺: 388.1672, found: 388.1673.

(R)-1-Benzoyl-3-cinnamyl-3-methyl-1,3-dihydro-2*H*-pyrrol-2-one (II.3z)



MW: 317.1416 g.mol⁻¹

Molecular Formula: C₂₁H₁₉NO₂

Compound **II.3z** was synthesized according to the general method from {2-[(*tert*-butyldimethylsilyl)oxy]-3-methyl-1*H*-pyrrol-1-yl}(phenyl)methanone **II.1o** (63.0 mg, 0.2 mmol) and cinnamyl benzoate **II.2e** (71.4 mg, 0.3 mmol, 1.5 equiv). Compound **II.3z** was isolated as a white solid (39.3 mg, 62%) after purification by flash column chromatography over silica gel (PE/Et₂O = 10:1).

Mp: 96–97 °C.

[α]²⁰_D = −145.0 (*c* = 1.23, CHCl₃), ee = 66% (determined by SFC).

SFC: AD-H column, pressure = 100 bar, eluent = CO₂/MeOH (90:10), flow rate = 4.0 mL/min, detection wavelength = 220 nm, *t*_{R1} = 4.40 (minor), *t*_{R2} = 10.40 (major).

IR (neat): 2928, 1757, 1677, 1600, 1493, 1449, 1376, 1353, 1304, 1202, 1180, 1074, 1030, 967 cm⁻¹.

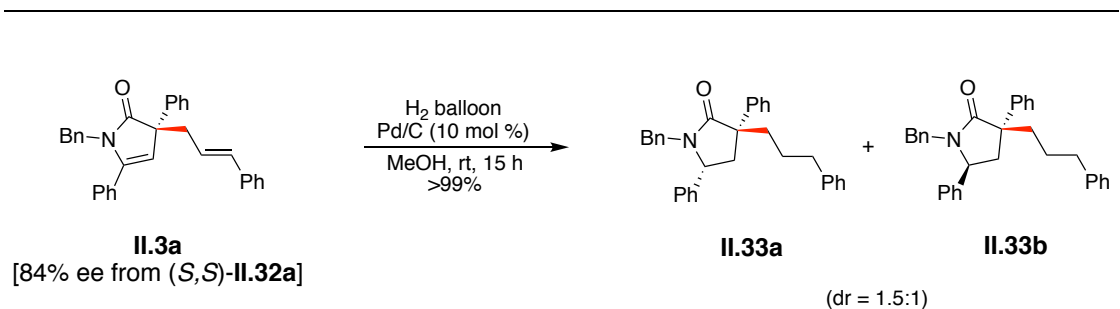
¹H NMR (400 MHz, CDCl₃) δ 7.50 – 7.42 (m, 3H, H_{Ar}), 7.30 – 7.13 (m, 8H, H_{Ar} and H₄), 6.44 (d, *J* = 15.7 Hz, 1H, H₁₃), 6.09 – 6.01 (m, 1H, H₁₂), 5.54 (d, *J* = 5.3 Hz, 1H, H₃), 2.54 – 2.42 (m, 2H, H₁₁), 1.26 (s, 3H, H₁₀).

¹³C NMR (101 MHz, CDCl₃) δ 179.4 (s, C₁), 167.9 (s, C₅), 137.0 (s, C_{Ar}), 134.5 (s, C₁₃), 133.4 (s, C_{Ar}), 132.6 (s, C_{Ar}), 129.4 (s, 2C, C_{Ar}), 128.8 (s, 2C, C_{Ar}), 128.3 (s, C₁₇), 128.0 (s, 2C, C_{Ar}), 127.8 (s, C₄), 126.4 (s, 2C, C_{Ar}), 123.9 (s, C₁₂), 117.6 (s, C₃), 52.9 (s, C₂), 41.3 (s, C₁₁), 22.5 (s, C₁₀).

HRMS (ESI) *m/z*: calculated for C₂₁H₁₉NO₂Na [M+Na]⁺: 340.1308, found: 340.1318.

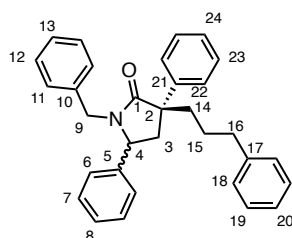
Post-functionalization:

1. Synthesis of chiral pyrrolidinone derivatives **II.33** from the α-allylated product **II.3a**:



To a solution of **II.3a** (50 mg, 0.11 mmol) in MeOH (3 mL) was added Pd/C (11 mg, 0.011 mmol, 10 wt %). The reaction mixture was stirred under 1 atm of H₂ at rt. After 15 h, the hydrogen balloon was removed. The mixture solution was filtered through Celite and washed by CH₂Cl₂, the solvent was removed under reduced pressure and purification of the crude mixture product by flash column chromatography over silica gel (PE/Et₂O = 10:1) afforded the two diastereomers in quantitative yield with 1.5:1 ratio.

(3*R*)-1-Benzyl-3,5-diphenyl-3-(3-phenylpropyl)pyrrolidin-2-one **II.33**



MW: 445.2406 g.mol⁻¹

Molecular Formula: C₃₂H₃₁NO

The data of major diastereomer of II.33 (28 mg, 58%)

[α]²⁰_D = −43.0 (*c* = 0.5, CHCl₃), ee = 84% (determined by SFC).

SFC: AD-H column, pressure = 100 bar, eluent = CO₂/MeOH (85:15), flow rate = 5.0 mL/min, detection wavelength = 220 nm, *t*_{R1} = 5.16 (minor), *t*_{R2} = 5.63 (major).

IR (neat): 2938, 1686, 1602, 1494, 1454, 1403, 1318, 1280, 1213, 1157, 1078, 1003, 973, 933, 912 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.45 – 7.43 (m, 2H, H_{Ar}), 7.38 – 7.30 (m, 5H, H_{Ar}), 7.27 – 7.23 (m, 3H, H_{Ar}), 7.18 – 7.06 (m, 8H, H_{Ar}), 6.74 (d, *J* = 7.2 Hz, 2H, H_{Ar}), 5.09 (d, *J*_{AB} = 14.5 Hz, 1H, H₉), 4.19 (dd, *J* = 9.6, 6.2 Hz, 1H, H₄), 3.48 (d, *J*_{AB} = 14.5 Hz, 1H, H₉), 2.85 (dd, *J* = 13.2, 6.2 Hz, 1H, H₃), 2.68 – 2.56 (m, 2H, H₁₆), 2.20 (td, *J* = 13.5, 13.0, 4.6 Hz, 1H, H₁₄),

2.07 (dd, $J = 13.2, 9.8$ Hz, 1H, H_3), 1.98 (td, $J = 13.4, 12.9, 4.7$ Hz, 1H, H_{14}), 1.72 – 1.53 (m, 2H, H_{15}).

^{13}C NMR (101 MHz, CDCl_3) δ 177.3 (s, C_1), 142.3 (s, C_{Ar}), 141.0 (s, C_{Ar}), 140.0 (s, C_{Ar}), 136.1 (s, C_{Ar}), 129.1 (s, 2C, C_{Ar}), 128.7 (s, 2C, C_{Ar}), 128.6 (s, 2C, C_{Ar}), 128.5 (s, 2C, C_{Ar}), 128.40 (s, 2C, C_{Ar}), 128.38 (s, 3C, C_{Ar}), 127.6 (s, 2C, C_{Ar}), 127.4 (s, C_{Ar}), 127.1 (s, C_{Ar}), 126.8 (s, 2C, C_{Ar}), 125.9 (s, C_{Ar}), 58.9 (s, C_4), 52.8 (s, C_2), 44.6 (s, C_9), 42.2 (s, C_3), 39.1 (s, C_{14}), 36.4 (s, C_{16}), 26.8 (s, C_{15}).

HRMS (ESI) m/z : calculated for $\text{C}_{32}\text{H}_{31}\text{NOH}$ [$M+H$]: 446.2478, found: 446.2487.

The data of minor diastereomer of II.33 (19 mg, 39%)

$[\alpha]_D^{20} = 39.1$ ($c = 0.75$, CHCl_3), ee = 84% (determined by SFC).

SFC: AD-H column, pressure = 100 bar, eluent = CO_2/MeOH (85:15), flow rate = 5.0 mL/min, detection wavelength = 220 nm, $t_{R1} = 4.65$ (minor), $t_{R2} = 6.76$ (major).

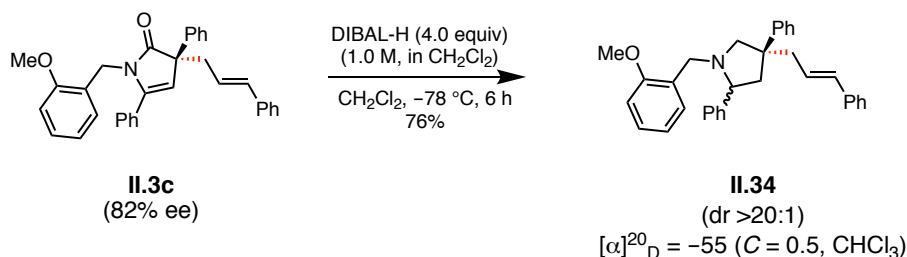
IR (neat): 2938, 1682, 1602, 1494, 1454, 1405, 1366, 1335, 1281, 1253, 1156, 1079, 1030, 934 cm^{-1} .

^1H NMR (400 MHz, CDCl_3) δ 7.57 (dd, $J = 7.6, 2.4$ Hz, 2H, H_{Ar}), 7.36 – 7.18 (m, 13H, H_{Ar}), 7.10 – 7.05 (m, 5H, H_{Ar}), 5.19 (dd, $J = 14.3, 2.6$ Hz, 1H, H_9), 4.28 (td, $J = 7.6, 2.6$ Hz, 1H, H_4), 3.48 (dd, $J = 14.3, 2.7$ Hz, 1H, H_9), 2.64 – 2.51 (m, 3H, H_3 and H_{16}), 2.32 (ddd, $J = 13.3, 7.7, 2.7$ Hz, 1H, H_3), 1.95 – 1.92 (m, 2H, H_{14}), 1.64 – 1.54 (m, 2H, H_{15}).

^{13}C NMR (101 MHz, CDCl_3) δ 177.2 (s, C_1), 143.4 (s, C_{Ar}), 142.0 (s, C_{Ar}), 140.5 (s, C_{Ar}), 136.4 (s, C_{Ar}), 129.02 (s, 2C, C_{Ar}), 129.0 (s, 2C, C_{Ar}), 128.7 (s, 2C, C_{Ar}), 128.5 (s, 2C, C_{Ar}), 128.4 (s, 4C, C_{Ar}), 128.2 (s, C_{Ar}), 127.7 (s, C_{Ar}), 127.4 (s, 2C, C_{Ar}), 126.8 (s, 2C, C_{Ar}), 126.6 (s, C_{Ar}), 125.9 (s, C_{Ar}), 58.5 (s, C_4), 51.7 (s, C_2), 44.8 (s, C_9), 42.6 (s, C_3), 39.3 (s, C_{14}), 36.1 (s, C_{16}), 26.3 (s, C_{15}).

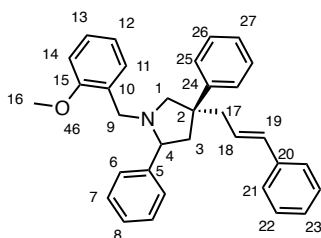
HRMS (ESI) m/z : calculated for $\text{C}_{32}\text{H}_{31}\text{NOH}$ [$M+H$]: 446.2478, found: 446.2479.

2. Synthesis of pyrrolidine derivatives II.6 from the α -allylated product II.3c:



To a solution of Compound **II.3c** (47 mg, 0.1 mmol) in CH_2Cl_2 at -78°C , DIBAL-H (0.4 mL, 4.0 equiv, 1.0 M in CH_2Cl_2) was added slowly. The reaction mixture was stirred at -78°C for further 6 h. After the reaction completely finished, NaOH (10 mol%) solution was added to quench the reaction, the aqueous layers were extracted with CH_2Cl_2 (3×5 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude product. After purification by flash column chromatography over silica gel ($\text{PE}/\text{Et}_2\text{O} = 12:1$), Compound **II.6** was isolated as a colourless oil in a single diastereomer (35 mg, 76%).

(4R)-4-cinnamyl-1-(2-methoxybenzyl)-2,4-diphenylpyrrolidine (II.34)



MW: 459.2562 $\text{g}\cdot\text{mol}^{-1}$

Molecular Formula: $\text{C}_{33}\text{H}_{33}\text{NO}$

$[\alpha]_D^{20} = -55.0$ ($c = 0.5$, CHCl_3).

IR (neat): 3026, 1600, 1492, 1463, 1376, 1286, 1241, 1158, 1090, 1070, 1049, 1030, 967, 909 cm^{-1} .

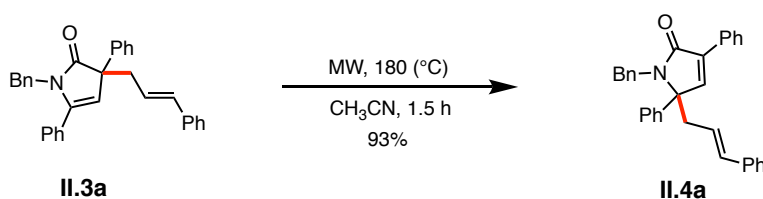
^1H NMR (400 MHz, CDCl_3) δ 7.62 (dd, $J = 7.5, 1.7$ Hz, 1H, H_{Ar}), 7.57 – 7.55 (m, 2H, H_{Ar}), 7.37 – 7.14 (m, 14H, H_{Ar}), 6.97 (td, $J = 7.4, 1.1$ Hz, 1H, H_{13}), 6.85 (dd, $J = 8.2, 1.1$ Hz, 1H, H_{14}), 6.28 (d, $J = 15.8$ Hz, 1H, H_{19}), 5.89 (ddd, $J = 15.5, 8.1, 6.9$ Hz, 1H, H_{18}), 3.78 (s, 3H, H_{16}), 3.75 (d, $J_{\text{AB}} = 14.6$ Hz, 1H, H_9), 3.69 (t, $J = 8.6$ Hz, 1H, H_4), 3.55 (d, $J = 9.1$ Hz, 1H, H_1), 3.40 (d, $J_{\text{AB}} = 14.6$ Hz, 1H, H_9), 2.90 (dd, $J = 13.2, 8.1$ Hz, 1H, H_{17}), 2.75 – 2.67 (m, 2H, H_3 and H_{17}), 2.57 (d, $J = 9.1$ Hz, 1H, H_1), 2.16 (dd, $J = 13.0, 8.0$ Hz, 1H, H_3).

^{13}C NMR (101 MHz, CDCl_3) δ 157.4 (s, C_{15}), 148.2 (s, C_{Ar}), 144.2 (s, C_{Ar}), 137.9 (s, C_{Ar}), 132.8 (s, C_{19}), 129.5 (s, C_{Ar}), 128.6 (s, 2C, C_{Ar}), 128.5 (s, 2C, C_{Ar}), 128.20 (s, 2C, C_{Ar}),

128.17 (s, C_{Ar}), 127.6 (s, 2C, C_{Ar}), 127.59 (s, 2C, C_{Ar}), 127.0 (s, C_{Ar}), 126.98 (s, 3C, C_{Ar}), 126.2 (s, 2C, C_{Ar}), 125.9 (s, C₁₈), 120.5 (s, C₁₃), 110.2 (s, C₁₄), 69.6 (s, C₄), 63.3 (s, C₁), 55.3 (s, C₁₆), 51.4 (s, C₉), 48.7 (s, C₂), 48.2 (s, C₁₇), 47.7 (s, C₃).

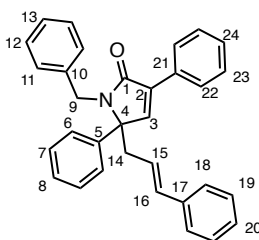
HRMS (ESI) *m/z*: calculated for C₃₃H₃₃NOH [M+H]⁺: 460.2635, found: 460.2642.

3. Synthesis of γ -allylated latam **II.4a** from α -allylated lactam **II.3a** via 1,3-migration:



A solution of compound **II.3a** (0.1 mmol, 1.0 equiv) in CH₃CN (1 mL) was heated at 180 °C for 1.5 h under microwave irradiation. The solvent was then removed under reduce pressure directly to afford the crude residue which was further purified by flash column chromatography over silica gel (PE/Et₂O = 15:1 to 10:1). The γ -allylated product **II.4a** was isolated as a colourless oil (41 mg, 93%).

1-Benzyl-5-cinnamyl-3,5-diphenyl-1,5-dihydro-2H-pyrrol-2-one (**II.4a**)



MW: 441.2093 g.mol⁻¹

Molecular Formula: C₃₂H₂₇NO

IR (neat): 3027, 2921, 1676, 1599, 1492, 1447, 1428, 1391, 1356, 1278, 1221, 1184, 1146, 1080, 1027, 1002, 965, 909 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.98 – 7.92 (m, 2H, C_{Ar}), 7.46 – 7.28 (m, 10H, C_{Ar}), 7.27 – 7.15 (m, 7H, C_{Ar}), 7.11 (dd, *J* = 6.8, 1.7 Hz, 2H C_{Ar}), 6.08 (d, *J* = 15.8 Hz, 1H, C₁₆), 5.72 (dt, *J* = 15.8, 7.0 Hz, 1H, C₁₅), 4.95 (d, *J* = 15.1 Hz, 1H, C₉), 3.85 (d, *J* = 15.2 Hz, 1H, C₉), 3.17 (ddd, *J* = 14.5, 6.7, 1.5 Hz, 1H, C₁₄), 2.89 (ddd, *J* = 14.4, 7.4, 1.4 Hz, 1H, C₁₄).

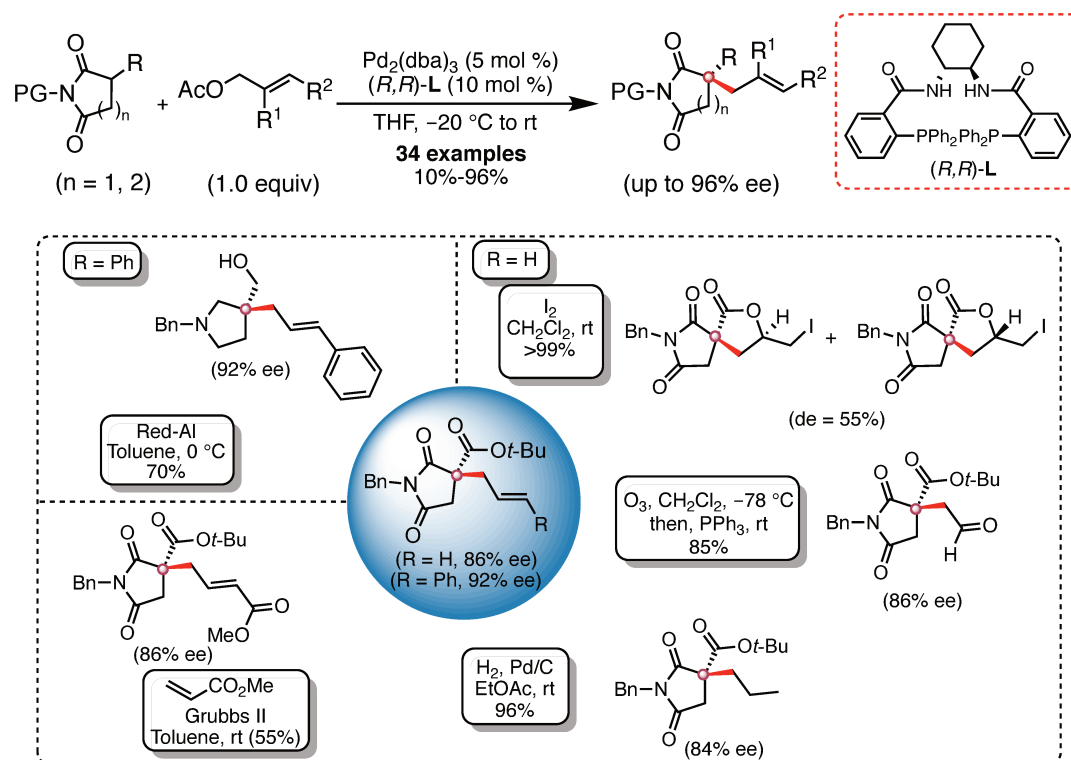
¹³C NMR (101 MHz, CDCl₃) δ 170.7 (s, C₁), 145.9 (s, C₃), 138.1 (s, C_{Ar}), 137.5 (s, C_{Ar}), 137.0 (s, C_{Ar}), 135.0 (s, C₁₆), 134.0 (s, C_{Ar}), 131.5 (s, C_{Ar}), 129.13 (s, 2C, C_{Ar}), 129.07 (s, 2C, C_{Ar}), 128.8 (s, C_{Ar}), 128.6 (s, 2C, C_{Ar}), 128.5 (s, 2C, C_{Ar}), 128.46 (s, C_{Ar}), 128.43 (s, 2C, C_{Ar}), 127.45 (s, 3C, C_{Ar}), 127.42 (s, C_{Ar}), 126.9 (s, 2C, C_{Ar}), 126.3 (s, 2C, C_{Ar}), 123.1 (s, C₁₅), 69.9 (s, C₂), 44.3 (s, C₉), 37.4 (s, C₁₄).

HRMS (ESI) m/z: calculated for C₃₂H₂₇NOH [M+H]⁺: 442.2165, found: 442.2163.0

General Conclusion

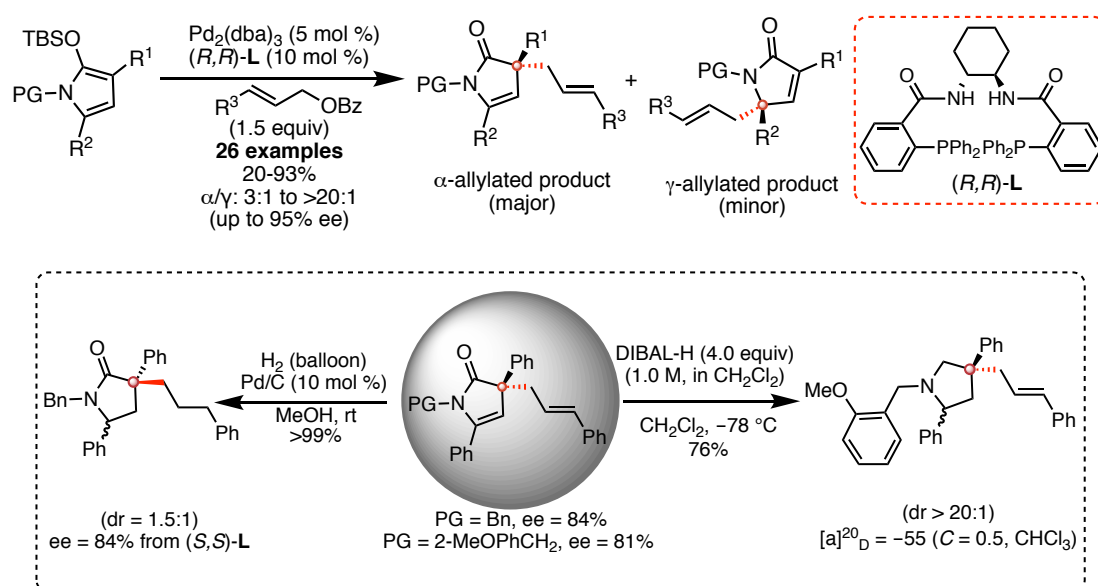
Asymmetric construction *N*-containing five-membered ring heterocycles bearing an all-carbon α -quaternary stereogenic center is a challenge in organic synthesis. In this thesis, we have successfully developed two mild synthetic methods to access the functionalized *N*-containing heterocycles, succinimides and γ -lactam derivatives, bearing an all-carbon α -quaternary center in high enantioselectivities through palladium-catalyzed **Asymmetric Allylic Alkylation (Pd-AAA)**.

In the first chapter, we have successfully developed an efficient base free, highly enantioselective Pd-AAA process to access the optically active succinimides bearing an all-carbon α -quaternary stereogenic center. A variety of monosubstituted succinimides and various functional allylic reagents were synthesized and applied to this Pd-AAA process, the corresponding allylated products were obtained in generally high yields and good to excellent enantioselectivities (up to 96% ee). More importantly, the optically active allylated succinimide derivatives could be converted to various useful building blocks through simple synthetic transformations



Scheme I. Synthesis of optically active succinimides bearing an all-carbon α -quaternary stereogenic center via Pd-AAA and their post-functionalization

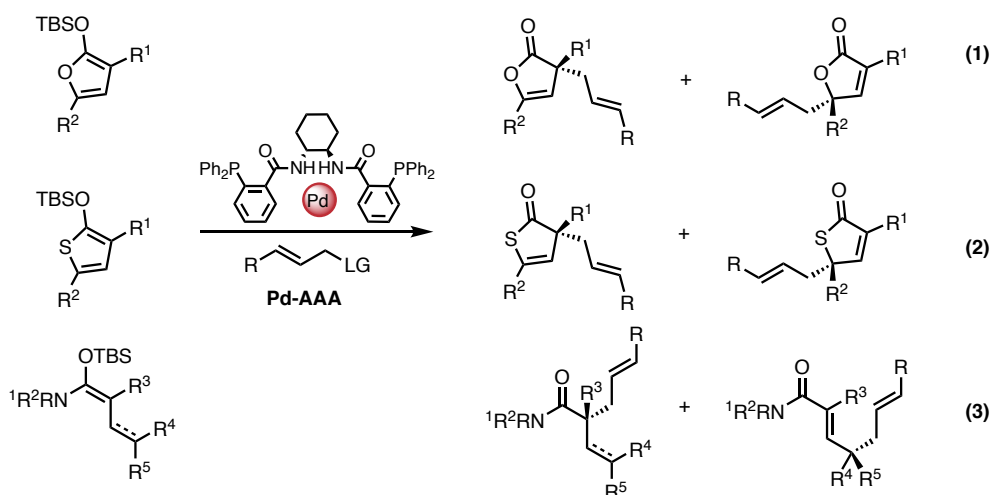
In the second chapter, various highly functionalized γ -lactam derivatives bearing an all-carbon α -quaternary stereogenic center were successfully obtained via an efficiently additive free Pd-**AAA** of 2-silyloxypyrroles. A variety of α,γ -disubstituted, α,β -unsaturated γ -lactams were synthesized and converted to the corresponding α,γ -disubstituted 2-silyloxypyrrole compounds which were applied to Pd-**AAA** under the optimized conditions. All of the corresponding allylated γ -lactam products were obtained in generally high yields, good to excellent regio- (3:1 to >20:1) and enantioselectivities (up to 95% ee). It's worth noting that the useful building blocks, pyrrolidinone and pyrrolidine derivatives, could be easily accessed from the corresponding allylated γ -lactam products by simple synthetic methods, respectively.



Scheme II. Synthesis of optically active γ -lactams bearing an all-carbon quaternary stereogenic center via Pd-AAA and their post-functionalization

Perspective

The palladium-catalyzed asymmetric allylic alkylation (Pd-AAA) is definitely one of the most efficient and versatile method to construct quaternary stereogenic centers through C-C or C-X (X = O, S, N, P) bond formation. We believe that a variety of heterocycles bearing a quaternary stereogenic center can be accessed using this key reaction (Scheme III, eq 1 and 2). In addition, saturated/unsaturated acyclic compound bearing a quaternary stereogenic center could also generated using this powerful reaction (Scheme III, eq 3).



Scheme III. Pd-AAA applied in the asymmetric construction of furan and thiophene derivative bearing a quaternary stereogenic center.

References

-
1. (a) Fredenhagen, A.; Tamura S. Y.; Kenny, P. T. M.; Komura, H.; Naya, Y.; Nakanishi, K. *J. Am. Chem. Soc.* **1987**, *109*, 4409-4411; (b) Coulter, D. A.; Huguenard, J. R.; Prince, D. A, *Br. J. Pharmacol.* **1990**, *100*, 800-806; (c) Malochet-Grivois, C.; Roussakis, C.; Robillard, N.; Biard, J. F.; D. Riou, D.; Debitus, C.; Verbist, J. F. *Anti-Cancer Drug Des.* **1992**, *7*, 493-502; (d) Hayashi, H.; Nishimoto, Y.; Nozaki, H. *Tetrahedron Lett.* **1997**, *38*, 5655-5658; (e) Todorovic, S. M.; Lingle, C. J. *J. Neurophysiol.* **1998**, *79*, 240-252; (f) Uddin, M. J.; Kokubo, K.; Ueda, K.; Suenaga, K.; Uemura, D. *J. Nat. Prod.* **2001**, *64*, 1169-1173; (g) Gomora, J. C.; Daud, A. N.; Weiergräber, M.; Perez-Reyes, E. *Mol. Pharmacol.* **2001**, *60*, 1121-1132. (h) Ando, Y.; Fuse, E.; Figg, W. D. *Clin. Cancer Res.* **2002**, *8*, 1964-1973; (i) Freiberg, C.; Brunner, N. A.; Schiffer, G.; Lampe, T.; Pohlmann, M.; Habich, D.; Ziegelbauer, K. *J. Biol. Chem.* **2004**, *279*, 26066-26073; (j) Isaka, M.; Rugserree, N.; Maithip, P.; Kongsaree, P.; Prabpai, S.; Thebtaranonth, Y. *Tetrahedron* **2005**, *61*, 5577-5583; (k) Bril, V.; Hirose, T.; Tomioka, S.; Buchanan, R. *Diabetes Care* **2009**, *32*, 1256-1260; (l) Sato, M.; Dander, J. E.; Sato, C.; Hung, Y.-S.; Gao, S.-S.; Tang, M.-C.; Hang, L.; Winter, J. M.; Garg, N. K.; Watanabe, K.; Tang, Y. *J. Am. Chem. Soc.* **2017**, *139*, 5317-5320.
 2. (a) World health Organization. WHO Fact Sheet No104. (b) Smith, C. V.; Shama, V.; Sacchettini, J. C. *Tuberculosis* **2004**, *84*, 45-55.
 3. (a) Cantrell, C. R.; Franzblau, S. G.; Fischer, N. H. *Planta Med.* **2001**, *67*, 685-694; (b) Duncan, K. *Tuberculosis* **2003**, *83*, 201-207. (c) Duncan, K., III; Barry, C. E. *Curr. Opin. Microbiol.* **2004**, *7*, 460-465.
 4. Uddin, M. J.; Kokubo, S.; Suenaga, K.; Ueda, K.; Uemura, D. *Heterocycles* **2001**, *54*, 1039-1047.
 5. Robert, F.; Gao, H. Q.; Donia, M.; Merrick, W. C.; Hamann, M. T.; Pettetier, J. *RNA* **2006**, *12*, 717-725.
 6. Gomora, J. C.; Daud, A. N.; Weiergräber, M.; Perez-Reyes, E. *Mol. Pharmacol.* **2001**, *60*, 1121-1132.
 7. Bril V, Buchanan R. A.; the AS-3201 Study Group *Diabetes Care* **2004**, *27*, 2369-2375.
 8. Chauhan, P.; Kaur, J.; Chimni, S. S. *Chem. Asian. J.* **2013**, *8*, 328-346.
 9. Bartoli, G.; Bosco, M.; Carlone, A.; Cavalli, A.; Locatelli, M.; Mazzanti, A.; Ricci, P.; Sambri, L.; Melchiorre, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 4966-4970.
 10. Cucinotta, C. S.; Kosa, M.; Melchiorre, P.; Cavalli, A.; Gervasio, F. L. *Chem. Eur. J.* **2009**, *15*, 7913-7921.

-
11. a) Ye, W.; Jiang, Z.; Zhao, Y.; Li, S.; Goh, M.; Leow, D.; Soh, Y.-T.; Tan, C.-H. *Adv. Synth. Catal.* **2007**, *349*, 2454-2458; b) Jiang, Z.; Ye, W.; Yang, Y.; Tan, C.-H. *Adv. Synth. Catal.* **2008**, *350*, 2345-2351; c) Jiang, Z.; Pan, Y.; Zhao, Y.; Ma, T.; Lee, R.; Yang, Y.; Huang, K.-W.; Wong, M. W.; Tan, C.-H. *Angew. Chem. Int. Ed.* **2009**, *48*, 3627-3631; d) Qin, Y.; Yang, G.; Yang, L.; Li, J.; Cui, Y. *Catal. Lett.* **2011**, *141*, 48-488; e) Shirakawa, S.; Terao, S. J.; He, R.; Maruoka, K. *Chem. Commun.* **2011**, *47*, 10557-10559; f) Gómez-Torres, E.; Alonso, D. A.; Gómez-Bengoa, E.; Nájera, C. *Org. Lett.* **2011**, *13*, 6106-6109; g) Wang, J.-J.; Dong, X.-J.; Wei, W.-T.; Yan, M. *Tetrahedron: Asymmetry* **2011**, *22*, 690-696; h) Liao, Y.-H.; Liu, X.-L.; Wu, Z.-J.; Du, X.-L.; Zhang, X.-M.; Yuan, W.-C. *Adv. Synth. Catal.* **2011**, *353*, 1720-1728; i) Bai, J.-F.; Wang, L.-L.; Peng, L.; Guo, Y.-L.; Jia, L.-N.; Tian, F.; He, G.-Y.; Xu, X.-Y.; Wang, L.-X. *J. Org. Chem.* **2012**, *77*, 2947-2953; j) Lattanzi, A.; Fusco, C. D.; Russo, A.; Poater, A.; Cavallo, L. *Chem. Commun.* **2012**, *48*, 1650-1652.
12. a) Alcaide, B.; Almendros, P.; Cabrero G.; Ruiz, M. P. *Org. Lett.* **2005**, *7*, 3981-3984; b) Alcaide, B.; Almendros, P.; Cabrero G.; Ruiz, M. P. *Chem. Commun.*, **2007**, 4788-4790.
13. Domingo, L. R.; Aurell, M. J.; Arnó, M. *Tetrahedron* **2009**, *65*, 3432-3440.
14. Li, G.-Q.; Li, Y.; Dai, L.-X.; You, S.-L. *Org. Lett.* **2007**, *9*, 3519-3521.
15. a) Liu, Y.-Y.; Zhang, W.-B. *Angew. Chem. Int. Ed.* **2013**, *52*, 2203-2206; b) Liu, Y.-Y.; Gridnev, I. D.; Zhang, W.-B. *Angew. Chem. Int. Ed.* **2014**, *53*, 1901-1905.
16. Han, Z.; Li, P.; Zhang, Z.; Chen, C.; Wang, Q.; Dong, X.-Q.; Zhang, X. *ACS Catal.* **2016**, *6*, 6214-6218.
17. Tajaya, Y.; Ogasawara, M.; Hayashi, T.; Sakai, M.; Miyaura, N. *J. Am. Chem. Soc.* **1998**, *120*, 5579-5580.
18. a) Shintani, R.; Ueyama, K.; Yamada, I.; Hayashi, T. *Org. Lett.* **2004**, *6*, 3425-3427; b) Shintani, R.; Duan, W.-L.; Nagano, T.; Okada, A.; Hayashi, T. *Angew. Chem. Int. Ed.* **2005**, *44*, 4611-4614; c) Duan, W.-L.; Iwamura, H.; Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2007**, *129*, 2130-2138.
19. Le Boucher d'Herouville, F.; Millet, A.; Scalone, M.; Michelet, V. *J. Org. Chem.* **2011**, *76*, 6925-6930.
20. Thaler, T.; Guo, L.-N.; Steib, A. K.; Raducan, M.; Karaghiosoff, K.; Mayer, P.; Knochel, P. *Org. Lett.* **2011**, *13*, 3182-3185.
21. Berhal, F.; Wu, Z.; Genet, J.-P.; Ayad, T.; Ratovelomanana-Vidal, V. *J. Org. Chem.* **2011**, *76*, 6320-6326.

-
22. Korenaga, T.; Ko, A.; Shimada, K. *J. Org. Chem.* **2013**, *78*, 9975-9980.
23. a) Liu, Y.; Han, S.-J.; Liu, W.-B.; Stoltz, B. M. *Acc. Chem. Res.* **2015**, *48*, 740-751; b) Quasdorf, K. W.; Overman, L. E. *Nature* **2014**, *516*, 181-191; c) Marek, I.; Minko, Y.; Pasco, M.; Mejuch, T.; Gilboa, N.; Chechik, H.; Das, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 2682-2694; d) Hong, A. Y.; Stoltz, B. M. *Eur. J. Org. Chem.* **2013**, 2745-2759; e) Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369-396; f) Christoffers, J.; Baro, A. *Adv. Synth. Catal.* **2005**, *347*, 1473-1482; g) Peterson, E. A.; Overman, L. E. *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 11943-11948; h) Christoffers, J.; Mann, A. *Angew. Chem. Int. Ed.* **2001**, *40*, 4591-4597; i) Corey, E. J.; Guzman-Perez, A. *Angew. Chem. Int. Ed.* **1998**, *37*, 388-401; j) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037-2066.
24. a) Feng, J.; Holmes, M.; Krische, M. J. *Chem. Rev.* **2017**, *117*, 12564-12580; b) Singh, S.; Bruffaerts, J.; Vasseur, A.; Marek, I. *Nat. Commun.* **2017**, *8*, 14200-14209; c) Pupo, G.; Properzi, R.; List, B. *Angew. Chem. Int. Ed.* **2016**, *55*, 6099-6102; d) Roy, S. R.; Didier, D.; Kleiner, A.; Marek, I. *Chem. Sci.* **2016**, *7*, 5989-5994; e) Zhang, F.-G.; Eppe, G.; Marek, I. *Angew. Chem. Int. Ed.* **2016**, *55*, 714-718; f) Trost, B. M.; Donckele, E. J.; Thaisrivongs, D. A.; Osipov, M.; Masters, J. T. *J. Am. Chem. Soc.* **2015**, *137*, 2776-2784; g) Eppe, G.; Didier, D.; Marek, I. *Chem. Rev.* **2015**, *115*, 9175-9206; h) Delaye, P.-O.; Didier, D.; Marek, I. *Angew. Chem. Int. Ed.* **2013**, *52*, 5333-5337.
25. Peng, X.-P.; Cao, Z.-Y.; Wang, Y.-H.; Zhou, F.; Zhou, J. *Chem. Rev.* **2016**, *116*, 7330-7396.
26. Shintani, R.; Duan, W.-L.; Hayashi, T. *J. Am. Chem. Soc.* **2006**, *128*, 5628-5629.
27. a) Song, T.; Li, L.; Zhou, W.; Zheng, Z. J.; Deng, Y.; Xu, Z.; Xu, L. W. *Chem. Eur. J.* **2015**, *21*, 554-558; b) Chen, M. Y.; Song, T.; Zheng, Z. J.; Xu, Z.; Cui, Y. M.; Xu, L. W. *RSC Adv.* **2016**, *6*, 58698-58708.
28. Wang, L.; Ni, Q.-J.; Blümel, M.; Shu, T.; Raabe, G.; Enders, D. *Chem. Eur. J.* **2015**, *21*, 8033-8037.
29. Wilsily, A.; Fillion, E. *Org. Lett.* **2008**, *10*, 2801-2804.
30. Hayashi, Y.; Kawamoto, Y.; Honda, M.; Okamura, D.; Umemiya, S.; Noguchi, Y.; Mukaiyama, T.; Sato, I. *Chem. Eur. J.* **2014**, *20*, 12072-12082.
31. Tsuji, J.; Takahashi, H.; Morikawa, Masanobu. *Tetrahedron Lett.* **1965**, *49*, 4387-4388.
32. Trost, B. M.; Fullerton, T. J. *J. Am. Chem. Soc.* **1973**, *95*, 292-294.

-
33. Selected reviews, see: a) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.*, **1996**, *96*, 395-422; b) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921-2944; c) Lu, Z.; Ma, S. *Angew. Chem., Int. Ed.*, **2008**, *47*, 258-297; d) Trost, B. M.; Zhang, T.; Sieber, J. D. *Chem. Sci.*, **2010**, *1*, 427-440; e) Trost, B. M. *Org. Process Res. Dev.* **2012**, *16*, 185-194.
34. Hayashi, T.; Kanehira, K.; Hagihara, T.; Kumada, M. *J. Org. Chem.* **1988**, *53*, 113-120.
35. Sawamura, M.; Nagata, H.; Sakamoto, H.; Ito, Y. *J. Am. Chem. Soc.* **1992**, *114*, 2586-2592.
36. Trost, B. M.; Radinov, R.; Grenzer, E. M. *J. Am. Chem. Soc.* **1997**, *119*, 7879-7880.
37. Rios, I. G.; Rosas-Hernandez, A.; Martin, E. *Molecules* **2011**, *16*, 970-1010.
38. a) Tsuji, J.; Minami, I.; Shimizu, I. *Tetrahedron Lett.* **1983**, *24*, 1793-1796; b) Tsuji, J.; Shimizu, I.; Minami, I.; Ohashi, Y.; Sugiura, T.; Takahashi, K. *J. Org. Chem.* **1985**, *50*, 1523-1529; c) Tsuji, J.; Minami, I. *ACC. Chem. Res.* **1987**, *20*, 140-145.
39. Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044-15045
40. a) Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 2846-2847 b) Trost, B. M.; Xu, J.; Schmidt, T. *J. Am. Chem. Soc.* **2009**, *131*, 18343-18357.
41. Stereocenter generated at the allyl fragment as a tertiary center, see: Burger, E. C.; Tunge, J. A. *Org. Lett.* **2004**, *6*, 4113-4115.
42. Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2005**, *117*, 7084-7087.
43. a) Behenna, D. C.; Liu, Y.; Yurino, T.; Kim, J.; White, D. E.; Virgil, S. C.; Stoltz, B. M. *Nat. Chem.* **2012**, *4*, 130-133; b) Korch, K. M.; Eidamshaus, C.; Behenna, D. C.; Nam, S.; Horne, D.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2015**, *54*, 179-183.
44. For selected examples, see: a) Alexy, E. J.; Virgil, S. C.; Bartberger, M. D.; Stoltz, B. M. *Org. Lett.* **2017**, *19*, 5007-5009; b) Starkov, P.; Moore, J. T.; Duquette, D. C.; Stoltz, B. M.; Marek, I. *J. Am. Chem. Soc.* **2017**, *139*, 9615-9620; c) De Oliveira, M. N.; Fournier, J.; Arseniyadis, S.; Cossy, J. *Org. Lett.* **2017**, *19*, 14-17; d) Craig, R. A., II; Loskot, S. A.; Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M. *Org. Lett.* **2015**, *17*, 5160-5163; e) Fournier, J.; Lozano, O.; Menozzi, C.; Arseniyadis, S.; Cossy, J. *Angew. Chem. Int. Ed.* **2013**, *52*, 1257-1261; f) Weaver, J. D.; Ka, B. J.; Morris, D. K.; Thompson, W.; Tunge, J. A. *J. Am. Chem. Soc.* **2010**, *132*, 12179-12181; g) Trost, B. M.; Xu, J.; Schmidt, T. *J. Am. Chem. Soc.* **2009**, *131*, 18343-18357; h) Nakamura, M.; Hajra, A.; Endo, K.; Nakamura, E. *Angew. Chem. Int. Ed.* **2005**, *44*, 7248-7251.

-
45. a) Khan A.; Marson, C. M.; Porter, R. A. *Synth. Commun.* **2001**, *31*, 1753-1764; b) Smith, A. M.; Rzepa, H. S.; White, A. J.; Billen, D.; Hii, K. K. *J. Org. Chem.* **2010**, *75*, 3085-3096.
46. Dr. Marllon Nascimento de Oliveira synthesized and generously share some substituted allyl acetates he had prepared, see: De Oliveira, M. N.; Arseniyadis, S.; Cossy, J. *Chem. Eur. J.* **2018**, *24*, 4810-4814.
47. See a review for the mechanism of Wittig reaction: Byrne, P. A.; Gilheany, D. G. *Chem. Soc. Rev.*, **2013**, *42*, 6670-6696.
48. Trost, B. M.; Xu, J.; Schmidt, T. *J. Am. Chem. Soc.* **2009**, *131*, 18343-18357.
49. Trost, B. M., *Org. Prog. Res. Dev.* **2012**, *16*, 185-194.
50. Tao Song, Stellios Arseniyadis, Janine Cossy, *Chem. Eur. J.* **2018**, *24*, 8076-8080.
51. Ding, G. N.; Lu, B.; Li, Y.-Y.; Wan, J.; Zhang, Z. G.; Xie, X. M, *Adv. Synth. Catal.* **2015**, *357*, 1013-1021.
52. Espinosa-Jalapa, N. A.; Kumar, A.; Leitus, G.; Diskin-Posner, Y.; Milstein, D. *J. Am. Chem. Soc.*, **2017**, *139*, 11722-11725.
53. Smith, A. M.R.; Rzepa, H. S.; White, A. J. P.; Billen, D; Hii, K. K.; *J. Org. Chem*, **2010**, *75*, 3085-3096.
54. Shi, S. C.; Szostak, M. *Org. Lett.* **2015**, *17*, 5144-5147.
55. Allous, I.; Comesse, S.; Daïch, A. *Lett. Org. Chem.*, **2008**, *5*, 73-78.
56. Agejas, J.; Ortega, L. *J. Org. Chem.* **2015**, *80*, 6509-6514.
57. Korenaga, T.; Ko, A.; Shimada, K. *J. Org. Chem.* **2013**, *78*, 9975-9980.
58. Dakarapu, U. S.; Bokka, A.; Asgari, P.; Trog, G.; Hua, Y.; Nguyen, H. H.; Rahman, N.; Jeon, J. *Org Lett*, **2015**, *17*, 5792-5795.
59. Zhang, H.; Huang, X. *Adv. Synth. Catal.* **2016**, *358*, 3736-3742.
60. Fontán, N.; García-Domínguez, P.; Álvarez, R.; de Lera, Á. R. *Bioorg. Med. Chem.* **2013**, *21*, 2056-2067.
61. Felpin, F.-X.; Miqueu, K.; Sotiropoulos, J.-M.; Fouquet, E.; Ibarguren, O.; Laudien, J. *Chem. Eur. J.* **2010**, *16*, 5191-5204.
62. Su, Y.-H.; Wu, Z.; Tian, S.-K. *Chem. Commun.* **2013**, *49*, 6528-6530
63. Kinsman, A. C.; Kerr, M. A. *J. Am. Chem. Soc.* **2003**, *125*, 14120-14125.
64. Peng, D.-J.; Zhang, M.-T.; Huang, Z. *Chem. Eur. J.* **2015**, *21*, 14737-14741.
65. Shintai, R.; Takatsu, K.; Takeda, M.; Hayashi, T. *Angew. Chem., Int. Ed*, **2011**, *50*, 8656-8659.

-
66. Kim, E.; Koh, M.; Lim, B. J.; Park, S. B.; *J. Am. Chem. Soc.* **2011**, *133*, 6642-6649.
67. Jobson, N. K.; Spike, R.; Crawford, A. R.; Dewar, D.; Pimlott, S. L.; Sutherland, A. *Org. Biomol. Chem.* **2008**, *6*, 2369-2376.
68. Vyas, D. J.; Oestreich, M. *Chem. Commun.* **2010**, *46*, 568-570.
69. Schmidt, B.; Hölter, F.; Kelling, A.; Schilde, U. *J. Org. Chem.* **2011**, *76*, 3357-3365.
70. Miyamura, H.; Choo, G. C. Y.; Yasukawa, T.; Yoo, W.-J.; Kobayashi, S.; *Chem. Commun.* **2013**, *49*, 9917-9919.
71. Reichl, K.; Dunn, N. L.; Fastuca, N. J.; Radosevich, A. T. *J. Am. Chem. Soc.* **2015**, *137*, 5292-5295.
72. Bober, Ashley.; Proto, Justin. T.; Brummond, K. M. *Org. Lett.* **2017**, *19*, 1500-1503.
73. Kinsman, A. C.; Beutner, G. L.; Grubbs, R. H. *J. Org. Chem.* **2006**, *71*, 7813-7825.
74. Su, Y.; Jiao, N. *Org. Lett.* **2009**, *11*, 2980-2983.
75. Pan, D.; Yu, M.; Chen, W.; Jiao, N. *Chem. Asian J.* **2010**, *5*, 1090-1093.
76. Ding, F. Q.; William, R.; Wang, F.; Liu, W. X. *Chem. Commun.*, **2012**, *48*, 8709-8711.
77. a) Engman, M.; Diesen, J. S.; Paptchikhine, A.; Andersson, P. G. *J. Am. Chem. Soc.* **2007**, *129*, 4536-4537; b) Procopiou, P. A.; Baugh, S. P. D.; Flack, S.; Inglis, G. A. *J. Org. Chem.* **1998**, *63*, 2342-2347.
78. Al-Masum, M.; Yamamoto, Y. *J. Am. Chem. Soc.*, **1998**, *120*, 3809-3810.
79. a) Saha, A.; Ranu, B. C. *Tetrahedron Lett.* **2010**, *51*, 1902-1905; b) Pan, D.; Chen, A.; Su, Y.; Zhou, W.; Li, S.; Jia, W.; Xiao, J.; Liu, Q.; Zhang, L.; Jiao, N. *Angew. Chem. Int. Ed.* **2008**, *47*, 4729-4732; c) You, S.-L.; Z, X-Z; L, Y-M; Hou, X.-L.; Dai, L.-X. *J. Am. Chem. Soc.* **2001**, *123*, 7471-7472; d) Iwasaki, M.; Kobayashi, Y.; Li, J.-P.; Matsuzaka, H.; Ishii, Y.; Hidai, M. *J. Org. Chem.* **1991**, *56*, 1922-1927.
80. a) L, L; Chase, C. E.; West, F. G. *Chem. Commun.* **2008**, *34*, 4025-4027; b) Cooper, J. A.; Cornwall, P.; Dell, C. P.; Knight, D. W. *Tetrahedron Lett.* **1988**, *29*, 2107-2110.
81. Wang, T.L.; Yao, W. J.; Zhong, F. R.; Pang, G. H.; Lu, Y. X. *Angew. Chem. Int. Ed.* **2014**, *53*, 2964-2968
82. Rammah, M. M.; Othman, M.; Rammah, M. B. *Journal de la Société Chimique de Tunisie*, **2008**, *10*, 11-21.
83. Bao, D. H.; Gu, X. S.; Xie, J. H.; Zhou, Q. L. *Org. Lett.* **2017**, *19*, 118-121.

-
84. For a review, see: Caruano, J.; Muccioli, G. G.; Robiette, R. *Org. Biomol. Chem.* **2016**, *14*, 10134-10156.
85. Schwartz, R. E.; Helms, G. L.; Bolessa, E. A.; Wilson, K. E.; Giacobbe, R. A.; Tkacz, J. S.; Bills, G. F.; Liesch, J. M.; Zink, D. L.; Curotto, J. E.; Pramanik, B.; Onishi, J. C. *Tetrahedron*, **1994**, *50*, 1675-1686.
86. Aoki, S.-Y.; Tsukude, T.; Miyazaki, Y.; Takao, K.-I.; Tadano, K. I. *Heterocycles*. **2006**, *69*, 49-54.
87. Ōmura, S.; Fujimoto, T.; Otoguro, K.; Matsuzaki, K.; Moriguchi, R.; Tanaka, H.; Sasaki, Y. *J. Antibiot.*, **1991**, *44*, 113-117.
88. a) Corey, E. J.; Reichard, Gregory A. *J. Am. Chem. Soc.* **1992**, *114*, 10677-10678; b) Corey, E. J.; Li, W.; Nagamitsu, T. *Angew. Chem., Int. Ed.*, **1998**, *37*, 1676-1679; c) Corey, E. J.; Li, W.-D. *Z. Chem. Pharm. Bull.*, **1999**, *47*, 1-10.
89. a) Ho Kang, S.; Jun, H.-S. *Chem. Commun.*, **1998**, 1929-1930; b) Ooi, H.; Ishibashi, N.; Iwabuchi, Y.; Ishihara, J.; Hatakeyama, S. *J. Org. Chem.*, **2004**, *69*, 7765-7768; c) Sunazuka, T.; Hirose, T.; Ōmura, S. *Acc. Chem. Res.* **2008**, *41*, 302-314.
90. Feling, R. H.; Buchanan, G. O.; Mincer, T. J.; Kauffman, C. A.; Jensen, P. R.; Fencial, W. *Angew. Chem., Int. Ed.*, **2003**, *42*, 355-357.
91. a) Reddy, L. R.; Saravanan, P.; Corey, E. J. *J. Am. Chem. Soc.*, **2004**, *126*, 6230-6231; b) Reddy, L. R.; Fournier, J.-F.; Subba Reddy, B. V.; Corey, E. J. *J. Am. Chem. Soc.*, **2005**, *127*, 8974-8976; c) Ma, G.; Nguyen, H.; Romo, D. *Org. Lett.*, **2007**, *9*, 2143-2146; d) Takahashi, K.; Midori, M.; Kawano, K.; Ishihara, J.; Hatakeyama, S. *Angew. Chem., Int. Ed.*, **2008**, *47*, 6244-6246; e) Satoh, N.; Yokoshima, S.; Fukuyama, T. *Org. Lett.*, **2011**, *13*, 3028-3031.
92. a) Zhu, X. Z.; Li, X.-Y.; Liu, J. *Eur. J. Pharmacol.*, **2004**, *500*, 221-230; b) Ning, N.; Hu, J.-F.; Sun, J.-D.; Han, N.; Zhang, J.-T.; Chen, N.-H. *Eur. J. Pharmacol.*, **2012**, *682*, 50-55; c) Chu, S.; Zhang, J. *Acta Pharmaceutica Sinica B.*, **2014**, *4*, 417-423.
93. Chu, S.; Liu, S.; Duan, W.; Cheng, Y.; Jiang, X.; Zhu, C.; Tang, K.; Wang, R.; Xu, L.; Wang, X.; Yu, X.; Wu, K.; Wang, Y.; Wang, M.; Huang, H.; Zhang, J. *Pharmacol. Ther.*; **2016**, *162*, 179-187.
94. Liu, D.; Yu, X.; Huang, L. *Chin. J. Chem.*, **2013**, *31*, 344-348.
95. selected examples, a) Barnes, D. M.; Bhagavatula, L.; DeMattei, J.; Gupta, A.; Hill, D. R.; Manna, S.; McLaughlin, M. A.; Nichols, P.; Premchandran, R.; Rasmussen, M. W.;

- Tian, Z.; Wittenberger, S. J. *Tetrahedron: Asymmetry* **2003**, *14*, 3541-3551; b) Gheorghe, A.; Schulte, M.; Reiser, O. *J. Org. Chem.* **2006**, *71*, 2173-2176; c) Suga, H.; Takemoto, H.; Kakehi, A. *Heterocycles* **2007**, *71*, 361-371; d) Sartori, A.; Curti, C.; Battistini, L.; Burreddu, P.; Rassu, G.; Pelosi, G.; Casiraghi, G.; Zanardi, F. *Tetrahedron* **2008**, *64*, 11697-11705; e) Curti, C.; Sartori, A.; Battistini, L.; Rassu, G.; Zanardi, F.; Casiraghi, G. *Tetrahedron Lett.* **2009**, *50*, 3428-3431.
96. For a review, see: Casiraghi, G.; Zanardi, F.; Battistini, L.; Rassu, G. *Synlett* **2009**, *10*, 1525-1542.
97. Suga, H.; Takemoto, H.; Kakehi, A. *Heterocycles* **2007**, *71*, 361-371.
98. a). Shepherd, N.E.; Tanabe, H.; Xu, Y.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.*, **2010**, *132*, 3666-3667; b) Tanabe, H.; Xu, Y. J.; Sun, B.; Matsunaga, S.; Shibasaki, M. *Heterocycles*, **2012**, *86*, 611-621.
99. Selected examples of asymmetric vinylogous Michael addition reaction, see: a) Feng, X.; Cui, H.-L.; Xu, S.; Wu, L.; Chen, Y.-C. *Chem. Eur. J.* **2010**, *16*, 10309-10312; b). Lin, J.; Zhang, J.; Ma, X.; Fu, X.; Wang, R. *Org. Lett.*, **2011**, *13*, 6410-6413; c) Huang, H.; Jin, Z.; Zhu, K.; Liang, X.; Ye, J. *Angew. Chem., Int. Ed.*, **2011**, *50*, 3232-3235; d). Wang, Z.-H.; Wu, Z.-J.; Yue, D.-F.; You, Y.; Xu, X.-Y.; Zhang, X.-M.; Yuan, W.-C. *Org. Biomol. Chem.*, **2016**, *14*, 6568-6576.
100. a) Curti, C.; Sartori, A.; Battistini, L.; Rassu, G.; Zanardi, F.; Casiraghi, G. *Tetrahedron Lett.* **2009**, *50*, 3428-3431; b) Curti, C.; Ranieri, B.; Battistini, L.; Rassu, G.; Zambrano, V.; Pelosi, G.; Casiraghi, G.; Zanardi, F. *Adv. Synth. Catal.* **2010**, *352*, 2011-2022.
101. a) Frings, M.; Atodiresei, I.; Runsink, J.; Raabe, G.; Bolm, C. *Chem. Eur. J.* **2009**, *15*, 1566-1569; b) Frings, M.; Atodiresei, I.; Wang, Y.; Runsink, J.; Raabe, G.; Bolm, C. *Chem. Eur. J.* **2010**, *16*, 4577-4587.
102. For a review, see: Casiraghi, G.; Battistini, L.; Curti, C.; Rassu, G.; Zanardi, F. *Chem. Rev.* **2011**, *111*, 3076-3154.
103. a) Denmark, S. E.; Beutner, G. L. *J. Am. Chem. Soc.* **2003**, *125*, 7800-7801. b) Denmark, S. E.; Heemstra, J. R., Jr. *Synlett* **2004**, 2411-2416. c) Denmark, S. E.; Beutner, G. L.; Wynn, T.; Eastgate, M. D. *J. Am. Chem. Soc.* **2005**, *127*, 3774-3789. d) Denmark, S. E.; Heemstra, J. R., Jr. *J. Am. Chem. Soc.* **2006**, *128*, 1038-1039; e) Denmark, S. E.; Heemstra, J. R., Jr. *J. Org. Chem.* **2007**, *72*, 5668-5688.

-
104. Del Corte, X.; Maestro, A.; Vicario, J.; de Marigorta, E. M.; Palacios, F. *Org. Lett.* **2018**, *20*, 317-320.
105. Ghorai, M. K.; Tiwari, D. P. *J. Org. Chem.* **2010**, *75*, 6173-6181.
106. For a review, see: Ye, L.-W.; Shu, C.; Gagosz, F. *Org. Biomol. Chem.*, **2014**, *12*, 1833-1845.
107. Rhee, J. U.; J. Krische, M. *J. Am. Chem. Soc.* **2006**, *128*, 10674-10675.
108. Kanbayashi, N.; Takenaka, K.; Okamura, T.-A.; Onitsuka, K. *Angew. Chem., Int. Ed.*, **2013**, *52*, 4997-5001.
109. Singha Roy, S. J.; Mukherjee, S. *Org. Biomol. Chem.*, **2017**, *15*, 6921-6925.
110. Lv, H.; Tiwari, B.; Mo, J., Xing, C.; Robin Chi, Y. *Org. Lett.*, **2012**, *14*, 5412-5415.
111. Arlt, A.; Toyama, H.; Takada, K.; Hashimoto, T.; Maruoka, K. *Chem. Commun.*, **2017**, *53*, 4779-4782.
112. For a review, see: Groaning, M. D.; Meyers, A. I. *Tetrahedron*, **2000**, *56*, 9843-9873.
113. a) Burgess, L. E.; Meyers, A. I. *J. Am. Chem. Soc.* **1991**, *113*, 9858-9859; b) Burgess, L. E.; Meyers, A. I. *J. Org. Chem.* **1992**, *57*, 1657-1662.
114. Hayashi, M.; Bachman, S.; Hashimoto, S.; Eichman, C. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2016**, *138*, 8997-9000.
115. Seki, T.; Tanaka, S.; Kitamura, M. *Org. Lett.*, **2012**, *14*, 608-611.
116. Behenna D.C.; Liu, Y., Yurino, T.; Kim, J.; White, D. E.; Virgil, S. C.; Stoltz, B. M. *Nat Chem.* **2012**, *4*, 130-133.
117. Aginagalde, M.; Bello, T.; Masdeu, C.; Vara, Y.; Arrieta, Ana.; Cossío, F. P. *J. Org. Chem.* **2010**, *75*, 7435-7438.
118. Jiang, X. Y.; Hartwig, J. F. *Angew. Chem., Int. Ed.*, **2017**, *56*, 8887-8891.
119. a) Fleige, M.; Glorius, F. *Chem. Eur. J.* **2017**, *23*, 10773-10776; b) Jiang, Q.; Jia, J.; Xu, B.; Zhao, A.; Guo, C.-C. *J. Org. Chem.*, **2015**, *80*, 3586-3596.
120. Chan, C.-K.; Tsai, Y.-L.; Chang, M.-Y. *Tetrahedron*, **2017**, *73*, 3368-3376.
121. a) Lin, C.; Achtenhagen, M.; Szostak, M. *Org. Lett.*, **2016**, *18*, 2375-2378; b) Zhang, S., Wang, L.; Feng, X.; Bao, M. *Org. Biomol. Chem.*, **2014**, *12*, 7233-7237.
122. Ganesan, P.; Ranganathan, R.; Chi, Y.; Liu, X.-K.; Lee, C.-S.; Liu, S.-H.; Lee, G.-H.; Lin, T.-C.; Chen, Y.-T.; Chou, P.-T. *Chem. Eur. J.* **2017**, *23*, 2858-2866.
123. Stroba, A.; Schaeffer, F.; Hindiel, V.; Lopez-Garcia, L.; Adrian, I.; Fröhner, H. R. W.; Biondil, R. M.; E, M. *J. Med. Chem.* **2009**, *52*, 4683-4693.

-
124. Larionov, V. A.; Markelova, E. P.; Smol'yakov, A. F.; Savel'yeva, T.; Maleev, V. L.; Belokon, Y. N. *RSC. Adv.* **2015**, *5*, 72764-72771.
125. Wang, J.; Liu, C.; Yuan, J.; Lei, A. *Angew. Chem. Int. Ed.* **2013**, *52*, 2256-2259.
126. Frost, J. R.; Cheong, C. B.; Akhtar, W. M.; Caputo, D. F. J.; Stevenson, N. G.; Donohoe, T. J. *J. Am. Chem. Soc.*, **2015**, *137*, 15664-15667.
127. Hino, K.; Nagai, Y.; Uno, H.; Masuda, Y.; Oka, M.; Karasawa, T. *J. Med. Chem.*, **1988**, *31*, 107-117.
128. Hino, K.; Nagai, Y.; Uno, H.; Masuda, Y.; Oka, M.; Karasawa, T. *J. Med. Chem.*, **1988**, *31*, 107-117.
129. Tomita, R.; Mantani, K.; Hamasaki, A.; Ishida, T.; Tokunaga, M. *Chem. Eur. J.* **2014**, *20*, 9914-991.
130. B. Delvos, L.; J. Vyas, D.; Oestreich, M. *Angew. Chem. Int. Ed.* **2013**, *52*, 4650-4653.
131. Li, C.; Xing, J.; Zhao, J.; Huynh, P.; Zhang, W.; Jiang, P.; Zhang, Y.-J. *Org. Lett.*, **2012**, *14*, 390-393.
132. Yuan, Q. J.; Yao, K.; Liu, D. L.; Zhang, W. B. *Chem. Commun.*, **2015**, *51*, 11834-11836.
133. Chun, S.; Chung, Y. K. *Org. Lett.*, **2017**, *19*, 3787-3790.
134. Niwa, T.; Nakada, M. *J. Am. Chem. Soc.*, **2012**, *134*, 13538-13541.
135. Stanely, L. M.; Bai, C.; Ueda, M.; Hartwig, J. F. *J. Am. Chem. Soc.*, **2010**, *132*, 8918-8920.
136. Lim, S.; Ji, M.; Wang, X.; Lee, C.; Jang, H.-Y. *Eur. J. Org. Chem.* **2015**, *3*, 591-595.
137. Chen, Z.-S.; Huang, X.-Y.; Gao, J.-M.; Ji, K. *Org. Lett.*, **2016**, *18*, 5876-5879.
138. Seo, H.; Hirsch-Weil, D.; Abboud, K. A.; Hong, S. *J. Org. Chem.*, **2008**, *73*, 1983-1986.
139. Zhang, Y.; Li, Z.; Liu, Z.-Q. *Org. Lett.*, **2012**, *14*, 226-229
140. Mahajan, P. S.; Gonnade, R. G.; Mhaske, S. B. *Eur. J. Org. Chem.* **2014**, *36*, 8049-8054.

Résumé

Le développement d'outils synthétiques permettant le contrôle de centres stéréogènes quaternaires reste un défi important en synthèse organique. Dans ce contexte, l'alkylation allylique asymétrique pallado-catalysée est apparue comme une méthode particulièrement efficace. Le premier chapitre de cette thèse est consacré à l'application de cette réaction d'alkylation allylique asymétrique à des dérivés de type succinimides. Cette méthode, convergente, nous a permis d'accéder à un grand nombre de composés de type succinimide comportant un centre stéréogène quaternaire en position α avec de bons rendements et d'excellents excès énantiomériques. Par ailleurs, afin de démontrer l'intérêt synthétique de la méthode, ces composés allylés ont pu être transformés en diverses briques moléculaires d'intérêt parmi lesquelles des pyrrolidines et des dérivés spirocycliques optiquement actifs. Le second chapitre à quant à lui été consacré à l'application de cette même réaction d'alkylation allylique asymétrique à des dérivés de type 2-siloxypyrroles α,γ -disubstitués dans le but de pouvoir accéder à des γ -lactames enantioenrichies comportant un centre quaternaire en position α de manière efficace. Ces derniers ont par la suite pu être convertis en pyrrolidines et des pyrrolidinones optiquement actives.

Mots Clés

Catalyse asymétrique, alkylation allylique, palladium, succinimides, lactames, centre stéréogène quaternaire

Abstract

The development of new synthetic tools allowing to create quaternary stereogenic centers remains an important challenge in synthetic organic chemistry. In this context, the palladium-catalyzed asymmetric allylic alkylation has become a particularly effective tool. The first chapter of this thesis is focused on the application of this key reaction to succinimide type compounds. This convergent method has allowed us to access a number of succinimide derivatives bearing a quaternary stereogenic center in high yields and excellent enantioselectivities. Moreover, in order to demonstrate the synthetic utility of the method, the resulting α -quaternary succinimides were converted to various useful building block including pyrrolidines and spirocyclic frameworks. The second chapter is focused on the application of the palladium-catalyzed asymmetric allylic alkylation to α,γ -disubstituted 2-siloxypyrroles in order to access γ -lactams bearing an α -quaternary stereogenic center in high yields and enantioselectivities. The latter were eventually converted to the corresponding pyrrolidines and pyrrolidinones

Keywords

asymmetric catalysis, allylic alkylation, palladium, succinimides, lactams, all-carbon quaternary stereogenic centers

