A Novel Radical Access to Benzazepinones, Naphthylamides and Naphthylhydrazides

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A Novel Radical Access to Benzazepinones, Naphthylamides and Naphthylhydrazides

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Contents

Abbreviation

Ac	acetyl
AIBN	2,2'-azo-bis-isobutyronitrile
APTS	paratoluensulfonique acid
Ar	aryl
Bn	benzyl
Boc	tert-butoxycarbonyl
DCE	1,2-dichloroethane
DCM	dichloromethane
DLP	dilauryl peroxide
DMAP	4-dimethylaminopyridine
DMF	N,N-dimethylformamide
DMSO	dimethylsulfoxyde
DTBP	di-tert-butyl peroxide
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
DS	Dean-Stark
EP	petroleum ether
Et	ethyl
EtOAc	ethylacetate
EDG	electron donating group
EWG	electron withdrawing group
Hal	halogene
HOMO	highest occupied molecular orbital
i-Pr	isopropyl
LDA	lithium diisopropylamide
LUMO	lowest occupied molecular orbital
m-CPBA	meta-chloroperoxybenzoic acid
Me	methyl
NBS	N-bromosuccinimide
Ph	phenyl
PhCl	chlorobenzene
PhCH3	toluene
Phth	phtalimide
Piv	pivaloyl
Pd/C	palladium on carbon
PG	protecting group
Pyr	pyridine
SET	mono-electronic transfert
SOMO	singly occupied molecular orbital

S_N	nucleophilic substitution
t-Bu	tert-butyl
TEA	triethylamine
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydric
TMS	trimethylsilyl
Ts	tosyl
Xa	O-ethyl xanthate
aq.	aqueous
atm	atmosphere
cat.	catalytic quantity
^oC	degree Celsius
e^-	electron
eq.	equivalent
quant.	quantitative
sat.	saturated
rt	room temperature
D	heating
Hz	hertz
kcal	hour
h	kilocalorie
IR	infrared
In	initiator
min	minute
M	mole per liter
NMR	nuclear magnetic resonance
Nu	nucleophile
Ox.	oxidation
Ppm	parts per million
Hv	photochemical irradiation
Red.	reduction
TLC	thin layer chromatography

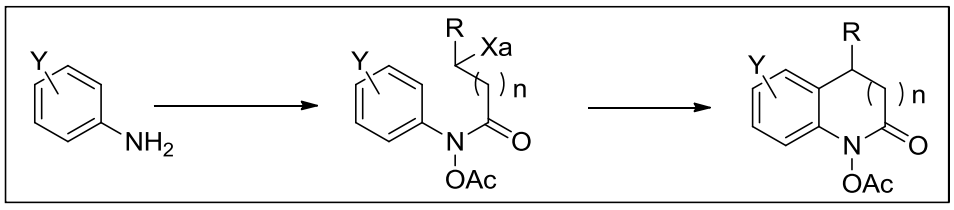
General Introduction

The first radical was described experimentally by Gomberg in 1900[1] from the reaction of triphenylmethyl chloride with zinc. Thirty years later, a radical chain process was explained by Kharasch[2] in a remarkable work showing the effect of oxygen or peroxides on the anti-Markovnikov addition of hydrogen bromide on alkenes. From that time, huge applications of radical chemistry were found in polymerization; however the use of radicals in organic synthesis was limited due to their high reactivity, which was believed to be uncontrollable and unpredictable. Ceaseless efforts have been devoted to study the nature of this chemistry over the years especially by kineticists and physical organic chemists. From a synthetic standpoint, the development of the radical chemistry of stannanes played an important role, yet there are some constraints on the usage of organotin derivatives, in an industrial setting due to the perceived toxicity and difficult purification problems. For many years, our laboratory has been developing a novel radical chemistry based on xanthates and selected functional groups. This chemistry is easy to implement and allows constructing complex structures which cannot be accessed easily by other methods. It also provides a powerful tool to introduce a broad diversity into molecular architectures.

The objective of this thesis is to show the potential of xanthates for the synthesis of nitrogen-containing cyclic structures. This manuscript consists of 4 chapters.

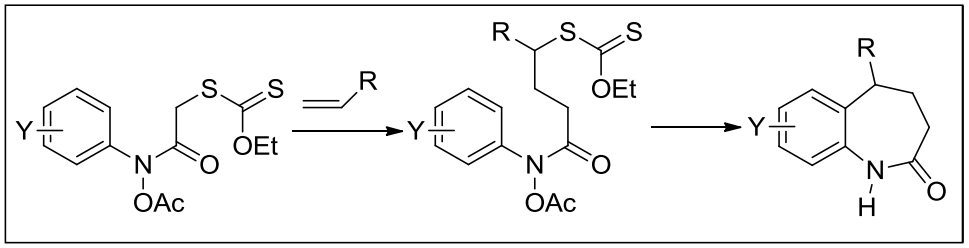
The first chapter introduces briefly the general use of radical chemistry in organic synthesis and then the chemistry of xanthates. This chapter provides the fundamental and indispensable knowledge for further discussion of our work.

The second chapter will focus on our first project which originally was the study of a radical-based approach to the cyclic hydroxamic acids.



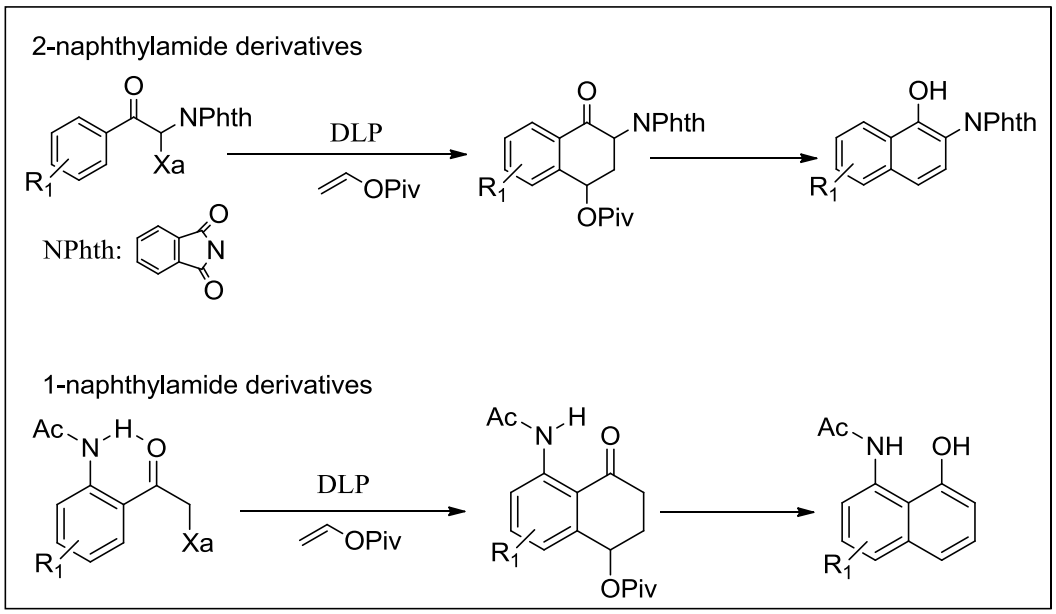
[1]Gomberg, M *J. Am. Chem. Soc*. **1900**, *22*, 757.
[2]Kharasch, M. S.; Mayo, F. R. *J. Am. Chem. Soc*. **1933**, *55*, 2468.

This objective was not attained but we made an unexpected observation, which after allowed us to develop an efficient route to *N*-unsubstituted benzazepinones. The mechanism of this process was also studied.



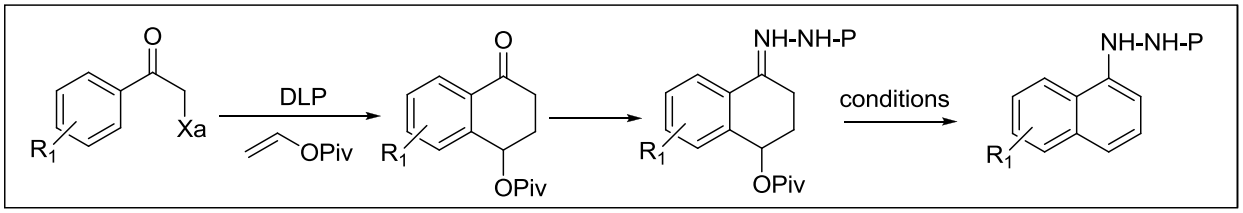
Synthesis of *N*-unsubsituted benzazepinones

The third chapter concerns the synthesis of protected naphthylamine derivatives. It starts with an introduction to some applications of naphthylamine derivatives and the synthetic routes to access this family. The preparation of regioselectively substituted naphthylamides via the α-tetralone intermediates is next presented. The preparation of the xanthate precursors required for the α-tetralone synthesis is also discussed as in some cases particular difficulties were encountered.



Synthesis of regioselectively substituted naphthylamides

The final chapter concentrates on the preparation of naphthylhydrazides again using xanthate chemistry. The conditions for aromatizing the intermediate hydrazones derived from the α–tetralones were optimized and applied successfully thus extending the general scope.



Synthesis of regioselectively substituted naphthylhydrazides

Chapter 1

Introduction to radical chemistry and to the radical chemistry of xanthates

I. General introduction to radical chemistry

1. Generalities on radical
2. Radical chain process
    i. Triorganotin hydride chemistry
    ii. Barton decarboxylation
    iii. Group transfer reactions

II. The radical chemistry of xanthates

1. Barton-McCombie deoxygenation
2. The degenerative xanthate transfer process
    i. Preparation of xanthates
    ii. Synthetic potential of xanthates

III. Conclusion

I. General introduction to radical chemistry

1. Generalities on radicals

A free radical can be defined as a chemical species possessing a single unpaired electron. In contrast to anions and cations, which normally react only with molecules with the opposite charge, free radicals can couple with each other very rapidly, sometimes as fast as the difussion rate since radical-radical interactions are almost barrierless.

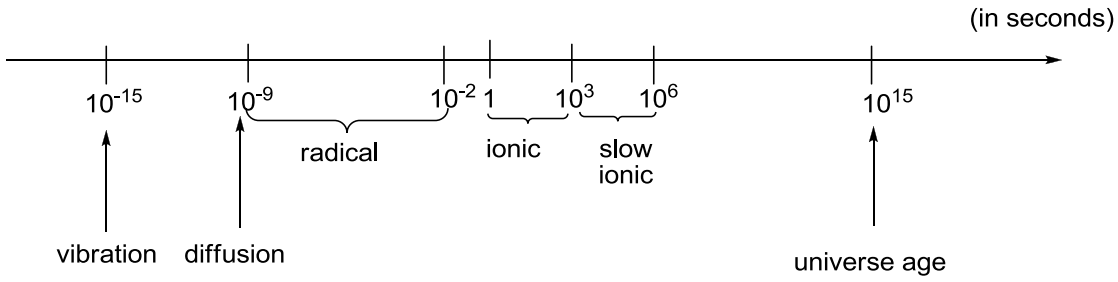


Figure I-1

Even though a radical is very reactive, it can be kinetically stabilized by steric hindrance thermodynamically stabilized by hyperconjugation and resonance effect. In fact, the stability of a radical is sometimes a result of all of these factors. Generally, the more a radical is substituted, the more stable it is. That is to say, a tertiary radical is more stable than a secondary radical which is more stable than a primary radical. Besides, the stability of a radical can also be enhanced by conjugation with electron-donating or electron-withdrawing atoms or groups attached to the radical center.

One illuminating example of a stable radical is TEMPO. Compared to the piperidine *N*-oxyl radical, the commercially available radical TEMPO is much more persistent. While both radicals enjoy the same electronic stabilization, the TEMPO radical cannot undergo disproportionation because of the absence of hydrogens on the two carbons attached to the nitrogen atom (**Figure I-2**).[3]

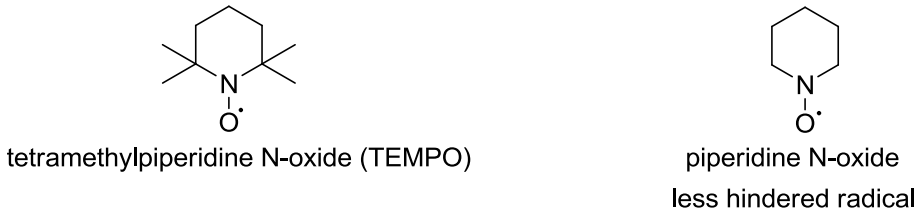


Figure I-2

[3]Clayden, J.; Greeves, N.; Warren, S.; Wothers, P. *Organic Chemistry Second Edition***2001**, Oxford University

With respect of structure, radicals can adopt in two extreme forms: planar or a shallow pyramid. A radical that has planar structure is known as a π type radical, when the unpaired electron occupies a p orbital. A radical with a pyramidal structure is known as a σ type radical. In the aliphatic series, σ radicals are obtained when the carbon bearing the unpaired electron is substituted with electrons active elements. For example, the trifluoromethyl radical is a σ radical. Since the interconversion occurs fast between two pyramidal forms, the stereochemical information of the substrate is lost in the radical process (**Figure I-3**).

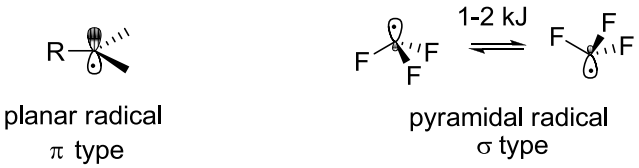


Figure I-3

In principle, a radical is neutral and in most cases reacts with uncharged molecule. However, depending on electron withdrawing or donating groups present, a radical may possess an electrophilic or a nucleophilic character respectively. Interaction with an electron-withdrawing group lowers the SOMO of the radical whereas interaction with an electron-rich substituent raises the SOMO energy level. In both cases, the whole system is stabilized as shown in **Fig. I-4**.

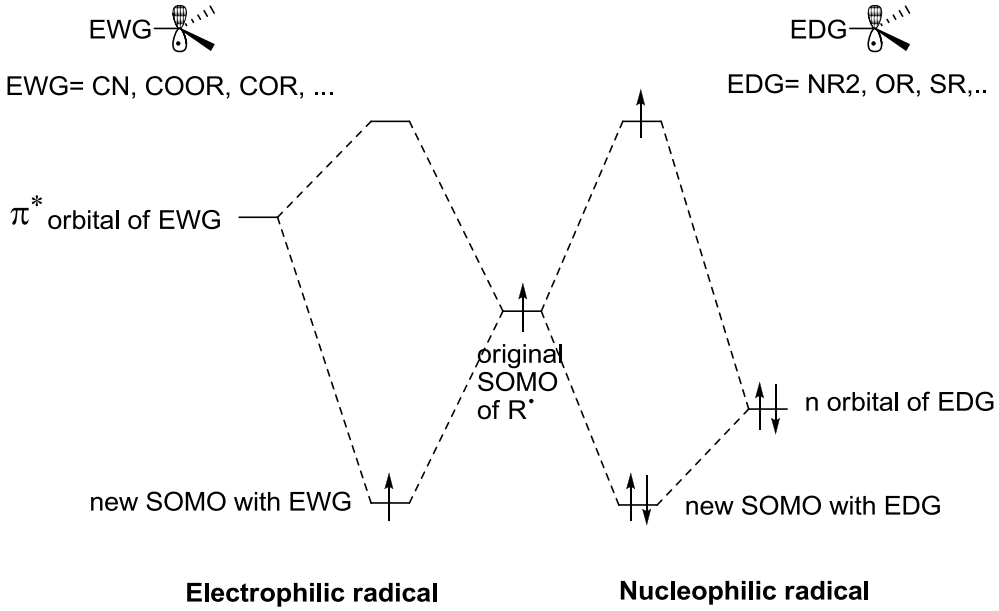


Figure I-4

In the case of radical addition to a double bond, it is important to create the largest interaction between the SOMO of the radical and the orbital of the olefin; in consequence, when SOMO is

lowered in energy, the SOMO-HOMO interaction become more favorable, which means that electrophilic radicals prefer to react with electron-rich olefins. On the contrary, the SOMO-LUMO interaction dominates when SOMO is higher in energy, which means that nucleophilic radicals prefer to react with electron-poor olefins (**Figure I-5**).

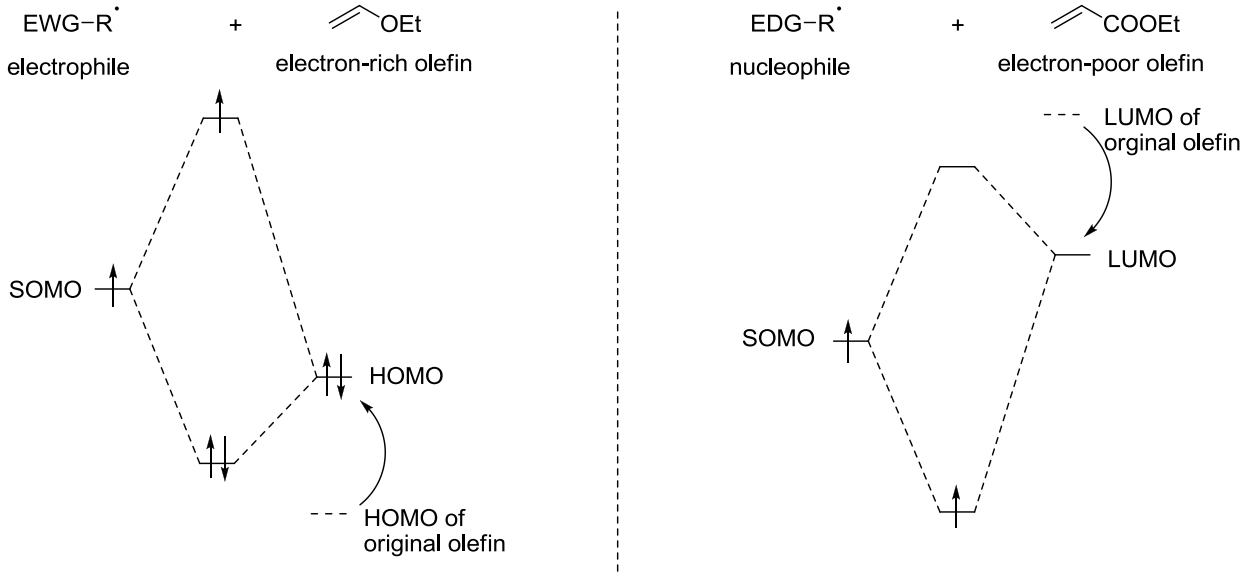


Figure I-5

After a brief general introduction of radicals, we now focus on radical chain processes.

2. Radical chain processes

A radical reaction proceeding by chain process includes 3 different steps: initiation, propagation and termination.

In the initiation step, a radical is generated by the homolysis of a weak bond in the initiator molecule through a thermal, a photochemical or redox process. The choice of initiators will be based on their half lifetime at the reaction temperature and the nature of liberated radical. The table **I-1** below depicts some common chemical initiators used in radical chemistry.

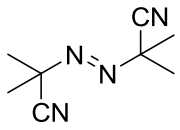
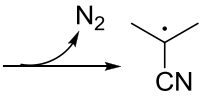
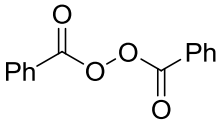
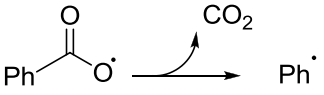
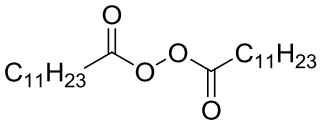
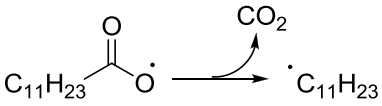
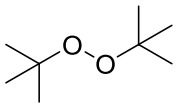
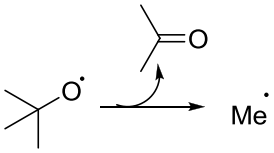
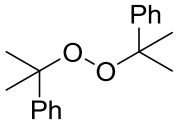
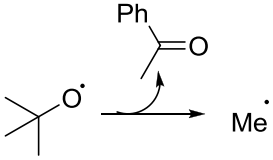
Initiators	Name	$t_{1/2}$	Radical products
	Azobisisobutyronitrile (AIBN)	1h at 85 °C	
	Dibenzoyl peroxide (DBP)	1h at 95 °C	
	Dilauryol peroxide (DLP)	1h at 85 °C	
	Ditertbutyl peroxide (DTBP)	1h at 150 °C	
	Dicumyl peroxide (DCP)	1h at 130 °C	

Table I-1

The next step is the propagation; it is a succession of elementary transformations which lead to the generation of the same starting radical to begin another chain; therefore, only a small amount of an initiator is needed.

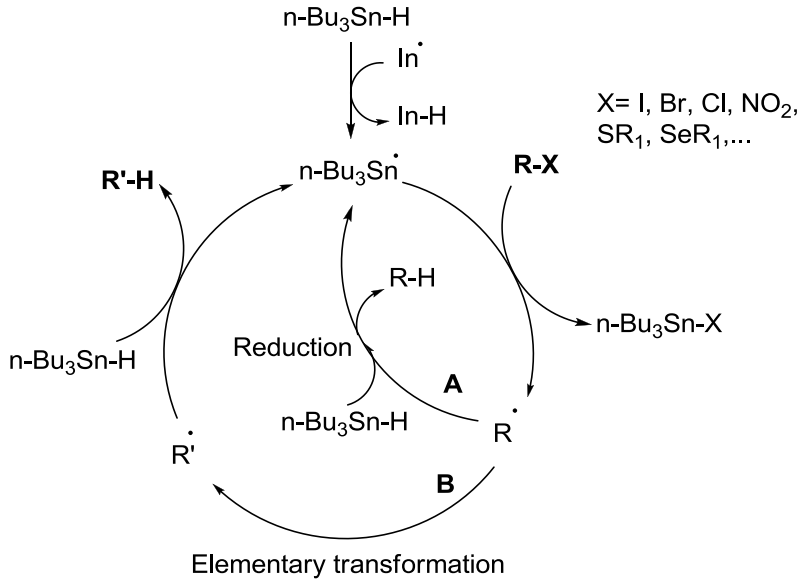
Generally, elementary reactions are addition to unsaturated bonds, elimination (fragmentation, β-elimination, α-scission), cyclisation, ring opening, rearrangement, transfer of atom or group, etc.

Finally, termination is the last phase of a chain reaction. It leads to the formation of non radical species by disproportionation, combination or reduction/oxidation. In order to avoid these chain-breaking steps, the concentration of the radicals in solution must be kept low.

Some classical radical chain processes will be presented in this chapter to provide a fundamental comprehension about the radical reactions.

i. Triorganotin hydride chemistry

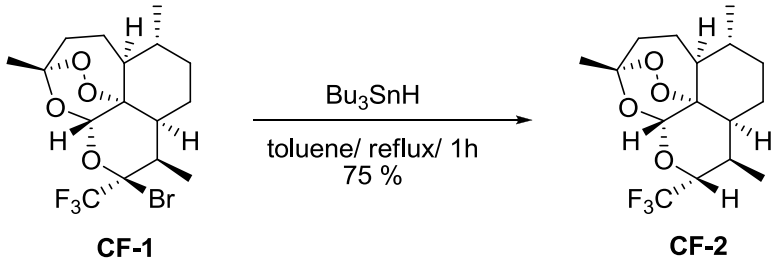
Tin chemistry has played a tremendously important role in the history of the development of radical chemistry. These triorganotin hydride reagents are used for converting the organic halides and other derivatives into the corresponding hydrocarbons. The most frequently used is tri-n-butyltin hydride Bu_3SnH. S**cheme I-6** represents the general mechanism of this method.



Scheme I-6

The initiation step starts with the formation of radicals $Bu_3Sn^{\bullet}$ due to the relative weak Sn-H bond (bond dissociation energy of Sn-H bond in Bu_3**Sn-H** is 74 kcal/mol, compared to the value of C-H bond in CH_2=CH**CH_2-H** is 89 kcal/mol). The tin radicals then react with R-X such as bromides, iodides, chlorides, sulfides, selenides or nitro compounds to liberate radicals $R^{\bullet}$. As shown in **Scheme I-6**, the radical $R^{\bullet}$ can follow two pathways **A** and **B.** In pathway **A**, it can abstract hydrogen from Bu_3SnH to form reduced compound RH and tin radical to propagate the chain. This indicates that Bu_3SnH is a very efficient radical reducing agent. This direct reduction route is absolutely very convenient and powerful due to its selectivity and compatibility with various functionalities. For example, the first synthesis of (trifluoromethyl)deoxoartenisinin**CF-2** by the Begue group was accomplished by debromination using tributyltin hydride as a key step. The delicate O-O bond in **CF-1** was unaffected under the mild reaction conditions (**Scheme I-7**).[4]

[4]Chorki, F.; Grellepois, F.; Crousse, B.; Hoang, V. D.; Hung, N. V.; Bonnet-Delpon, D.; Begue, J. P. *Org. Lett.***2002**, *4*, 757.

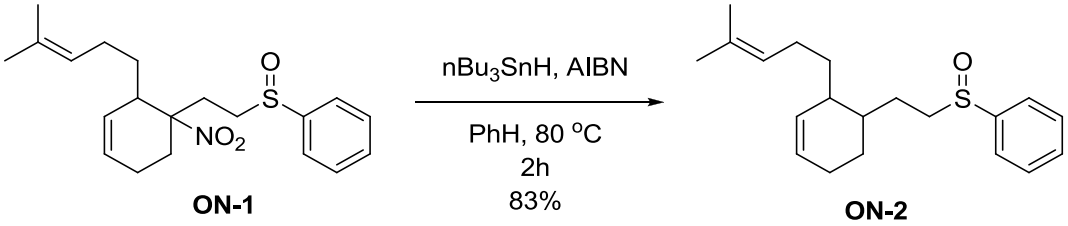


Scheme I-7

In pathway **B**, radical $R^{\bullet}$ can undergo elementary transformations, such as an addition to an alkene, before being reduced. In this case, the reaction becomes more complex since the intermediate radicals may still be reduced by Bu_3SnH, which leads to a competition. In order to avoid the formation of side products, a good comprehension of the kinetics of each reaction is required. Because the rate constant for hydrogen abstraction from Bu_3SnH is $2*10^6$ $M^{-1}s^{-1}$ at 20^oC, a staggering desired pathway B could be easily overtaken by a premature hydrogen abstraction. The concentration of Bu_3SnH present in the medium must therefore be well controlled to diminish the competitive direct reduction. This is the main reason why this method is used principally in intramolecular radical processes, indeed, the intermolecular radical additions can only be achieved when the olefin is activated and used in excess.

In any case, this method is particularly important in respect of its reactivity and flexibility in radical reduced transformations. The examples below illustrate the efficiency of this chemistry.

The first example is the denitration of compound **ON-1** to **ON-2** in a good yield (83 %). It is worthy of note that the intermediate radical was reduced before undergoing 5-exo cyclisation on the internal double bond (**Scheme I-8**).[5]

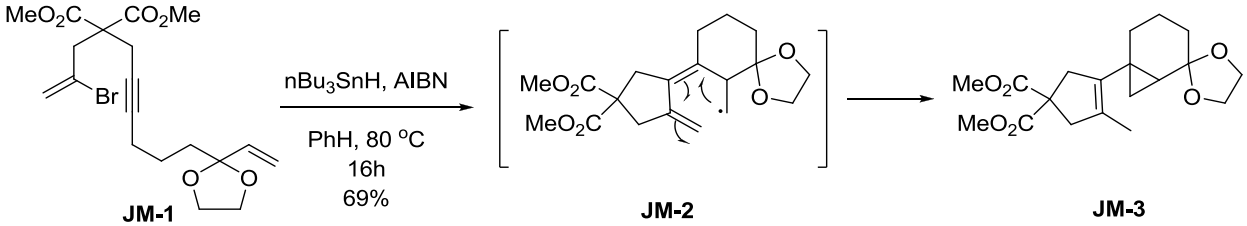


Scheme I-8

In 1994, Journet and Malacria succeeded in performing a succession of radical reactions in the synthesis of **JM-3**.[6] The vinyl radical generated from the corresponding bromide derivative **JM-1** underwent a 5-exo cyclisation to form radical **JM-2**, which subsequently underwent a 6-exo

[5]Ono, N.; Kamimura, A.; Miyake, I.; Kaji, A. *J. Org. Chem.***1985**, *50*, 3692.
[6] Journet, M.; Malacria, M. *J. Org. Chem.***1994**, *59*, 718.

cyclisation and then hydrogen abstraction to furnish final product **JM-3**. In regards to the complexity of this transformation, the 69% yield could be considered as excellent (**Scheme I-9**).

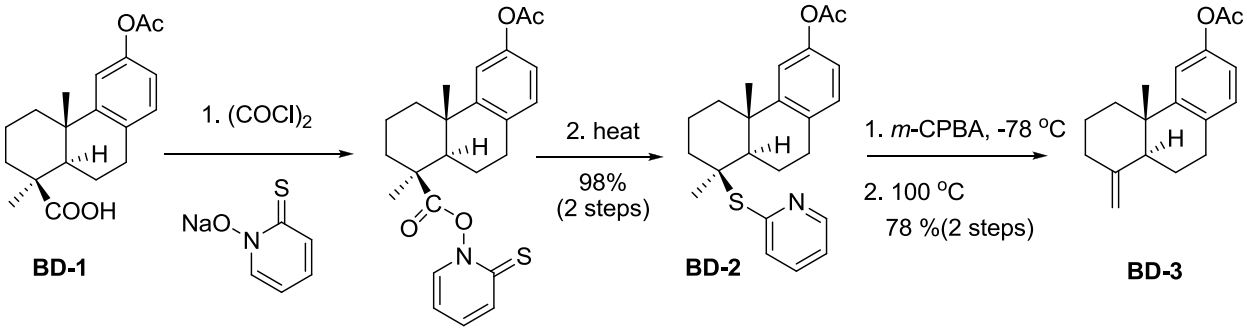


Scheme I-9

However, so far problems related to the toxicity of organic derivatives and the difficult purification have limited the development of tin chemistry to mostly at laboratory level. Even though, sometimes tris(trimethylsilyl)silane[7] may be as an alternative reducing agent, its price and difference in reactivity have limited its widespread applications.

ii. Barton decarboxylation

The Barton decarboxylation[8] was discovered in 1980s by Sir Derek Barton. It involves in the transformation of a carboxylic acid into the corresponding thiohydroxamate ester or Barton ester then decarboxylation, which allows the chemists to access to a broad range of transformations. In its original version, as displayed in **Scheme I-10,** the starting carboxylic acid **BD-1** was transformed into the corresponding thiohydroxamate ester **BD-2**.[9] Generally, Barton esters are generated in situ by different methods[10] since they are sensitive to light.



Scheme I-10

[7]Chatgilialoglu, C.; Griller, D.; Lesagel, M. *J. Org. Chem***1988**, *53*, 3641

[8] (a) Barton, D. H. R.; Crich, D.; Motherwell, W. B. *J. Chem. Soc., Chem. Commun.***1983**, 939.*Tetrahedron***1985**, *41*, 3901. (b) Barton, D. H. R. Half a Century of Free Radical Chemistry, Cambridge University Press, Cambridge, **1993**, p. 91.

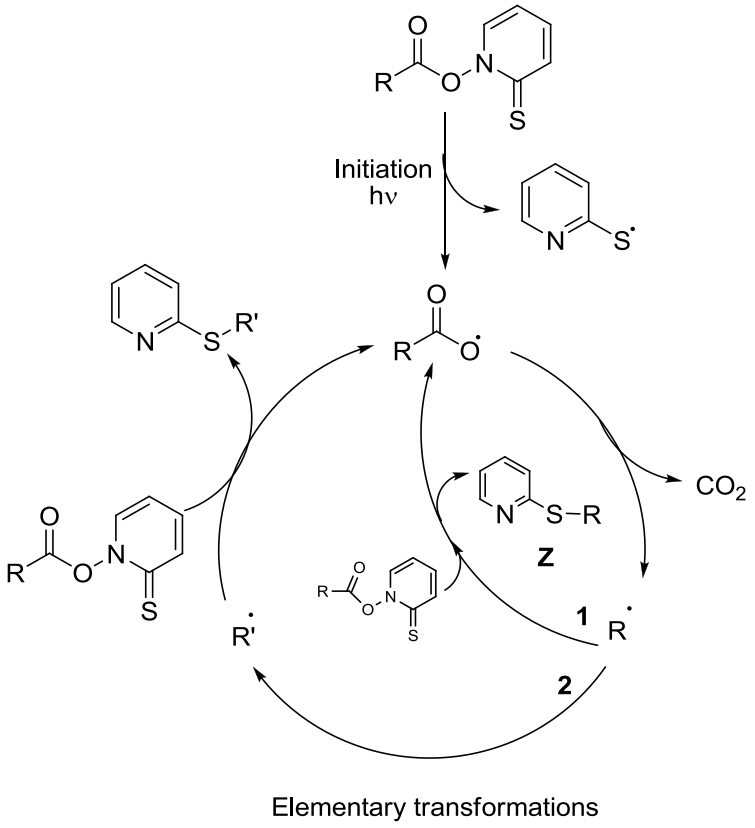
[9]Barton, D. H. R.; Bridon, D.; Zard, S. Z. *Tetrahedron***1987**, *43*, 2733.

[10](a) Crich D. *Aldrichimica Acta***1987**, *20*, 35. (b) Barton, D. H. R.; Zard, S. Z. *Pure Appl. Chem.***1986**, *58*, 675. (c) Barton, D. H. R.; Motherwell, W. B. *Heterocycles***1984**, *21*, 1.

The flexibility in controlling the generation of radical species from these thiohydroxamate esters is one of the most interestingly attractive features for various synthetic strategies. So far, this chemistry has been widely applied in the synthesis of numerous biologically active compounds such as carbohydrates, amino acids, vitamins and terpenoids.[11]

The detailed mechanism of this decarboxylation is outlined below in S**cheme I-11**.

The initiation step involves in the homolytic rupture of weak N-O bond of the Barton ester and the driving force is the aromatisation of pyridine ring. The high energy carbonyloxy radical $RCO_2^{\bullet}$ thus created extrudes a CO_2 molecule irreversibly and generates radical $R^{\bullet}$. If there is no radical trap in the system, radical $R^{\bullet}$ can attack the starting Barton ester to give **Z** and a new carbonyloxy radical $RCO_2^{\bullet}$ to propagate the chain (pathway **1**). The example above followed this pathway.



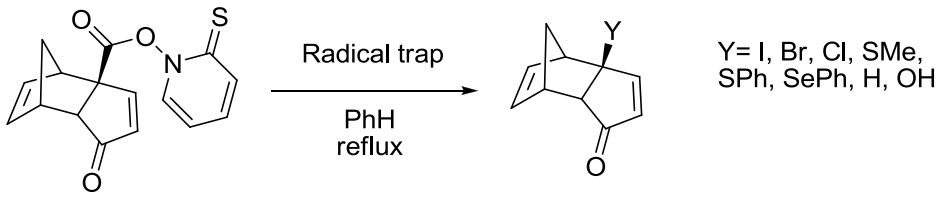
Scheme I-11

In the presence of radical traps, radical $R^{\bullet}$ can partake in one or more elementary transformations before reacting with the Barton ester (pathway **2**). For example, in the case where Bu_3SnH is

[11]For a review on the Barton ester chemistry, see: Saraiva, M. F.; Couri, M. R. C.; Le Hyaric, M.; de Almeida, M. V. *Tetrahedron***2009**, *65*, 3563.

used as a radical trap, radical $R^{\bullet}$ reacts with Bu_3SnH to furnish RH and radical $Bu_3Sn^{\bullet}$ which propagates the chain. Even though in this case, radical $R^{\bullet}$ can proceed along two pathways **1** and **2**, modifications of the temperature and the concentration of the Barton ester can favor pathway **2.** Normally, using a low concentration of Barton ester and low temperature, pathway **1** can be curtailed.

Apart from reduction with Bu_3SnH, the initial carboxylic acid can also be transformed into numerous other functional groups by using various radical traps such as Bu_3SnH, HCI_3, $BrCCl_3$, *t*-BuOCl, $(MeS)_2$, $(PhS)_2$, $(PhSe)_2$, *t*-BuSH, $H_2O/O_2/(PhSn)_3Sb$. Depending on the choice of radical traps, various functional groups can be introduced into the structure such as halide, sulfide, selenide or even hydroxyl group. A simple interesting example carried out by the Zwanenburg group illustrates how versatile this chemistry is (**Scheme I-12**).[12]



Radical trap: HCI_3, $BrCCl_3$, *t*-BuOCl, $(MeS)_2$, $(PhS)_2$, $(PhSe)_2$, *t*-BuSH, $H_2O/O_2/(PhSn)_3Sb$

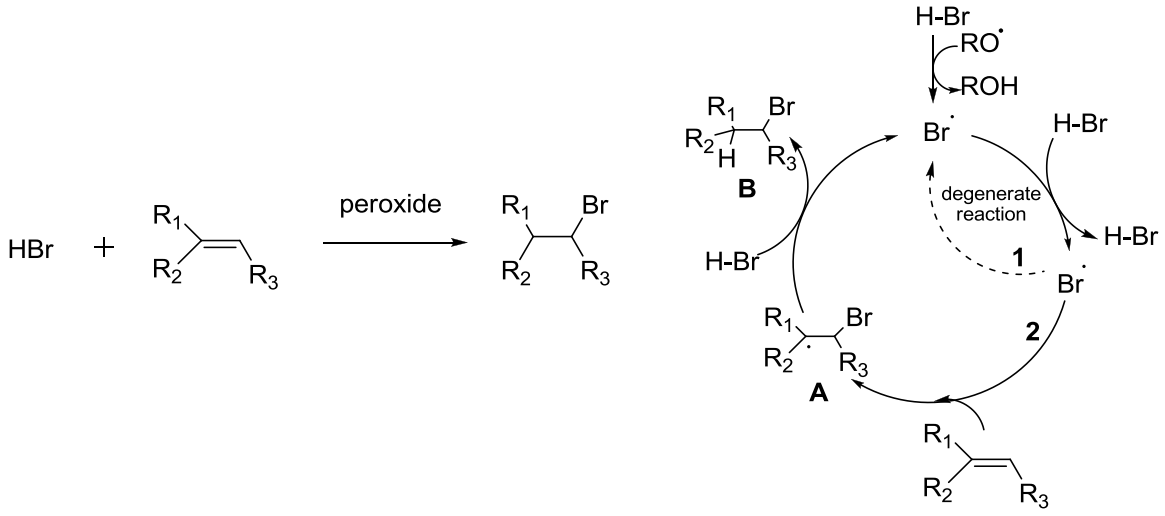
Scheme I-12

iii. Group transfer reaction

Another important and tremendously useful radical process is the group transfer, which is characterized by the transfer of a group from the precursors to the products. This type of reaction was studied initially by Kharasch, namely the addition of hydrogen bromide to olefins in the presence of peroxide, known as the 'peroxide effect' (**Scheme I-13**).[13] In this process, radical $Br^{\bullet}$, liberated from the reaction of peroxide radical $RO^{\bullet}$ and H-Br, adds to the double bond to form radical **A** that subsequently abstracts a hydrogen atom from H-Br to produce the anti-Markovnikov product **B** and radical $Br^{\bullet}$, which propagates the chain.

[12]Zu, J.; Klunder, A. J. H.; Zwanenburg, B. *Tetrahedron***1995**, *51*, 5099.

[13] (a) Kharasch, M. S.; Jensen, E. V.; Urry, W. H. *Science* **1945**, *102*, 128. (b) Kharsch, M. S.; Skell, P. S.; Fisher, P. J. *J. Am. Chem. Soc.* **1948**, *70*, 1055. (c) Kharsch, M. S.; Freiman, M.; Urry, W. H. *J. Org. Chem.* **1948**, *13*, 570.

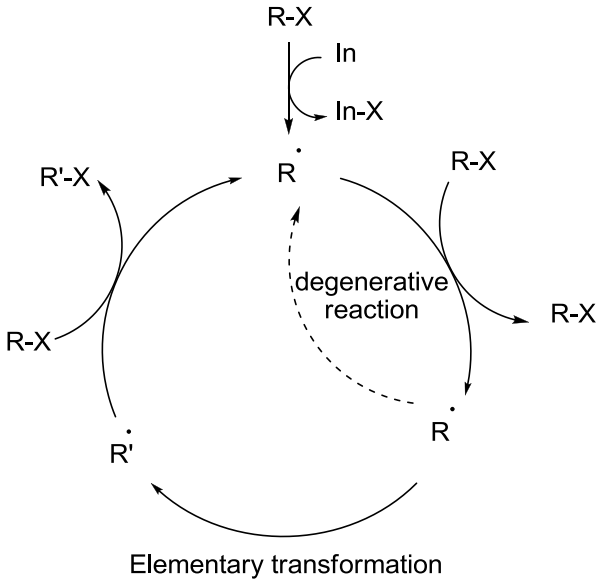


Scheme I-13

The reaction of radical Br$^{\bullet}$, with H-Br is an identity reaction. This reversible reaction is also called degenerate and is not observed at the macroscopic level.

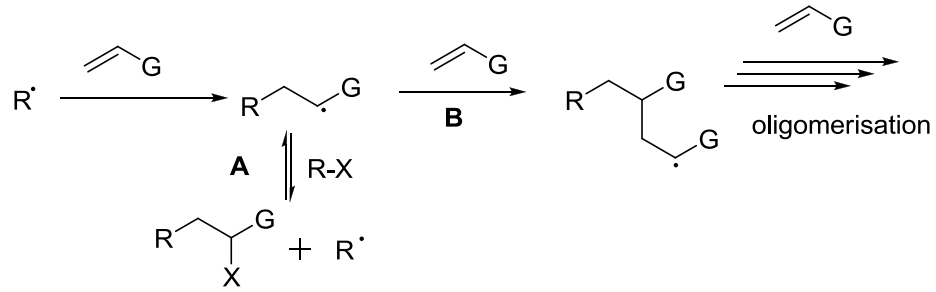
From this basic concept, the radical mechanism by the group transfer process may be generalized and as depicted in **Scheme I-14.**

In the group transfer process, the fact that radical R$^{\bullet}$ undergoes the degenerate reaction brings numerous advantages to the system. Since the equilibrium does consume the radicals, it increases its effective lifetime in the medium. Because of this property, radical R$^{\bullet}$ can perform transformations difficult to accomplish with stannane.



Scheme I-14

It is important to remember that radical R• must be more stable than radical R'• generated from in pathway **2** otherwise the reversible exchange of X step becomes inefficient. In the case of addition to alkens, a greater stability of R'• compared to R• will cause oligomerisation of the alkene (**SchemeI-15**). Therefore radicals R• such as primary, vinyl and aromatic radicals are not efficient in such process.



Scheme I-15

II. The radical chemistry of xanthate

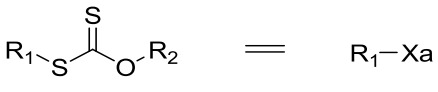
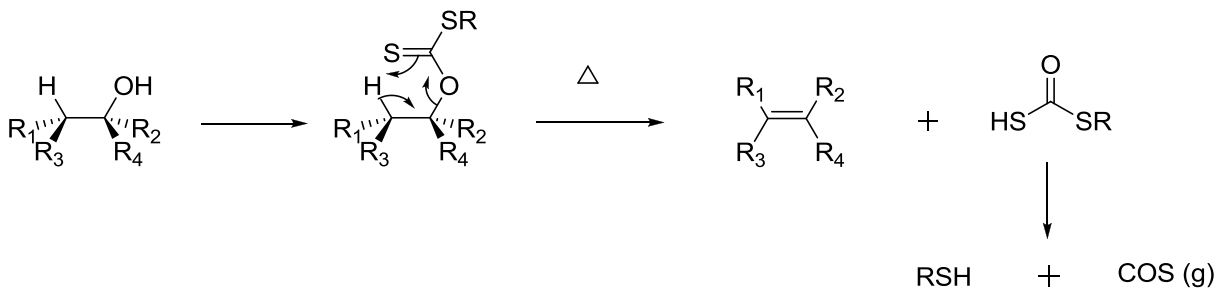


Figure II-1 The xanthate functional group

Dithiocarbonates, known as xanthates[14] (**Figure II-1**), were initially used in the Chugaev elimination,[15] which involves the elimination of COS from a secondary xanthate to produce alkenes and a thiol, and hence as a method to dehydrate a secondary alcohol (**Scheme II-1**). Apart from this reaction, the chemistry of xanthate was little exploited over for a relatively long period of time, until the recent discovery of its radical reactivity.

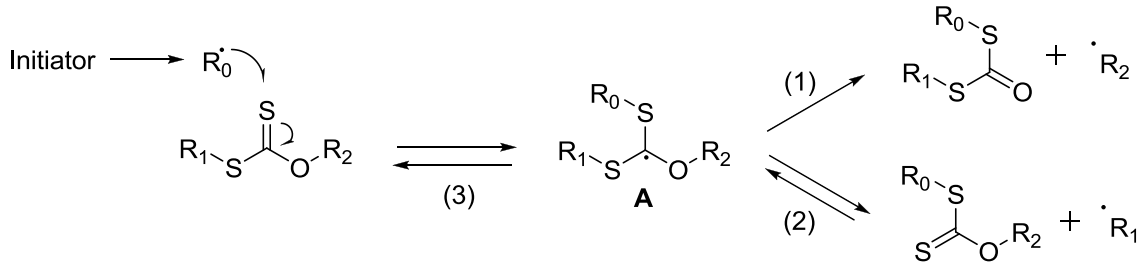
[14]Zeise, W. C. *J.Chem. Phys.* **1822**, *35*, 173; **1822**, *36*, 1
[15] Chugaev, L. *Ber Dtsch. Chem. Ges.* **1899**, *32*, 3332.



Scheme II-1

The development of the radical chemistry of xanthates in synthesis may be traced to the early 1970s with the reporting of the Barton-McCombie deoxygenation[16], which will be presented later. In fact, part of the radical chemistry of xanthate belongs to the more general field of group transfer that we introduced in the previous section.

As a consequence of the radicophilicity of the thiocarbonyl group, the first step involves the attack of a radical $R_0^{\bullet}$ on the sulfur of C=S double bond. This step is fast and reversible, as demonstrated in the study of the mechanism of the Barton-McCombie deoxygenation.[17] The intermediate radical **A** generated from this step is the key in discussing of this chemistry (**Scheme II-2**).



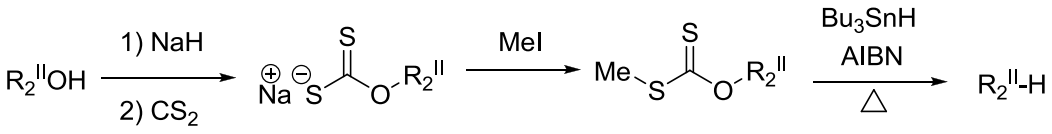
Scheme II-2

Except from the degenerate reaction (pathway **3**), this radical has the possibility to fragment in two different manners, depending on the nature of two groups R_1 and R_2. One pathway is the fragmentation of the C-O bond (pathway **1**), which leads to Barton-McCombie deoxygenation reaction, whereas the other pathway is the fragmentation of the C-S bond (pathway **2**), which is central to our study.

[16] Barton, D. H. R; McCombie, S. *J. Chem.Soc. Perkin. Trans. 1* 1975, 1574.
[17] Barton, D. H. R.; Crich, D.; Lobberding, A.; Zard, S. Z. *Tetrahedron* **1986**, *42*, 2329

1. Barton-McCombie deoxygenation

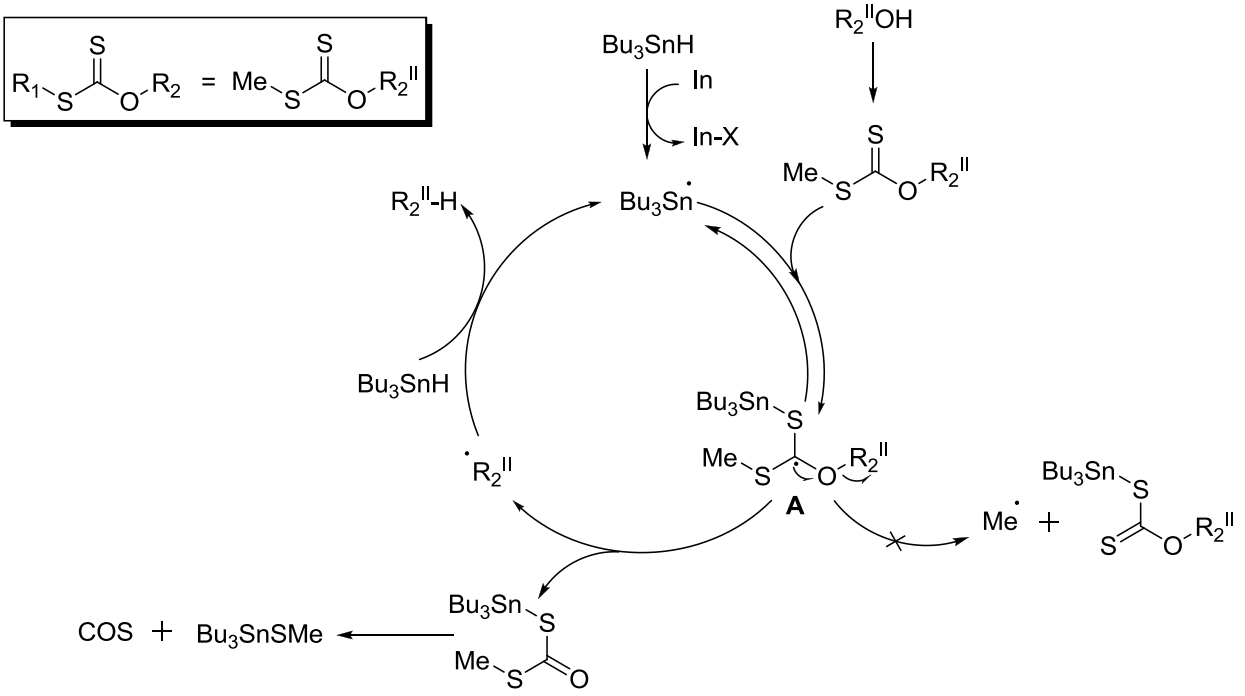
Discovered by Barton and McCombie in 1975, this method, first used to deoxygenate secondary alcohols, involves the initial transformation of a secondary alcohol into the corresponding xanthate, followed by the treatment with Bu_3SnH through a radical chain process to furnish the deoxygenated product (**Scheme II-4**).[18] It has been so far the most popular application of xanthates, particularly in the field of carbohydrates and aminoglycosides.



Scheme II-3

As illustrated in S**cheme II-4**, radical $Bu_3Sn^{\bullet}$ generated after the initiation step attacks the sulfur of the C=S bond in a rapid and reversible manner, which leads to intermediate radical **A**. As the R_1 group is a methyl group and the R_2 group is a secondary alkyl group, the fragmentation of **A** occurs only to the side of the C-O bond leading to more stable secondary radical. Subsequently, radical $R_2^{\bullet}$ reacts with Bu_3SnH to generate reduced product RH and stannyl radical $Bu_3Sn^{\bullet}$ which propagates the chain. The driving force of this process is the formation of a strong S-Sn bond and the conversion of a C=S bond into a stronger C=O bond.

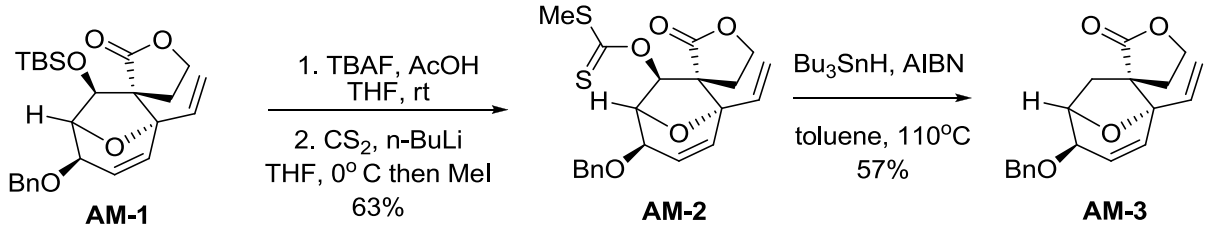
[18] Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc. Perkin Trans.1***1975**, 1574.



Scheme II-4

The Barton-McCombie reaction has proved to be the most suitable deoxygenation method for alcohols in organic synthesis. Since its discovery, the original publication has been cited more than 1400 times, and its applications are found widely in total synthesis and in the systematic modification of natural products. This transformation provides a good alternative to ionic methods which are frequently less selective and efficient.

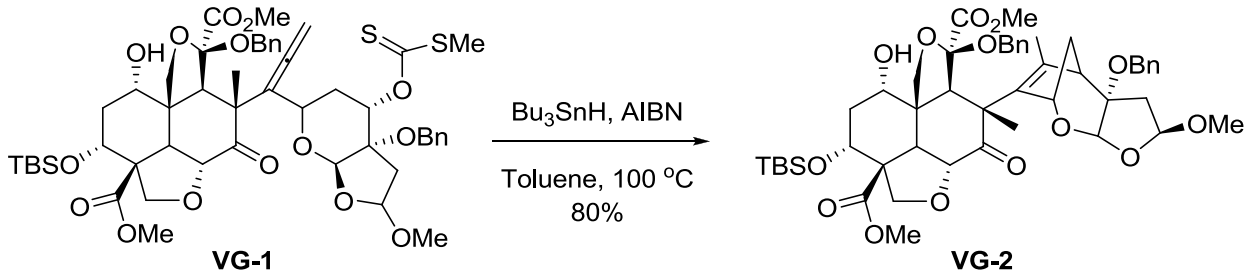
For example, in a recent total synthesis of Polygalolide A by Nishikawa's group in 2011[19], the key intermediate **AM-3** was obtained by conversion of the protected alcohol functional group of **AM-1** into thiocarbonate **AM-2,** whichwas then transformed into **AM-3** by treatment with Bu_3SnH (**Scheme II-5**).



Scheme II-5

[19]Adachi, M; Yamada, H.; Isobe, M.; Nishikawa, T. *Org. Lett.***2011**, *13*, 6532.

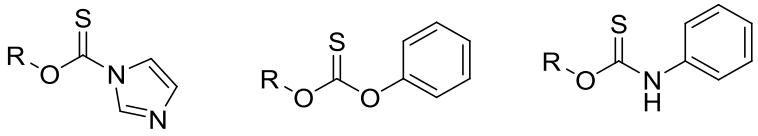
Another elegant example concerns access to the very complex precusor of azadirachtine.[20] After fragmentation of the C-O bond, the radical derived from **VG-1** underwent a 5-exo cyclisation on an allene to furnish an allylic radical which then abstracted hydrogen from Bu_3SnH to give rise to **VG-2**. This example demonstrates the high functional group tolerance of this method (**Scheme II-6**).



Scheme II-6

Not limited to secondary alcohols, the Barton-McCombie reaction can sometimes be applied for the primary and tertiary alcohols by modifying the conditions, even though with much less generalities than in the case of secondary alcohols.

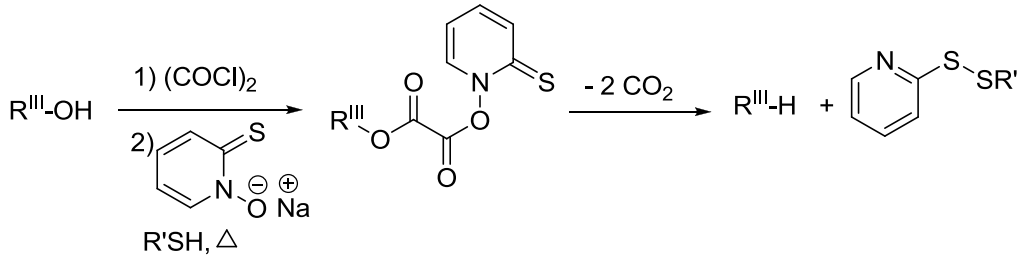
For instance, for the primary alcohols, the rupture of C-S bond, which produces the methyl radical, will be in the competition with the desired rupture of C-O bond since both of fragmentations leads to the formation of primary radicals. To solve the problem, the thiomethyl group is replaced by an imidazole, a phenol or an aniline.[21] In these cases, the undesired fragmentation becomes incompatible since a very high energy radical would be generated; therefore, the deoxygenation provides a good yield even for primary alcohol (**Scheme II-7**).



Scheme II-7

[20]Veitch, G. E.; Beckmann, E.; Burke, B. J.; Boyer, A.; Maslen, S.; Ley, S. V. *Angew. Chem. Int. Ed.***2007**, *46*, 7629.
[21]Barton, D.H.R.; Motherwell, W. B.; Stange, A. *Synthesis***1981**, 743.

In the case of tertiary alcohols, the corresponding xanthates undergo the Chugaev elimination[22] under the experimental conditions. For such alcohols, a better variant is to perform a reductive decarboxylation on the hemioxalate as shown in **Scheme II-8**.[23]



Scheme II-8

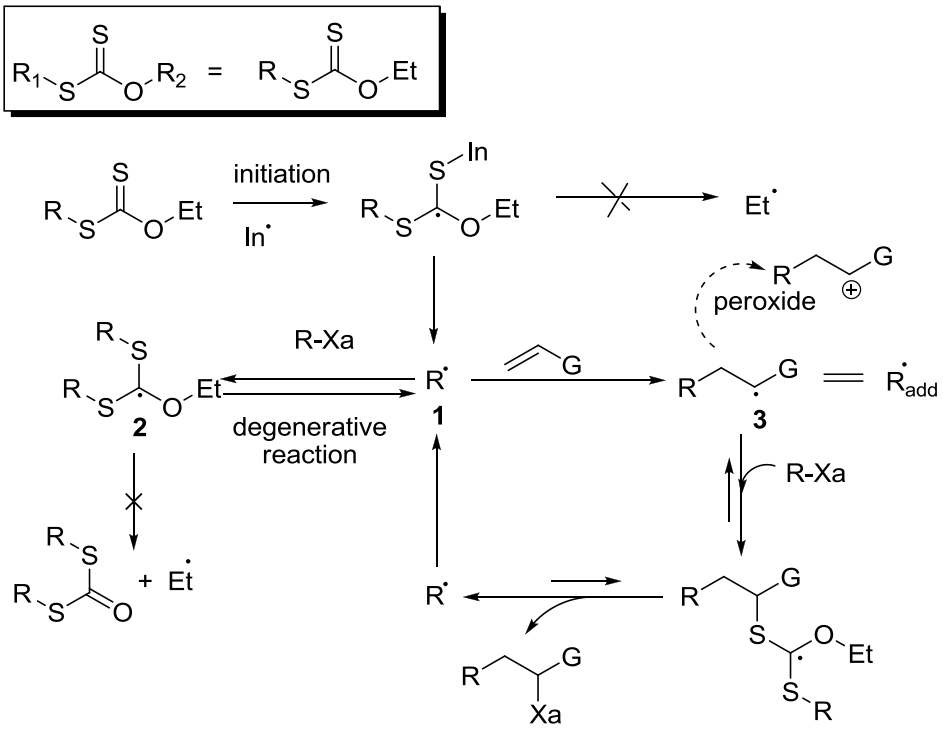
2. The degenerative xanthate transfer process

Originally developed from a detailed study on the mechanism of Barton-McCombie deoxygenation, yet in contrast to the cleavage of C-O bond in the deoxygention method, the radical chemistry by transfer of a xanthate is based on the cleavage of C-S bond. In this case, in order to prevent the fragmentation of the C-O bond, the R_1 group is generally a primary alkyl (an ethyl group is normally used). As the matter of fact, the chemistry of group transfer allows both intermolecular and intramolecular additions. The simplified general mechanism manifold for the addition of R-Xa to an olefin is presented in **Scheme II-9**.

In this process, it is important to emphasize two crucial necessary conditions for the efficiency of the whole system:

- $R^{\bullet}$ radical must be equally, or better, more stable than an ethyl radical so that the fragmentation occurs only to the side of C-S bond.
- $R_{add}^{\bullet}$ radical**3** must be less stable than $R^{\bullet}$ radical so that the problem of oligomerisation is obviated and the chain propagates.

[22]Nace, H. R. *Org React.***1962**, *12*, 57.
[23] (a) Barton, D.H.R.; Crich, D. *J. Chem. Soc. Chem. Commun.***1984**, 774. (b) *J. Chem. Soc. Perkin. Trans.1* **1986**, 1603.



Scheme II-9

In this respect, the key element to the success of the xanthate chemistry is due to the degenerate reaction leading to radical **2**. Radical R• is stocked in the form of the more stable tertiary radical **2**, in consequence, the concentration of radical R• remains very low in solution yet its lifetime is at the same time increase. The low concentration of radical R• decreases the importance of the termination steps. This makes this process unique and, in contrast to most other radical methods, the degenerative xanthate transfer process can be performed in a very concentrated solution, thus favoring even sluggish bimolecular processes. This is also an advantage for applications in industry since it is easy to scale up the reactions.

The radical addition reactions can be accomplished even with unactivated olefins. Indeed, the xanthate transfer process represents a good solution to the longstanding problem in organic synthesis of creating C-C bonds in an intermolecular fashion with non-activated alkenes.

In some special cases, the initiator peroxides can oxidize the intermediate radical R_{add}• to the corresponding cation, which can then undergo typical ionic transformations.[24]

[24]For reviews on the xanthate radical transfer reaction, see: (a) Zard, S. Z. *Angew. Chem., Int. Ed*. **1997**, *36*, 672. (b) Quiclet-Sire, B.; Zard, S. Z. *Chem. Eur. J*.**2006**, *12*, 6002. (c) Quiclet-Sire, B.; Zard, S. Z. *Top. Curr.Chem*.**2006**,

This process offers numerous advantages:

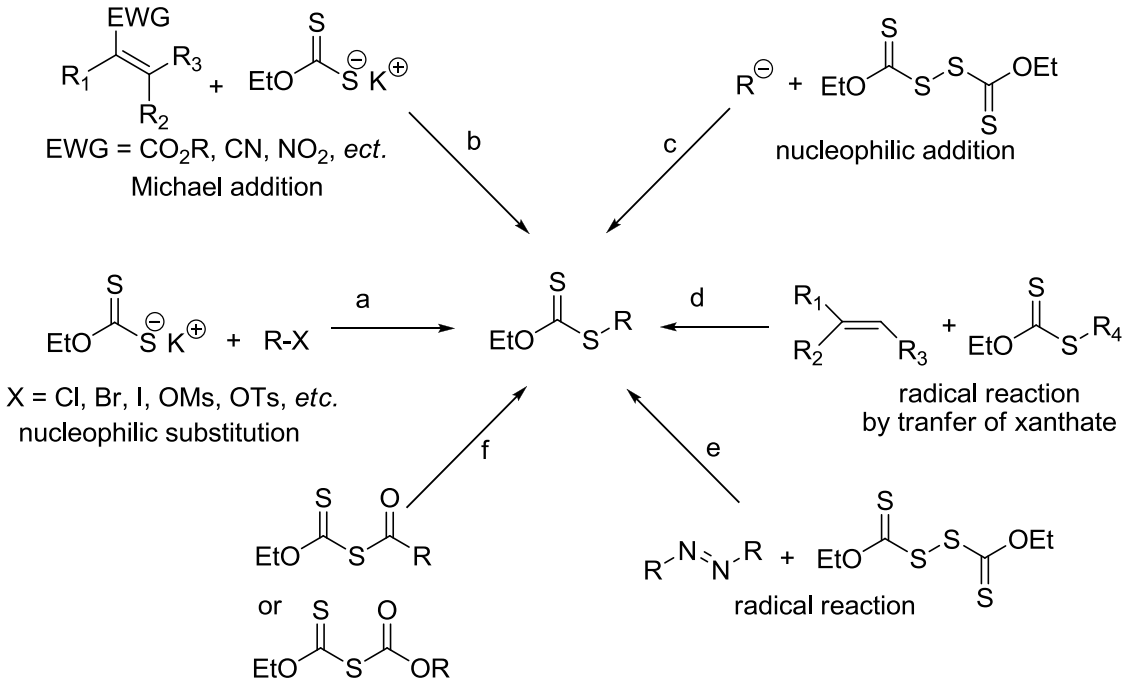
- It does notinvolve heavy metals such as tin or mercury.
- There is no fast competing reduction as with the stannane chemistry.
- It is easy to accessxanthates, which are generally stable.
- Difficult transformations– can be accomplished, in particular intermolecular additions to unactivatedolefins and cyclisations onto aromatic rings.
- It is easy to implement experimentally. Moreover, xanthates possess physical characteristics suitable for analyzing the products: they are visible under a UV lamp and exhibit characteristic NMR signals.
- The processes are safe and easy to scale up.
- The products of additions to alkenes are also xanthates. It is often possible to use them in a second radical transformation or convert them into other functional groups.
- This chemistry has a remarkable tolerance to a variety of functional groups, which allows an easy access to an assembly of richly functionalised structures.

i. Preparation of xanthates

Numerous methods to access xanthates have been developed and depending on the nature or the substitution of the desired xanthate, a given route may be preferred. As mentioned above, the ethyl group is placed to prevent the fragmentation of the C-O bond; in fact this choice is only based on a practical facility, because potassium *O*-ethyl xanthate salt is commercially available and cheap. The ethyl group can obviously be replaced by another alkyl group if necessary.

S**cheme II-10** portrays a summary of routes to xanthates.

264, 201. (d) Zard, S. Z. *Aust. J. Chem.***2006**, *59*, 663. (e) Quiclet-Sire, B.; Zard, S. Z. *Pure Appl. Chem.* **2011**, *83*, 519.

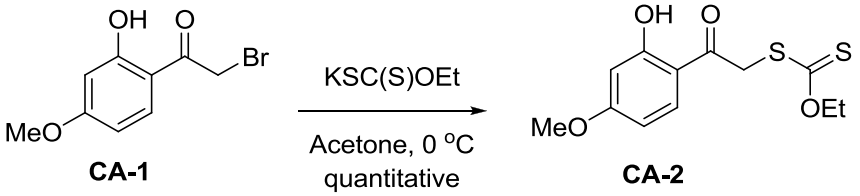


Scheme II-10

By ionic methods:

1/ The most popular method is the nucleophilic substitution of a leaving group by potassium *O*- ethyl xanthate salt. Most of the starting xanthates used in our group are synthesized by this method. It is efficient for the synthesis of primary or secondary xanthates, but it generally fails for tertiary xanthates.

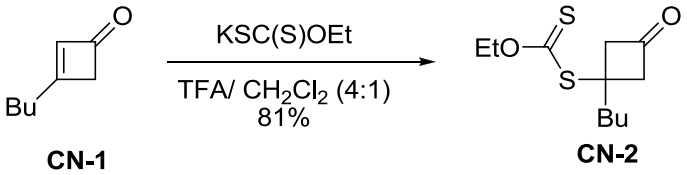
For example, xanthate **CA-2** is obtained in excellent yield from the corresponding bromide (**Scheme II-11**).[25]



Scheme II-11

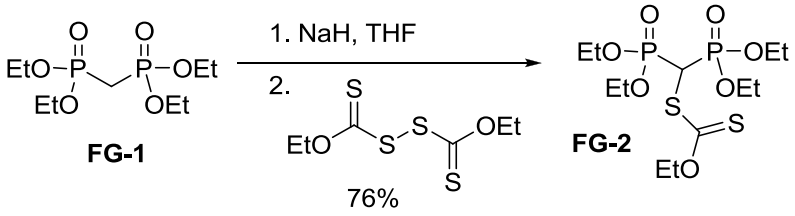
2/ Certain tertiary xanthates an be prepared by Michael addition to an electrophilic alkene as shown in **Scheme II-13**. However, it is necessary to operate under acidic conditions to avoid the retro-Michael reaction, and this introduced a limitation.[26]

[25]Cordero-Vargas, A.; Quiclet-Sire, B.; Zard, S. Z. *Org. Lett.***2003**, *5*, 3717.
[26]Charrier, N.; Gravestock, D.; Zard, S. Z. *Angew.Chem. Int. Ed.***2006**, *45*, 6520.



Scheme II-12

3/ An alternative method is the nucleophilic attack of an anion on a bis-xanthate. For example, in our laboratory, the highly functionalized xanthate **FG-2** is produced in high yield 76% by Fabien Gagosz (**Scheme II-13**). However, this approach is limited because a second addition of xanthate can take place for primary and secondary carbanions.

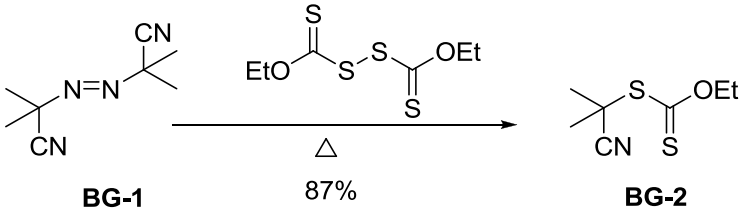


Scheme II-13

By radical methods:

1/ The most general method is the addition of a xanthate to an olefin by transfer of xanthate (examples will be presented in the following section). This strategy allows us to access to very complicated xanthates. By modifying the xanthate precursors and olefin traps, the number of generated xanthates is unlimited.

2/ Reacting a radical derived from an azo compound with a bis-xanthate also generates xanthates. This method is employed to form tertiary xanthates but is limited by the availablility of the azo component.[27]

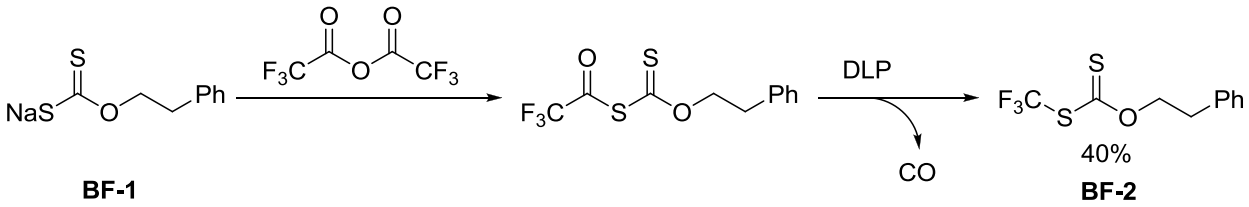


Scheme II-14

3/ The photolysis of *S*-acyl xanthate can furnish tertiary xanthates through the extrusion of a CO_2 or a CO molecule. It is sometimes necessary to use this process in some specific cases. For example, *S*-triluoromethyl xanthates cannot be prepared by a normal nucleophic substitution,

[27]Bouhadir, G.; Legrand, N.; Quiclet-Sire, B.; Zard, S. Z *Tetrahedron Lett.***1999**, *40*, 277.

but the procedure involving the decarbonylation of *S*-trifluoroacetyl xanthate proved to be a successful route. Thus, Bertrand could obtain the *S*-xanthate of trifluromethyl **BF-2** in moderate yield (40%) as shown in **Scheme II-15**. [28]



Scheme II-15

ii. Synthetic potential of xanthates

Xanthates have a huge potential in organic synthesis as they allow the construction of a vast array of different structures. The main types of reactions that can be accomplished by the xanthate chemistry are listed below:

a. Intermolecular additions

b. Ring-closure onto internal alkenes

c. Ring-closure onto aromatic derivatives

d. Fragmentation reactions

e. Transformation of xanthates

f. Application of xanthate in total synthesis

By going through these reactions, we will clarify how powerful and versatile this chemistry is.

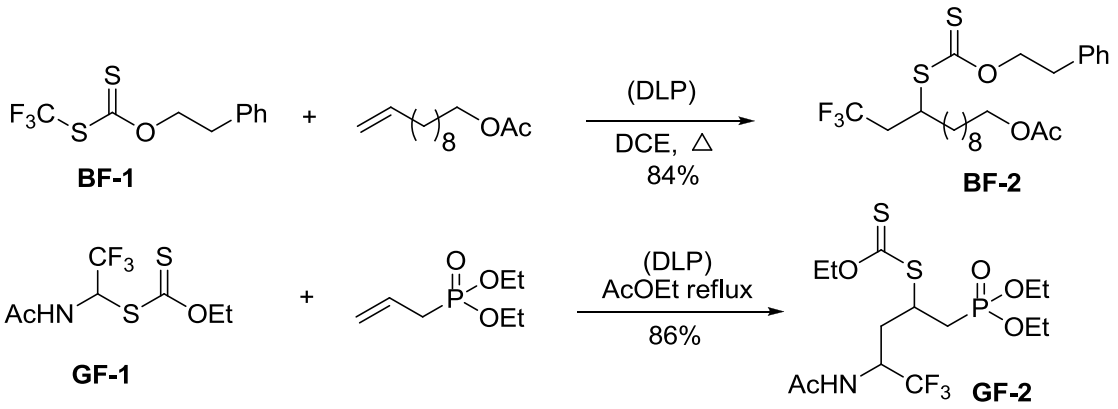
From now on, in this thesis, placing lauroyl peroxide in parentheses indicates that it is used as the initiator in substoichiometric amounts, while no parentheses means that the peroxide is used both as initiator and as a stoichiometric oxidant.

a. Intermolecular additions:

As stated above, the ability of xanthates to mediate intermolecular C-C bond formation to non-activated olefins is one of the main hallmarks of this chemistry.

[28] Bertrand, F.; Pevere, V.; Quiclet-Sire, B.; Zard, S. Z. *Org. Lett.* **2001**, *3*, 1069.

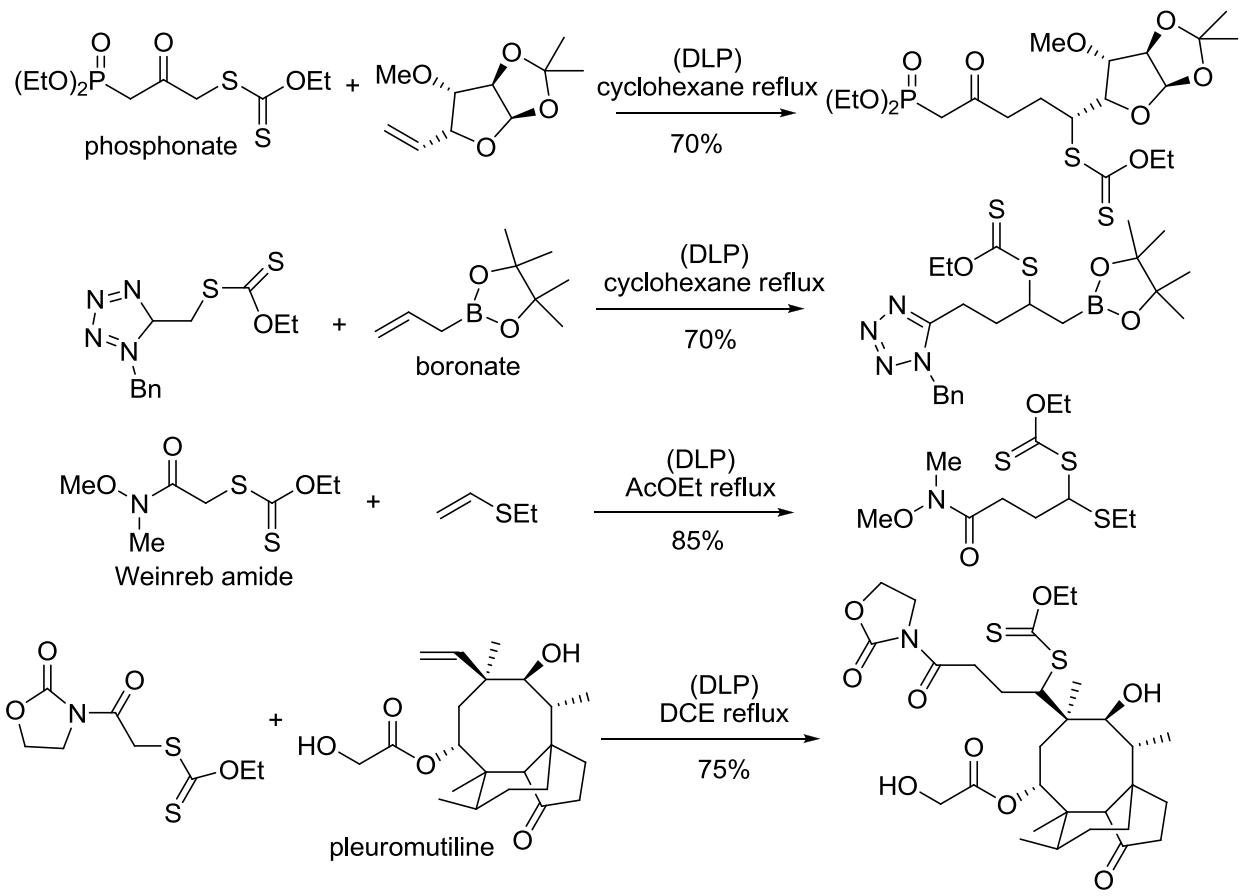
The first example in **Scheme II-16** is the addition of the xanthate of trifluoromethyl.[29] In this case, the ethyl group is replaced by a phenylethyl group to reduce the volatility of the compound. After reaction, the trifluoromethyl motif is introduced to the structure efficiently in 84% yield. In the same way, the α-trifluoromethylamine motif[30] can be introduced efficiently by using the corresponding xanthate **GF-1**. With these reactions, a variety of fluorinated structures important for their potential pharmaceutical applications can be obtained.



Scheme II-16

An important observation is that this chemistry is compatible with various functional groups demonstrated by the examples in **Scheme II-17.** The last example involving pleuromutiline and possessing unprotected alcohol groups is particularly noteworthy.

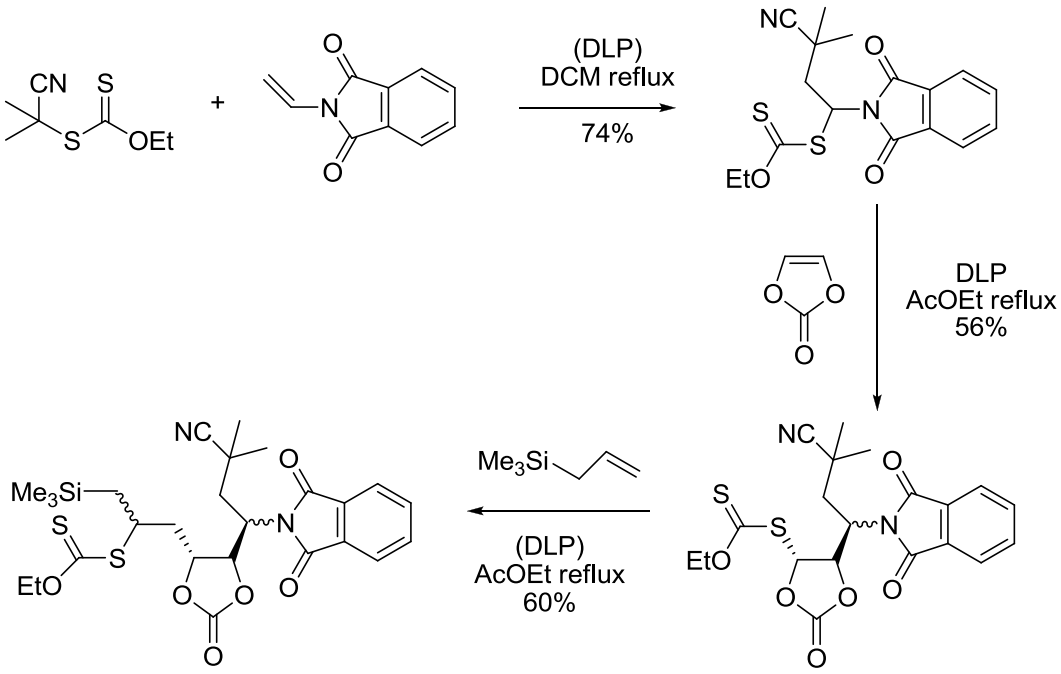
[29]Bertrand, F; Pevere, V; Quiclet-Sire, B.; Zard, S. Z. *Org. Lett.***2001**, *3*, 1069.
[30] (a) Gagosz, F.; Zard, S. Z. *Org. Lett.***2003**, *5*, 2655. (b) Quiclet-Sire, B; Zard, S. Z. *Chem. Eur. J.***2006**, *12*, 6002.



Scheme II-17

Besides, the resulting xanthate can often react with another olefin to generate a new xanthate. A succession of addition reactions can sometimes be performed to construct, a complex and highly functionalised structures. Such an example is displayed in **Scheme II-18**.[31]

[31]Quiclet-Sire, B.; Revol, G.; Zard, S. Z. *Tetrahedron***2010**, *66*, 6565.

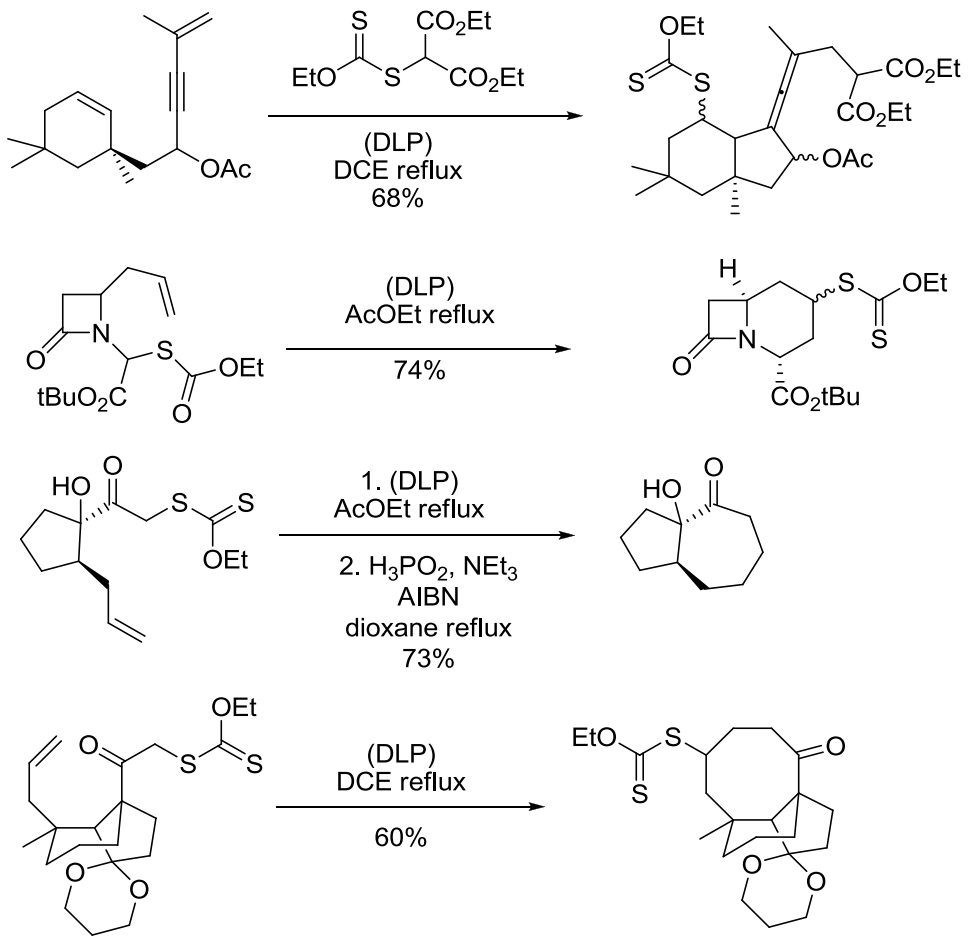


Scheme II-18

b. Ring-closure onto internal alkenes:

Xanthates can also be used to mediate efficient cyclisations if the substrate bears a suitable located internal alkene. So far, besides the easy formation of five[32] or six-member-rings,[33] even the difficult and problematic formation of seven[34] or even eight-member-rings[35] can sometimes be achieved (**Scheme II-19**). This method opens up an easy access to carbocycles as well as to heterocycles.

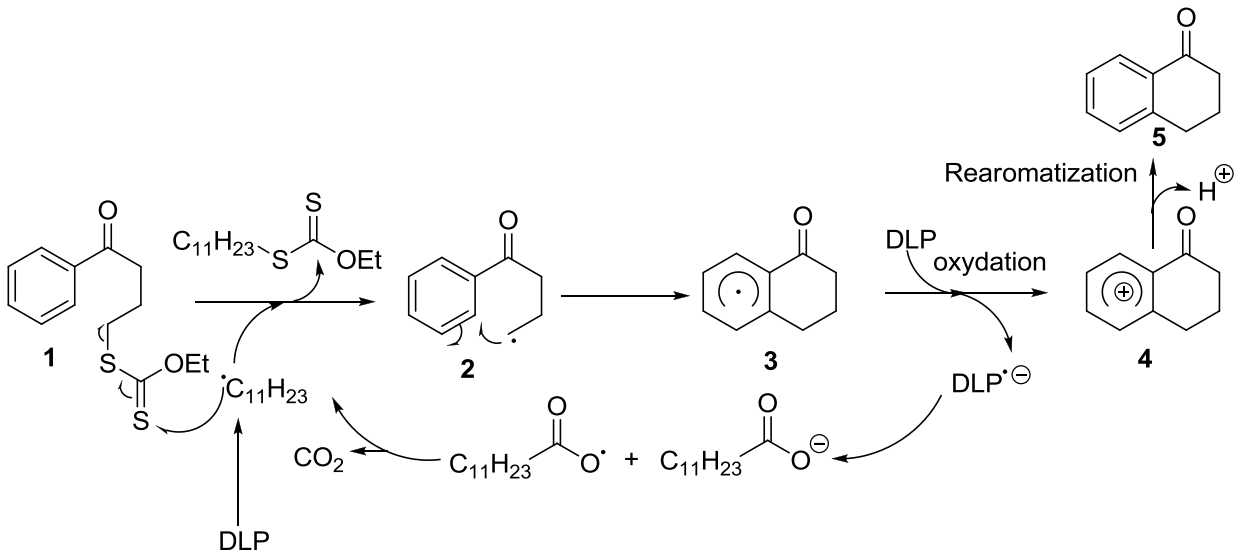
[32](a) Alamenda-Angulo, C.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron***2006**, *47*, 913. (b) Denieul, M.-P.; Quiclet-Sire, B.; Zard S. Z. *Tetrahedron Lett.***1996**, *37*, 5495.
[33] Boiteau, L.; Boivin, J.; Quiclet-Sire, B.; Saunier, J.B.; Zard, S. Z. *Tetrahedron***1998**, *54*, 2087
[34]Heng, R; Zard, S. Z. *Org. Biomol.Chem.***2011**, *9*, 3396.
[35]Bacque, E.; Pautrat, F.; Zard, S. Z. *Org. Lett.***2003**, *5*, 325.



Scheme II-19

c. Ring-closure onto aromatic derivatives:

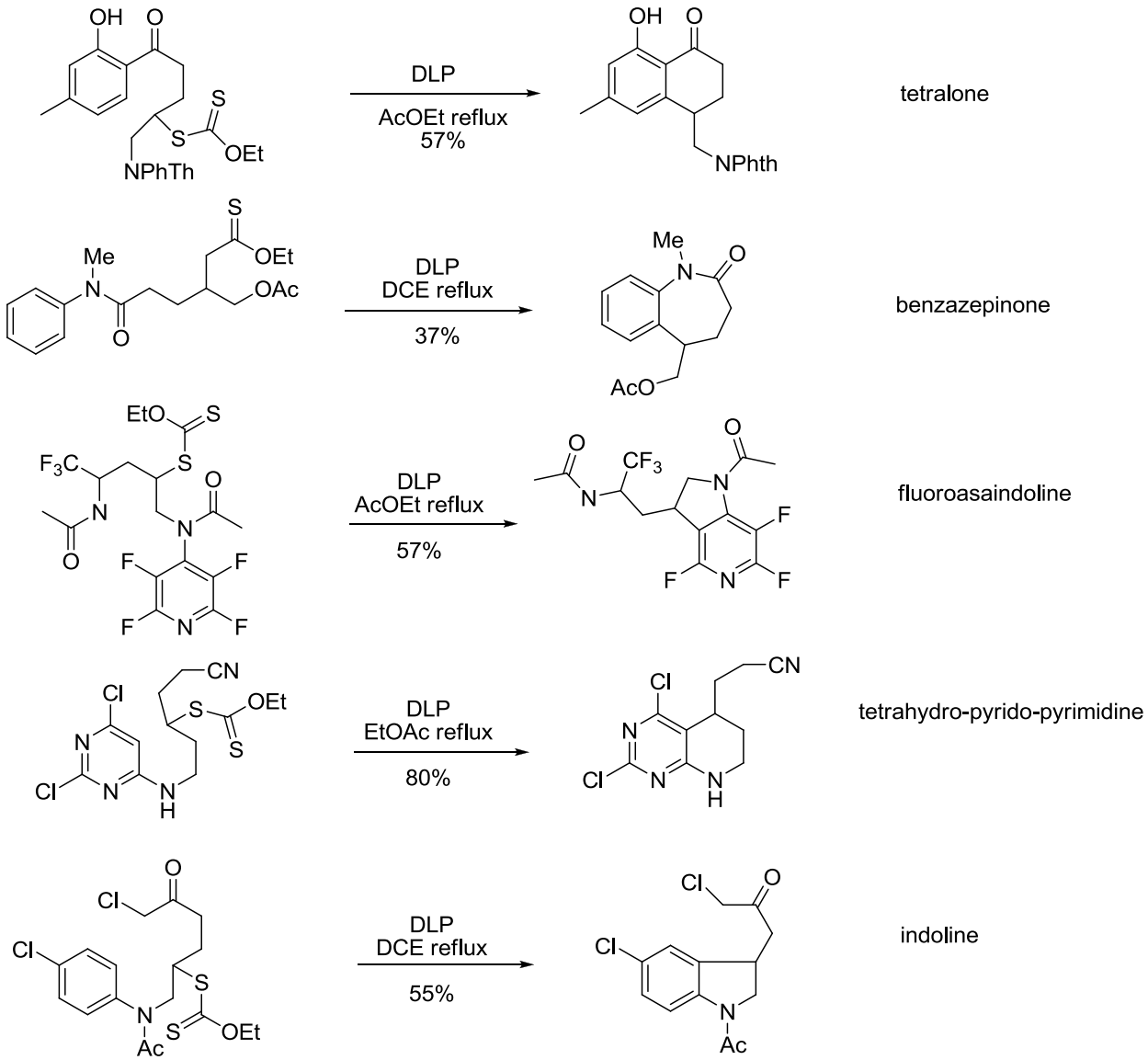
The intramolecular addition can also take place on an aromatic nucleus, but in this case, the reaction proceeds without transfer of the xanthate group. As shown in S**cheme II-20**, the cyclohexadienyl radical thus generated is oxidized to a carbocation by electron transfer to the peroxide, followed by aromatisation through loss of a proton. The peroxide therefore acts as both an initiator and an oxidant. The principal side reaction in this process is the premature reduction of radical **2**.



Scheme II-20

This reaction mode allows the application of xanthate to the systhesis of a wide variety of substituted cyclic systems such as α-tetralones,[36] benzazepinones,[37] fluoroazaindolines,[38] indulines,[39] tetrahydro-pyrido-pyrimidines[40]… These ring-closures to aromatic and heteroaromatic derivatives allow access to highly functionalised molecular architectures as illustrated by the examples in **Scheme II-21**. The precursors in these examples were themselves made by an intermolecular addition of a xanthate to a simple alkene. In some cases, both steps can be performed in the same pot without isolation of the adduct.

[36]Petit, L.; Zard, S. Z. *Chem. Commun***2010**, *46*, 5148.
[37]Kaoudi, T.; Quiclet-Sire, B.; Seguin, S.; Zard, S. Z. *Angew.Chem. Int. Ed.***2000**, *39*, 731.
[38]Laot, Y.; Petit, L.; Zard, S. Z. *Org. Lett.***2010**, *12*, 3426.
[39]Bereot, O.; Corsi, C.; El Qacei, M.; Zard, S. Z. *Org. Biomol.Chem.***2006**, *4*, 278.
[40]Liu, Z.; Qin, L.; Zard, S. Z. *Org. Lett.***2012**, *14*, 5976.

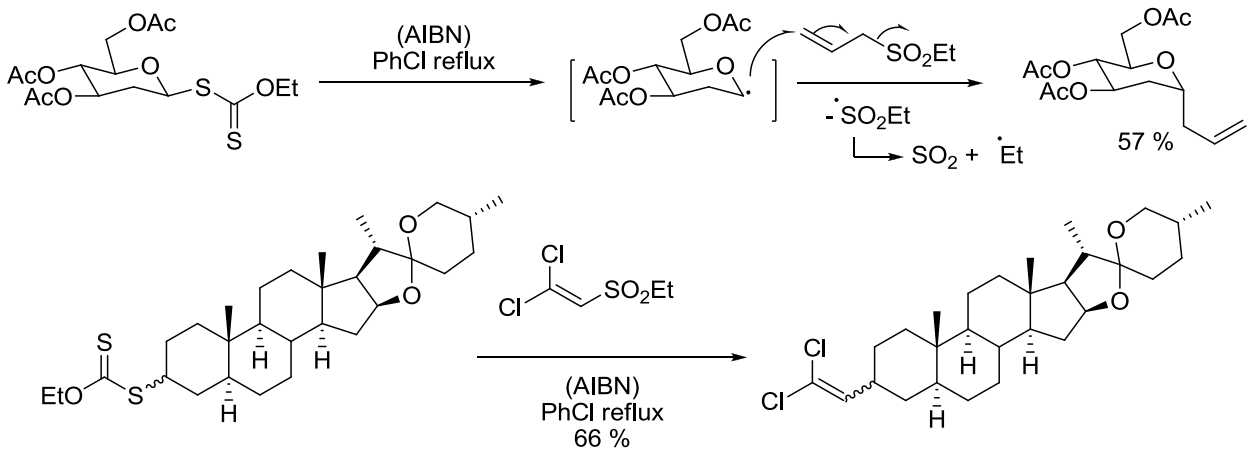


Scheme II-21

d. Fragmentation reactions:

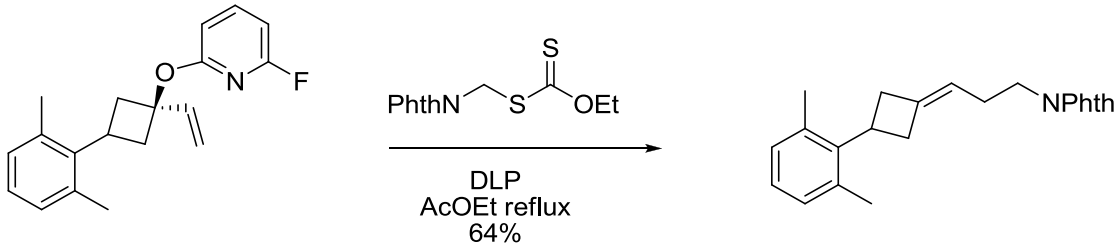
Following the addition or cyclisation step, a radical can sometimes undergo a fragmentation and generate a new radical, which may then propagate the chain.

One of the more interesting fragmentations is the case of allylic[41] and vinylic sulfones;[42] in the latter case, the dichloro vinyl derivative obtained can be transformed into an alkyne by the well-known Corey-Fuchs reaction (**Scheme II-22**).



Scheme II-22

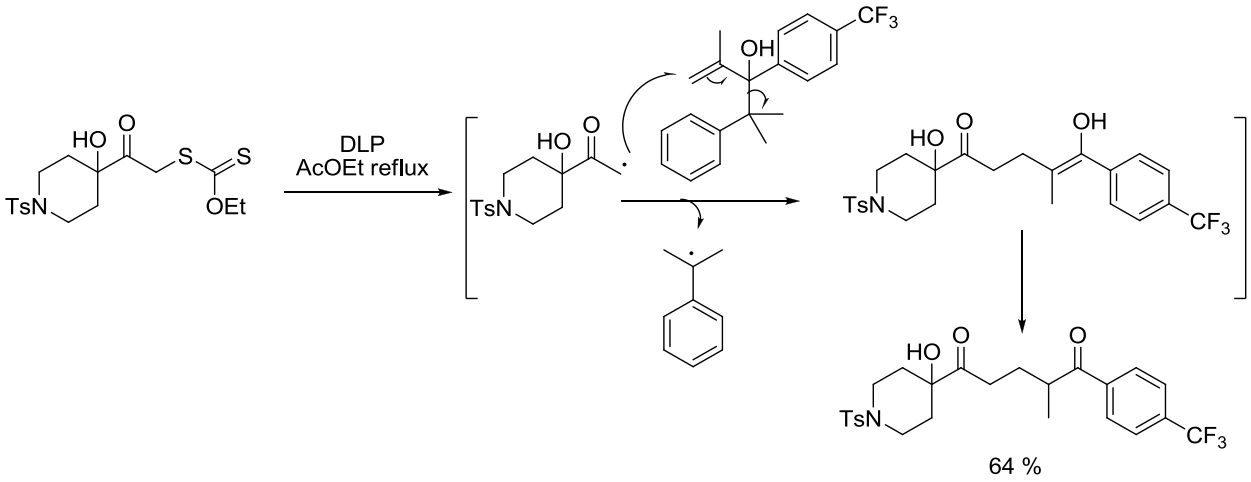
The 2-fluoro-6-hydroxypyridinyloxy group has recently been developed in our laboratory as a means for cleaving by homolysis the C-O bond of alcohols. This fragmentation allows access to di, tri- or even tetrasubstituted olefins. The latter are generally difficult to obtain by more traditional methods such as the Wittig olefination. In this case, a stoichiometric amount of peroxide is needed because the fluoro pyridyloxyl radical, generated from the fragmentation, does not propagate the chain (**Scheme II-23**).[43]



Scheme II-23

[41]Quiclet-Sire, B.; Zard, S. Z. *Angew.Chem. Int. Ed.***1998**, *37*, 2864.
[42](a) Bertrand, F.; Quiclet-Sire, B.; Zard, S. Z. *Angew.Chem. Int. Ed.***1998**, *38*, 1943. (b) Li, Z.; Zard, S. Z. *Tetrahedron Lett.* **2009**, *50*, 6973.
[43] Charrier, N; Quiclet-Sire, B.; Zard, S. Z. *J. Am. Chem. Soc*.**2008**, *130*, 8898.

In the course of extending the scope of this approach, another interesting fragmentation was discovered involving the rupture of a C-C bond to generate cumyl radical, as described in **Scheme II-24**. This discovery provides a synthetic route to useful ketones.[44]



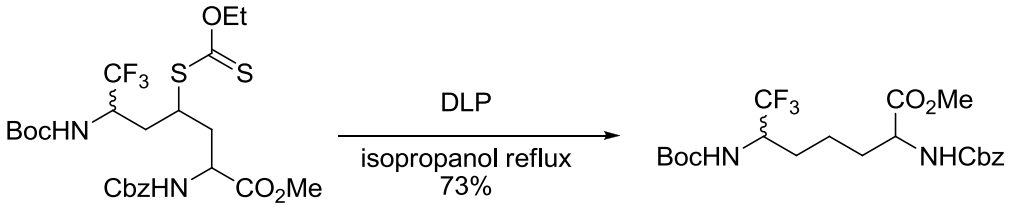
Scheme II-24

e. Transformations of xanthate:

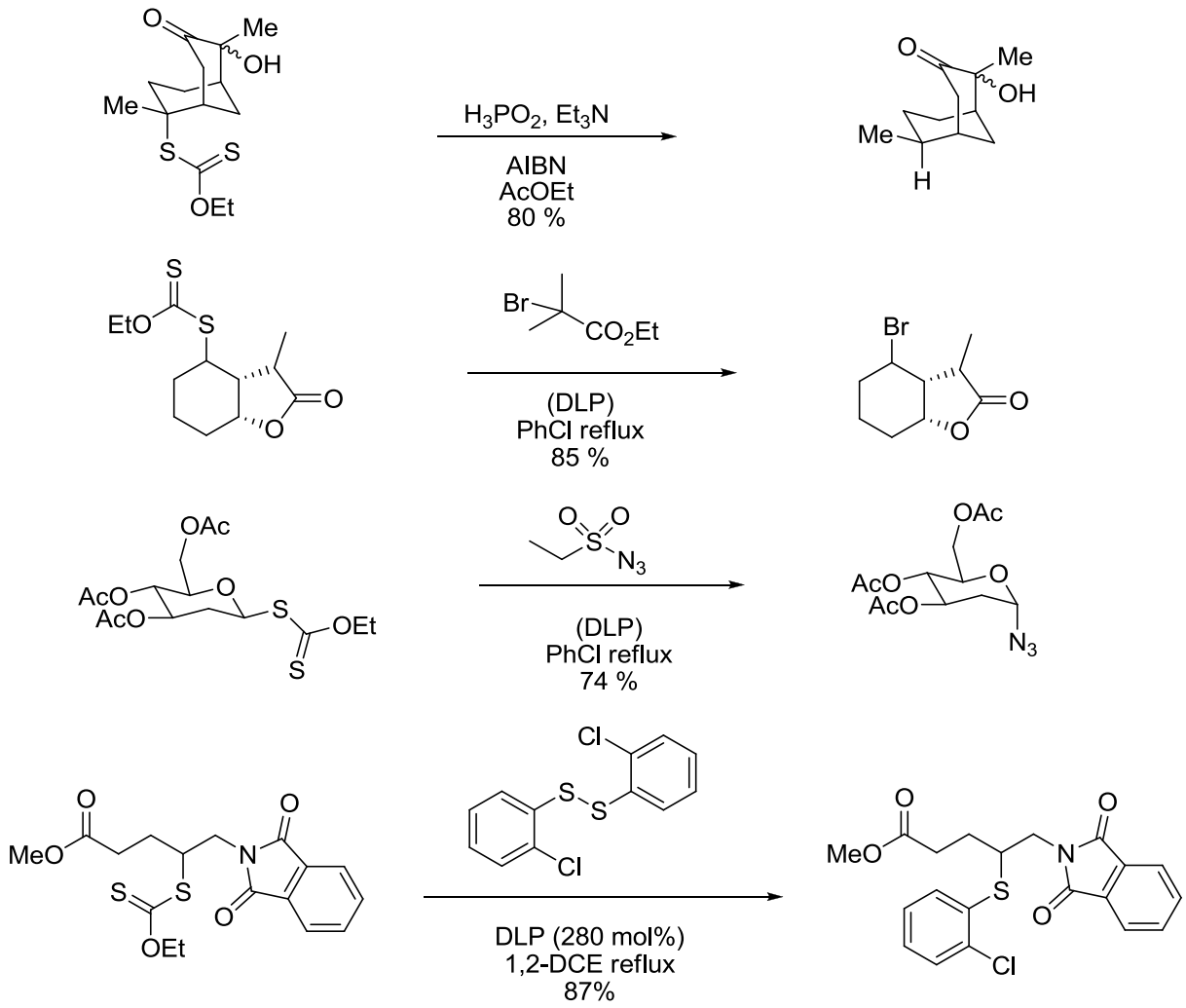
Since the final products of the normal addition to alkenes contain a xanthate, it is possible to transform it into numerous other functional groups by using both radical and ionic processes.

(1) Radical transformations

Using radical chemistry, the xanthate can be reduced easily by the DLP/isopropanol couple[45] or by a the mixture of H_3PO_2/Et_3N/AIBN[46]. The xanthate may also be converted into a bromide[47] using ethyl bromo isobutyrate with di-*t*-butyl-peroxide or into an azide via a peroxide initiated reaction with ethylsulfonylazide;[48] or, finally, into a chlorophenyl sulfide by reacting with DLP/bis(2-chlorophenyl)disulfide.[49]Some examples are displayed in **Scheme II-25**.



[44]Debien, L.; Zard, S. Z. *J. Am. Chem. Soc.* **2013**, *135*, 3808.
[45]Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.***1998**, *39*, 9435.
[46]Braun, M.-G.; Heng, R.; Zard, S. Z. *Org. Lett.***2011**, *13*, 1230.
[47] Barbier, F.; Pautrat, F.; Quiclet-Sire, B.; Zard, S. Z. *Synlett***2002**, 811.
[48]Olivier, C.; Renaud, P. *J. Am. Chem. Soc.***2000**, *122*, 6496.
[49]Corbet, M; Ferjancic, Z.; Quiclet-Sire, B.; Zard, S. Z. *Org. Lett.***2008**, *10*, 3579.

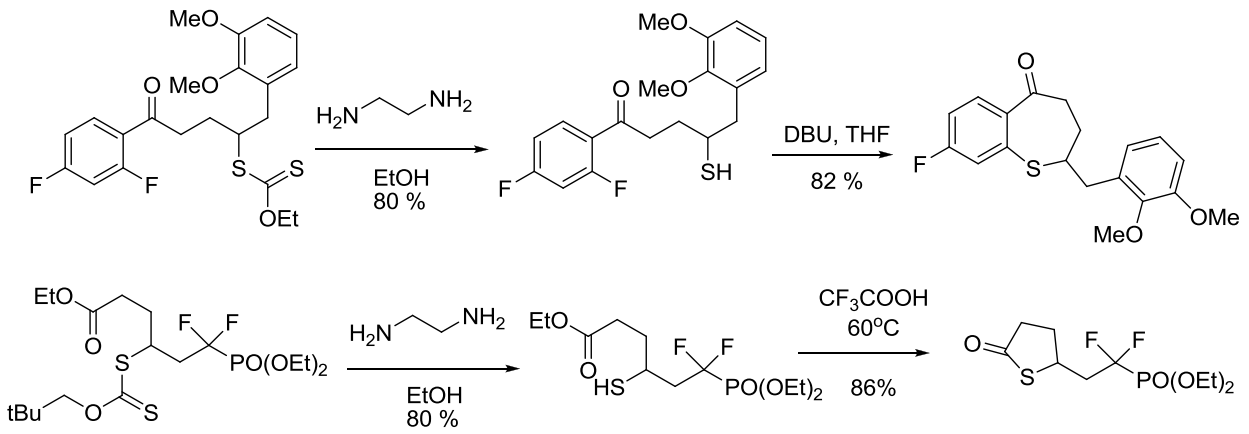


Scheme II-25

(2) Ionic transformations

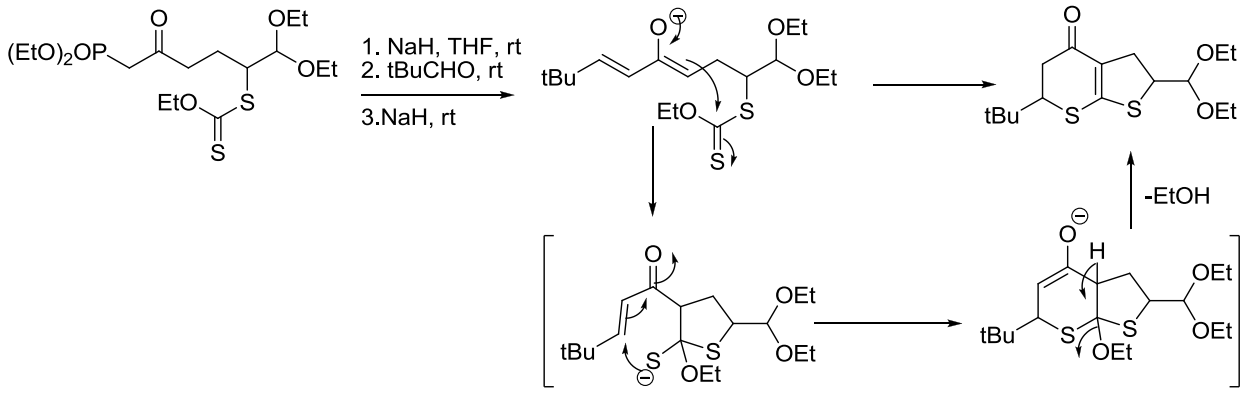
It is possible to transform a xanthate into a thiol group by cleavage with ethylenediamine in ethanol under an inert atmosphere. The resulting thiol may then be incorporated into various ionic under either basic[50] or acidic[51] conditions to create interesting sulfur-containing cyclic or acylic products (**Scheme II-26**).

[50]Boutillier, P.; Quiclet-Site, B.; Zafar, S.; Zard, S. Z. *Tetrahedron-Asymmetry***2010**, *21*, 1649.
[51]Boivin, J.; Ramos, L.; Zard, S. Z. *Tetrahedron Lett.***1998**, *39*, 6877.



Scheme II-26

If an electrophilic alkene is present in the compound, then a Michael can occur as in the example in **Scheme II-27**.[52]

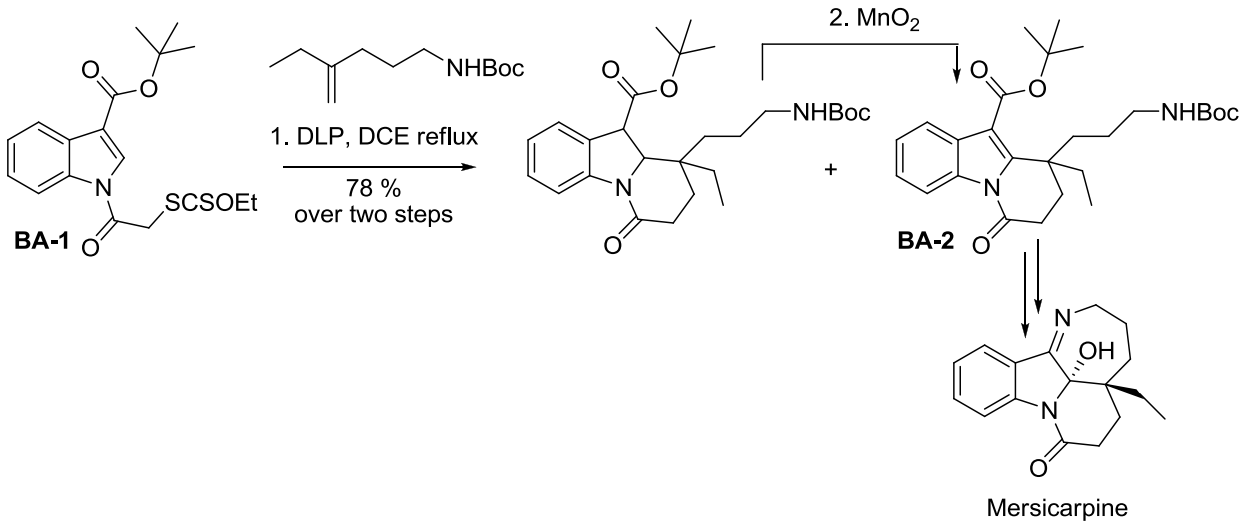


Scheme II-27

f. Application of xanthantes in total synthesis

To further illustrate the utility of xanthates in some applications in the total synthesis of natural products are briefly presented. The first example is an intermolecular radical addition-cyclisation cascade in the synthesis of the key intermediate **BA-2** towards mersicarpine (**Scheme II-28**). The precursor **BA-1** underwent a one-pot addition-cyclisation sequence, to give a crude product, which was oxidized by treatment with MnO_2 as the lauroyl peroxide was not sufficient to rearomatise completely the system. In this way, the tricyclic intermediate **BA-2** was obtained in good yield (78%).[53]

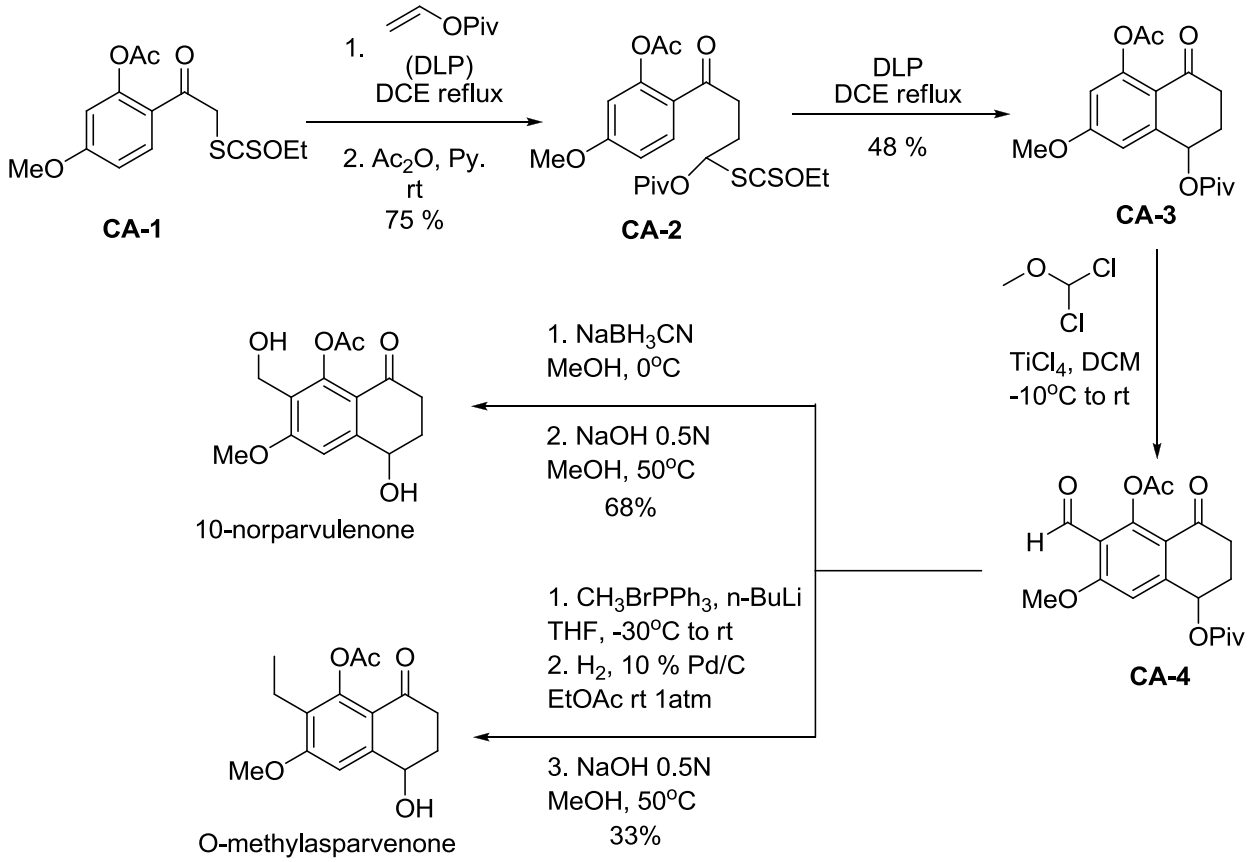
[52]Corbet, M.; Zard, S. Z. *Org. Lett.***2008**, *10*, 2861.
[53]Biechy, A.; Zard, S. Z. *Org. Lett.***2009**, *11*, 2800.



Scheme II-28

Another example is the systhesis of 10-norpavulenone and *O*-methylasparvenone where the α-tetralone framework was constructed the chemistry of xanthates.[54] As shown in **Scheme II-29**, the formation of tetralone **CA-3** started with addition of **CA-1** to vinyl pivalate, followed by cyclisation of the resulting addition product **CA-2**. Subsequently, the formyl substituent was introduced in nearly quantitative yield by exposure of a cold (-10^{o}C) solution of intermediate **CA-3** to $TiCl_4$ and dichloromethyl methyl ether. From this common intermediate **CA-4**, two sequences were implemented. In the first, reduction of the aldehyde in **CA-4** to the alcohol followed by saponification of the pivalate furnished 10-norpavulenone. In the second, the conversion of the same aldehyde into a vinyl group, followed by hydrogenation and saponification of the pivalate led to *O*-methylasparvenone. The synthesis of 10-norpavulenone was accomplished in five steps in 14% unoptimized overall yield, whereas the synthesis of *O*-methylasparvenone required 6 steps and proceeded in 7% overall yield. This approach can be modified to provide to a flexible access to various analogs functionalised at various positions around the structure.

[54]Cordero-Vargas, A.; Quiclet-Sire, B.; Zard, S. Z. *Org. Lett.***2003**, *5*, 3717.



Scheme II-29

III. Conclusion

This chapter presented a brief introduction to radical chemistry in general and to the degenerative xanthate transfert process in particular, which is center to this work. This knowledge is fundamental and indispensable for understanding the topics of the following chapters.

In respect to the xanthate chemistry, the above examples illuminate the reactivity, stability, and diversity of xanthates in the various transformations leading to complex structures. The mild and easy-to-perform conditions underscore its compatibility with a wide range of common functional groups.

Some important applications of xanthates such as RAFT (Reversible Addition Fragmentation Transfer) and MADIX (Macromolecular Design by Interchange of Xanthate) controlled polymerization technologies are not included in this presentation.

The next chapter will focus on the application of xanthates for the synthesis of benzazepinones and discusses how this route was unexpectedly dicovered.

Chapter 2

Synthesis of benzazepinones

I. Introduction

1. Some aspects of the chemistry of hydroxamic acids
2. Brief review of the Smiles rearrangement
2. Introduction to benzazepinones
    i. The importance of benzazepinones
    ii. Recent syntheses of benzazepinones

II. Original plan and unexpected results

1. Original plan
2. Unexpected results
    i. An attempt at five-membered ring construction
    ii. An attempt at six-membered ring construction

II. Results and discussion

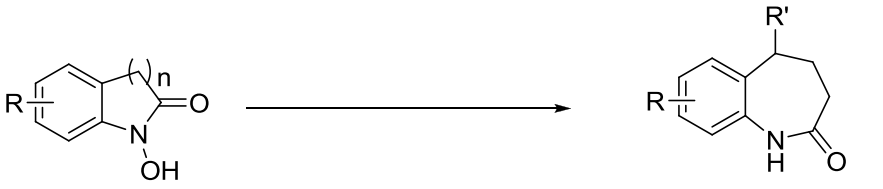
1. Investigation of the mechanism
2. Preliminary results on the synthesis of benzazepinones (seven-membered ring)

III. Application to the synthesis of benzazepinones

IV. Conclusion

I. Introduction

Our original plan was to synthesize the hydroxamic acids, but, unexpectedly, we found an interesting route to access *N*-Unsubstituted benzazepinones.



hydroxamic acids benzazepinones

In the course of this work, we also found that a radical Smiles rearrangement occurred under our experimental conditions, which helped us resolve the mechanism of this unexpected transformation. Therefore, in this introduction, we shall first present some aspects of the chemistry of hydroxamic acids, then a brief review of the Smiles rearrangement and, finally, we will discuss benzazepinones and recent syntheses of members of this family. This will constitute the main part of this section.

1. Some aspects of the chemistry of hydroxamic acids

Hydroxamic acids are an important class of compounds which exhibit a wide spectrum of biological activities such as antibiotic, antifungal, anti-inflammatory, anticancer and enzyme inhibitory activities. The strong chelating ability of hydroxamic acids toward metal ions such as zinc and iron has made them popular targets for medicinal chemists. This class has therefore received a considerable attention from chemists in industry. Numerous members of this family have indeed been reported as potent inhibitors of histone deacetylase (HDAC) and matrix metalloproteinases. Among the many clinical agents explored in the pharmaceutical industry; suberoylanilidehydroxamic acid SAHA has emerged as a new potential drug. SAHA displays antitumor activity in several *in vivo* models of cancer. In 2006, the Merck Company launched the production of SAHA for the treatment of cutaneous T-cell lymphoma. It is currently in advanced clinic trials. Moreover, hydroxamic acids have been applied in therapy treatment of iron overload diseases due to their possibility to complex and transport the ferric ion. For example, desferrioxamine B (Desfaeral), produced by Novartis, is used to treat iron poisoning, which can arise by following blood transfusion to patients with genetic blood diseases (**Figure 1**).[55]

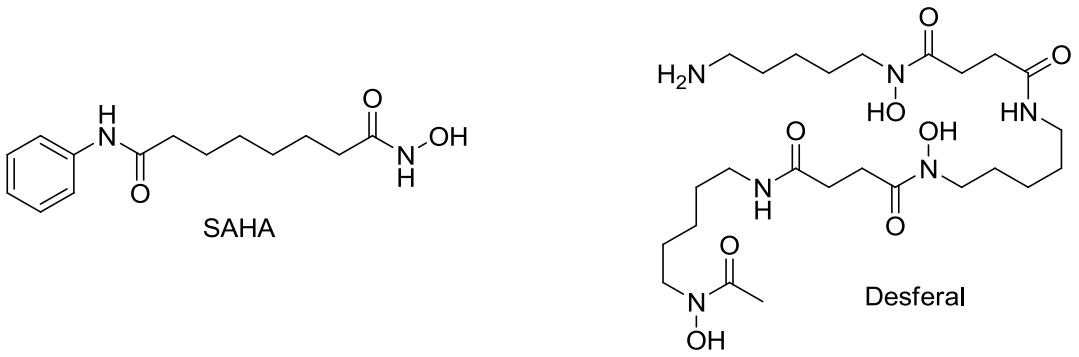


Figure 1

Not only linear hydroxamic acids are important, cyclic hydroxamic acids have also attracted more and more attention nowadays. The cyclic hydroxamic acids are present in a variety of natural products, which also display biological activities. For example, Mycobactin T and Cobactin T are siderphore growth promoters isolated from mycobacteria. Current discovery in the aspect of drug resistance in strains of tuberculosis has simulated the research in mycobatin

[55]Nandurkar, S. N.; Petersen, R.; Qvortrup, K.; Komnatnyy, V. V.; Taveras, K. M.; Le Quement, S. T.; Frauenlob, R. ; Givskov, M.; Nielsen, T. E. *Tetrahedron Lett.***2011**, *52*, 7121.

analogs in order to investigate the iron metabolic mechanisms and mycobactin-drug conjugates for better drug delivery. Structurally related mycobactins, amamistatins A7 and B8, natural products isolated from a strain of Nocardia,exhibit an antiproliferative effect against several human tumor cell lines.[56]Another example includes PF-04859989 developed by Pfizer, which is used for treating schizophrenia due to its capacity as an irreversible kynurenine aminotransferase II inhibitor (**Figure 2**).[57]

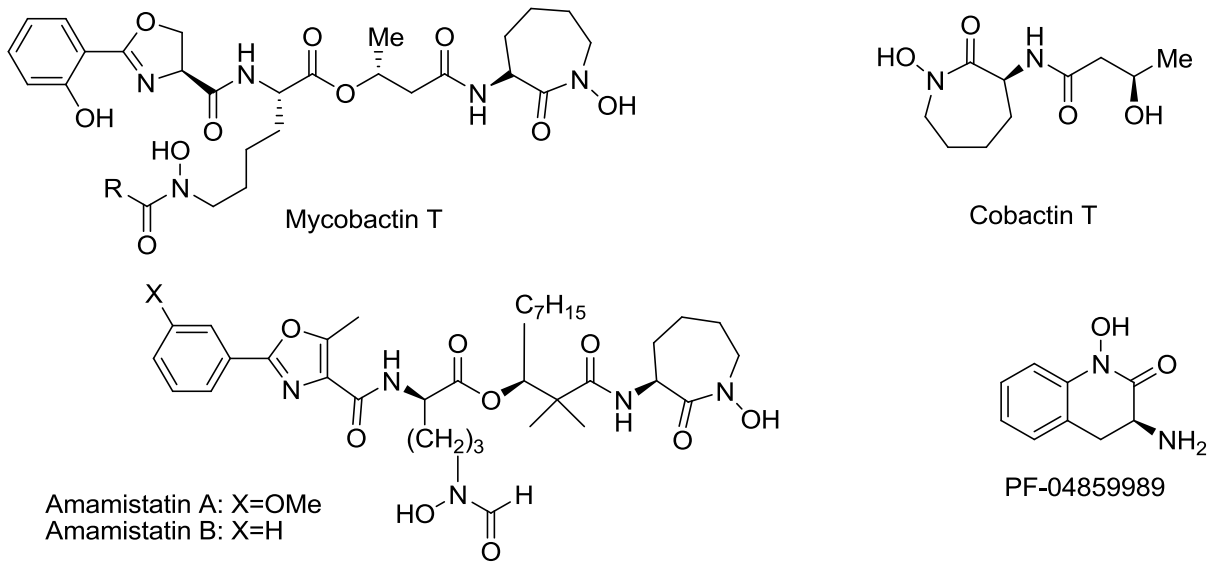


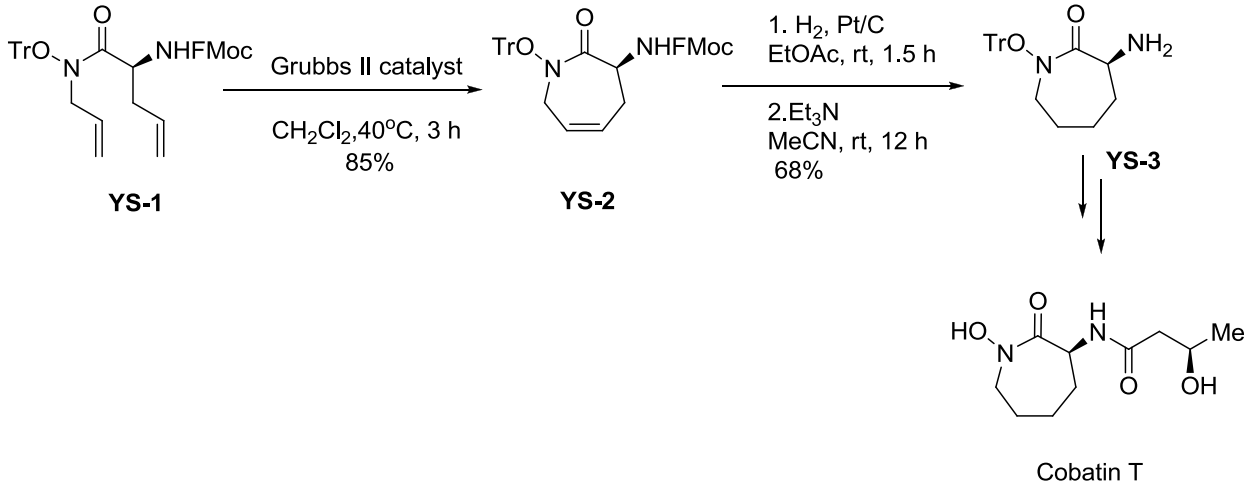
Figure 2

As indicated, the incredible pharmaceutical relevance of hydroxamic acids has promoted the search to establish useful methods for their incorporation into a variety of complex structures. Since our original work focused on the synthesis of cyclic hydroxamic acids, the recent methods to access cyclic hydroxamic acids are briefly presented.

[56]Fennell, K. A.; Mollmann, U.; Miller, M. J. *J. Org. Chem.***2008**, *73*, 1018.

[57] Dounay, A. B.; Anderson, M.; Bechle, B. M.; Campbell, B. M.; Claffey, M. M.; Evdokimov, A.; Evrard, E.; Fonseca, K. R.; Gan, X.; Ghosh, S.; Hayward, M. M.; Horner, W.; Kim, J. _Y.; McAllister, L. A.; Pandit, J.; Paradis, V.; Parikh, V. D.; Reese, M. R.; Rong, S. B.; Salafia, M. A.; Schuyten, K.; Strick, C. A.; Tuttle, J. B.; Valentine, J.; Wang, H.; Zawadzke, L. E.; Verhoest, P. R. *ACS Med. Chem. Lett.* **2012**, *3*, 187.

Synthesis of Cobactin T pictured in **Scheme I-1** was reported by the Yang group. In this work, the key seven-membered ring lactam intermediate **YS-2** was synthesized by the ring closing metathesis of **YS-1** using Grubbs II ruthenium catalyst in refluxing CH_2Cl_2.[58]



Scheme I-1

The seven-membered ring was also constructed by the cyclisation reaction of a hydroxylamine and an acid. In the course of development of therapeutically useful antihypertensive agents, the Miller group synthesized novel hydroxamic acid-derived azepinones by using nitrone precursors **WA-1 (Scheme I-2)**. The stable and storable nitrone **WA-1** was converted to the hydroxylamine by an exchange reaction with hydroxylamine hydrochloride. The amide coupling was accomplished by EDC/ HOAt-mediated cyclisation to give rise to hydroxamic acid **WA-2**.[59]

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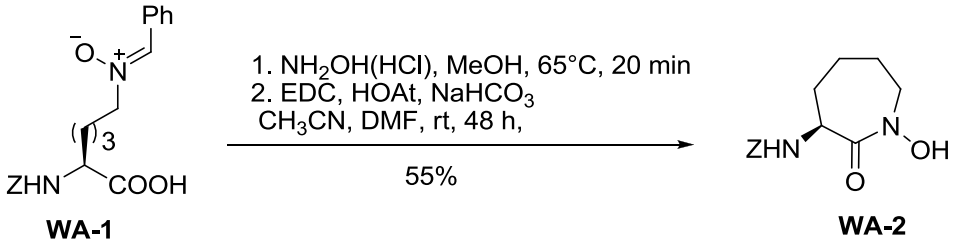


Scheme I-2

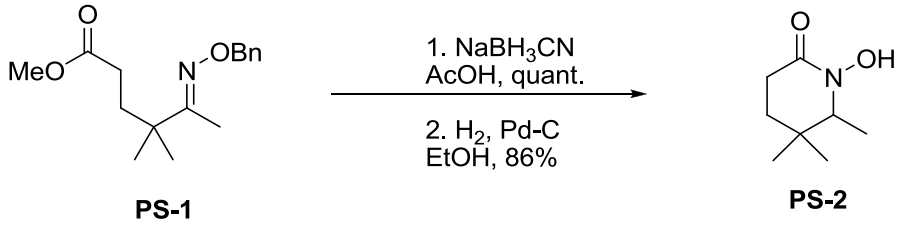
[58]Yang, S.-M.; Lagu, B.; Wilson, L. J. *J. Org. Chem.***2007**, *72*, 8123.

[59](a) Walz. A. J.; Miller, M. J. Org. Lett. 2002, 4, 2047. (b) Jingdan Hu and Marvin J. Miller *J. Am. Chem. Soc.***1997**,*119*, 3462.

Cyclic hydroxamic acids can be obtained by oxidation of secondary amines. As shown in S**cheme I-3**, treatment of 1,2,3,4-tetrahydroquinolines with 30% aqueous hydrogen peroxide in the presence of tungstate catalyst gave the hydroxamic acids in the yield varying from 52% to 85%. This synthesis allows accessing cyclic hydroxamic acids bearing a variety of different functional groups such as bromide, chloride, cyanide, methyl and methoxy group.[60]

Scheme I-3

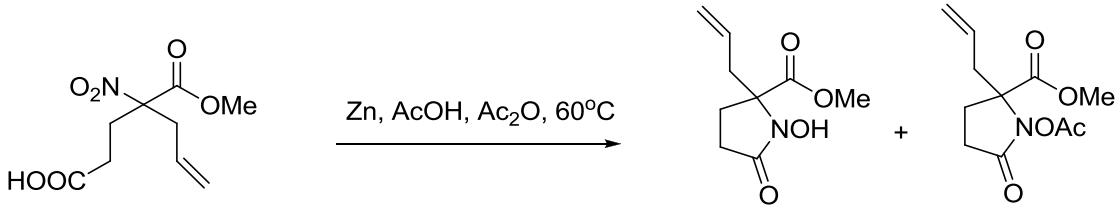
In fact, the most frequently used method to construct cyclic hydroxamic acids involves the formation of amine bond by reductive cyclisation of a suitable oxime. For example, the group of Spino reported the cyclisation after the reduction of **PS-1** by $NaBH_3CN$, as described in **Scheme I-4**.[61]



PS-1 **PS-2**

Scheme I-4

The nitro group can also be converted into hydroxylamine group. In the case of compound **CP-1** in **Scheme I-5**, the nitro group was reduced by zinc/AcOH/Ac_2O to give directly cyclic hydroxamic acid **CP-2** (55%) and its *O*-acetyl derivative **CP-3** (40%).[62]

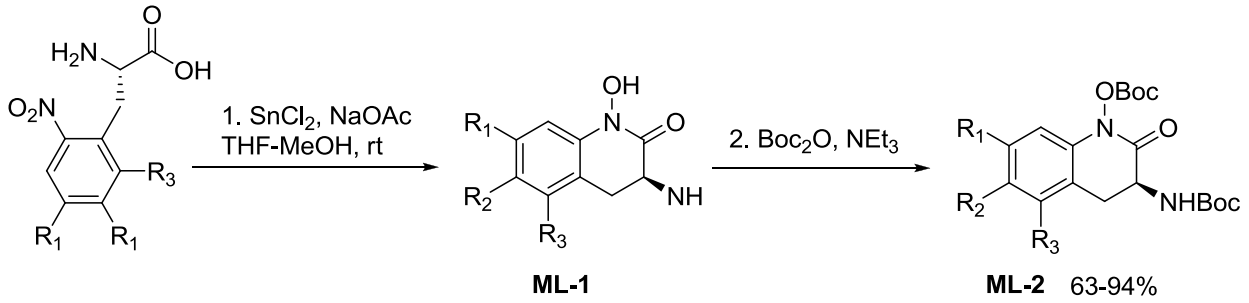


CP-1 **CP-2** 55% **CP-3** 40%

Scheme I-5

[60]Marahashi, S.-I.; Ode, T.; Sugahara, T.; Masui, Y. *J. Org. Chem.***1990**, *55*, 1744.
[61] Pichette, S.; Aubert-Nicol, S.; Lessard, J.; Spino, C. *J. Org. Chem.***2012**, *77*, 11216
[62]Chittari, P.; Thomas, A.; Rajappa, S. *Tetrahedron Lett.***1994**, *35*, 3793.

An alternative reductive cyclisation system is $SnCl_2$/NaOAc. This reagent allows the synthesis of substituted cyclic hydroxamic acids bearing a wide range of substituents R_2, R_3, and R_4 with different electronic properties (Me, CF_3, Cl, OMe, OCF_3, F). The nitro group is reduced partially to the corresponding hydroxylamine, followed by cyclisation to generate bicyclic structures **ML-1**. For ease of isolation and purification, the crude amino hydroxamic acids **ML-1** were protected in situ to furnish **ML-2** as the di-Boc derivatives. This method is very efficient; the yields varied from 63 to 94% (**Scheme I-6**).[63]

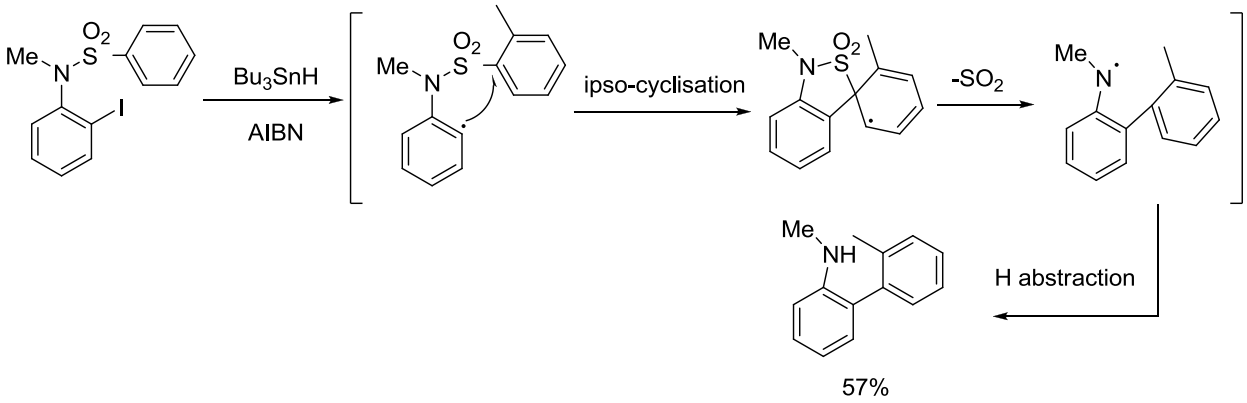


Scheme I-6

2. A brief review on the radical Smiles rearrangement

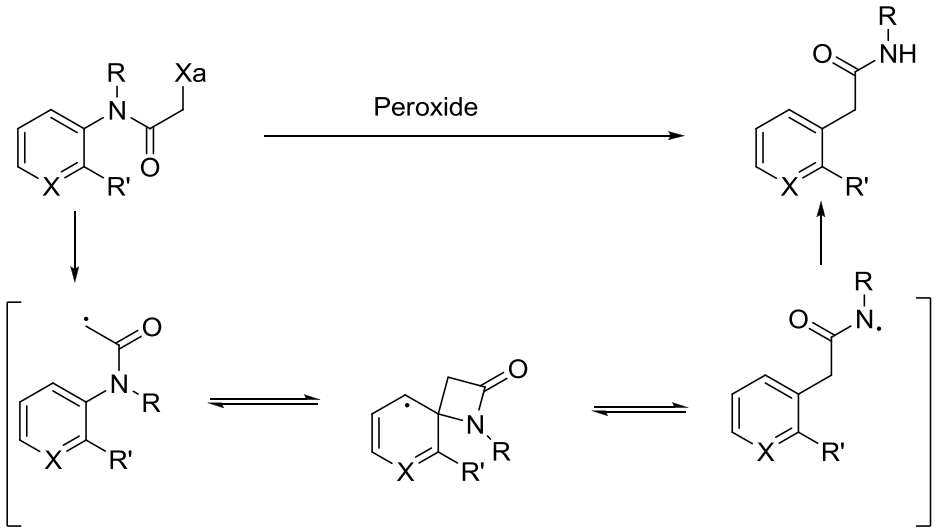
The origin of the Smiles rearrangement comes from an intramolecular nucleophilic aromatic substitution.[64] The first radical Smiles rearrangement, also known as 1,4-arylradical rearrangement, was observed by Speckamp.[65] In principle, this rearrangement starts with a free radical attack at the *ipso* position of sulfonates or sulfonamides, followed by the extrusion of sulfur dioxide molecular and terminated by hydrogen abstraction to generate final product with 1,4-aryl migration and the loss of SO_2. This mechanism is described in detail in **Scheme I-7** in the synthesis of biaryl derivatives reported by Motherwell and coworkers. This transformation and its variants have been applied for the preparation of numerous interesting structures.

[63] McAllister, L. A.; Bechle, B. M.; Dounay, A. B.; Evrard, E.; Gan, X.; Ghosh, S.; Kim, J.-Y.; Parikh, V. D.; Tuttle, J. B.; Verhoest, P. R. *J. Org. Chem.***2011**, *76*, 3484.
[64]Levy, A. A.; H. C. Rains; Smiles, S.*J. Chem. Soc.*, **1931**, 3264.
[65]*(a)* Loven, R.; Speckamp,W. N. *Tetrahedron Lett.*, 1972, 13, 1567. (*b*) Köhler, J. J.; Speckamp, W. N. *Tetrahedron Lett.*,**1977**, *18*, 631.



Scheme I-7

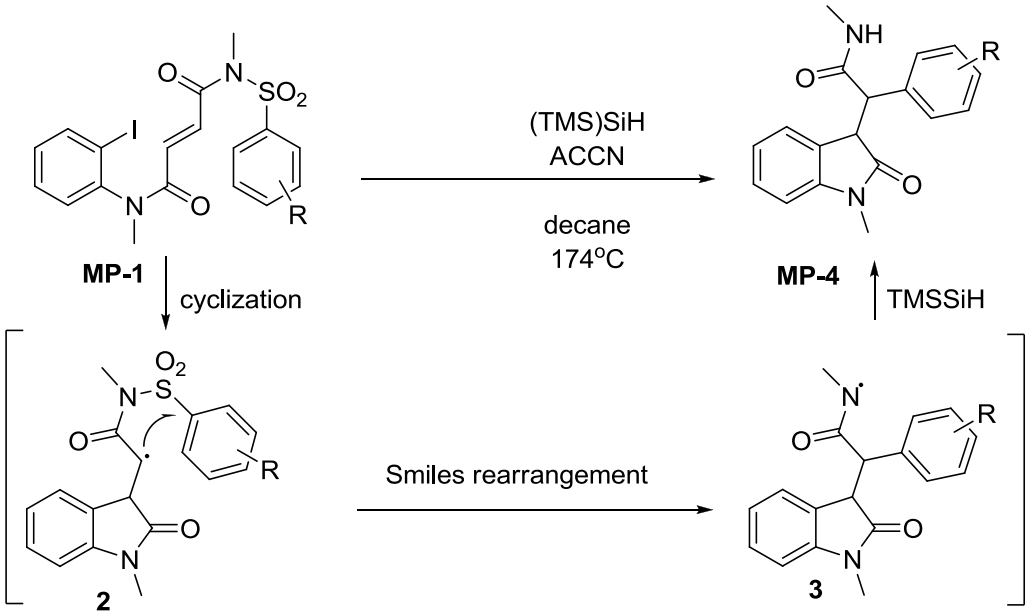
Recently, our group discovered an unusual radical Smiles rearrangement of *N*-(α-xantyl)acetylaminopyridines proceeding via a spiro azetidinone intermediate (**Scheme I-8**).[66]



Scheme I-8

The domino radical cyclisation/Smiles rearrangement cascade exemplified in **Scheme I-9** was achieved by Sapi and co-workers to furnish 3-(2'-aryl-*N*-methyl acetamido)indolin-2-ones **MP-4**. Exposure of **MP-1** to 2,2'-azocyclohexanecarbonitrile (ACCN), a liposoluble radical initiator, triggered the cyclisation followed by a Smiles rearrangement to give the desired product **MP-2**.[67]

[66]Bacqué,E.; El Qacemi, M.; Zard,S. Z. *Org. Lett.*, **2005**, *7*, 3817.
For a review on radical aryl migration reactions, see: A. Studer and M. Bossart, *Tetrahedron*, **2001**, *57*, 9649.
[67]Pudlo, M.; Allart-Simon, I.; Tinant, B.; Gerard, S.; Sapi, J.*Chem. Commun.*, 2012, **48**, 2442.



Scheme I-9

3. Introduction to benzazepinones

i. The importance of benzazepinones

Benzazepinones and other molecules possessing similar structures (bicyclic lactams such as benzazepines and paullones) are an important class in medicinal chemistry and the pharmaceutical industry (**Figure 1**). These ubiquitous structural units are found in a large spectrum of bioactive natural products and therapeutic agents. They exhibit a large array of biological activities for the treatment of cardiovascular, neuropathic pain, cancer, Alzheimer's diseases, etc. Therefore, these compounds have been the targets of intensive synthetic efforts over the years.

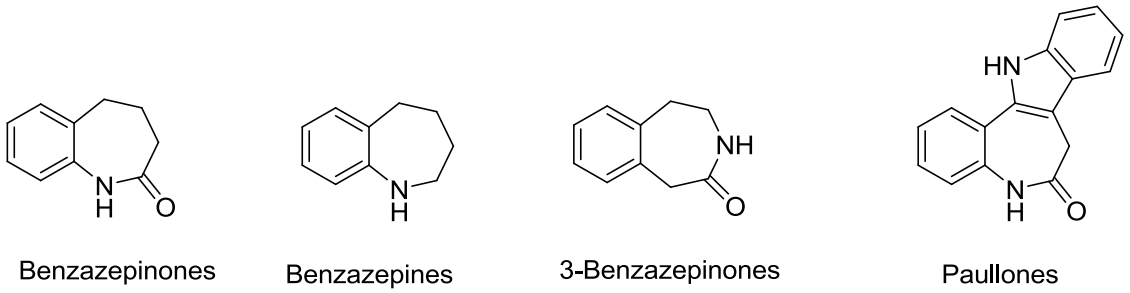


Figure 1

For example, paullones constitute a new family of benzazepinones exhibiting promising antitumoral properties. They also appear to have some potential for the study and possibly for the treatment of neurodegenerative and proliferative disorder in Alzheimer's disease.[68]

Some benzazepinones are also important as sodium channel blockers and have been investigated as a treatment for neuropathic pain. **Figure 2** displays some representative examples. For instance, the weak selective sodium channel blocker carbamazepine demonstrates clinical efficacy in the therapeutic treatment for neuropathic pain. Later, the Hoyt group found that the benzazepinone derivatives **1** and **2** show even more selectivity as $Na_v1.7$ blockers and are orally efficacious in a preclinical rat model of neuropathic pain.[69]

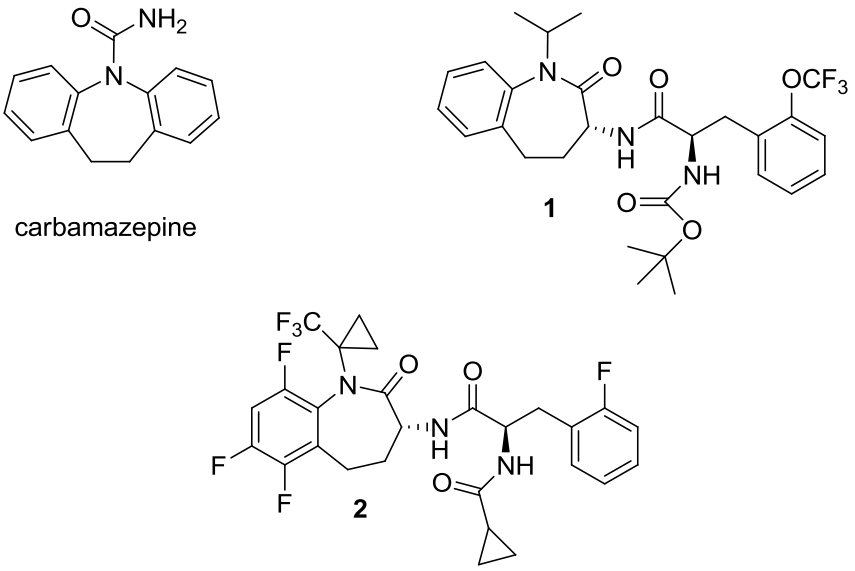


Figure 2

Recently, compound **3** bearing a benzazepinone motif was identified by Griebenow's group as a potent squalene synthase inhibitor (**Figure 3**). These inhibitors belong to a promising drug class

[68]Leost, M.; Schultz, C.; Link, A.; Wu, Y-Z.; Biernat, J.; Mandelkow, E.-M.; Bibb, J. A.; Snyder, G. L.; Greengard, P.; Zaharevitz, D. W.; Gussio, R.; Senderowicz, A. M.; Sausville, E. A.; Kunick, C.; Meijer, L. *Eur. J. Biochem.* **2000**, *267*, 5983.

[69] Hoyt, S. B.; London, C.; Ok, H.; Gonzalez, E.; Duffy, L. J.; Abbadie, C.; Dean, B.; Felix, J. P.; Garcia, M. L.; Jochnowitz, N.; Karanam, B. V.; Li, X.; Lyons, K. A.; McGowan, E.; MacIntyre, D. E.; Martin, W. J.; Priest, B. T.; Smith, M. M.; Tshirret-Guth, R.; Warren, V. A.; Williams, B. S.; Kaczorowski, G. J.; Parsons, W. H. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4630. (b)Hoyt, S. B.; London, C.; Abbadie, C.; Felix, J. P.; Garcia, M. L.; Jochnowitz, N.; Karanam, B. V.; Li, X.; Lyons, K. A.; McGowan, E.; Priest, B. T.; Smith, M. M.; Warren, V. A.; Thosmas-Fowlkes, B. S.; Kaczorowski, G. J. *Biorg. Med. Chem. Lett.***2013**, *23*, 3640

for cholesterol lowering and used for the treatment of hyerlipidemia and atherosclerosis. This discovery encouraged the study of other derivatives and, as a result, benzazepinone derivative **4** was found to exhibit the expected biological activity and has been progressed further to in vivo animal studies.[70]

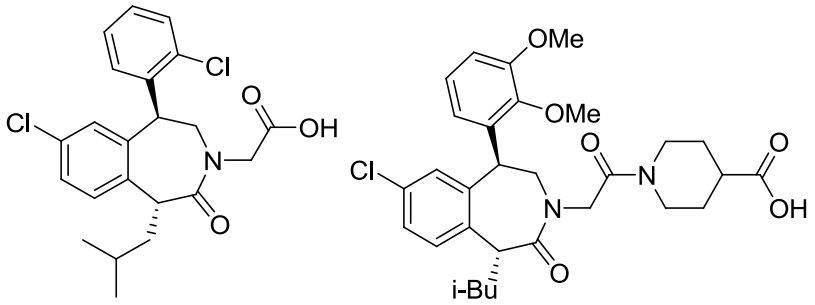


Figure 3

Recently, a high-throughput screen of a corporate compound library carried out by Donnel's group led to the identification of benzazepinone **5** as a novel XIAP BIR2-selective inhibitor, which is a potential target for cancer therapy. Later, benzoxazepinone **6** was discovered during the continuous search for increasing BIR2 potency and overcoming high *in vivo* clearance. It is indeed a potent BIR2-selective inhibitor with good *in vivo* pharmacokinetic properties (**Figure 4**).[71]

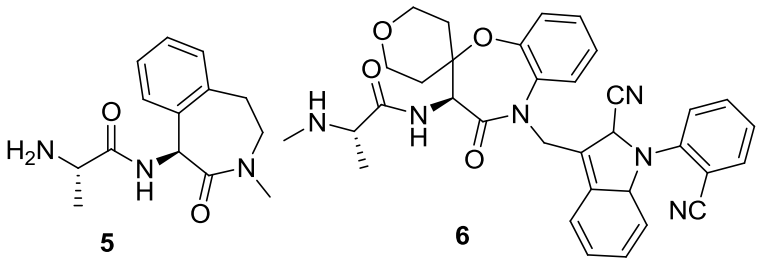
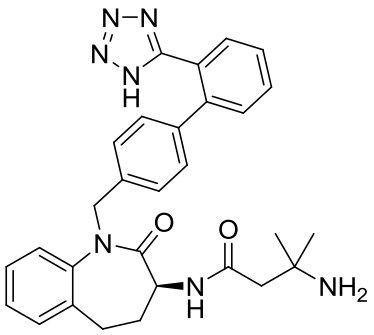


Figure 4

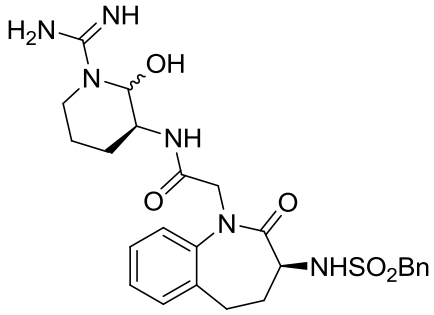
[70]Griebenow, N.; Flessner, T.; Buchmueller, A.; Raabe, M.; Bischoff, H.; Kolkhof, P. *Biorg. Med. Chem. Lett.***2011**, *21*, 2554.

[71]Donnell, A. F.;Michoud,C.;Rupert, K. C.; Han, X.;Aguilar, D.; Frank, K. B.; Fretland, A. J.; Gao, L.; Goggin, B.; Hogg, J. H.; Hong, K.; Janson, C. A.; Kester, R. F.; Kong, N.;Le, K.; Li, S.; Liang, W.; Lombardo, L. J.; Lou, Y.; Lukacs, C.M.; Mischke, S.; Moliterni, J. A.; Polonskaia, A.; Schutt, A. D.; Solis, D. S.; Specian, A.; Taylor, R. T.; Weisel, M.; Remiszewski, S. W. *J. Med. Chem.***2013**, *56*, 7772.

The benzazepinones are appealing candidates for advanced clinical trials. For example, the benzazepinone L-692,428[72]is a stimulating agent for releasing growth hormone (GH) and benzazepinone CVS-1778[73] is used as an antithrombotic agent (**Figure 5**).



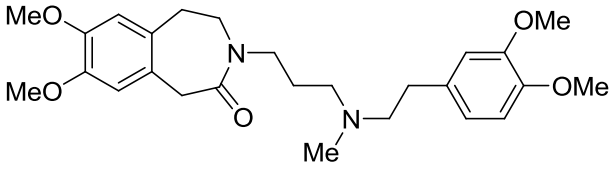
L-692428



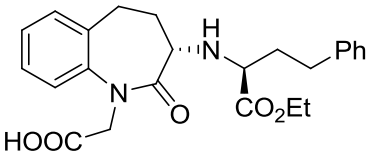
CVS-1778

Figure 5

Not only limited to the academic field, some benzazepinones have found their way to the pharmaceutical market. As shown in **Figure 6**, Zatebradine is an antianginal and belongs to a novel class of specific bradycardic agents.[74] The antihypertensive drug Benazepril, sold under the brand name Lotensin, is commonly used for the control of high blood pressure.[75]



Zatebradine



Benazepril

Figure 6

[72] (a) Smith, R. G.; Cheng, K.; Schoen, W. R.; Pong, S. S.; Hickey, G.; Jacks, T.; Butler, B.; Chan, W. W. S.; Chaung, L. Y. P.; Judith, F.; Taylor, J.; Wyvratt, M. J.; Fisher, M. H. *Science***1993**, *260*, 1640–1643; (b) Schoen, W. R.; Pisano, J. M.; Prendergrast, K.; Wyratt, M. J.; Fisher, M. H.; Cheng, K.; Chan, W. W. S.; Butler, B.; Smith, R. G.; Ball, R. G. *J. Med. Chem.***1994**, *37*, 897.

[73] Tamura, S. Y.; Goldman, E. A.; Bergum, P. W.; Semple, J. E. *Bioorg. Med. Chem. Lett.***1999**, *9*, 2573.

[74](a) P. Tyrer, Lancet **1974**, 709. (b) Dictionary of Drugs (Eds.: J. Elks, C. R. Ganellin), Chapman and Hall, London, **1990**. (c) A. Bombard, A.; Reiffen M.; Heider, J.; Psiorz, M.; Lillie, C.; *J. Med. Chem.***1991**, *34*, 942. (d) Drugs Fut. **1997**, *22*, 933.

[75] (a) Ciba-Geigy Corporation, US 4410520A1, **1983.** (b) Ciba- Geigy Corporation, US 4473575A1, **1984.** (c) Ciba-Geigy Corporation, US 4575503A1, **1986**.

At the beginning of this year, Hoffmann-La Roche released a patent on the synthesis of a variety of benzazepinones aimed at controling and treating cancer (**Figure 7**).[76]

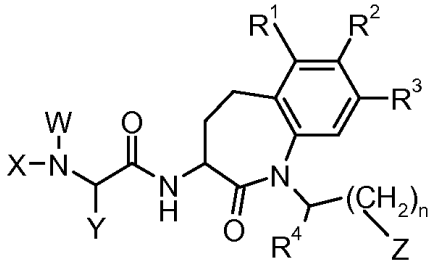


Figure 7

ii. Recent syntheses of benzazepinones

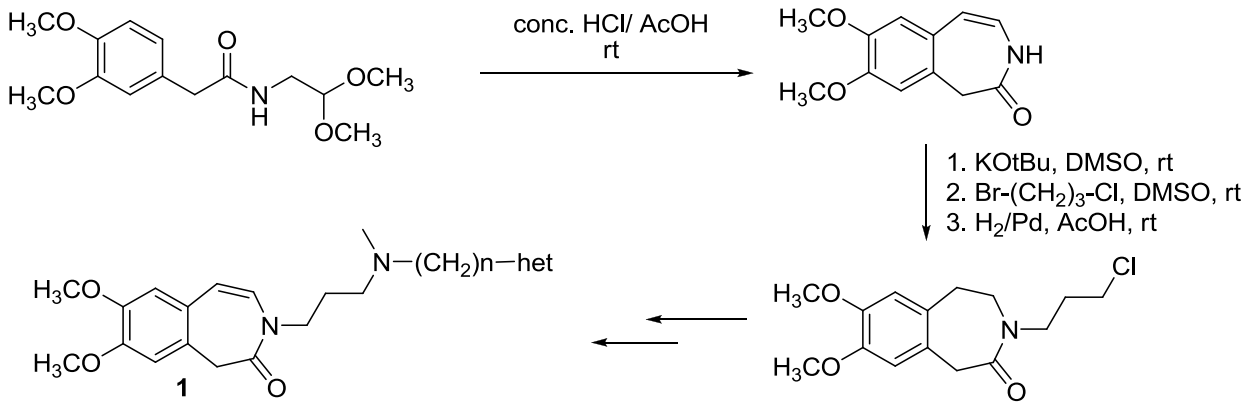
In view of the importance of benzazepinones, numerous methods for the construction of this structural motif have been explored by synthetic chemists and a variety of approaches have been reported in the literature. Some of the more important routes are listed below.

- Friedel-Crafts cyclisations
- Condensation cyclisations
- Transition-metal catalysed cyclisations
- Radical reactions
- Rearrangements

a. Friedel-Crafts cyclisations

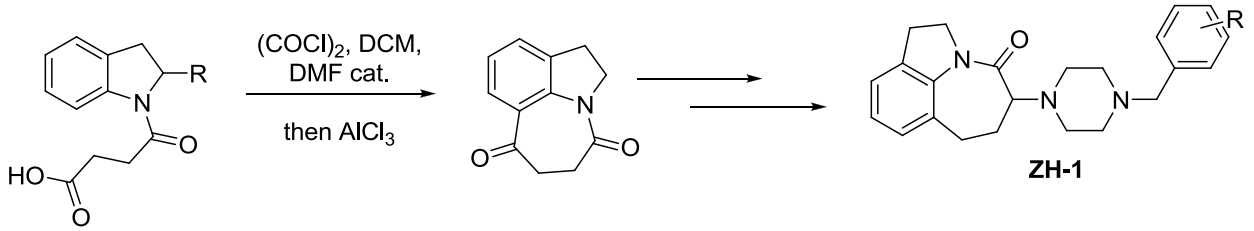
Even though the Friedel-Crafts reaction has been extensive applied for the alkylation and acylation of aromatic systems, examples related to the preparation of benzazepinones by this method are not common. In search of specific bradycardic agents with various pharmacokinetic profiles, Bomhard and co-workers synthesized the analog **1** by using a Friedel-Crafts based cyclisation (**Scheme I-10**).[77]

[76] F Hoffmann-La Roche AG**;** Hoffmann-La Roche Inc.; Han, X.; Lou, Y.; Michoud, C.; Mischke, S. G.; Remiszewski, S.; Rupert, K. C. Patent**:** WO2014/9495 A1, **2014**.
[77]Bomhard, A.; Reiffen, M.; Heider, J.; Psiorz, M.; Lillie, C. *J Med. Chem.***1991**, *34*, 942.



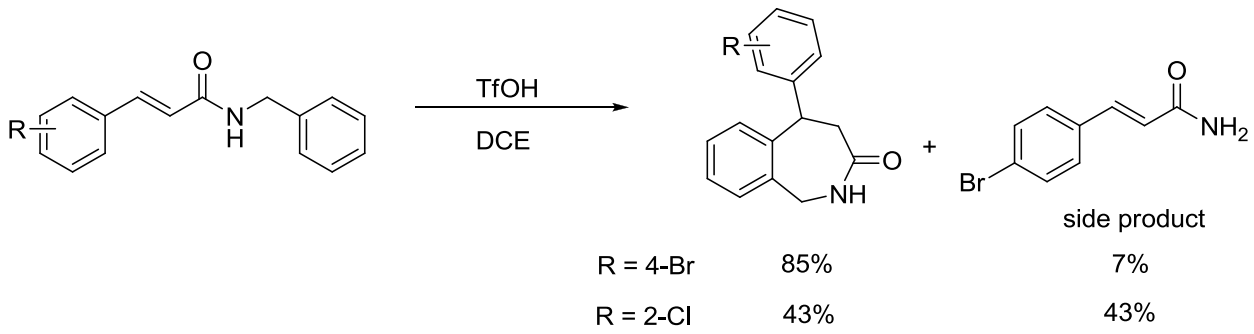
Scheme I-10

Zhao *et al.* used this strategy to synthesise piperazinyl-benzazepinones **ZH-1**, which are antagonists of the D2 and D4 receptors of dopamine. The synthetic route is presented in **Scheme I-11**.[78]



Scheme I-11

King and Caddick reported the cyclisation of *N*-benzyl-cinnamamides under TfOH catalysis to give the corresponding benzazepinones, as shown in **Scheme I-12**. In most cases, there was the formation of cinnamamides as side products; the yield was good when the phenyl ring of the cinanmamides was substituted.[79]



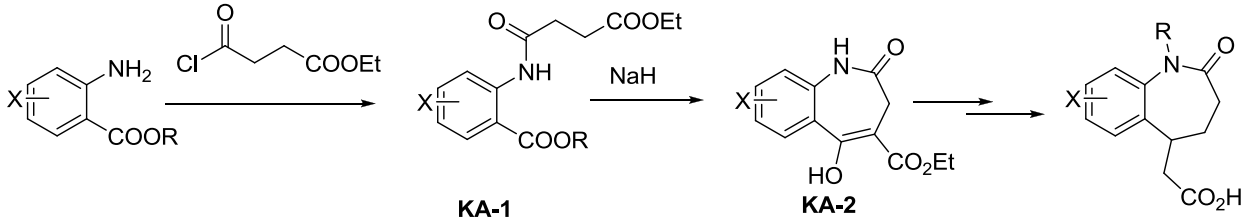
Scheme I-12

[78] Zhao, H.; Zhang, X.; Hodgetts, K.; Thurkauf, A.; Hammer, J.; Chandrasekhar, J.; Kieltyka, A.; Brodbeck, R.; Rachwal, S.; Primus, R.; Manly, C. *Biorrg. Med. Chem. Lett.***2003**, *13*, 701.
[79]King, F. D.; Caddick, S. *Tetrahedron***2013**, *69*, 487.

In Friedel-Crafts based strategy, the need for a large excess of acid usually causes problems during workup, hazardous waste generation and could lead to side products with complex structures. In addition, the fact that the aromatic system needs to be electron rich also limits its application.

b. Condensation cyclisations

Benzazepinones can be prepared by a Dieckmann condensation, which is a very efficient method to construct five, six or seven-membered-rings from two ester groups in the molecule. Kling *et al.* applied this route to the synthesis of **KA-2** by the treatment of functionalised aniline **KA-1** with NaH (**Scheme I-13**).[80]

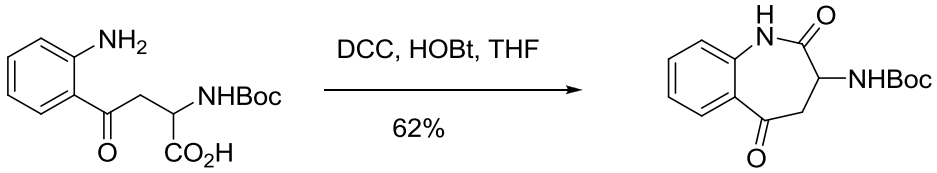


KA-1 **KA-2**

Scheme I-13

Even though the reaction is efficient, it is worth noting that the strong basic conditions are not always compatible with other functions present in the precursors.

Another popular condensation is the peptide coupling reaction; this method is used widely to prepare benzazepinones. The simplest examples are the intramolecular-coupling of functionalised anilines. Van Niel *et al.* performed a peptide coupling of aniline **VN-1** to afford product**VN-2 (Scheme I-14)**.[81]



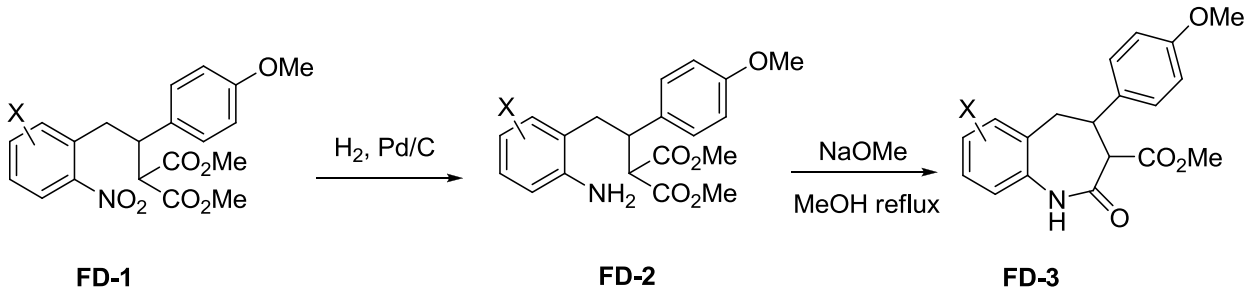
VN-1 **VN-2**

Scheme I-14

[80]Kling, A.; Backfish, G.; Delzer, J.; Geneste, H.; Graef, C.; Hornberger, W.; Lange, U. E. W.; Lauterbach, A.; Seitz, W.; Subkowski, T. *Bioorg.Med. Chem.***2003**, *11*, 1319.

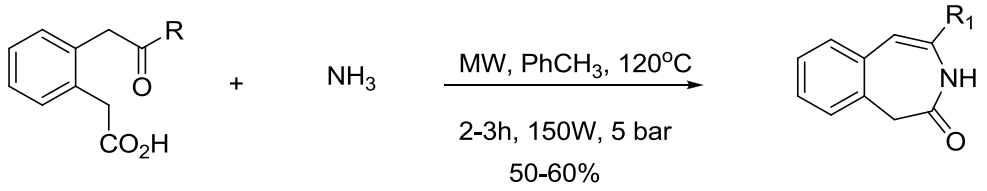
[81] Van Niel, M. B.; Freedman, S. B.; Matassa, V. G.; Patel, S.; Pengilley, R. R.; Smith, A. J. *Bioorg. Med. Chem. Lett.***1995**, *5*, 1421.

In the same manner, as reported by the group of Floyd, the reduction of precursors **FD-1** into anilines **FD-2,** followed by cyclisation furnished products **FD-3 (Scheme I-15)**.[82]



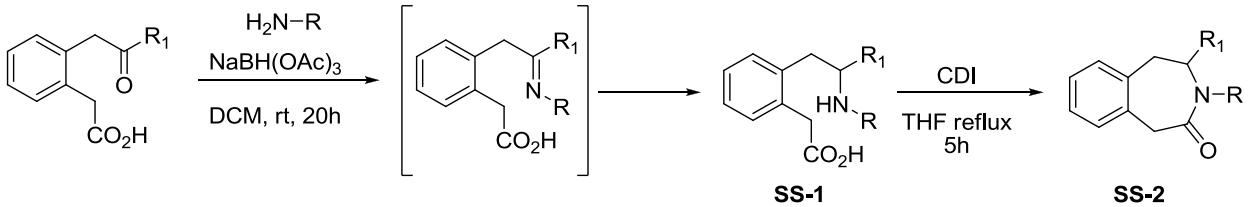
Scheme I-15

As described in **Scheme I-16**, Sarkar *et al.* reported a direct seven-membered-ring construction using the microwave assisted condensation of primary amines with keto acids. This method provides the desired products in good yield if the amine is NH_3, otherwise the yield drops dramatically. It is an easy route to access simple benzazepinone skeletons.[83]



Scheme I-16

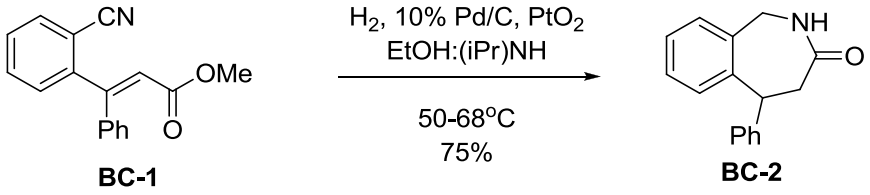
When amines with larger substituents such as butyl or benzyl groups are used, a two-step sequence can be applied (**Scheme I-17**). The sequence starts with the condensation of the ketone and primary amine, followed by reduction with $NaBH(OAc)_3$ to generate amino acid intermediates **SS-1,** which can be cyclised to give rise to the desired benzazepinones **SS-2.**[84]



Scheme I-17

[82]Floyd, D. M.; Kimball, S. D.; Krapcho, J.; Das, J.; Turk, C. F.; Moquin, R. V.; Lago, M. W.; Duff, K. J.; Lee, V. G.; White, R. E.; Ridgewell, R. E.; Moreland, S.; Brittain, R. J.; Normandin, D. E.; Hedberg, S. A.; Cucinotta, G. G. *J. Med. Chem.***1992**, *35*, 756.
[83] Sarkar, S.; Hussain, S. M.; Schepmann, D.; Frohlich, R.; Wunsch, B. *Tetrahedron***2012**, *68*, 2687.
[84] Sarkar, S; Schepmann, D.; Kohler, J.; Frohlich, R.; Wunsch, B. Eur. *J. Org. Chem.***2012**, 5980.

Busaccca and Johnson applied this strategy on starting material **BC-1**, the catalytic reductive cyclisation in a mixture of ethanol and diisopropylamine led to the formation of lactam **BC-2** in good yield (**Scheme I-18**).[85]

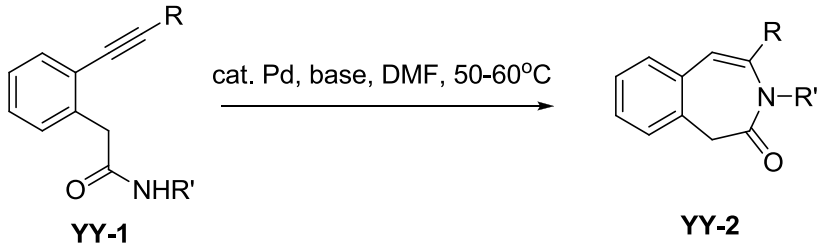


Scheme I-18

c. Transition-metal catalysed cyclisations

The metal transition-catalysed cyclisations are frequently used to prepare numerous different scaffolds since they allow the formation of carbon-carbon bonds or carbon-heteroatom bonds. Because of their easy-to-perform procedures, their applications are very numerous in organic synthesis.

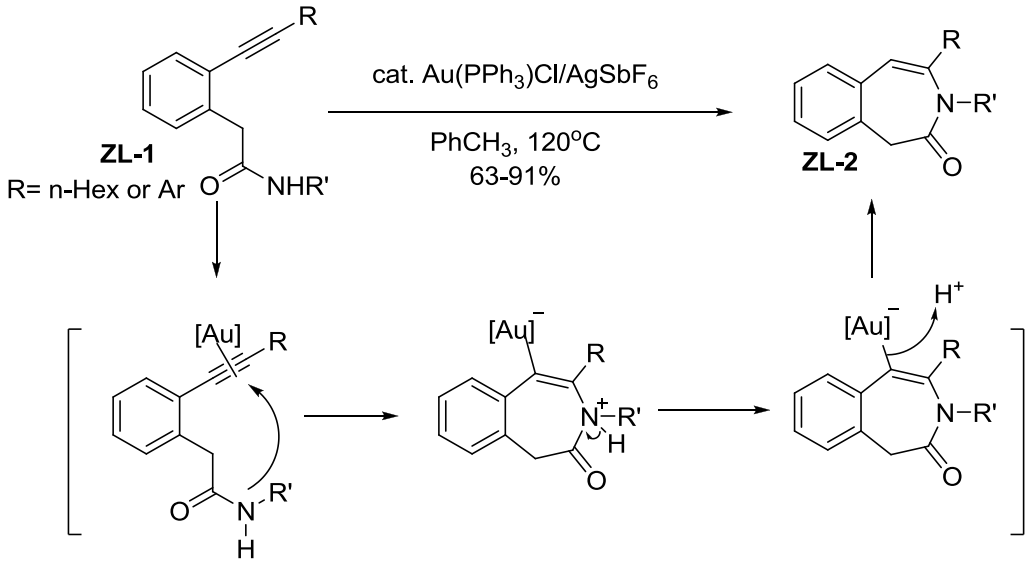
This strategy for intramolecular nitrogen ring formation is not only limited to common five or six-membered-ring such as pyrrols and indoles, but can be extend to seven-membered-ring analogs. For example, the synthesis of 3-benzazepinones by palladium-catalysed intramolecular addition of an amide to an alkyne was reported by Yu and co-workers (**Scheme I-19**). Depending on the 2-(1-alkynyl)phenylacetamide precursors **YY-1**, the palladium catalyst could be $Pd(PPh_3)_2(OAc)_2$, $Pd(PPh_3)_2Cl_2$ or $Pd(Ph\text{-}CN)_2Cl_2$ while the base could be KOH, NaH or NaOEt. The synthesis is most efficient when the starting material has an acetamide and an alkyl substituent on the acetylene unit.[86]



Scheme I-19

[85]Busacca, C. A.; Johnson, R. E.*Tetrahedron Lett.***1992**, *33*, 165.
[86]Yu, Y.; Stephenson, G. A.; Mitchell, D. *Tetrahedron Lett.***2006**, *47*, 3811.

The construction of 3-benzazepinones can also be achieved with the use of a gold catalyst. As illustrated in **Scheme I-20**, the Liu group extended the scope by using $Au(PPh_3)Cl/AgSbF_6$ as the catalyst instead of palladium to accomplish the regioselective hydroamidation of 2-(1-alkynyl)phenylacetamides **ZL-1**. This method is applicable to a broad range of aryl alkynyl substituents, and provides the desired products **ZL-2** in moderate to good yields (63-89%).[87]

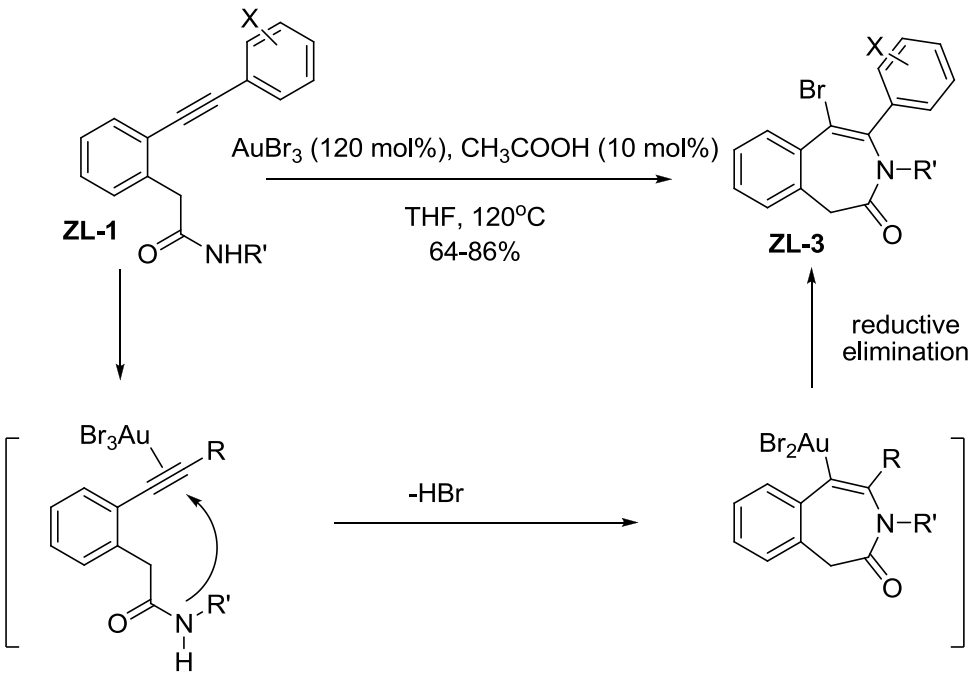


Scheme I-20

During this work, Zang and co-workers unexpectedly found that the gold-mediated process can transform **ZL-1** into the more synthetically versatile 5-bromo-3-benzazepinones **ZL-3**, in which $AuBr_3$ acts as both activation role and reactant (**Scheme I-21**). This discovery is very useful since it allows diversifying the molecular structure and therefore opens up access to new members of this family.

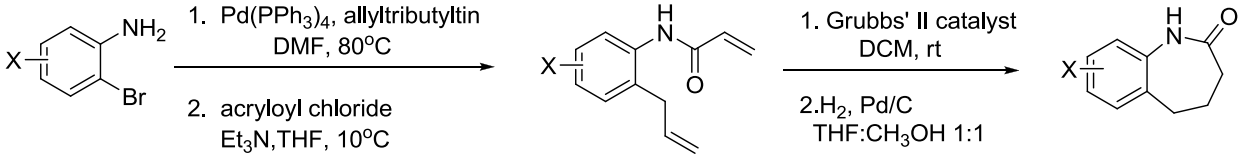
In this study, no examples with substituents on the aromatic ring of the 3-benzazepinones were carried out.

[87] Zang, L.; Ye, D.; Zhou, Y.; Liu, G.; Feng, E.; Jiang, H.; Liu, H. *J. Org. Chem.***2010**, *75*, 3671.



Scheme I-21

The last strategy to prepare the seven-membered ring involves in the use of ring-closing olefin metathesis. Thus, Hoyt and coworkers synthesized various benzazepinones bearing electron deficient groups (such as fluoride, trifluoromethyl, trifluoromethoxy and methylsulfone) since such compounds are expected to be resistant to metabolic oxidation. The yield for this closure using Grubbs' catalyst was generally high and varied from 60 to 87%. This approach is very practical and multigramme scale was achieved easily (**Scheme I-22**).[88]



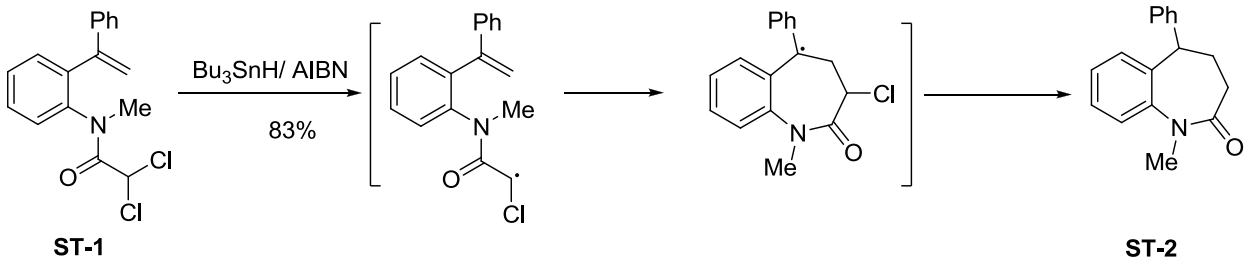
Scheme I-22

d. Radical cyclisations

In comparison to ionic chemistry, the construction of seven-membered rings by radical-based methods is rare. The reason is mainly because the desired cyclisation is too slow to compete with other pathways such as premature reduction of intermediate radical. If the cyclisation is by the intramolecular addition of a radical to an olefin, then there will be a competition between 6-exo

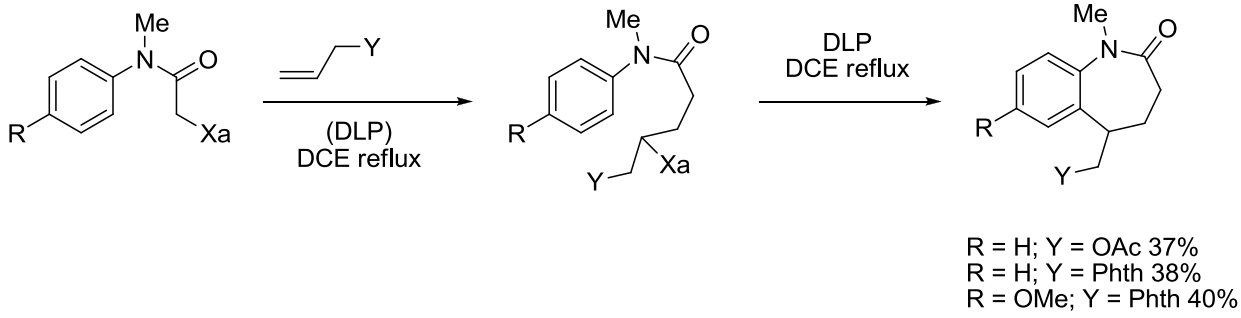
[88]Hoyt, S. B.; London, C.; Park, M. *Tetrahedron Lett.***2009,***50*, 1911

and 7-endo cyclisations. Normally, the former is more favored. Nevertheless, some substrates can cyclise selectively via a 7-endo closure by treatment with Bu_3SnH. Ikeda *et al.* reported that cyclisation of **ST-1** followed a 7-endo pathway exclusively when a phenyl group was present at the 1-position since the 6-exo closure is slowed by steric hindrance and the resulting radical from the cyclisation is stabilized (**Scheme I-23**).[89]



Scheme I-23

The chemistry of xanthates helps resolve the problem of 6-exo cyclisation. The synthesis of *N*-methyl benzazepinones was successfully achieved in moderate yield as shown in **Scheme I-24**. This strategy provides a powerful tool to access diverse structures because the choice of olefin and the substitution of the aromatic ring can be easily modified.[90]

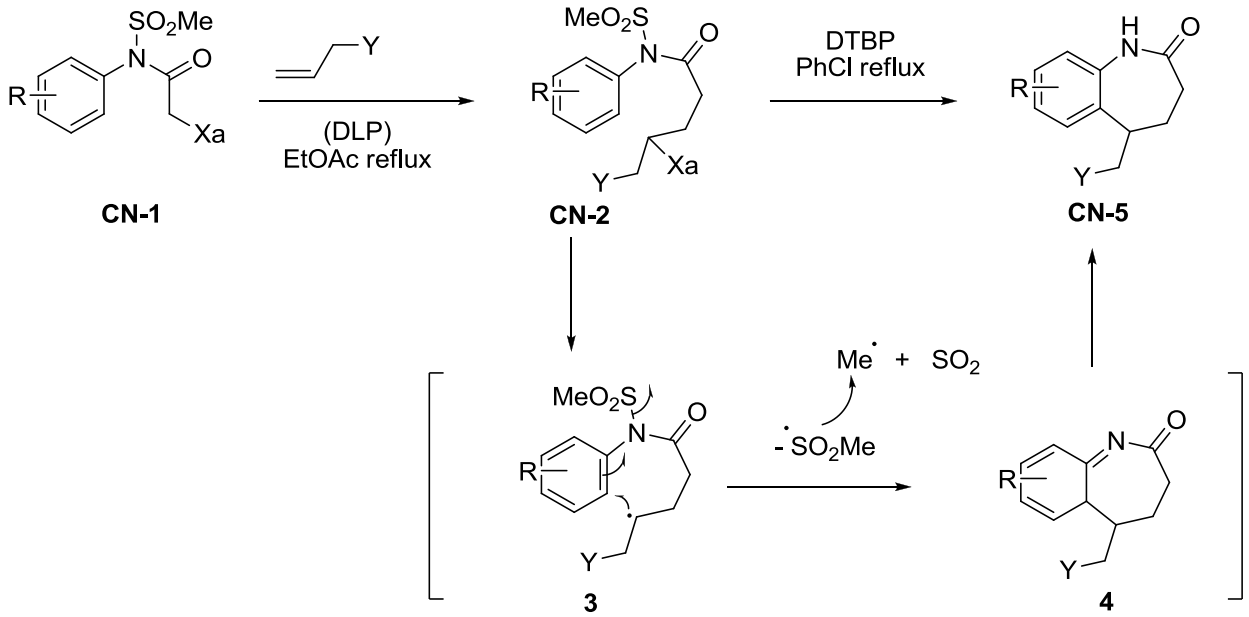


Scheme I-24

During a study aimed at establishing an easy access to arylpiperidones via benzazepinone intermediates, the *N*-unprotected benzazepinone could be formed efficiently by the unexpected

[89]Sato, T.; Ishida, S.; Ishibashi, H.; Ikeda, M. *J. Chem. Soc. Perkin Trans. I***1991**, 353
[90]Kaoudi, T; Quiclet-Sire, B.; Seguin, S.; Zard S. Z. *Angew.Chem. Int. Ed.***2000**, *39*, 731.

loss of a sulfonyl radical,[91] as outline in **Scheme I-25**. Thus the radical generated from xanthate adduct **CN-2** underwent cyclisation and fragmentation to generate a methanesulfonyl radical. The latter extruded SO_2 and generated a methyl radical which is able to propagate the chain. Rearomatisation furnishes products **CN-5** (**Scheme I-25**).



Scheme I-25

This method allows the introduction of a broad range of functional groups into the benzazepinone skeleton (R can be halide groups, trifluoromethyl or trifluoromethoxy group while Y can be $SiMe_3$, NHBoc, OAc, etc…) (**Figure I-8**). By modifying the combination of the xanthate precursor and the olefin, an easy entry to numerous structures becomes possible. Post-modification of the substituents is another tool for increasing diversity. This flexibility and convergence is valuable for the exploration of bioactivity around the lactam core and for pharmacological studies.

[91]Charrier, N.; Liu, Z.; Zard, S. Z. *Org. Lett.***2012**, *14*, 2018.

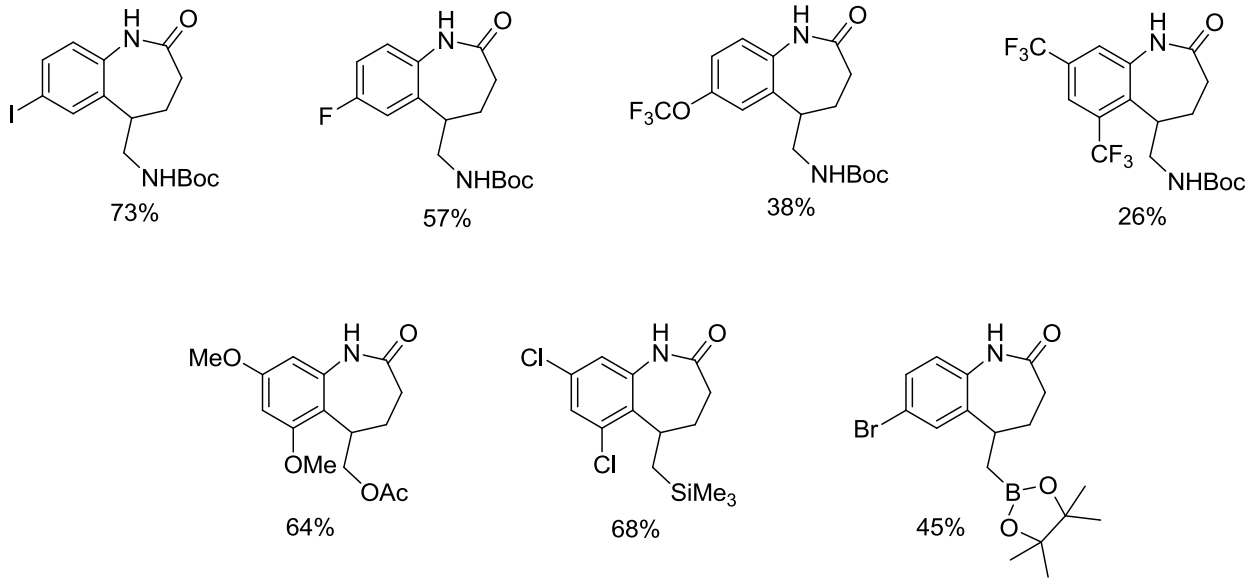
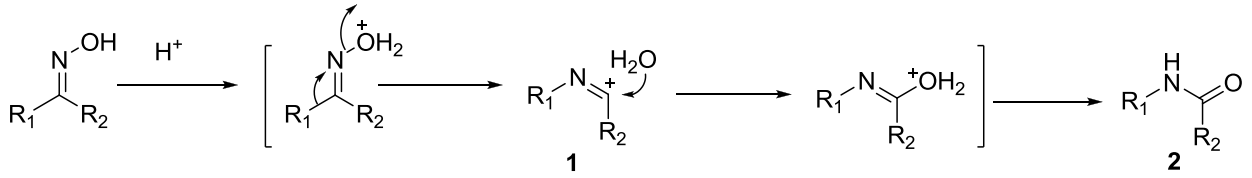


Figure I-8

e. Rearrangements

i. Beckmann rearrangement

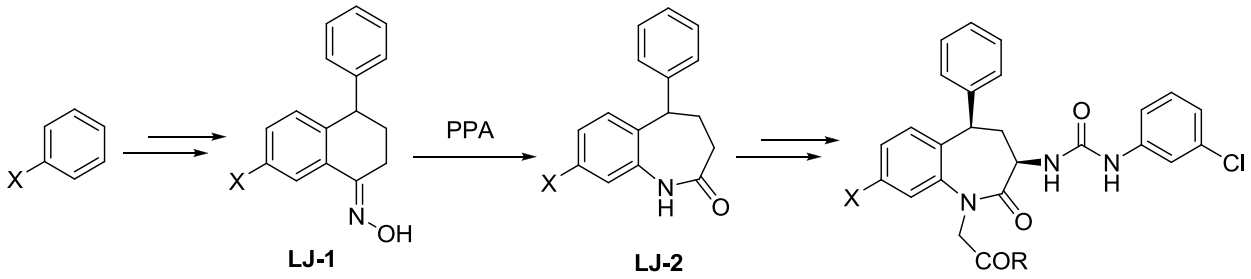
The Beckmann rearrangement is a very useful method to access to medium-ring lactams. It involves the rearrangement of an oxime in acidic medium to furnish the corresponding amide. It allows the rupture of C-C bond and formation of C-N bond in one step. Numerous reagents such as PCl_5, H_2SO_4, HCOOH, $SOCl_2$, $POCl_3$ or PPA can perform this transformation. The mechanism of the reaction is depicted in S**cheme I-26**. During the rearrangement, iminium **1** is first formed, and then it is attacked by water in the medium or upon work up to give finally amide **2**.



Scheme I-26

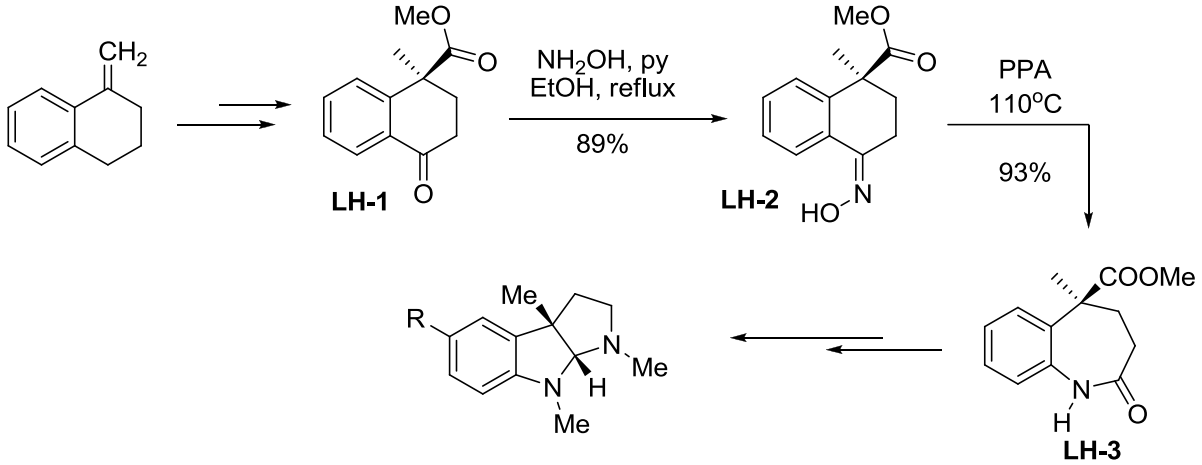
The Beckmann rearrangement of an oxime derived from anα-tetralone was applied for the preparation of benzazepinones and benzazepines. Lowe *et al.* employed this strategy for the synthesis of Cholecystokinin-B Receptor Antagonists as indicated in simplified **Scheme I-27**. In

this case, PPA was used to convert **LJ-1** into **LJ-2,** which was then transformed into the final product.[92]



Scheme I-27

Rajanbabu and co-workers accomplished the synthesis of anticholenergic pyrrolidinoindolines via the formation of benzazepinone intermediate **LH-3,** as described in **Scheme I-28**. The condensation of hydroxylamine with ketone **LH-1** afforded the corresponding oxime **LH-2** which underwent the Beckmann ring expansion to furnish **LH-3** in excellent yield.[93]

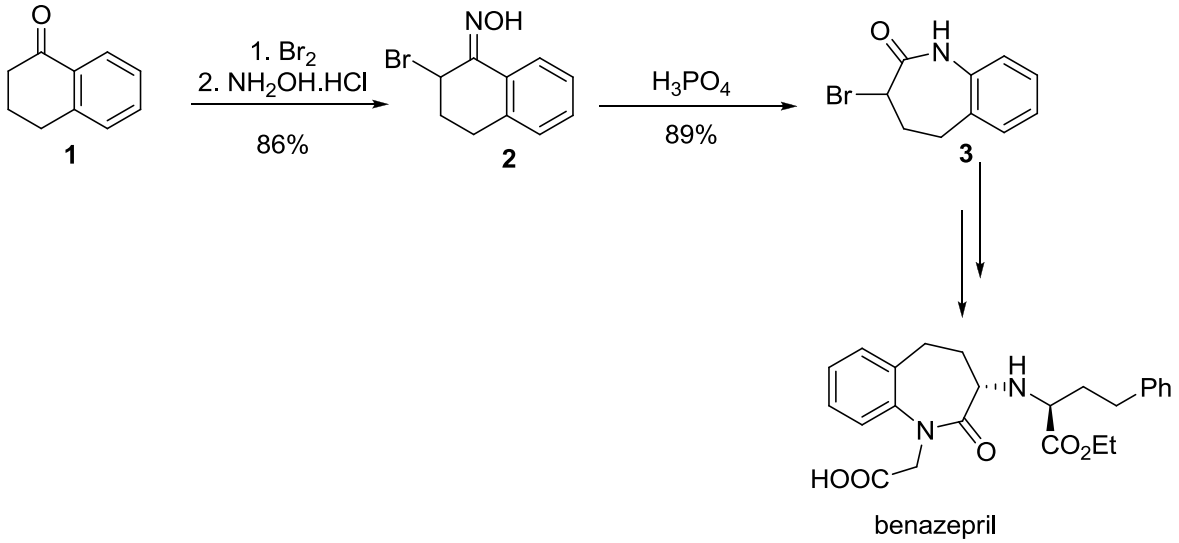


Scheme I-28

Obviously, this method is very efficient and versatile since a variety of reagents can be used to perform this transformation. This strategy has been applied in industry for the synthesis of benzazepinone portion of benazepril. As shown in **Scheme I-29**, the sequence started with the treatment of precursor **1** with bromine, followed by condensation with hydroxylamine to furnish

[92]Lowe, J. A.; Hageman, D. L.; Drozda, S. E.; McLean, S.; Bryce, D. K.; Crwford, S. Z.; Morrone, J.; Bordner, J. *J. Med. Chem.***1994**, *37*, 3789.
[93]Lim, H. J.; RajanBabu T. V.*Org. Lett.*, **2011**, *13*, 6596.

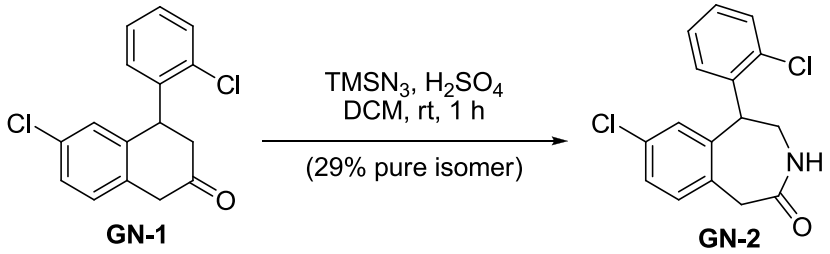
oxime **2** in good yield. Exposure of **2** to phosphoric acid led to intermediate **3** via a Beckmann rearrangement in good yield.[94]



Scheme I-29

ii. Schmidt rearrangement

The Schmidt rearrangement is very similar to Beckmann rearrangement, except that the reaction takes place from a carbonyl function by reaction hydrazoic acid. In principle, the reaction is catalysed by concentrated sulfuric acid. For example, in a study of squalene synthase inhibitors, Griebenow *et al.* synthesized **GN-2** from the substrate ketone **GN-1** via Schmidt rearrangement **(Scheme I-30)**. However the reaction conditions are harsh and it is important that the substituents on the substrates be compatible with these conditions.[95]

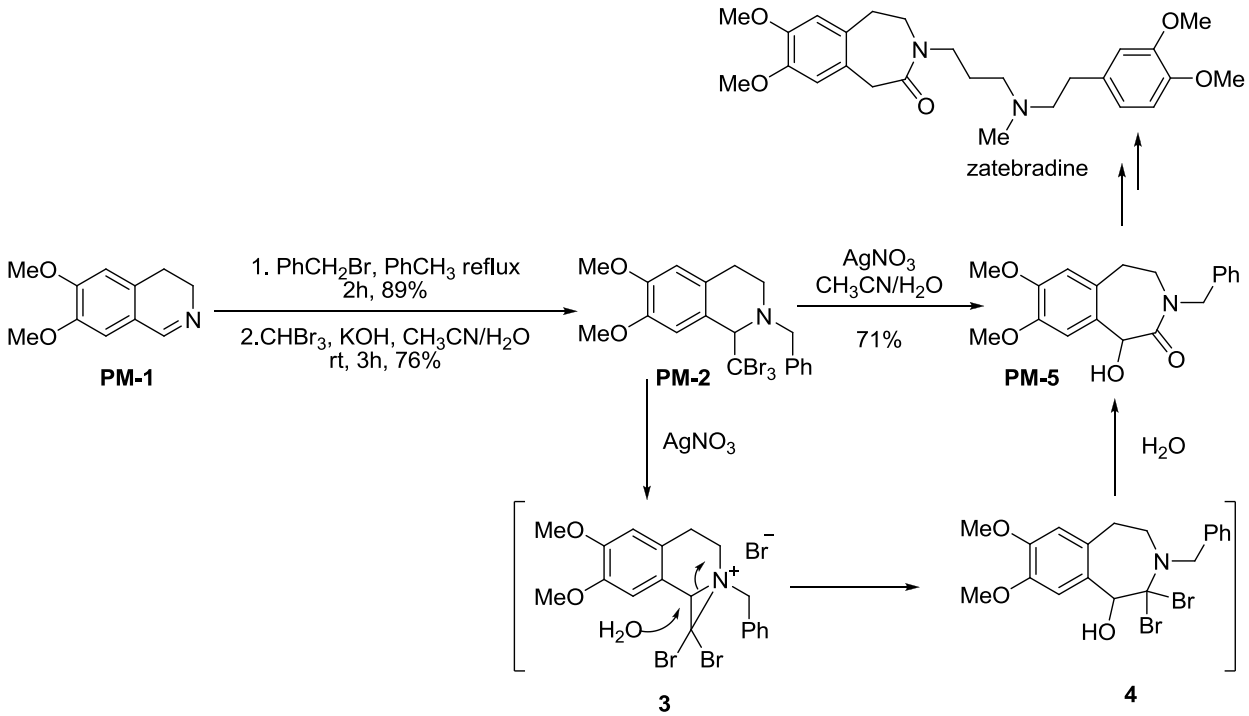


Scheme I-30

[94]Johnson, D. S.; Li, J. J.*The art of Drug synthesis***2007**.
[95]Griebenow, N.; Flessner, T.; Buchmueller, A.; Raabe, M; Bischoff, H.; Kolkhof, P. *Bioorg. Med. Chem. Lett.***2011**, *21*, 2554.

iii. Rearrangement of quinolinium salt

The Guingant group reported a ring enlargement method using $AgNO_3$ in the mixture of methanol and water to transform compound **PM-1** into benzazepinone **PM-5**. The rearrangement was be explained by the formation of aziridium intermediate **3** by treatment of **PM-2** with $AgNO_3$, followed by attack of water to produce dibromoamine **4**, which furnishes lactam **PM-5** after hydrolysis (**Scheme I-31**). This strategy was applied to the synthesis of the anti-anginal zatebradine.[96]



Scheme I-31

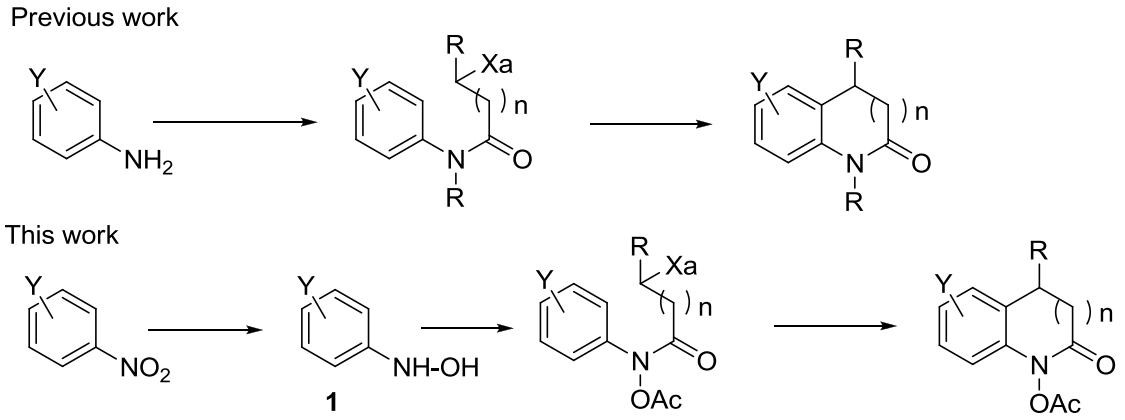
As we can see, a broad diversity of approaches has been studied for the synthesis of benzazepinone analogs. In the following section, we will report the results obtained from our research. Our approach complements existing methods used to access this important family of substances.

[96]Pauvert, M.; Collet, S.; Guingant, A. *Tetrahedron Lett.***2003**, *44*, 4203.

II. Original plan and unexpected results

1. Original plan

From previous experience, we learnt that the construction of lactams fused to aromatic or heteroaromatic rings could be accomplished directly by the xanthate-based radical cylization onto the aromatic core. Therefore, we decided to employ this approach for the synthesis of cyclic hydroxamic acids by simply changing the N-R bond into N-OAc bond, as shown in **Scheme II-1.** An attractiveaspect of this strategy is the ready availability of precursors **1** as they can be easily prepared by the partial reduction of nitroarenes.[97]



Scheme II-1

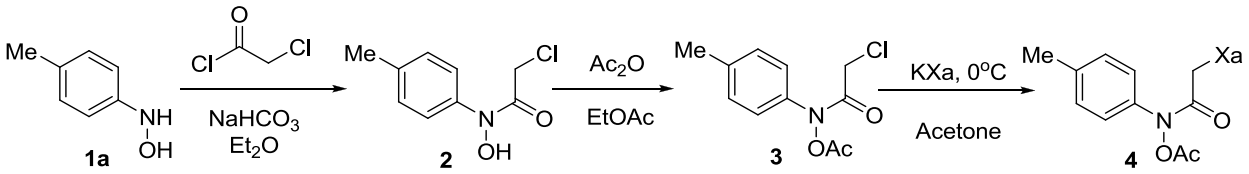
2. Unexpected results

i. An attempt at five-membered ring construction

In general, the formation of five-membered-rings by a radical process is the most efficient; we decided therefore to attempt the synthesis of five membered cyclic hydroxamic acids. The sequence synthesis of the required xanthate precursor for this cyclisation is presented in **Scheme II-2**. First, *p*-methyl-phenylhydroxylamine **1a** was chloroacetylated selectively on the nitrogen to furnish product **2.** The nitrogenis more nucleophilic than the oxygen of hydroxyl group.

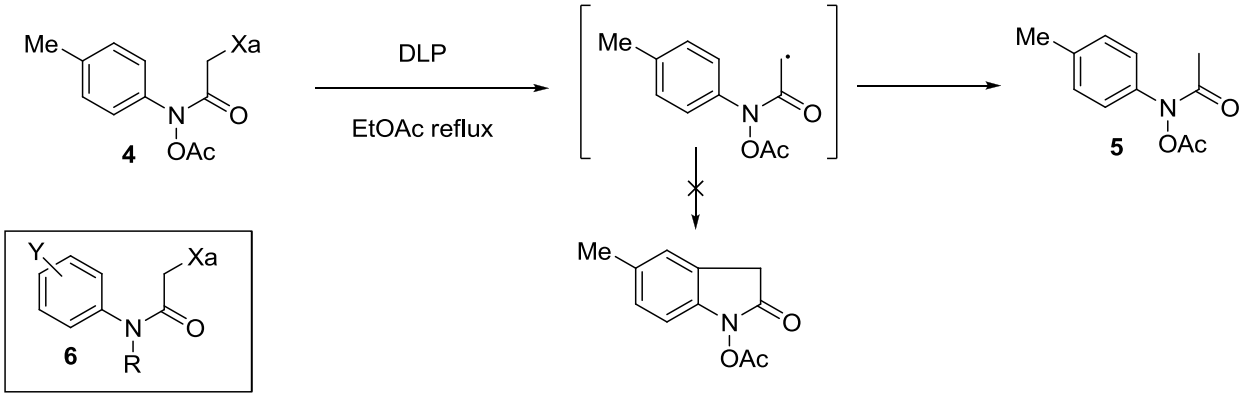
[97]Oxley, P. W.; Adger, B. M.; Sasse, M. J.; Forth, M. A. *Org. Synth.***1988**, *67*, 187.

Acetylation of **2** was followed by displacement of the chlorine with potassium *O*-ethyl xanthate to afford the desired xanthate **4**.



Scheme II-2

The cyclisation of **4** was carried out under the standard conditions: heating **4** in refluxing ethyl acetate, lauroyl peroxide was added portionwise in stoichiometric amount. Unfortunately, no cyclised product was formed, the only isolated product was the trivial reduced product **5** (95% yield) (**Scheme II-3**).



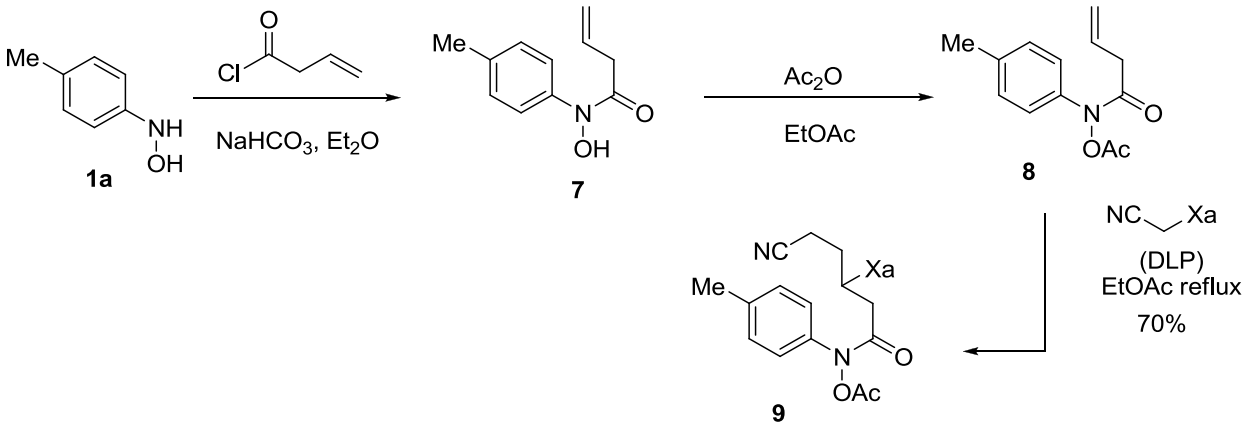
Scheme II-3

The reasons for this are not yet clear but perhaps it relates to the bond angles. Compared to the easy cyclisation of anilide **6** under the similar conditions, the cyclisation in this case must significantly slower.[98]

[98] (a) Axon, J.; Boiteau, L.; Boivin, J.; Forbes, J. E.; Zard, S. Z. *Tetrahedron Lett.***1994**, *35*, 1719. (b) Bacqu_e, E.; El Qacemi, M.; Zard, S. Z. Org. Lett. 2004, 6, 3671.(c) Bacque, E.; El Qacemi, M.; Zard, S. Z. *Heterocycles***2012**, *84*, 291. (d) El Qacemi, M.; Petit, L.; Quiclet-Sire, B.; Zard,S. Z. *Org. Biomol.Chem.***2012**, *10*, 5707.

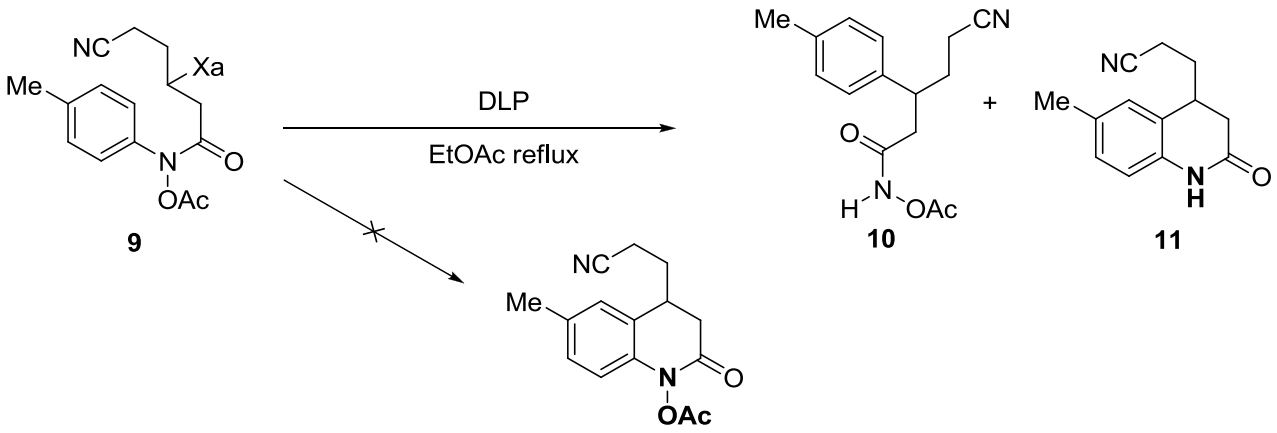
ii. An attempt at six-membered ring construction

We next examined access to six-membered-ring cyclic hydroxamic acides. First we synthesized xanthate precursor **9** by the sequence described in **Scheme II-4**. Compound **9** was prepared by radical addition of cyanomethyl xanthate to butenyl hydroxamate **8** in 70% yield.



Scheme II-4

Exposure of xanthate **9** to DLP in refuxing ethyl acetate furnished the desired cylization but not in the manner we had anticipated. Indeed, two major products were isolated after the reaction (**Scheme II-5**). The first product wasthe open chain hydroxamate **10**, obtained in 40% yield. The second product was dihydroquinolone **11**, isolated in 35% yield, which was the cyclised product but the acetoxy group of the hydroxamate moiety had been lost.



Scheme II-5

These results were different from what we had predicted and encouraged us to investigate the mechanism.

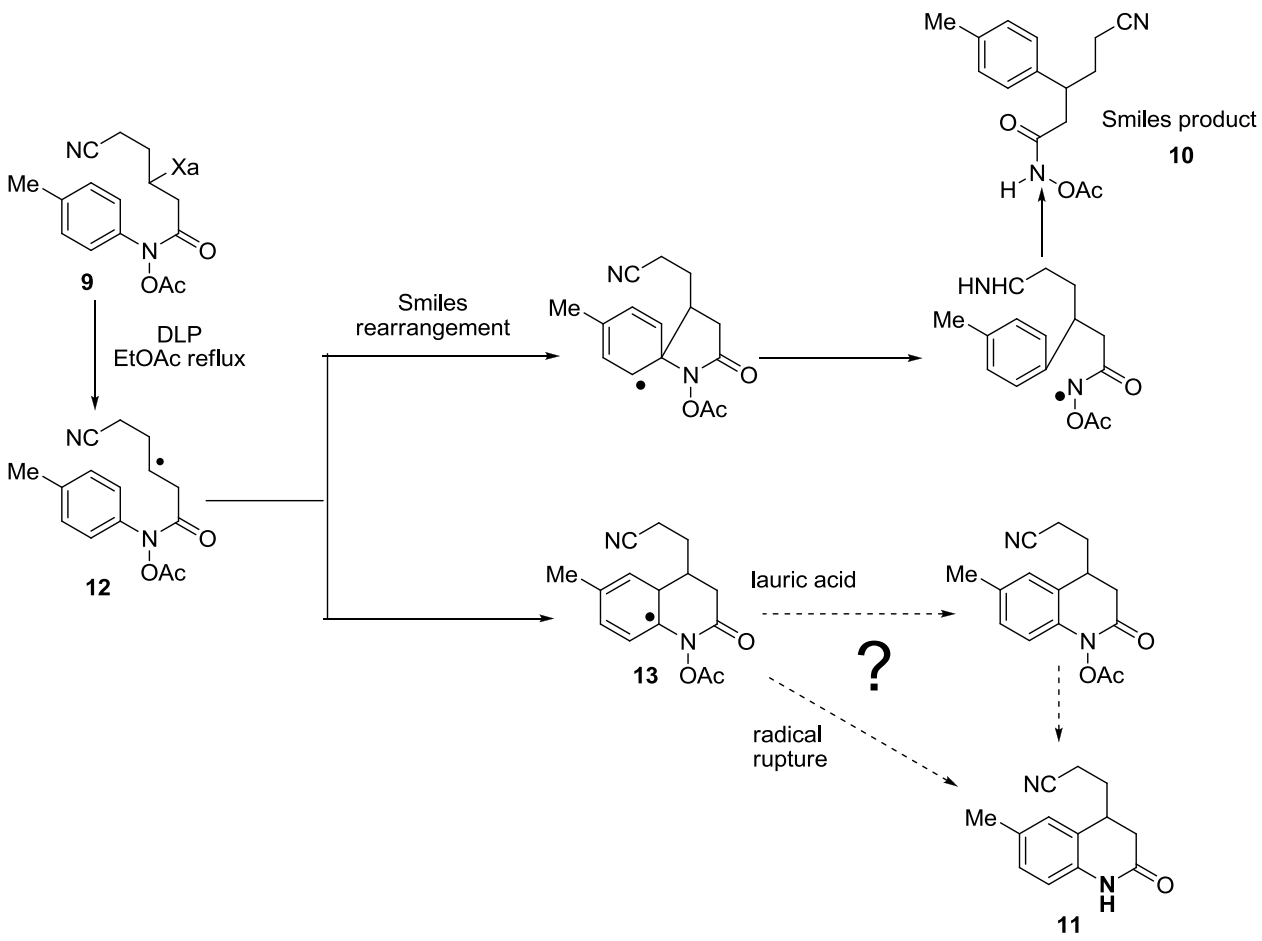
III. Results and discussions

1. Investigation of mechanism

Upon treatment with dilauroyl peroxide in refluxing ethyl acetate, xanthate **9** produces the radical **12**, which can follow two different pathways to furnish two products, as described in **Scheme II-6**.

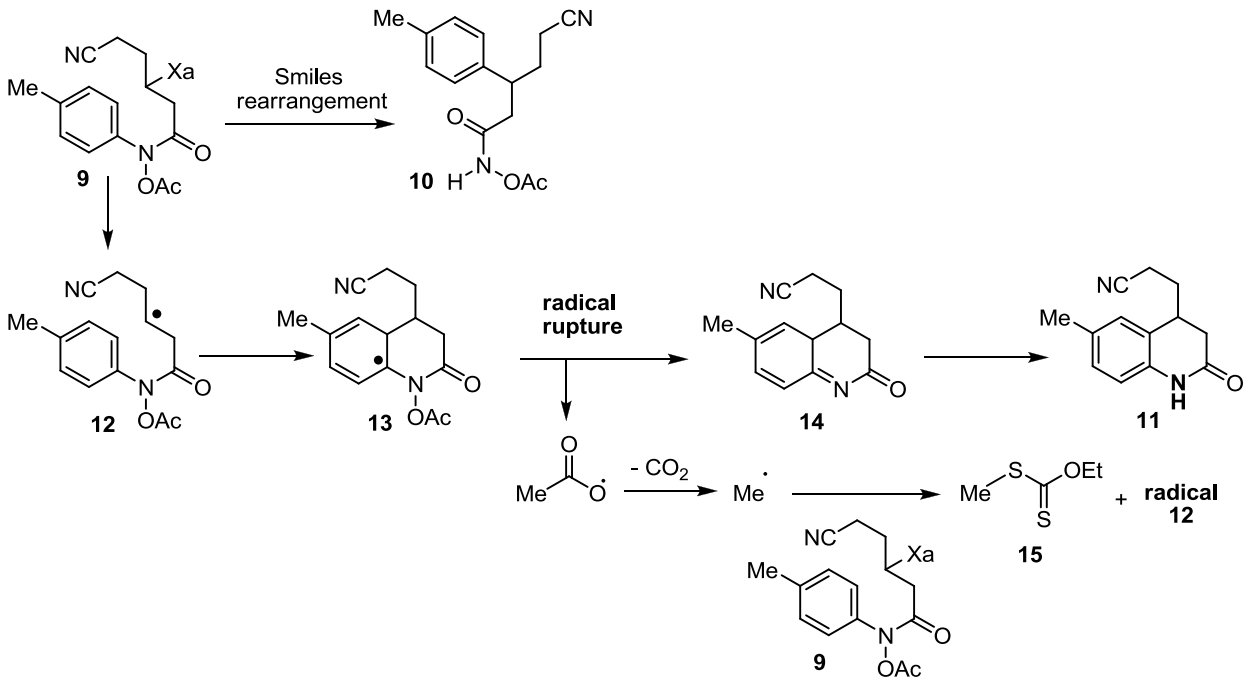
The open chain product **10** is apparently derived from the Smiles rearrangement. This transformation starts with a free radical attack at the*ipso* position of hydroxamate, followed by hydrogen abstraction to furnish product **10** through a 1,4-aryl migration.

The other pathway is the expected cyclisation to the aromatic ring to give radical **13**. However aromatisation occurs by cleavage of the N-O bond and not by electron-transfer to the peroxide as in the previous studies. The question was now whether the N-O bond was cleaved in ionic manner upon prolonged heating with lauric acid or whether the rupture involved homolysis.



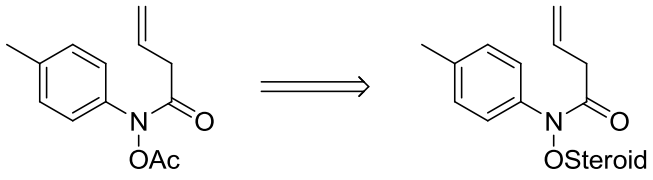
Scheme II-6

As presented in chapter 1, fragmentation occurs when a bond is weak or when a highly stable radical can be generated. The weak N-O bond is cleaved in the Barton decarboxylation process and the possibility of homolytic rupture of the N-OAc bond in our case is high. If homolysis takes place, as depicted in **Scheme II-7**, the radical adduct **13** should undergo β-scission of the weak N-O bond to produce intermediate **14** and acetyloxy radical. The latter would rapidly extrude carbon dioxide and generate a methyl radical, which could participate in xanthate transfer process by readily with the starting material **9** to give rise to radical **12** and S-methyl xanthate **16**. In principle, three products (Smiles rearrangement product **10** + unexpected cyclised **11** + S-methyl xanthate **15**) should have been isolated after the reaction if the rupture occurred by homolysis.



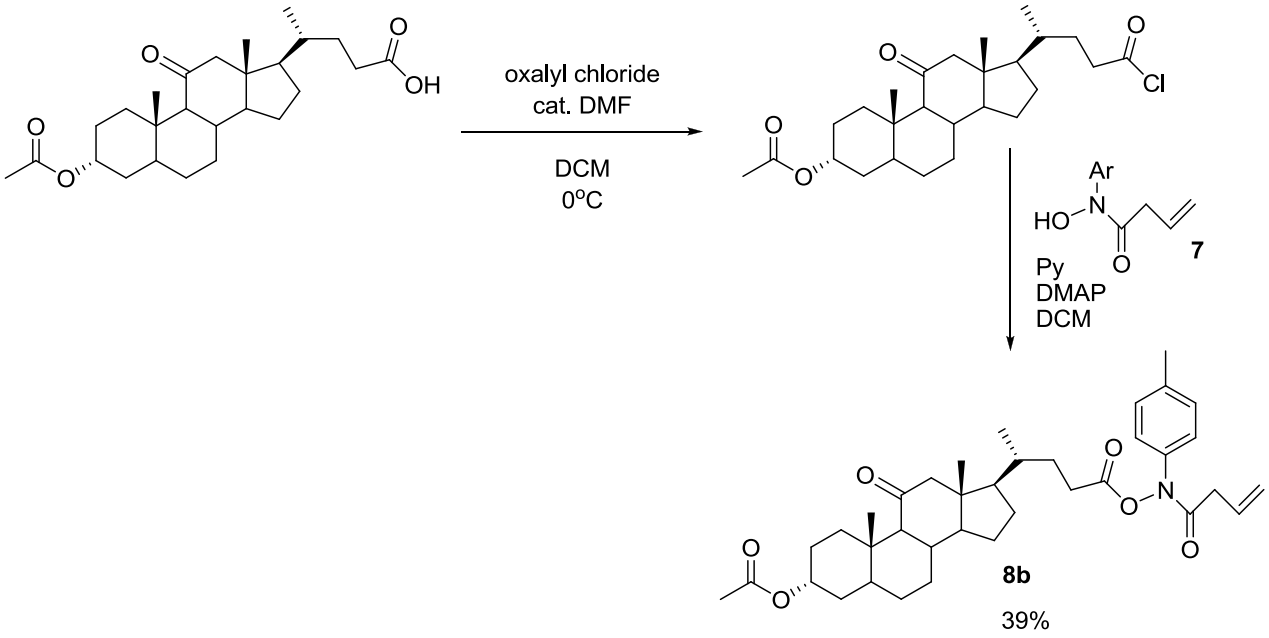
Scheme II-8

However, we could isolate only two products. The problem is that we could not detect the presence of S-methyl xanthate because it is volatile. Therefore, in order to investigate the mechanism of this reaction, we decided to use a very bulky ester so that we could detect the formation of the conresponding xanthate. We therefore selected a steroid ester as a non-volatile marker.



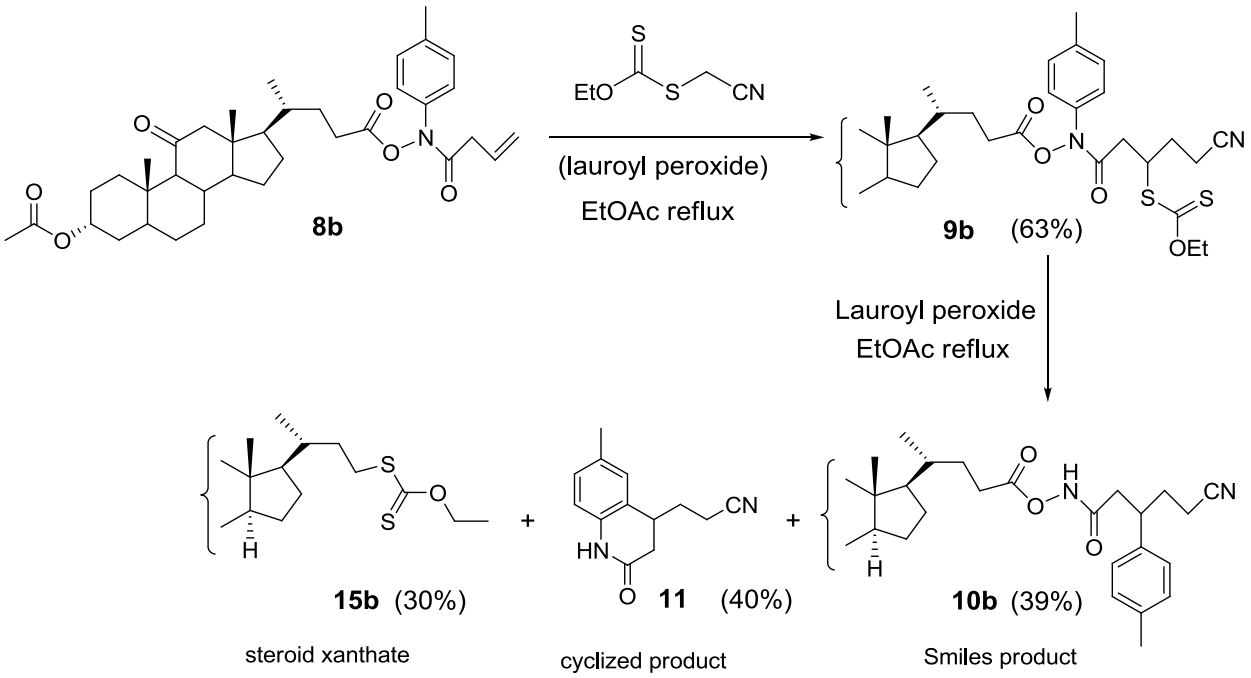
8 **8b**

The same sequence was applied to the synthesis of **8b**. Instead of using acetylchloride, we used an acyl chloride derived from a bile acid which had been prepared beforehand. The alkene bearing steroid moity **8b** was obtained in 39% yield (**Scheme II-9**).



Scheme II-9

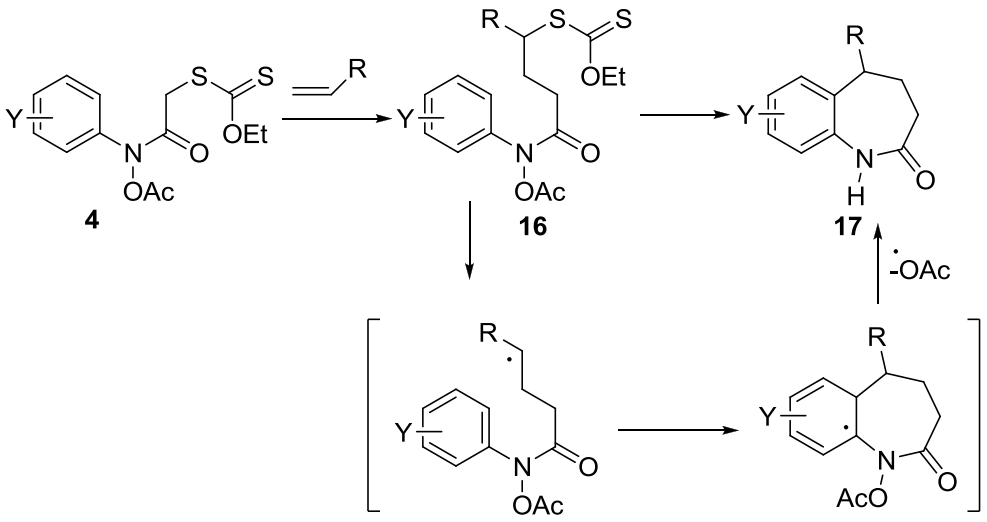
With the steroid hydroxamate **8b** in hand, we applied the same conditions for the cyclisation reaction. As outlined in **Scheme II-10**, the reaction furnished the expected open chain hydroxamate **10b** (39%) and dihydroquinolone **11** (40%), in addition to steroid xanthate **15b** (30%). The fact that three products were isolated including the presence of steroid xanthate **15b** is the solid evidence of a homolytic rupture of the N-O bond. This result also proved that decarboxylation of the labile carboxylic radical (Me-$CO_2^{\bullet}$ and Steroid-$CO_2^{\bullet}$) had indeed occurred in accord with the proposed mechanism pictured in **Scheme II-8**.



Scheme II-10

The cyclisation of xanthate **9** took place to form six-membered-ring**,** albeit in modest yield. This fact encouraged us to examine the possibility of seven-membered-ring closure which would lead to the formation of benzazepinones.

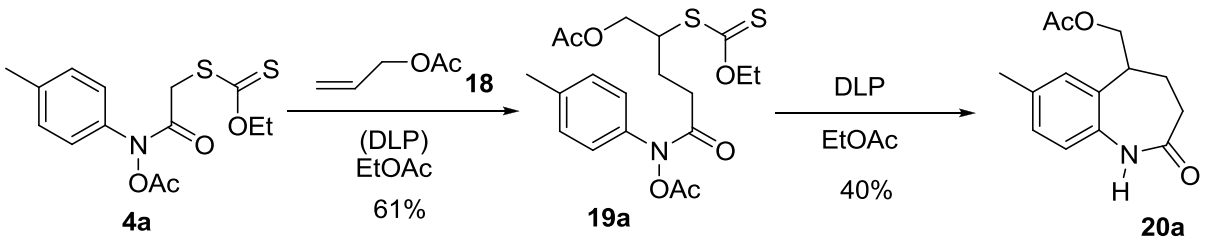
As we have seen in the introduction to benzazepinones, it is possible using xanthate chemistry to achieve the construction of seven membered rings by direct radical cyclisation onto an aromatic nucleus. Moreover, it is worth remembering that the radical derived from xanthate **4** did not cyclise, and this should allow it to undergo an efficient intermolecular radical addition to an alkene. As illustrated in S**cheme II-11**, this addition reaction would provide a direct and flexible access to starting xanthates **16** required for the preparation of benzazepinones **17**.



Scheme II-11

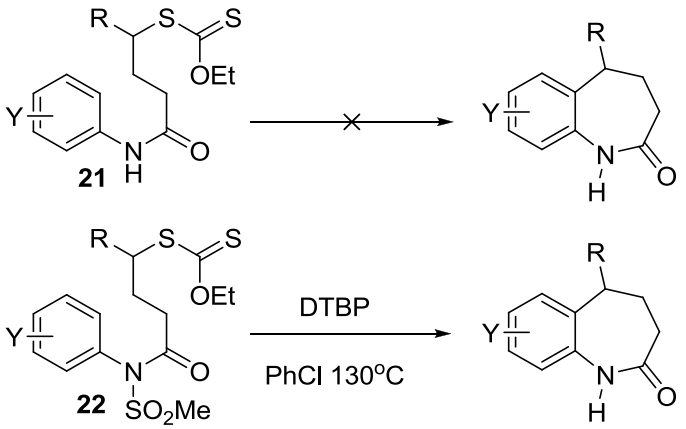
2. Preliminary results in the synthesis of benzazepinones (seven-membered ring construction)

We carried out the reaction between xanthate **4a** and allyl acetate **18**. The intermolecular addition to the unhindered terminal alkene proceeded in moderate yield (61%). The resulting xanthate **19a** was subjected to DLP in refluxing ethyl acetate. We were pleased to find that the cyclisation proceeded reasonably smoothly to produce cyclised product **20a** in 40% yield (**Scheme II-12**). In this case, in contrast to six-membered ring cyclisation, no product arising from a radical Smiles rearrangement was observed. This can be explained by the slower formation of a temporary six-membered ring for the Smiles rearrangement.



Scheme II-12

This approach is interesting because it provides a direct access to *N*-unsubstituted benzazepinones under mild conditions. Indeed, this family cannot be accessed by cyclisation of secondary amide xanthate **21** (**Scheme II-13**). This fact perhaps is due to the relatively high rotation barrier and the dominant presence of the rotamer with an unfavorable conformation for ring closure.[99]So far, the best method is the one using the methanesulfonamide of xanthate **22** mentioned earlier. This approach is efficient but requires high temperature for the cyclisation-fragmentation step.[100]



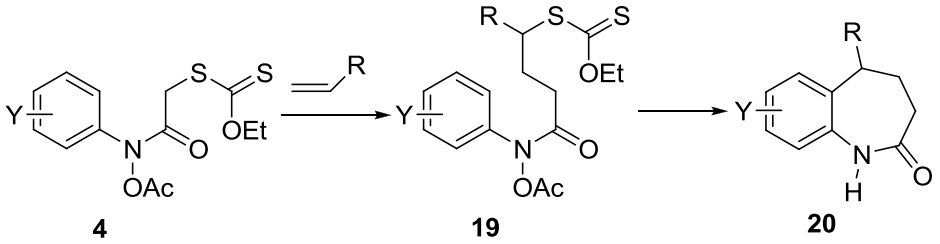
Scheme II-13

Our approach complements therefore the existing methods for the synthesis of benzazepinones. Since this building block has tremendous applications in medicinal chemistry, the expansion of the range of substrates is crucial.

[99](a) Kaoudi, T.; Quiclet-Sire, B.; Seguin, S.; Zard, S. Z. *Angew.Chem., Int. Ed.***2000**, *39*, 731. (b) Petit, L.; Botez, I.; Tizot, A.; Zard, S. Z. *Tetrahedron Lett.***2012**, *53*, 3220. (c) Yamasaki, R.; Tanatani, A.; Azumaya, I; Saito, S.; Yamaguchi,K.; Kagechika, H. *Org. Lett.***2003**, *5*, 1265.
[100]Charrier, N.; Liu, Z.; Zard, S. Z. *Org. Lett.***2012**, *14*, 2018.

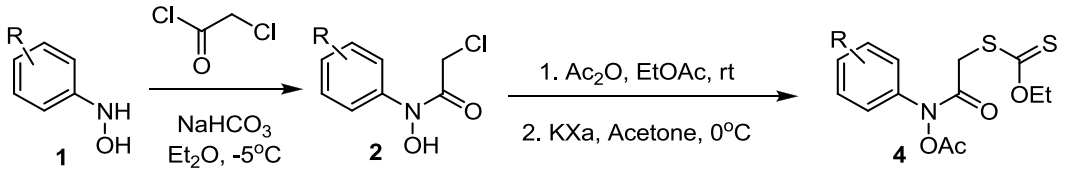
IV. Application to the synthesis of benzazepinones

The same addition/ cyclisation sequence was applied to synthesize a library of benzazepinones (**Scheme II-14**). By varying the substituents on the aromatic ring and the alkenes, numerous combinations diversifying the benzazepinone skeleton could be obtained.



Scheme II-14

First, the starting xanthates were synthesized as summarized in T**able II-1**.



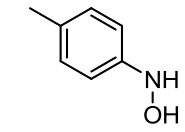
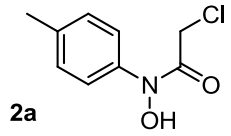
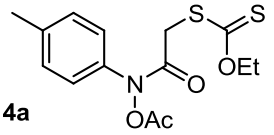
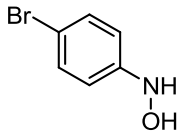
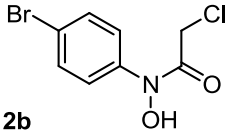
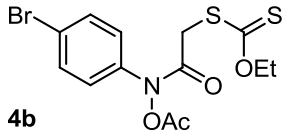
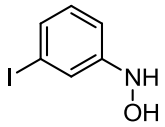
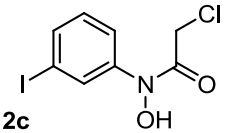
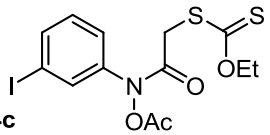
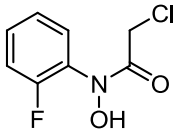
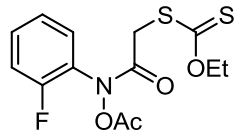
Substrate **1**	Compound **2**	Yield (%)	Xanthate **4**	Yield (%)
	 **2a**	78%	 **4a**	71%
	 **2b**	76%	 **4b**	70%
	 **2c**	82%	 **4c**	75%
	 **2d**	71%	 **4d**	77%

Table II-1

We chose to include precursors bearing a bromine (**4b**) and especially an iodine (**4c**) substituent as these groups allow further elaboration through the myriad transition metal catalysed couplings. The introduction of fluorine group (**4d**) is also interesting in view of the importance of organofluorine derivatives in medicinal chemistry. We examined all of the main substitutions on the ring: ortho (**4a** and **4b**), meta (**4c**) and para substituents (**4d**).

With these xanthates **4a-4d** in hand, the addition reactions to various olefins were carried out. We used the alkenes possessing a wide range of useful functional groups. For example, NPhth and NHBoc could be deprotected to provide the amine function; the cyano group could be transformed into the corresponding amine or carbonyl group; the boronate, phosphate or

carbohydrate motif would represent interesting indications for the tolerance of this transformation etc. (**Figure II-1**).

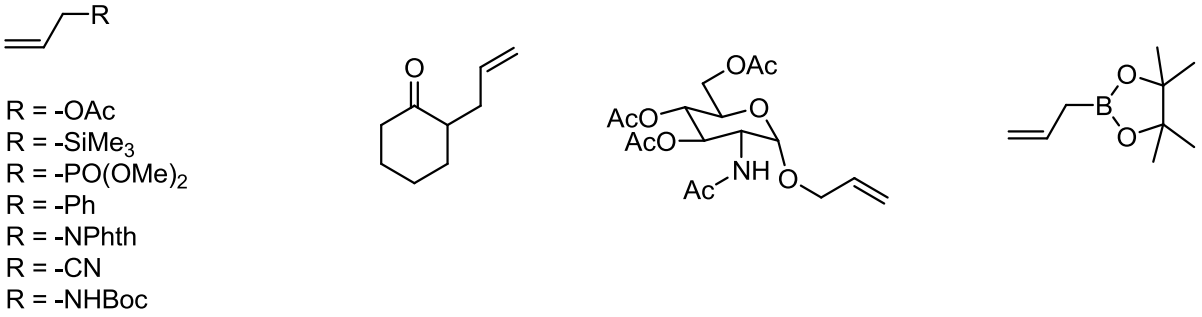
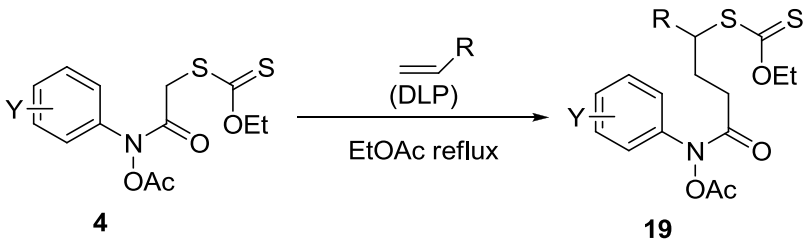


Figure II-1

The addition reactions of xanthate precursors **4** and alkenes were carried out in refluxing ethyl acetate with the addition of lauroyl peroxide portionwise until the complete consumption of starting xanthate **4** (around 10 to 15 mol% of DLP). The examples presented in **Table II-2** give a general idea of the scope and compatibility of this methodology towards various functional groups.



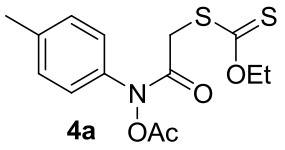
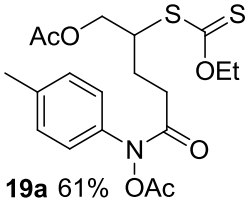
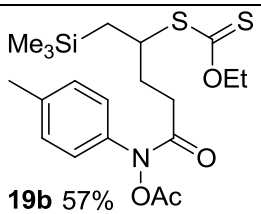
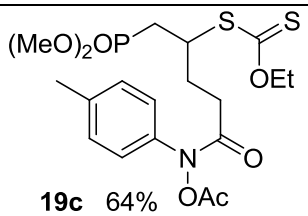
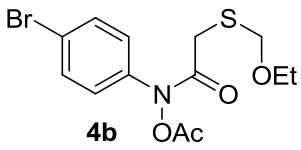
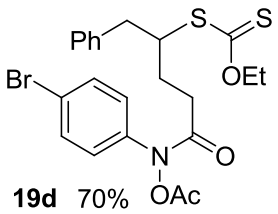
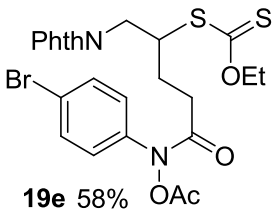
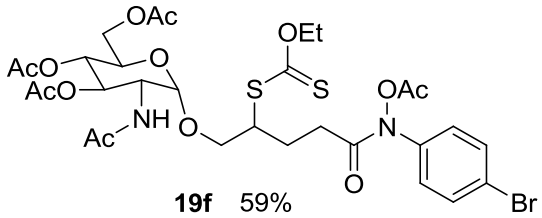
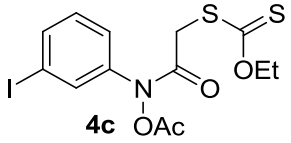
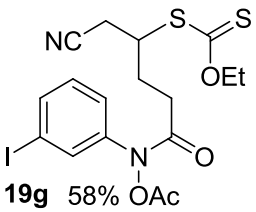
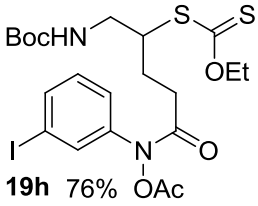
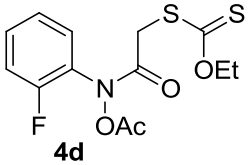
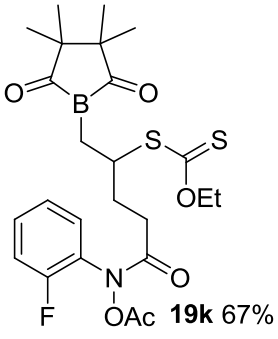
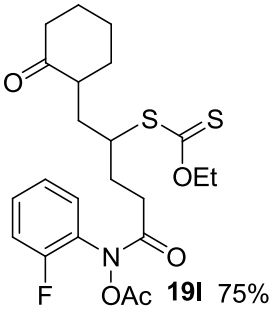
Xanthates **4**	Addition Products **19**		
 **4a**	 **19a** 61%	 **19b** 57%	 **19c** 64%
 **4b**	 **19d** 70%	 **19e** 58%	
	 **19f** 59%		
 **4c**	 **19g** 58%	 **19h** 76%	
 **4d**	 **19k** 67%	 **19l** 75%	

Table II-2

Adducts **19a-19l** were obtained easily in moderate to good yields (57% to 76%) and these results showed that the difference in the substitution pattern on the aromatic ring of the xanthate precursor **4** do not affect the radical addition process. Treatment of these xanthates with DLP in refluxing ethyl acetate furnished the corresponding benzazepinones in synthetically useful yields. **Figure II-2** displays the benzazepinones derivatives obtained by this method.

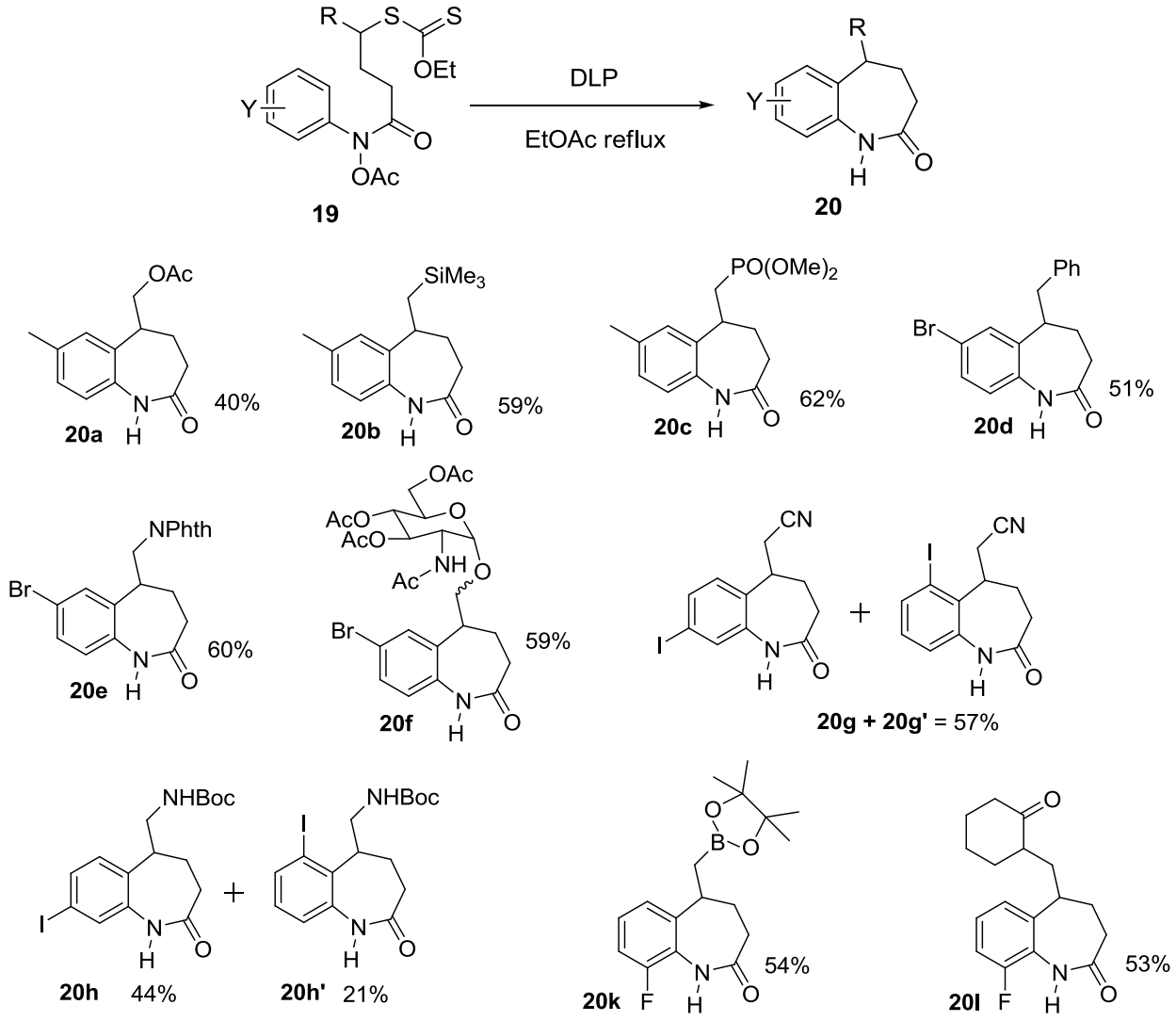


Figure II-2

As shown in **Figure II-2**, the cyclisation proceeded smoothly to give a unique cyclised product in cases where the substituent on the aromatic ring is at the *para* or *ortho* positions (*ortho*-

methyl, *ortho*-bromo, *para*-fluoro). After purification by silica gel column chromatography, these compounds were obtained as white solids in moderate yields varying from 40 to 62%. In contrast, a *meta*-iodo subtituent on the starting xanthate provided two products with only moderately regioselective (2:1 in favor of a distal cyclisation, examples of **20g**/**20g'** and **20h**/**20h'**). In the case of **20g**/**20g'**, the two regioisomers could not be separated by silica gel column chromatography but a pure sample of the major product **20g** could be collected from the oily mixture by crystallising from dicholoromethane.It is important to note that this method is totally compatible with the presence of halide subtituents. Another appealing aspect is that it is easy to introduce unusual functional groups such as a boronate (**20k**) or a complex carbohydrate motif (two seperable epimers **20f** and **20f'**), which would be tedious to prepare by other conventional synthetic approaches.

V. Conclusion

In summary, our method corresponds to a general radical approach to access the *N*-unsubstituted benzazepinones. It combines flexibility in the choice of reacting components with simplicity and mildness of the experimental procedure and provides a concise and cheap route to a highly valuable class of compounds for medicinal chemistry. It is easy to imagine numerous variations to expand the scope and variety in the structures.

Chapter 3 Synthesis of protected naphthylamine derivatives

I. Introduction

1. Applications of naphthylamines
2. Recent syntheses of naphthylamines
    i. Synthesis of naphthylamines from functionalized benzene precursors
    ii. Functionalisation of bicyclic systems

II. Synthesis of naphthylamides using xanthate chemistry

A. Synthesis of 2-naphthylamides

1. Previous work and our strategy
2. Results and discussion

B. Synthesis of 1-naphthylamides

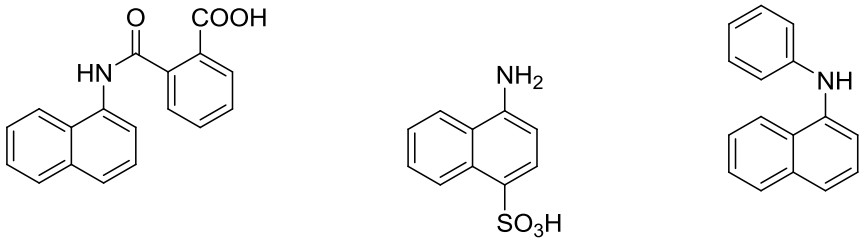
1. Previous work and our strategy
2. Preliminary results
3. Synthesis of the xanthate precursors
4. Results and discussion
5. An attempt to extend the scope

III. Conclusion

I. Introduction

1. Applications of naphthylamines

Naphthylamines, whose structure consists of two fused benzene rings bearing an amine functional group, belongs to a subfamily of naphthalene. In general, naphthalenes are important building blocks of many biologically active natural products, pharmaceutics and opto-electronic materials. It is not surprising, therefore, that a plethora of methods to access to substituted naphthalenes have been developed over the years. However, the synthesis of the naphthylamine subfamily remains a significant challenge, even though naphthylamine derivatives are found in numerous applications such as in the manufacture of dyes, agrochemicals, rubber stabilisers etc.[101] As shown in **Figure I-1**, *N*-1-naphthylphthalamic acid **I** is used as a selective herbicide for soybean, peanut, and vine crops; naphthionic acid (1-naphthylamine-4-sulphonic acid) **II** is employed as an important intermediate in the manufacture of dyes, such as Congo Red, Fast Dye A, azo dyes; and *N*-phenyl-1-naphthylamine **III** is antioxidation rubber additive.



I **II** **III**

Figure I-1

Besides, naphthylamine derivatives are reported as potentially useful structure in medicinal chemistry research. For example, compound **IV** is a potent binder of the chemokine receptor CCR8[102]; rifampicin **V**, a member of the ansa antibiotic family, is used clinically as a

[101] M. F. Wolfe, J. N. Seiber, *Arch. Environ. Contam.Toxicol.*1992, **23**, 137.

[102] Jenkins, T. J.; Guan, B.; Dai, M.; Li, G.; Lightburn, T. E.; Huang, S.; Freeze, B. S.; Burdi, D. F.; Jacutin-Porte, S.; Bennett, R.; Chen, W.; Minor, C.; Ghosh, S.; Blackburn, C.; Gigstad, K. M.; Jones, M.; Kolbeck, R.; Yin, W.; Smith, S.; Cardillo, D.; Ocain, T. D.; Harriman, G. C. *J. Med. Chem.*, **2007**, *50*, 566.

semisynthetic antibiotic[103] and the reactive fluorescent dye dansylamine has been widely utilised as a probe for carbonic anhydrases in addition to numerous other applications (**Figure I-2**).[104]

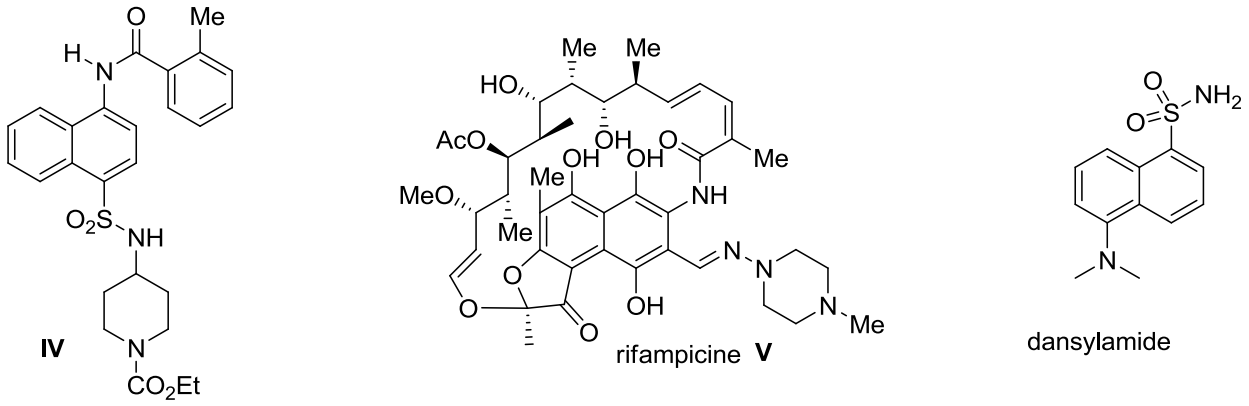


Figure I-2

The naphthylamine motif can also be found in drug for the treatment of inflammatory diseases, BIRB796 for example is the first p38 MAP kinase inhibitor that has advanced to clinical trials.[105] Recently, in course of research for selective bone seeking matrix metalloproteinase inhibitors, compound **VI** was shown to be a new promising agent for bone malignancy treatment (**Figure I-3**).[106]

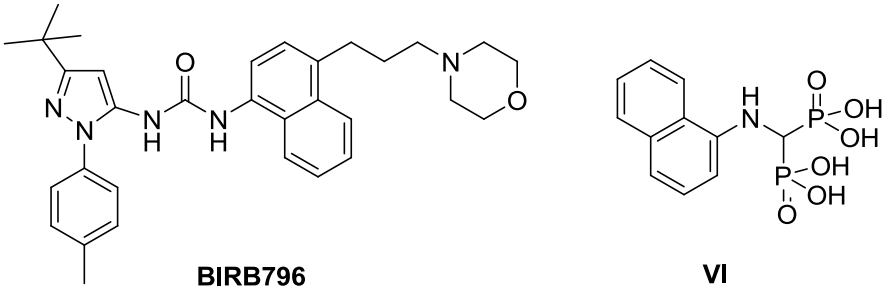


Figure I-3

[103]Rinehart Jr., K. L. *Acc. Chem. Res*. **1972**, *5*, 57.

[104] (a) Banerjee, A. L.; Tobwala, S.; Ganguli, B.; Mallik, S.; Srivastava, D. K. *Biochemistry*, **2005**, *44*, 3673. (b) Lesburg, C. A.; Huang, C.; Christianson D. W.; Fierke, C. A. *Biochemistry*, **1997**, *36*, 15780.(c) Clare B. W.; Supuran, C. T. *Eur. J. Med. Chem.*,**1997**, *32*, 311.

[105] Regan, J.; Breitfelder, S.; Ciirillo, P.; Gilmore, T.; Graham, A. G.; Hickey, E.; Klaus, B.; Madwed, J.; Moriak, M.; Moss, N.; Pargellis, C.; Pav, S.; Proto, A.; Swinamer, A.; Tong, L.; Torcellini, C. *J. Med. Chem.***2002**, *45*, 2994.

[106]Tauro, M.; Laghezza, A.; Loiodice, F.; Agamennone, M.; Campestre, C.; Tortorella, P. *Bioorg.Med. Chem.* **2013**, *21*, 6456.

The hydronaphthoquinone sulfonamides (analogs of **1**) were reported by the Lawrence group to be novel proteasome inhibitors displaying the bioactivity both *in vitro* and *in vivo*; moreover compound **VII,** another member**,** also inhibited breast tumor cell proliferation (**Figure I-4)**.[107]

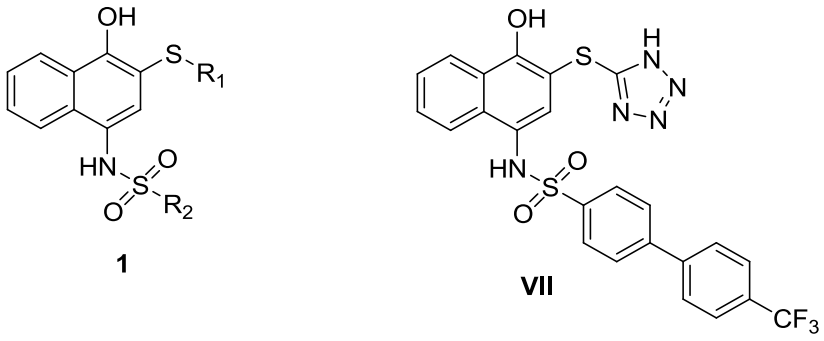
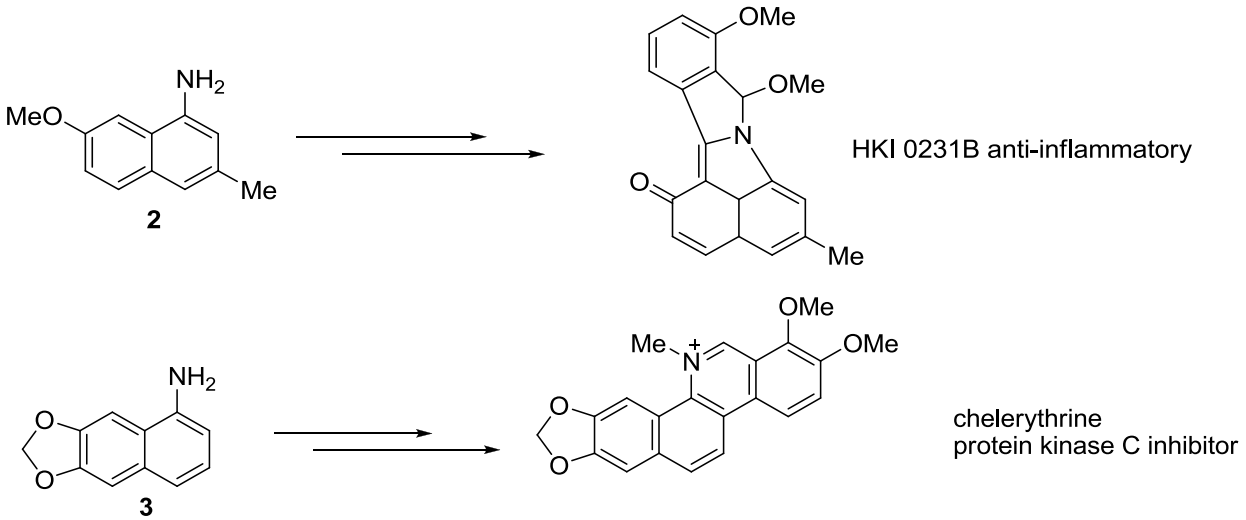


Figure I-4

Naphthylamines are also used as important intermediates in the synthesis of complex structures possessing biological activities. For example, the synthesis of the 3α-hydroxysteroid dehydrogenase inhibitor HKI0231B[108] and the potent *protein kinase C inhibitor* chelerythrine[109] proceeded via the intermediate aminonaphthalenes **2** and **3** respectively (**Scheme I-1**).



Scheme I-1

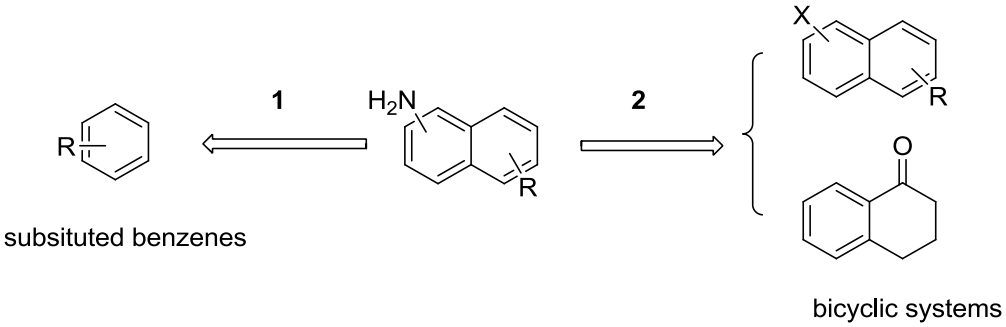
[107]Ge, Y.; Kazi, A.; Marsilio, F.;Luo, Y.; Jain, S.; Brooks, W.; Daniel, K. G.; Guida, W. C.; Sebti, S. M.; Lawrence H. R. *J. Med. Chem.***2012**, *55*, 1978**.**

[108]Scopton, A.; Kelly, T. R. *J. Org. Chem.***2005**, *70*, 10004.

[109] Kessar, S. V.; Gupta, Y. P.; Balakrishnan, P.; Sawal, K. K.; Mohammad, T.; Dutt, M. *J. Org. Chem.***1988**, *53*, 1708.

2. Recent syntheses of naphthalimines

Despite numerous contributions to the synthesis of substituted naphthalene derivatives, the preparation of naphthylamines has not been explored to the same extent and the synthetic routes to this subfamily are limited and lack generality. In principle, the strategies to access naphthylamines can be divided into two groups (**Scheme I-2**).



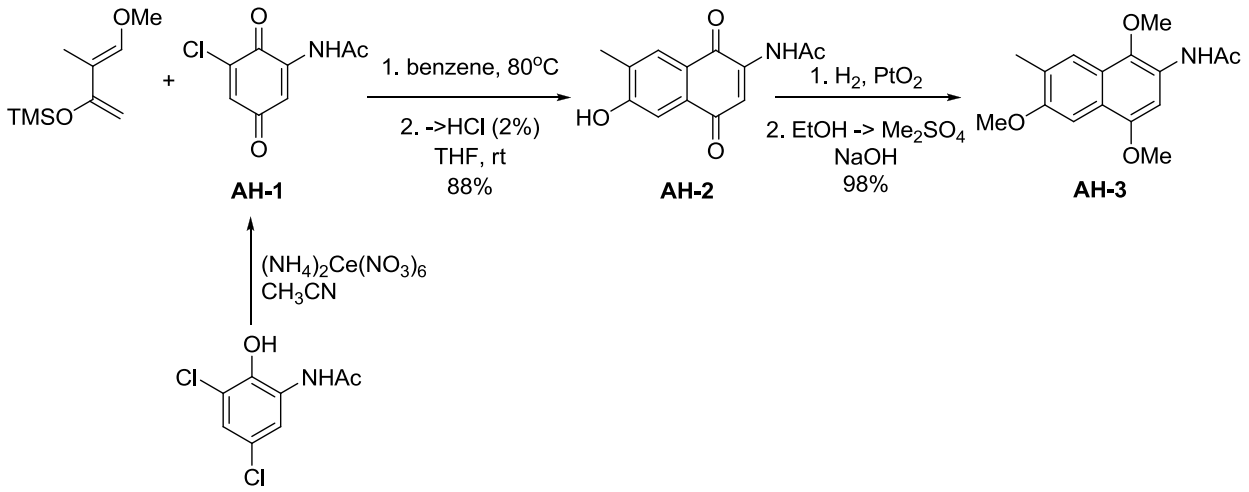
Scheme I-2

Strategy **1** hinges on the construction of the second ring from functionalized benzene precursors. Strategy **2** involves the functionalisation of precursors possessing already a bicyclic system; the most popular bicyclic systems are usually simple naphthalene derivatives or tetralones.

i. Synthesis of naphthylamines from functionalized benzene precursors

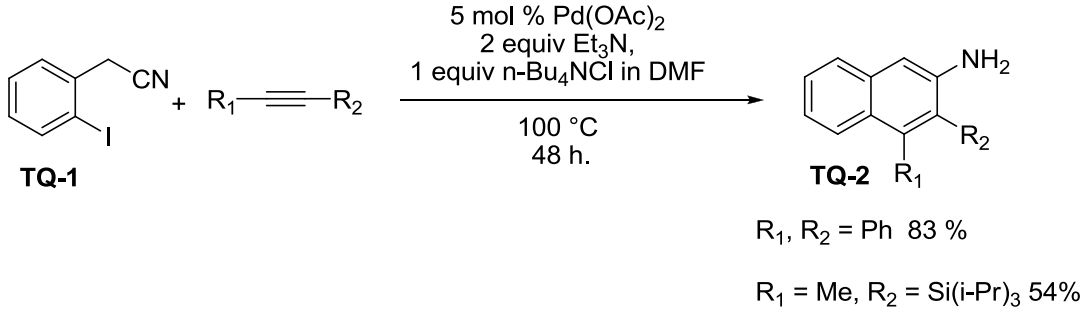
The Diels-Alder reaction is undoubtedly one of the most powerful and robust transformations for assembling carbocyclic and heterocyclic frameworks. The construction of 2-naphthylamines through Diels-Alder reactions can be accomplished using quinones and dienes. For example, Hager *et al.* described a very simple route to access naphthylamine **AH-3,** as indicated in S**cheme I-3**.[110] Quinone **AH-1** reacted with methyl-Danishefsky diene to give rise to intermediate **AH-2**, which was subjected to catalytic hydrogenation in the presence of PtO_2 in ethanol, followed by methylation to furnish the final compound **AH-3** in excellent yield. In this case, a single regioisomer Diels-Alder product was formed, but often a mixture of products is obtained.

[110]Hager, A.; Kuttruff, C. A.; Herrero-Gómez, E.; Trauner, D.*Tetrahedron Lett.***2014**, *55*, 59.



Scheme I-3

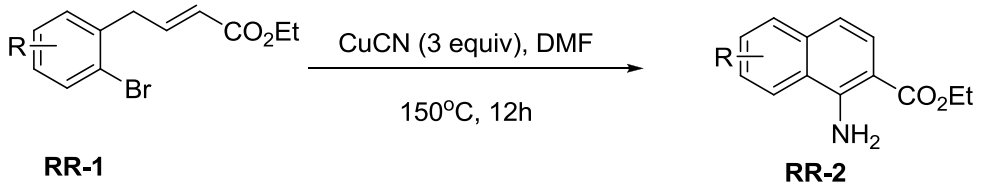
The application of transition metals in the organic synthesis provides plenty of solutions to numerous problems in organic synthesis, including the preparation of substituted naphthylamine derivatives. The Larock group thus developed an easy method to access naphthylamines using the palladium-catalysed coupling of 1-iodo-2-cyanomethylaryl and diaryl alkynes.[111] As displayed in **Scheme I-4**, the coupling between **TQ-1** and diaryl alkynes occurred smoothly to furnish **TQ-2** in high yield. This method provides a general strategy for the synthesis of 3,4-disubstituted 2-aminonaphthalenes. It is important to note that good results could only be achieved when the two substituents on the alkynes are aryl groups and, furthermore, if the two groups are different, then a mixture of products is usually obtained.



Scheme I-4

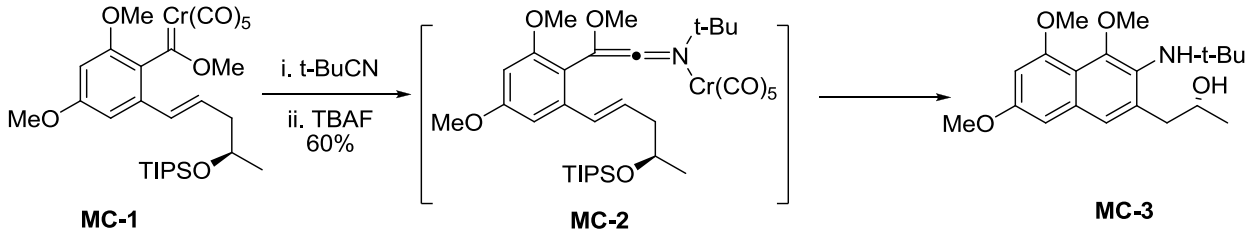
[111] Tian, Q. T.; Pletmev, A. A.; Larock, R. C. *J. Org. Chem.***2003**, *68*, 339.

Recently, a new approach using a CuCN-mediated cascade cyclisation was developed by Reddy and co-workers to prepare substituted amino naphthoate esters **RR-2** (**Scheme I-5**).[112]In this work, various substituents, such as fluorine, methoxy, nitro, methyl and benzo-fused group, were tolerated and the yields were high, ranging from 70% to 90%. However, this method cannot provide bromo-naphthylamine derivatives.



Scheme I-5

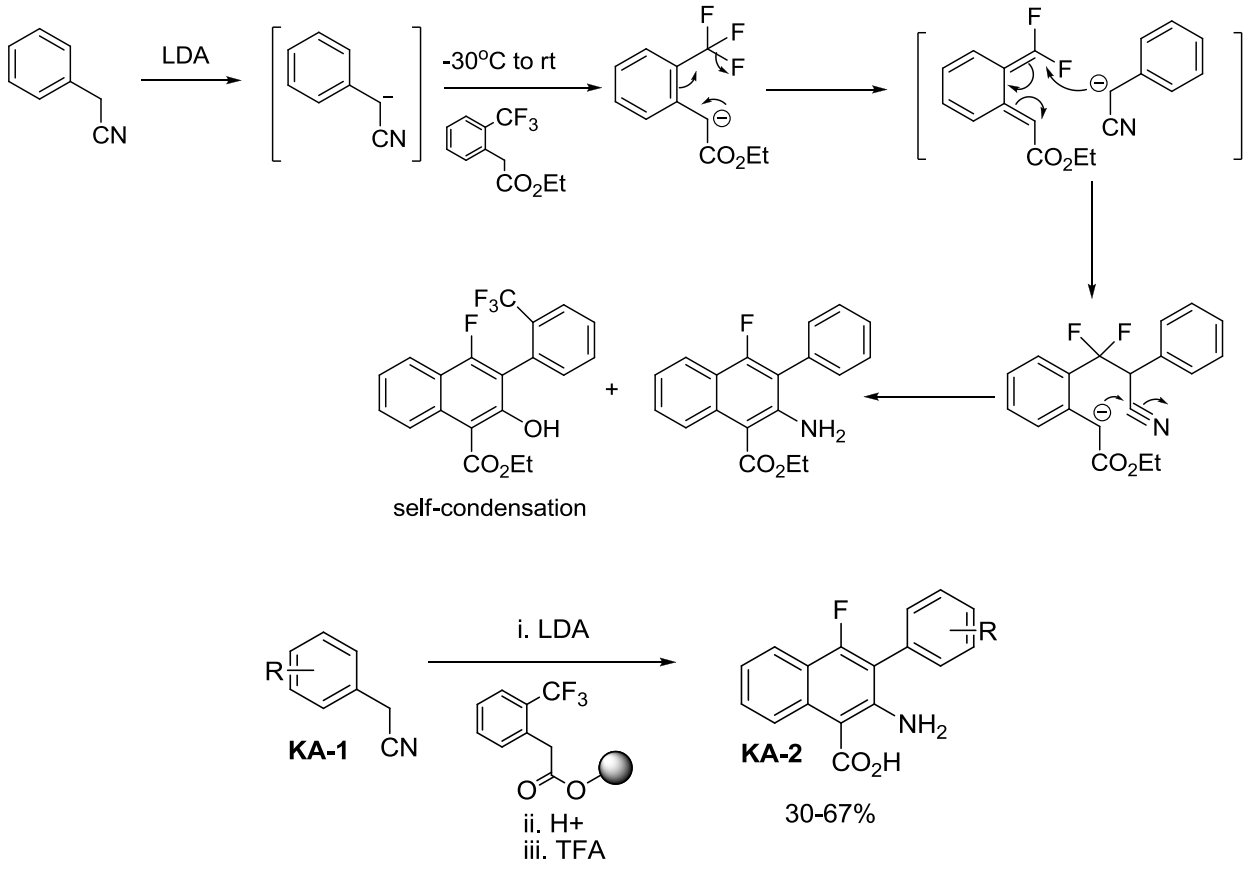
In the course of a study on the total synthesis of calphostil, Merlic and co-workers synthesised an important intermediate naphthylamine **MC-3** by using the Dotz reaction between chromium carbene **MC-1** and *t*-BuNC. As illustrated in **Scheme I-6**, the reaction proceeded through the intermediate ketenimine **MC-2,** which underwent thermal electrocyclisation to afford **MC-3** in 60% yield.[113] This method allows the preparation of highly functionalised naphthylamines, yet its limitation is related to the unstability of the starting carbene.



Scheme I-6

[112] Reddy, R. S.; Prasad, P. K.; Ahuja, B. B.; Sudalai A. *J. Org. Chem.***2013**, *78*, 5045.
[113](a) Merlic, C. A.; Aldrich, C. C.; albaneze-Walker, J.; Saghatelian, A. *J. Am. Chem. Soc.***2000**, *122*, 3224. (b)de Mejiere A.; Shirmer, H.; Duetsch, M. *Angew.Chem Int. Ed.***2000**, *39*, 3964.

A particular case in anionic ring annulations reported by Kiselyov is shown in **Scheme I-7**. In this synthesis, and in order to avoid the problem of self-condensation, ester component was connected to a solid support, allowing the formation of the highly substituted naphthalenes **KA-2** as the sole products in 30-67% yield.[114] To the best of our knowledge, no other examples have since been reported in the literature.



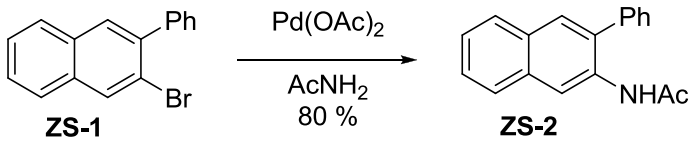
Scheme I-7

ii. Functionalisation of bicyclic systems

Naphthylamines can be constructed efficiently from the corresponding functionalised naphthalenes. An efficient and simple method to access naphthylamine derivatives from

[114] (a) Kiselyov, A. S. *Tetrahedron***2001**, *57*, 5321. (b) Kiselyov, A. S. *Tetrahedron Lett.***2001**, *42*, 3053.

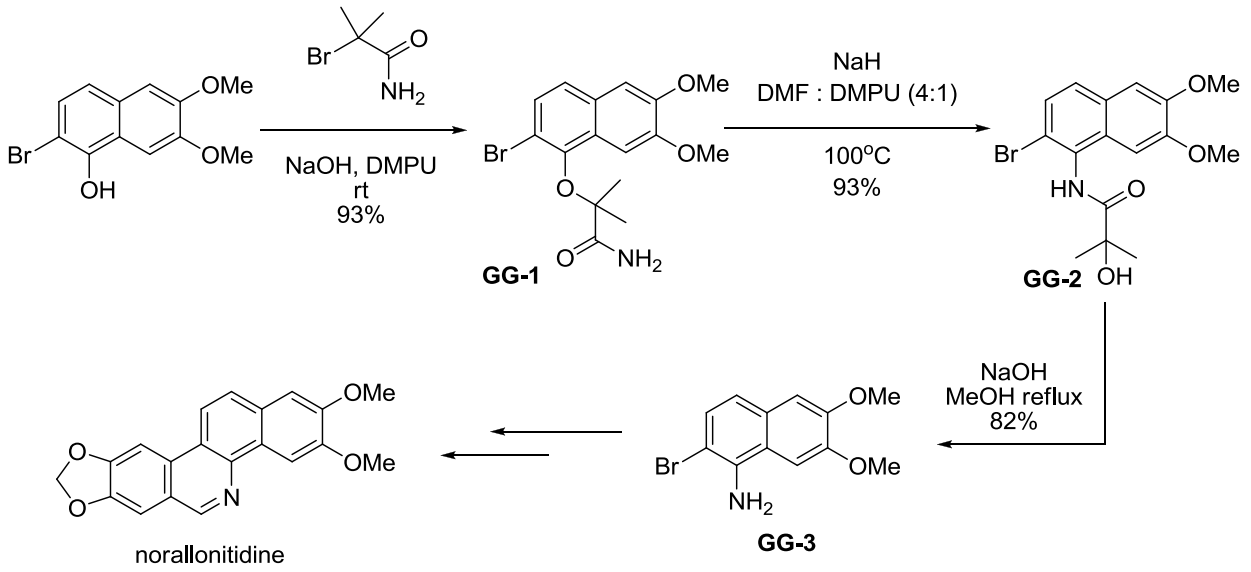
substituted naphthalenes is the Buchwald-Hartwig reaction which hinges on the use of palladium catalysed coupling between aryl halides and amines or ammonia. **Scheme I-8** shows a simple example of this method, the product **ZS-2** was obtained directly by the coupling of bromonaphthalene **ZS-1** and acetamide.[115] The naphthylamide **ZS-2** was obtained in good yield (80%) but a severe limitation of this strategy is that the precursors must possess a halide substituent and such derivatives are not ready available in the naphthalene series.



Scheme I-8

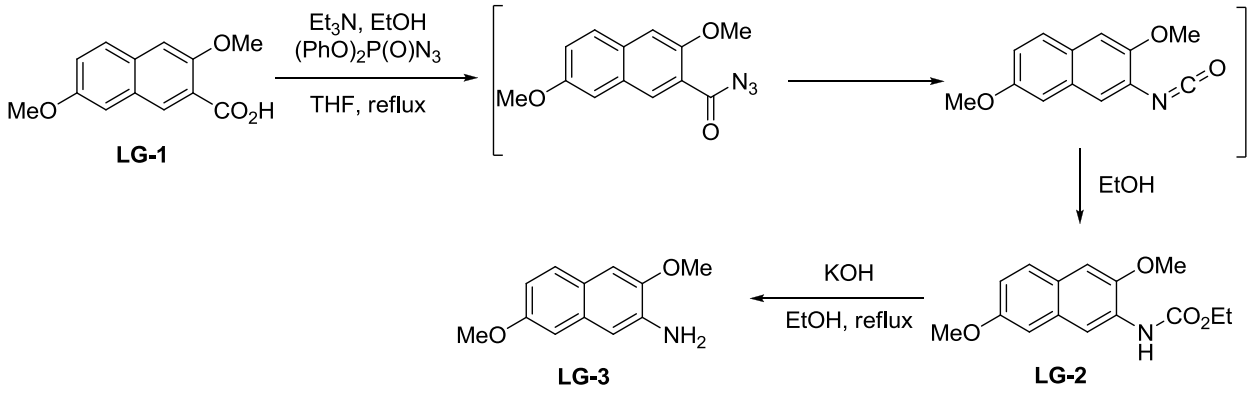
Another route to access naphthylamine derivatives is through a Smiles rearrangement. In the synthesis of the antitumor/anti-viral alkaloid norallonitidine reported by Green *et al.*, intermediate **GG-3** was prepared via Smiles rearrangement of naphthol **GG-1**.[116] As indicated in **Scheme I-9**,treatment of **GG-1** with NaH in a mixture of DMF: DMPU (4:1) at 100^{o}C, followed by deprotection of the amide furnished the corresponding naphthylamine **GG-3** in good yield. The limitation of this method relates to the availability of naphthol precursors.

[115]Zhu, S.; Xiao, Y.; Guo, Z.; Jiang, H. *Org. Lett.***2013**, *15*, 898.
[116]Geen, G. R.;Mann, I. S.; Mullane, M. V.*Tetrahedron***1998**, *54* ,9875.



Scheme I-9

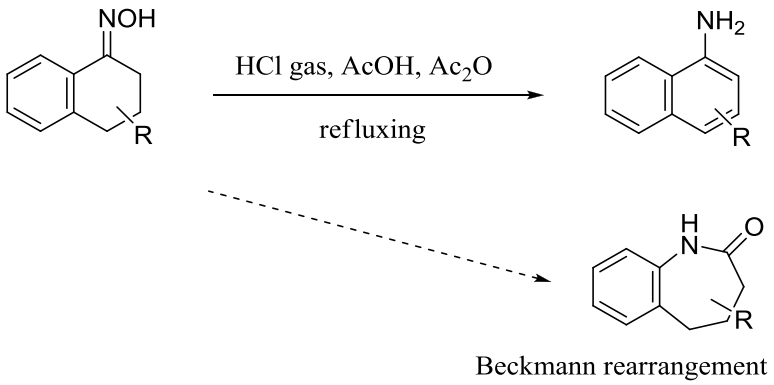
The Curtius rearrangement can be used to generate naphthylamines from the corresponding naphthoic acids. For example, the Kurti group applied this strategy to synthesize naphthylamine **LG-3**. As shown in **Scheme I-10**, the acid functional group in **LG-1** was transformed into the acyl azide, which underwent the Curtius rearrangement to afford an isocyanate. Attack by ethanol gave rise to intermediate **LG-2**, which was then hydrolysed to furnish the naphthylamine **LG-3**.[117] The drawback of this route is the limited availability of the acid precursors.



Scheme I-10

[117]Li, G.Q.; Gao, H.; Keene, C.; Devonas, M.; Ess, D. H.; Kurti, L. *J. Am. Chem. Soc.***2013**, *135*, 7414.

One of the most popular methods for preparation of naphthylamine derivatives is the nitration of naphthalenes followed by the reduction of the nitro group; unfortunately, the regioselectivity of this process is hard to control since the reaction conditions are relatively harsh. Beside nitration and reduction, 1-naphthylamines can also be synthesised by using the Semmler-Wolff/Schroeter aromatisation. As shown in **Scheme I-11**, this reaction consists in the dehydration of the oxime derived from the corresponding α-tetralone under acidic conditions using anhydrous HCl gas in refluxing AcOH/Ac_2O. Yet, because of the harsh conditions, the reaction frequently produces a lactam side-product resulting from a Beckmann rearrangement. Another disadvantage of this process is related to the limited availability of substituted α-tetralones (prior to the advent of our xanthate chemistry), therefore this method has rarely been used.[118]



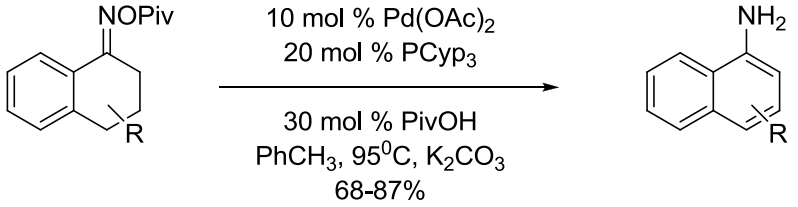
Scheme I-11

Recently, the Stahl group decided to employ Pd as the catalyst for the Semmler-Wolff reaction. Indeed, the efficiency of this process was improved and the α-tetralones can now be converted into naphthylamines in yields ranging from 68% to 87% (**Scheme I-12**).[119] The substituents can be methyl, methoxy, fluorine, nitro or a pivalate-protected alcohol. However, in the case of the

[118] (a) W. Semmler, *Ber. Dtsch. Chem. Ges.***1892**, *25*, 3352. (b) L.Wolff *Justus Liebigs Ann. Chem.***1902**, *332*, 351. (c) G. Schroeter, A. Gluschke, S. Götzky, J. Huang, G. Irmisch, E. Laves, O. Chrader, G. Stier, *G. Ber. Dtsch. Chem. Ges.***1930**, *63*, 1308.

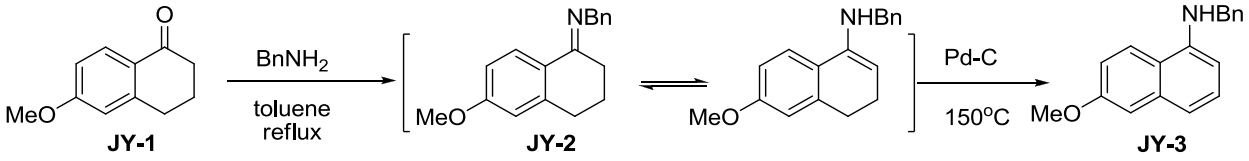
[119] W. P. Hong, A. V. Iosub, S. S Stahl, *J. Am. Chem. Soc.***2013**, *135*, 13664.

substrate possessing a bromine substituent, the reaction could not be accomplished since there was a competition of oxidative addition of the bromoarenes to the palladium complex. This limitation prevented access to bromo or iodo-naphthylamines. As we can see, the preparations of naphthylamine derivatives based on transition metal are efficient; however the availability of the precursors limits its application.



Scheme I-12

The intermediateα-tetralones can be transformed into *N*-substituted naphthylamines by reacting with other amines instead of hydroxylamine but a subsequent oxidative step is necessary. As shown in **Scheme I-13**, the α-tetralone **JY-1**is condensed with benzylamine to afford intermediate **JY-2**, which then is aromatised with Pd-C to furnish the corresponding naphthylamine **JY-3**.[120]



Scheme I-13

Indeed, α-tetralones are very useful bicyclic systems for the synthesis of naphthylamines and naphthalene derivatives more generally since they can be functionalized and aromatised.

Apart from the few methods involving transition metals, no general and simple approaches for the regioselectivitive synthesis of substituted naphthylamines have been established yet. Most of the earlier routes are adapted to specifically strcutres but lacks generality. Since the chemistry of xanthate provides easy approaches to the preparation of α-tetralones structures, it can therefore

[120]Janin, Y. L.; Bisagni, E. *Synthesis***1993**, 53.

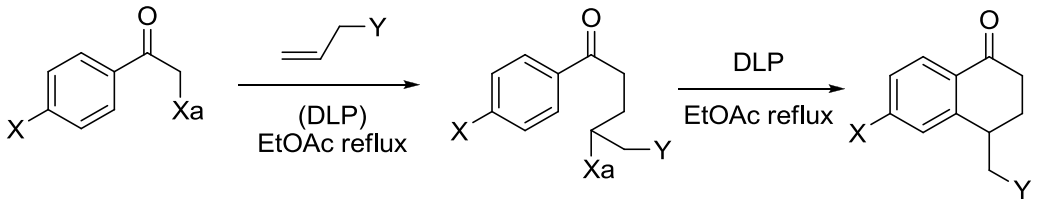
also be applied to access naphthylamines. In the following section, we will present the synthesis of regioselectively substituted naphthylamides by a radical based strategy.

II. Synthesis of naphthylamides using xanthate chemistry

A. Synthesis of 1-naphthylamides

1. Previous work and our strategy

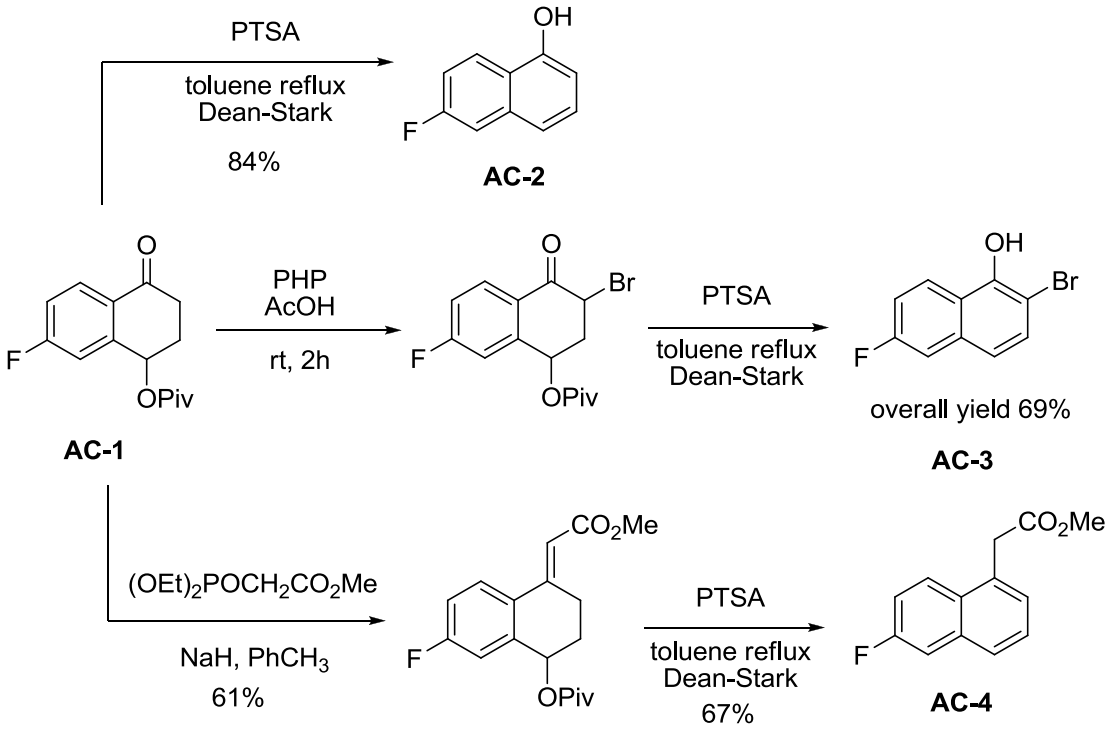
As described in the first chapter, it is possible to construct α-tetralones by a xanthate radical addition-cyclisation sequence under mild conditions (**Scheme II-A1**).[121]



Scheme II-A1

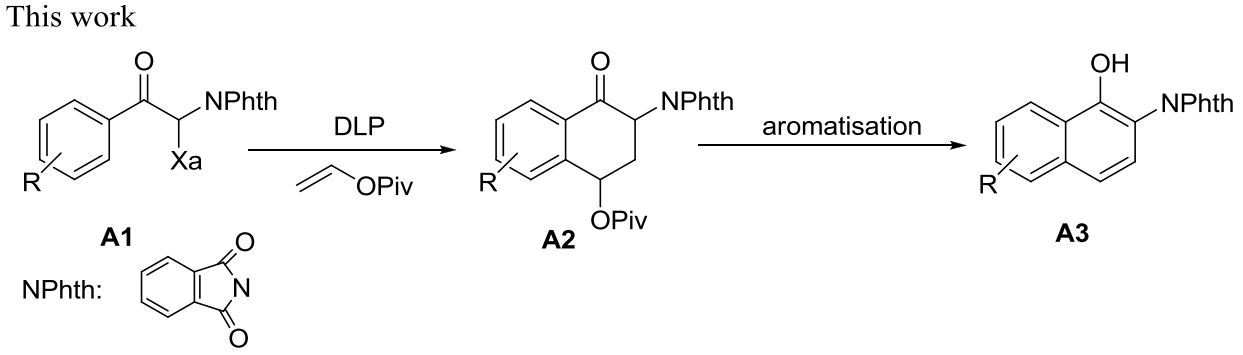
Recently, our group reported the synthesis of regioselectively substituted naphthalenes by aromatisation of α-tetralones. The construction of more complex naphthalenes by functionalizing the α-tetralones beforehand was also accomplished. As illustrated in **Scheme II-A2**, various naphthalenes can be prepared by aromatising simple α-tetralone **AC-1** or modified α-tetralones. For example, α-tetralone **AC-1** underwent the bromination by pyridinium hydrobromide perbromide (PHP) or Wittig reaction before aromatization to afford highly functionalised naphthalenes **AC-3** and **AC-4** respectively. It is useful to have a bromine substituent since it can be later incorporated into various organometallic couplings.[122]

[121] Liard, A.; Quiclet-Sire, B.; Saicic, R. N.; Zard, S. Z. *Tetrahedron Lett.* **1997**, *38*, 1759.
[122] (a) (b) Cordero-Vargas, A.; Pérez-Martin, I.; Quiclet-Sire, B.; Zard, S. Z. *Org. Biomol. Chem.* **2004**, *2*, 3018.



Scheme II-A2

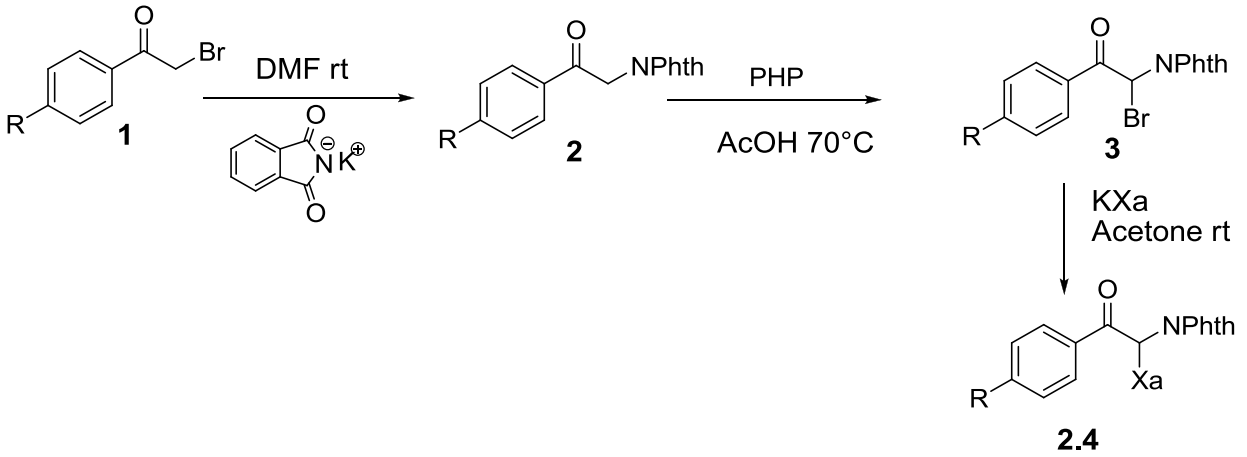
We believed that we could exploit the utility of the xanthate chemistry for the regioselective synthesis of the naphthylamide subfamily. As indicated in **Scheme II-A3,** in order to access 2-naphthylamides,it is necessary to introduce an amino group in the guise of an *N*-phtalimide on the α-position to the carbonyl group in the starting xanthate. These xanthate precursors **A1** would participate in the radial sequence to afford the corresponding substituted α-tetralones **A2**, which would be aromatised to give rise to 2-naphthylamide derivatives **A3**.



Scheme II-A3

2. Results and discussion

The general synthetic route we adopted[123] is displayed in **Scheme II-A4**. The sequence started with the treatment of readily available α-bromoacetophenone precursors**1** with potassium phtalimide in DMF at room temperature to furnish compounds**2**. The solid products **2** were easily collected by filtration, followed by washing with water. The nucleophilic substitutionswere very efficient, with most yields over 90%.



Scheme II-A4

According to the literature, the bromination of **2**was accomplished with pyridinium hydrobromide perbromide (PHP) in acetic acid at 70°C.[124]After 4 hours heating, the conversion was around 60% (the bromide derivatives were identified by their single peak at 7.48 ppm in the ^{1}H NMR.The reaction was stopped because no further progress was observed after heating for longer time. After work-up, it was not necessary to purify the crude mixtures; they were used directly to the following step.

The substitution of α-bromine in compounds **3** by potassium *O*-ethyl xanthate in acetone was carried out smoothly at room temperature rather than at 0^{o}C so that intermediates **3** could be better dissolved. Xanthates **2.4** were isolated by silica gel column chromatography. These xanthates were obtained as white or light pink solids.

[123]Thesis of Nadajda Stoeva Spassova 2000 in DCSO Ecole Polytechnique.

[124](a) Liu, Y.; Jiang, B.; Zhang, W.; Xu Z.*J. Org. Chem.* **2013**, *78*, 966. (b) Low, D. W.; Pattison, G.; Wieczysty, M. D.; Churchill, G. H.; Lam, H. W. *Org. Lett.***2012**, *14*, 2548. (c) Arrieta, A.; Ganboa, I.; Palomo, C. *Synthetic Comm.***1984**, *14*, 939.

The results are summarised in **Table II-A1**; xanthates **2.4a – 2.4e** were easily synthesised in moderate yields after the 3-step-sequence. These xanthate precursors are stable and easy to handle. Except for the xanthate product **2.4a (**57% yield) bearing no substituent, the other xanthates have various subsituents such as *p*-fluoro (**2.4b**, 54% yield), *p*-bromo (**2.4c**, 54% yield), *p*-chloro (**2.4d**, 55% yield) and *p*-CF_3 (**2.4e**, 53% yield). These substituents was chosen because they could be useful for other transition-metal-catalysed couplings (Br, Cl) or for applications in medicinal chemistry (F, CF_3). In addition, as we mentioned above, the preparation of bromonaphthylamine was not feasible by methods involving transition metals. The choice of bromide substituent would highlight the generality of this xanthate-based methodology.

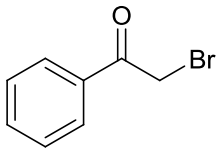
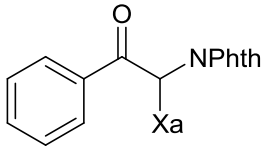
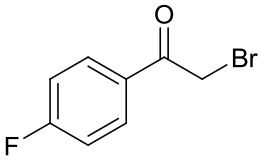
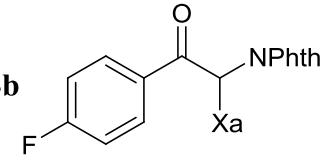
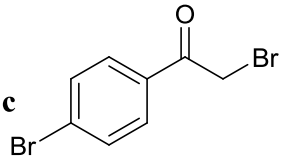
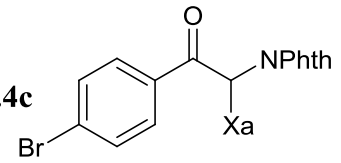
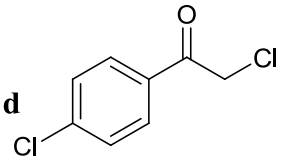
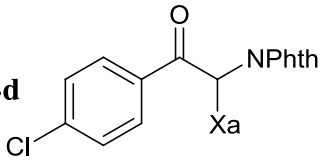
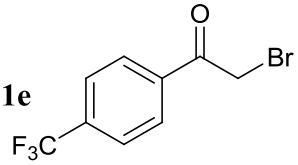
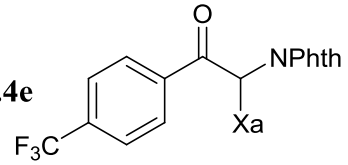
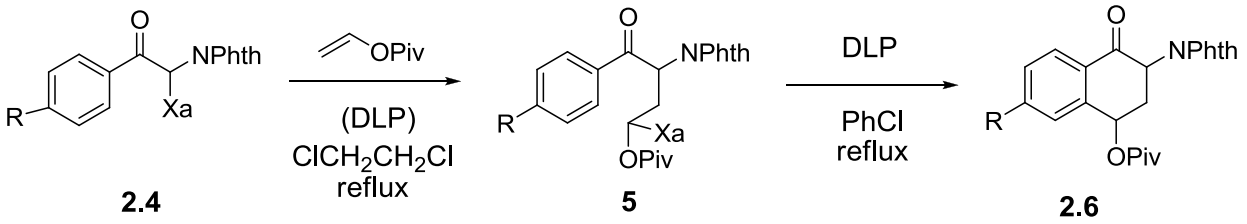
Precusors 1	Xanthate 2.4	Yield (%)
1a 	**2.4a** 	57
1b 	**2.4b** 	54
1c 	**2.4c** 	54
1d 	**2.4d** 	55
1e 	**2.4e** 	53

Table II-A1

With the starting xanthates **2.4** in hand, we carried out the addition-cyclisation sequence (**Scheme II-A5**). Vinyl pivalate was chosen as the olefin for this process since it is volatile so one-pot sequence can be used,furthermore, the conditions for aromatisation of α-tetralones **A2** would be simpler. The radical addition of xanthates **2.4**to vinyl pivalate generated adducts **5**after using 25-30 mol% of initiator dilauroyl peroxide (DLP). Normally, the required amount of DLP to finish radical addition reaction for the substrates non-bearing *N*-phthalimide group was only 10 mol%. In this work, to finish the reaction addition, more DLP was needed.



2.4 **5** **2.6**

Scheme II-A5

After the complete consumption of starting xanthates **2.4**, the solvent and excess of vinyl pivalate were evaporated. The resulting xanthates **5** were used as precursors for the next cyclisation step. It is not necessary to isolate the addition adducts**5**. The residue was taken up in chlorobenzene, and treated with stoichiometric amounts of DLP. Under these conditions, the intermediates **5**underwent cyclisation to furnish the bicyclic structures **6.** The xanthate-based radical addition/cyclisation sequence was applied successfully for the construction of the desired tetralones **6**in moderate yields varying from 37% to 45%. The results are assembled in **Table II-A2**. These modest, albeit unoptimised yields are mostly due to the difficult cyclisation step. It is important to remember that the intermolecular addition to unactivated alkene such as vinyl pivalate as well as the cyclisation onto the aromatic ring are not trivial and cannot be easily accomplished by other conventional radical methods.

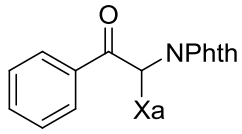
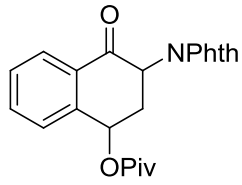
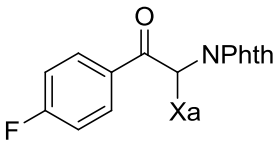
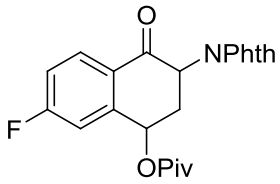
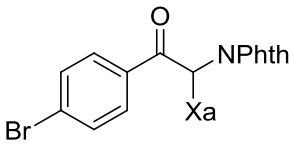
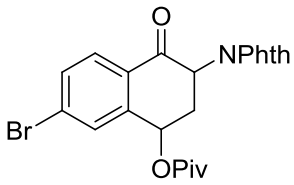
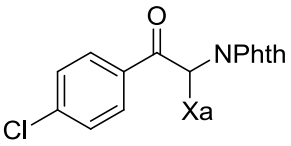
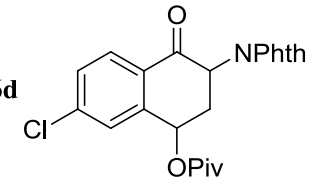
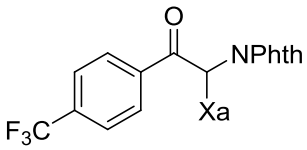
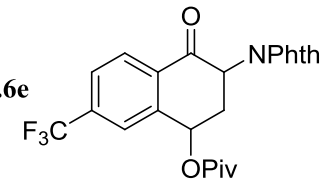
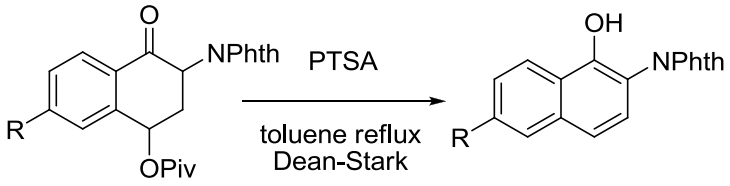
Xanthates 2.4	Tetralones 2.6	Yield (%)
2.4a 	**2.6a** 	42
2.4b 	**2.6b** 	45
2.4c 	**2.6c** 	40
2.4d 	**2.6d** 	37
2.4e 	**2.6e** 	41

Table II-A2

With these α-tetralones in hand, we next examined the aromatization step. According to the literature, numerous methods such as oxidation with DDQ or Pd-C at high temperature[125] or heating under acidic conditions[126]have been documented. In this study, we decided to heat these α-tetralones **2.6** under acidic conditions. The treatment of tetralones **2.6** with *p*-toluenesulfonic acid in refluxing toluene using a Dean-Stark apparatus for 3 hours furnished the protected naphthylamines**2.7** as expected (**Scheme II-A6**).

[125] (a) L. Martarello, D. Joseph, G. Kirsch, *Heterocycles*, **1996**, *43*, 367; (b) D. Joseph, L. Martarello, G. Kirsch, *J. Chem. Research (S)*, **1995**, 448. (c) S. Sekiguchi, M. Hirai, E. Ota, H. Hiratsuka, Y. Mori, S. Tanaka,*J. Org. Chem.* **1985**, *50*, 5105.

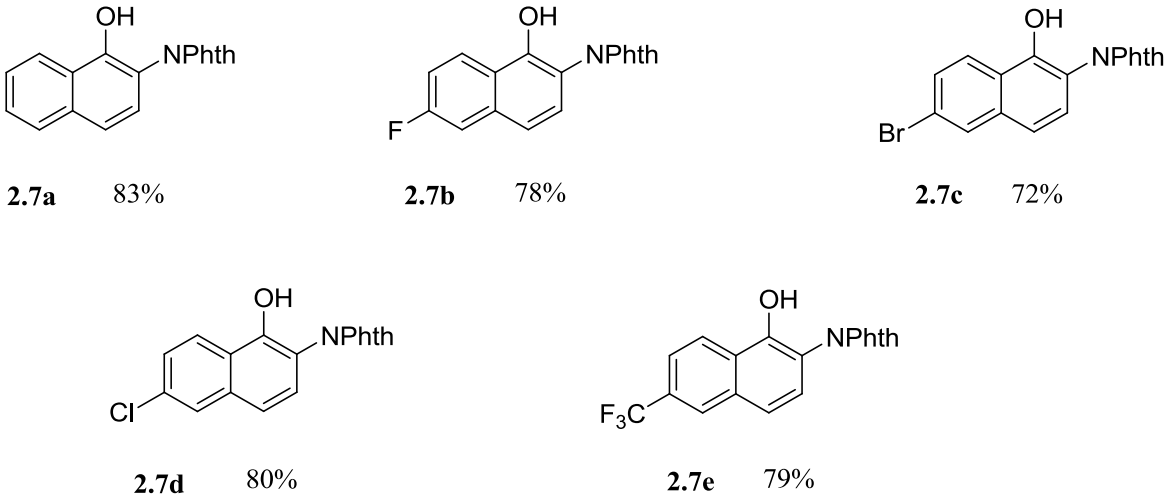
[126](a) Cordero-Vargas, A.; Pérez-Martin, I.; Quiclet-Sire, B.; Zard, S. Z.*Org. Biomol.Chem.***2004**, *2*, 3018.



2.6 **2.7**

Scheme II-A6

This aromatisation step was very efficient and the yields were high (up to 83% yield) (**Figure II-A1**). The purification process was very easy; no purification by silica gel column chromatography was required. After workup and evaporation, we only needed to wash the residues with pentane or dichloromethane, and the naphthylamide derivatives were collected as crystalline solids.



2.7a 83% **2.7b** 78% **2.7c** 72%

2.7d 80% **2.7e** 79%

Figure II-A1

Since 2-naphthylamines are generally carcinogenic, the removal of the phthalimide group was not affected. It is worth emphasizing that none of the substituted 2-amino-1-naphthols **2.7b-2.7e** has been described in the literature yet**.** Only the simplest unsubstituted 2-amino-1-naphthol corresponding to **2.7a** has been reported previously.

In conclusion, this step completed the six-step-sequence leading to the synthesis of 2-naphthylamides from the readily available 2-bromo-1-(4-substituted-phenyl)ethanones. Among

those steps, some of them did not require the isolation of intermediates. The simple and easy-to-perform synthesis allows us to access the 2-naphthylamide family which is not easily prepared by other methods. The substitution is regioselective and the final products have the unique structure of 2-amino-6-substituted-naphthol.

It is worth noting that the application of the radical chemistry of xanthate allows the presence of halide substituents, which are particularly valuable and not always easily accessible. Even though the yields of this method are not as high as those in recent methods involving to transition metals, this sequence provides a concise synthesis of regiocontrolled substituted 2-naphthylamides with a wide range of useful substituents. Moreover, this strategy starts with the α-bromoacetophenone precursors **1** many ofwhich are cheap and commercially available.

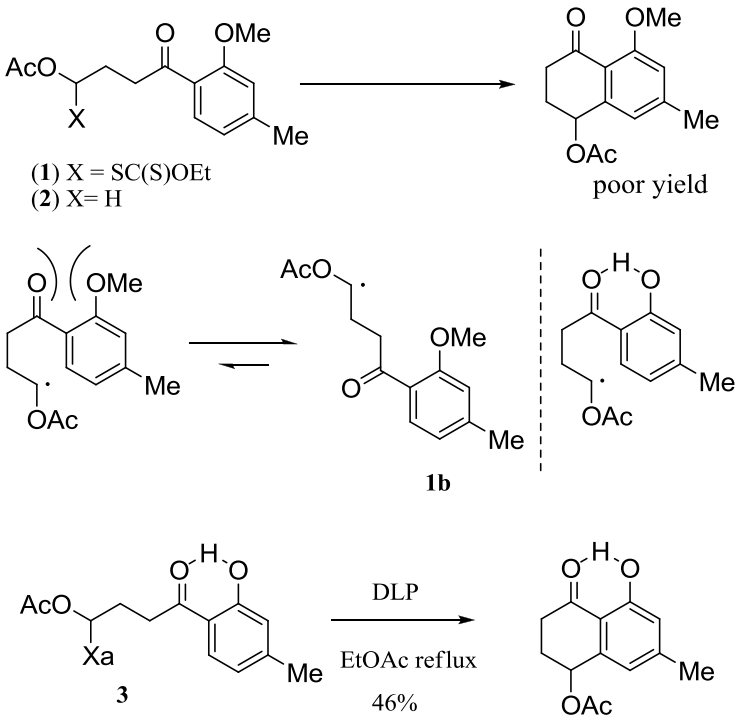
B. Synthesis of 1-naphthylamides by xanthate chemitry

1. Previous work and our strategy

From a previous study[127] on the synthesis of α-tetralones, we had found that when the substrate possessed an ortho-substituent to the acyl chain, especially a methoxy group, the cyclisation became very hard and the yield dropped dramatically. This factor can be explained by a combination of steric and dipole-dipole repulsions (**Scheme II-B1**). It was reamarkable to find out that this problem could be solved efficiently by simply using the naked phenol instead of a protected phenol. In this case, the yield attainted to 46% in the case of compound **3.** In fact, the naked phenol present in the compound **3** forms a strong intramolecular hydrogen bond with the oxygen of adjacent acyl chain. This hydrogen bond not only helps to freeze the structure in a favorable conformation for the cyclisation step but also helps to slow down the hydrogen abstraction rate from the phenol.[128] Indeed, the radical addition/ cyclisation sequence could be accomplished with unprotected phenol.

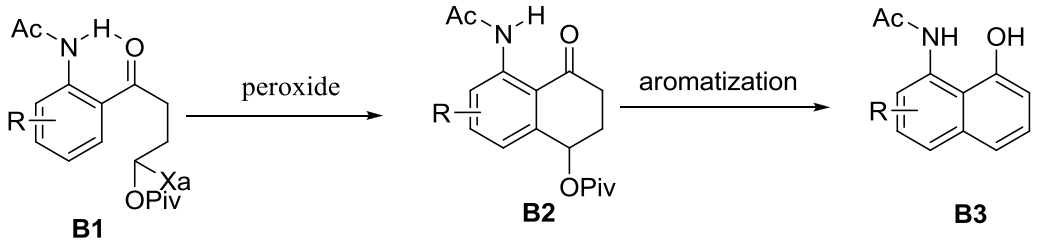
[127] L. Petit and S. Z. Zard, *Chem. Commun*., **2012**, *46*, 5148

[128](a) H. Zweifel, *Stabilization of Polymeric Materials*, Springer, Berlin, **1997**. (b) D. V. Avila, K. U. Ingold, J. Lusztyk, W. H. Green, D. R. Procopio, *J. Am. Chem. Soc*., **1995**, *117*, 2929.



Scheme II-B1

We decided to apply this observation in the synthesis of 1-naphthylamide derivatives. As presented in the **Scheme II-B2,** in the same manner, the acetamide group should display the same hydrogen bond which would facilitate the formation of bicyclic structure **B2**. After aromatisation, the systhesis of 1-naphthylamides **B3** would be accomplished.

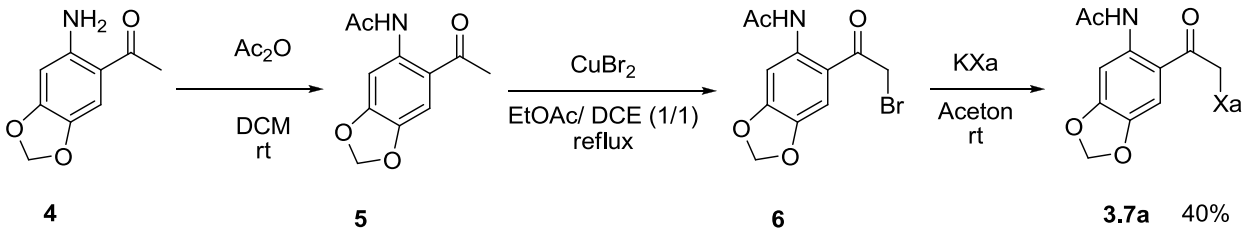


Scheme II-B2

2. Preliminary results

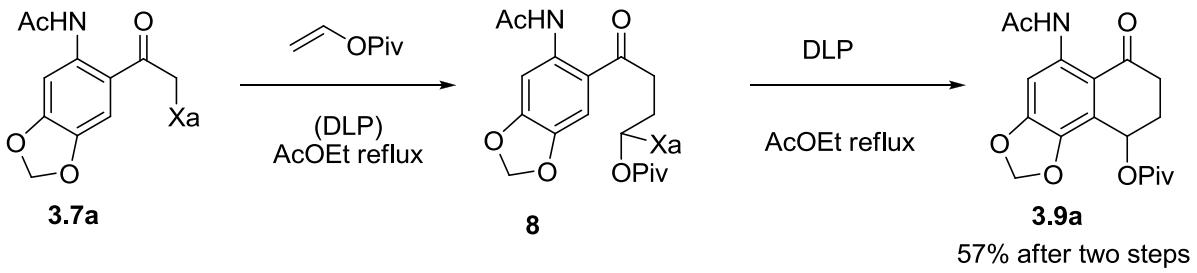
First of all, it was necessary to prepare a xanthate precursor to test our hyphothesis. We decided to start with readily available 1-(6-aminobenzo[d][1,3]dioxol-5-yl)ethanone **4** as a precursor. As depicted in **SchemeII-B3,** after the protection of the amine function by treatment with acetic

anhydride in dichloromethane at room temperature, the resulting product **5** was brominated with $CuBr_2$ in a refluxing mixture 1:1 of ethyl acetate and chloroform. We chose this method to brominate **5** since the aromatic nucleus is very electron rich and if Br_2 or pyridinium hydrobromide perbromide (PHP) were used, there would be the risk of also brominating the aromatic ring. The reaction proceeded smoothly to furnish bromide **6. T**he α-bromine in the compound **3** was easily substituted by potassium *O*-ethyl xanthate to provide the starting xanthate **3.7a** in quantitative yield. The overall yield for the three-step-sequence was 40%.



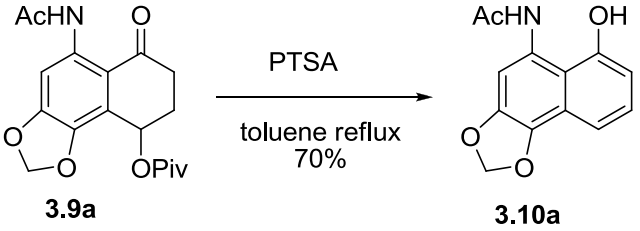
SchemeII-B3

With the xanthate **3.7a** in hand, we carried out the addition reaction. As for the synthesis of 2-naphthylamides, we decided to use the vinyl pivalate as the olefin so that the aromatisation would be easy to achieve under acidic conditions. The xanthate-based radical addition-cyclisation procedure of precursor **3.7a** is outline in **Scheme II-B4**. First, the addition of xanthate **3.7a** to vinyl pivalate furnished adduct **8**. After complete consumption of xanthate **3.7a**, the solvent and excess vinyl pivalate were evaporated. The addition was very efficient and xanthate **8** was clean enough to be used in the following step. To perform the cyclisation of compound **8,** the standard conditions were used as in the case of compound **3**, where hydrogen bond supports the formation of α-tetralone. Xanthate **8** was treated portion-wise with DLP (10 mol% in every hour) in refluxing ethyl acetate. The reaction was complete after the addition of 1 equivalent of DLP. We were pleased to find that the transformation of xanthate **8** into the bicylic system **3.9a** took place smoothly giving a 57% yield for the two steps. Compared to the case of synthesis of 2-naphthylamides, this reaction appears much more efficient. It is undeniable that the hydrogen bond has played a crucial role in this cyclisation.



Scheme II-B4

Finally, the exposure of **3.9a** to *p*-toluenesulfonic acid in refluxing toluene using Dean-Stark apparatus for 3 hours furnished 1-naphthylamide **3.10a** in good yield (70%) (S**cheme II-B5**).

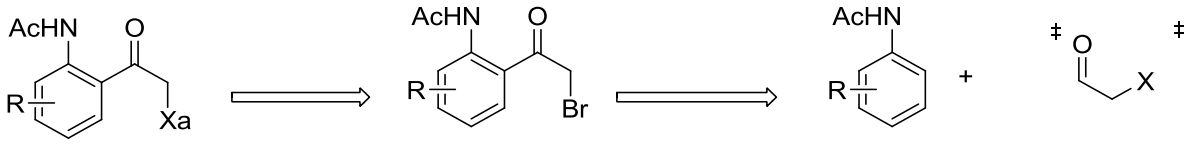


Scheme II-B5

With this promising result, we decided to explore the scope of this approach by modifying the substituents around the aromatic ring. First of all, we needed to synthesize the xanthate precursors as they are not commercially available.

3. Synthesis of the xanthate precursors

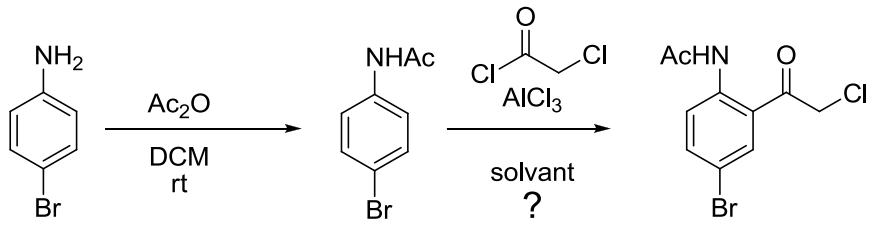
Numerous substituted anilines are commercial products and represent convenient pool of starting materials. The retrosynthesis of xanthate precursors is presented in **Scheme IV-B6**.



Scheme II-B6

i. Friedel-Crafts reaction

We first considered using a Friedel-Crafts reaction between the protected anilines and chloroacetyl chloride. If the reaction is successful, the synthesis of xanthate would be very simple. 4-Chloroaniline was chosen to test this possibility. However, the Friedel-Crafts acylation cannot be performed in the presence of an unprotected amine group since the basic nitrogen of amine group easily coordinates with the $AlCl_3$ Lewis acid, turning the system from being rich in electron to being poor in electron. As the consequence, the amine group was protected by treatment with acetic anhydride in dichloromethane at room temperature. This protected aniline, which is rather rich in electron because of the electron donating of acetamide group, was exposed to trichloroaluminium under several different conditions. The results are summarized in **Table II-B1**.



Solvent	Temperature	Result
DCM	rt	No reaction
DCE	90°C	No reaction
Nitropropane	130°C	No reaction

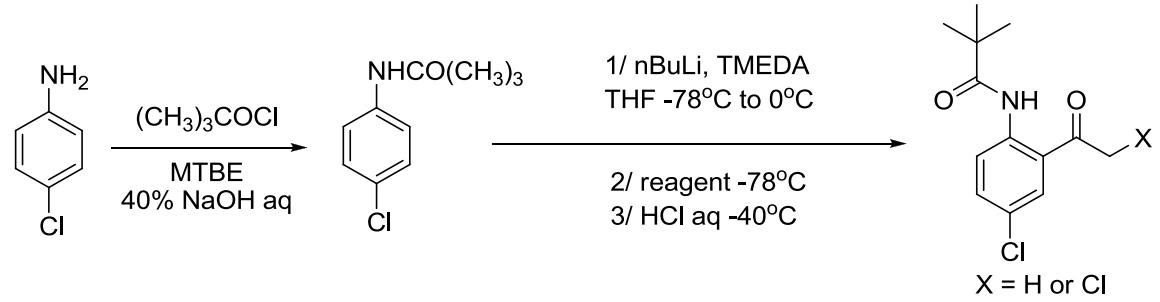
Table II-B1

Several other conditions were attempted without success. We also examined 4-methylaniline as the substrate since methyl group is an electron-donating group but no reaction occurred, and all we could obtain were the starting materials. One possible explanation is that even after

protection, the nitrogen still coordinates with Lewis acid $AlCl_3$ and deactivates the whole system completely towards a Friedel-Crafts acylation.

ii. nBuLi utilisation

Another approach to synthesize these precursors was investigated. Instead of using Lewis acid, the use of basic conditions was attempted. Recently the Zang group reported a sequence to attach an acetyl group onto the aromatic ring of protected anilines under basic conditions.[129] We repeated the same operation on 4-chloroaniline (**Scheme II-B7**), however the yield was much lower than the one reported in the literature (in the publication, the yields were all greater than 50% for various para-substituents such as bromine, methoxy, hydroxyl and trifluoromethyl).



Scheme II-B7

As assembled in the **Table II-B2**, several attempts were carried out, using the same reagent, ethyl acetate, as the Zang group afforded only 15% of desired product and the rest was starting material. Ethyl choloroacetate was also used but the yield was dropped to 10%. We moved to the more reactive reagent such as acetic anhydride and Weinreb amide but none of them gave satisfactory results (28% and 27% respectively). We also tried to increase the temperature to -40°C while adding the reagent, but the results turned out to be even worse.

[129]Zhu, L.; Miao, Z.; Sheng, C.; Guo, W.; Yao, J.; Liu, W.; Che, X.; Wang, W.; Cheng, P.; Zang, W. *Eur. J. Med. Chem.***2010**, *45*, 2726.

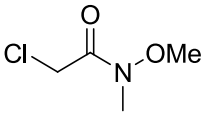
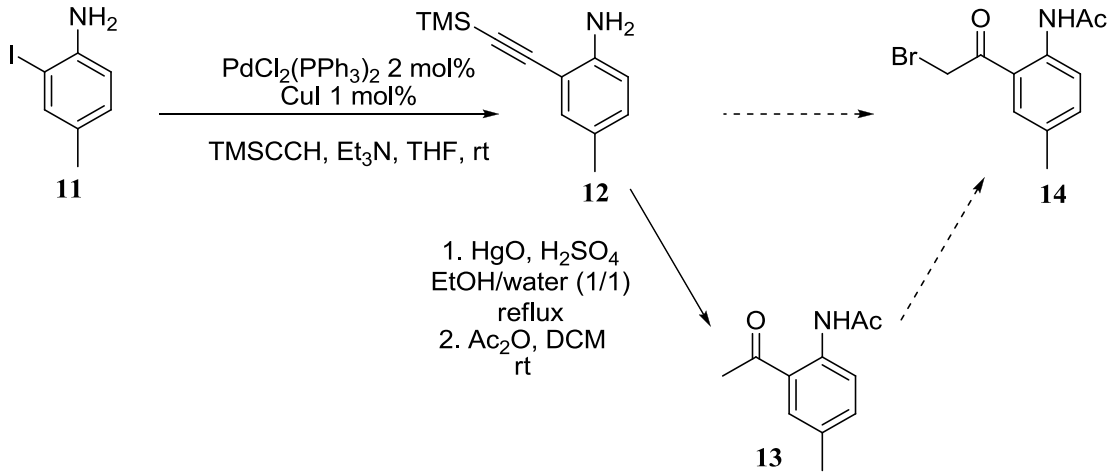
Reagent	Result
CH_3COOEt	15 %
$ClCH_2COOEt$	10 %
$(CH_3CO)_2O$	28 %
	27 %

Table II-B2

iii. Sonogashira coupling

To overcome the difficulties we encountered so far, we examined an alternative route which is longer but have a high possibility of being more efficient (**Scheme II-B8**). It also starts from the substituted anilines and employs the chemistry of palladium in a Sonogashira coupling to attach a trimethylsilyl acetylene to the substituted anilines. Indeed, product **12** was obtained in a quantitative yield from aniline **11**. Now our next task was to transform the triple bond into a bromoacetyl group. According to classic chemistry, it is possible to convert the triple bond into an acetyl group with a catalytic amount of HgO under acidic conditions. Indeed, treatment of substrate **12** with 3 mol% of HgO in the presence of H_2SO_4 in a refluxing mixture of 1:1 ethanol:water followed by acetylation of the amino group gave rise to adduct **13** in 90% yield.



Scheme II-B8

With compound **13** in hand, we tried to convert it into the requisite bromide **14**. This seemingly trivial transformation proved in fact much more problematic than expected. As shown in **Table II-B3**, the reaction with bromine furnished only a mixture of compounds and, furthermore, it proved difficult to isolate the products since all are crystalline and possess quite similar R_f.

Reagent	**T°**	**Equivalent**	**Results**
$Br_2/CHCl_3$	0°C	1.1	SM
$Br_2/CHCl_3$	rt	1.1	SM
$Br_2/CHCl_3$	90°C	1.1	SM + monobromo + dibromo
$Br_2/CHCl_3$	90°C	3	monobromo + dibromo (1:4)
PHP/AcOH	120°C	1.1	SM + monobromo + dibromo
PHP/AcOH	70°C	1.1	SM + monobromo
$CuBr_2$/AcOEt:$CHCl_3$	90°C	2.1	SM + monobromo + dibromo

Table II-B3

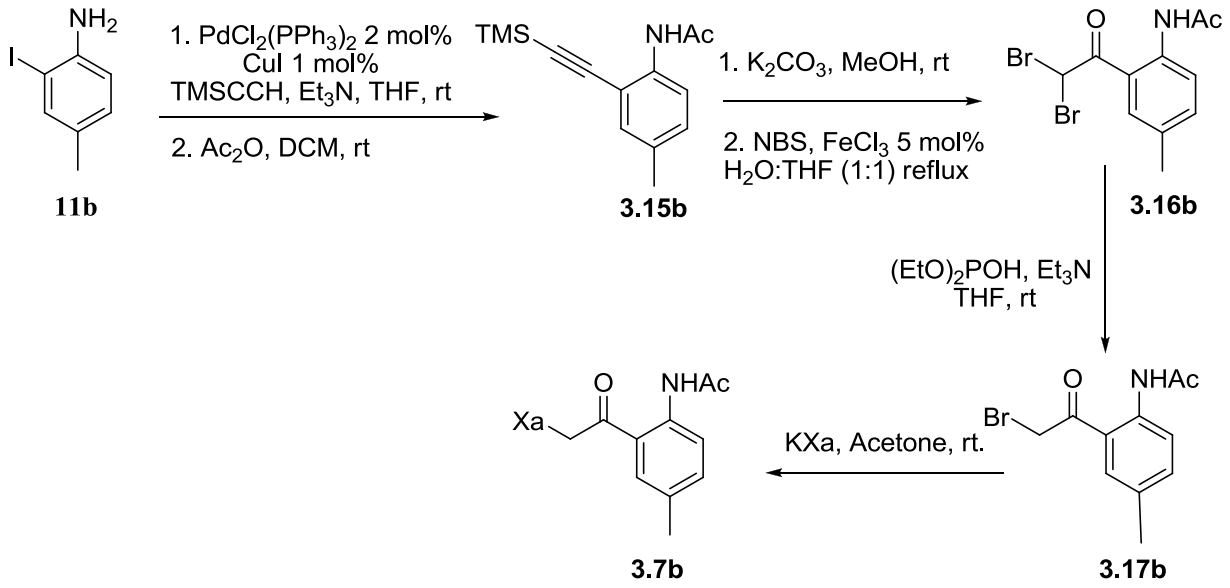
Therefore the crude mixture of the bromides was used directly for the xanthate substitution step. However, when the crude mixture of starting material and monobromide was reacted with

potassium *O*-ethyl xanthate, the resulting mixture could not be separated efficiently to give the corresponding xanthate because the xanthate and the starting acetophenone have nearly the same polarity.

An alternative was to reduce the crude mixture of monobromo and dibromoacetophenone with diethyl phosphite $(EtO)_2POH$ so as to convert the latter to the former and hus simplify the access to the desired xanthate. However, with the drawback of using toxic HgO in addition to a lack of route to the α-bromo acetyl derivative, we considered another pathway to transform the triple bond into bromoacetophenone.

iv. Final attempt: Sonogashira coupling and NBS oxidation

Several recent publications have described the conversion of terminal triple bond of arylalkynes into dibromoacetophenones with NBS.[130] This transformation could solve our problem in accessing the desired xanthate precursors. Our strategy is presented in **Scheme II-B9.**



Scheme II-B9

[130](a) Zu, Y.; Jie, F.; Liu, M.;Wu, A. *Org. Lett.*, **2012**, *14*, 4414. (b) Yadav, J. S.; Reddy, B. V. S.; Singh, A. P.; Basak, A. K. *Tetrahedron Lett.*, **2008**, *49*, 5880. (c) Yang, X.; Yuan, L.; Yamato, K.; Brown, A. L.; Feng, W.; Furukawa, M.; Zeng, X. C.; Gong, B. *J. Am. Chem. Soc.*, **2004**, *126*, 3148. (d) Liu, J.; Li, W.; Wang C.; Li, Z. *Tetrahedron Lett.*, **2001**, *52*, 4320.

The starting amine **11b** underwent clearly the Sonogashira coupling, and protection of the amino group furnished product **3.15b.** Treatment with potassium carbonate in methanol at room temperature cleaved the trimethylsilyl group. The terminal triple bond was then transformed into dibromoacetyl by heating with *N*-bromosuccinimide in the presence of iron trichloride catalyst in a refluxing mixture of water and tetrahydrofuran. This two-step sequence provided the intermediate α-dibromo derivative **3.16b** in 57% yield. This compound was easily reduced into the α-bromo derivative **3.17b** by exposure to diethyl phosphite $(EtO)_2POH$ and triethylamine in tetrahydrofuran at room temperature.[131] Subsequently, the substitution of the bromine by potassium *O*-ethylxanthate provided the xanthate precursor **3.7b** in almost quantitative yield after the two steps.

Compared to the sequence using n-BuLi, this sequence is longer, however most of its steps are every efficient, except for the transformation of the triple bond into dibromoacetyl group with a yield around 60%. It is worth noting that it is important to eliminate the dark color of product **3.15b** by chromatography or by recrystalisation before treating with NBS, otherwise the yield of this step drops dramatically. This sequence is general and practical for the synthesis of xanthate precursors. In the same manner, the xanthates bearing *p*-trifluoromethyl (**3.7c**) or *p*-bromide (**3.7d**) substituent were synthesized in 53% and 58% yields respectively (**Table II-B4**).

[131]Diwu, Z.; Beachdel, C.; Klaubert, D. H. *Tetrahedron Lett.*,**1998**, *39*, 4987.

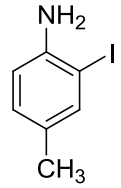
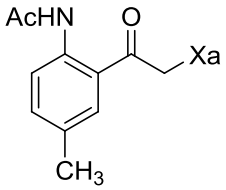
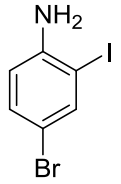
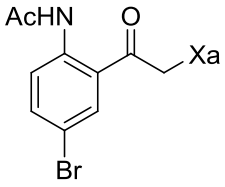
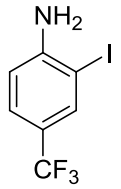
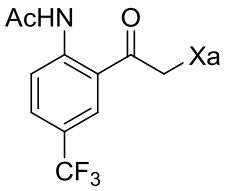
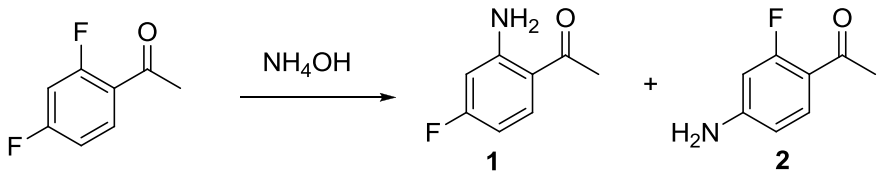
Precusors 11	Xanthate 3.7	Yield
11b 	**3.7b** 	49
11c 	**3.7c** 	53
11d 	**3.7d** 	48

Table II-B4

Apart from bromide and trifluoromethyl substitution, another interesting example is the fluoro derivative which was prepared from the 2,4-difluoroacetophenone by substitution of ammoniac. The presence of secondfluorine in the structure would allow further substitution later.

First of all, the substitution of fluorine by ammonia was carried out. As shown in the **Table II-B5**, the reaction between 2,4-difluoroacetophenone and ammonia in a mixture of 1,2-dimethoxyethane and water did not take place at room temperature. When the temperature was increased to 100^{o}C, the reaction advanced a little after 2 days: there were traces of product as judged by TLC, but much starting material remained. At 140^{o}C, reaction was complete after 15 hours. The change of solvent to a mixture of dimethylformamide and water did not affect. It has been known that microwave irradiation often leads to reduced reaction times and improved yields. We therefore heated the components in a microwave oven with the hope of speeding the process. Indeed, the reaction was complete after only 4 hours in dimethoxyethane and water, and was even faster when water was the only solvent. The most appropriate conditions for substitution of fluorine were the use of 25% ammonia under microwave irradiation at 130^{o}C and

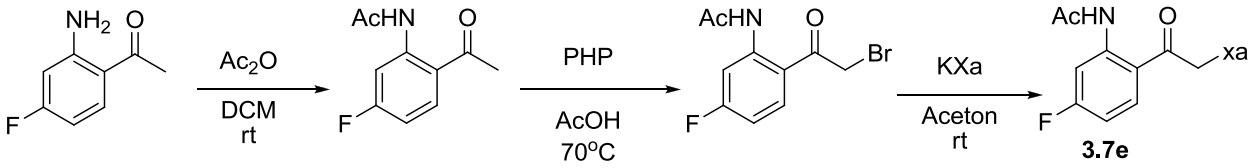
16 bars.The reaction time was 3hourscompared to 15 hours without microwave irradiation. In all cases, the mixture of the isomeric anilines **1** and **2** were obtained which were separated by chromatography.



Solvent	**T(^{o}C)**	**Time**	**Results (1:2)**
Dimethoxyethane/water (1/3)	rt	2 days	No reaction
Dimethoxyethane/water (1/3)	100	2 days	Trace of products
Dimethoxyethane/water (1/3)	140	15 h	1:2
DMF/water (1/3)	140	20 h	1:2.2
Dimethoxyethane/water (1/3)	120^{o}C and 16 bars	4 h	1:2
Water	130^{o}C and 16 bars	3 h	1:2.5

Table II-B5

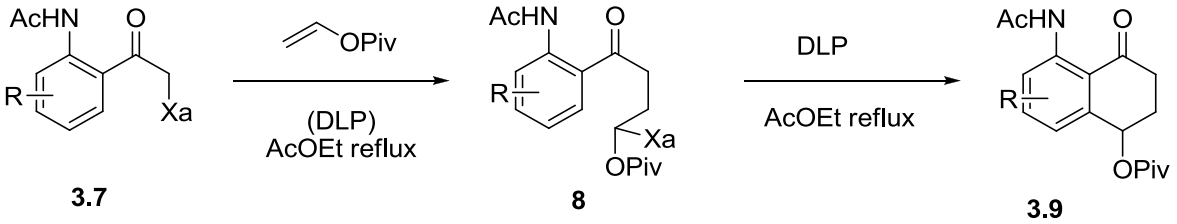
The2’-amino-4’-fluoroacetophenone**1** was acetylated and brominated with pyridinium hydrobromide perbomide in acetic acid at 70^{o}C. Subsequent substitution provided xanthate **3.7e (Scheme II-B10)**.



Scheme II-B10

4. Results and discussion

The same conditions for the radical addition and cyclisation employed in the case of**3.7a**(R = OCH_2O) were applied to the xanthate precursors **3.7b -3.7e (Scheme II-B11)**.



Scheme II-B11

In the case of **3.7d**(R = *p*-CF_3) and **3.7e**(R = *m*-F),the addition reactions were finished afteraddition of only 10 mol% of DLP resulting a fairly clean formation of addition products. In contrast, substrates**3.7b (**R = *p*-CH_3**)** and **3.7c (**R = *p*-Br**)**, the intermediate addition product started to cyclise after the consumption of around 40% ofthe starting material. In other words, the closure of the intermediate radical onto the aromatic ring occurred despite the presence of starting xanthates and olefins in the reaction mixture. In consequence, we decided to modify the procedure by adding portion-wise in 10 mol% amount a stochiometric amount of DLP to the mixture of xanthate and vinyl pivalate to generate directly the cyclised products **3.9b**and **3.9c**in a yield of48% and 51% respectively. The formation of desired bicyclic compound **3.7d** and **3.7e** were also accomplished in 60% and 65% overall yields respectively after exposure of intermediate addition product **8d** and **8e** to 1 equiv DLP (adding 10 mol% every hour) in refluxing ethyl acetate (**Table II-B6**). The obtained yields of these one pot procedures were higher than in the case of 2-naphthylamides. Based on these experimental results, we could

conclude that the role of intermolecular hydrogen bond is high beneficial for promoting the cyclisation onto the aromatic nucleus.

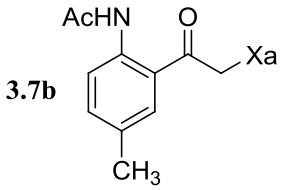
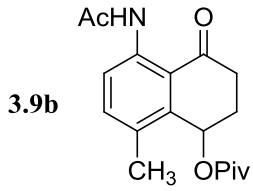
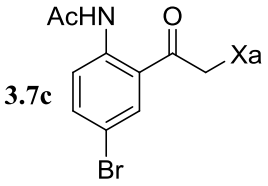
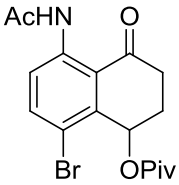
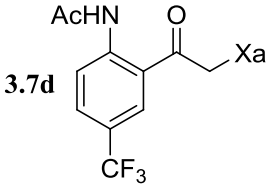
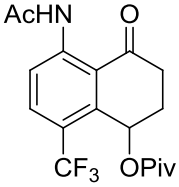
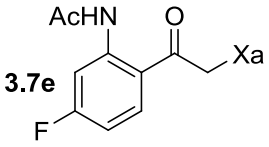
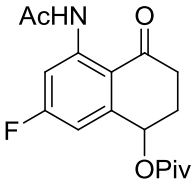
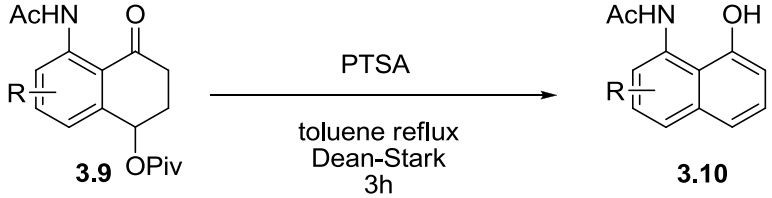
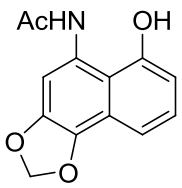
Xanthate 3.7	Tetralones 3.9	Yields
 **3.7b**	 **3.9b**	48%
 **3.7c**	 **3.9c**	51%
 **3.7d**	 **3.9d**	60%
 **3.7e**	 **3.9e**	65%

Table II-B6

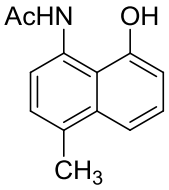
α-Tetralones **3.9b - 3.9e** possessing various substituents on the aromatic rings were treated with *p*-toluenesulfonic acid to furnish 1-naphthylamides **3.10b - 3.10e** in yields ranging from 60% to 74%. All the examples are assembled in the **Figure II-B2**.



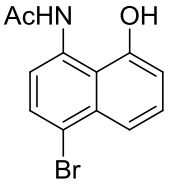
3.9 **3.10**



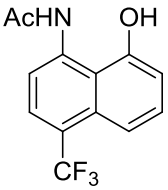
3.10a 70%



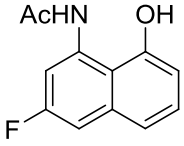
3.10b 74%



3.10c 72%



3.10d 74%



3.10e 60%

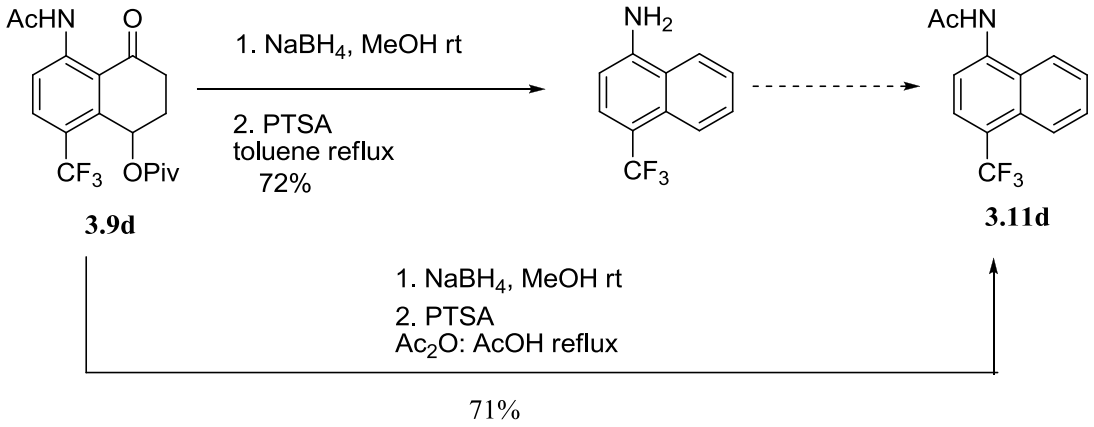
Figure II-B2

As reported above, the recent synthesis of 1-naphthylamine derivatives usingrearrangement with palladium catalyst or CuCN-mediated cannot produce the 1-naphthylamines bearing a bromine substituent since the halide substituents on the substrates such as bromine and iodine would be participate in coupling reactions. In our case, the bromine substituent is tolerated in the xanthate chemistry as seen in the case of product **3.7c**. The trifluoromethyl groupin product **3.10d**is also noteworthy in view of the importance of fluorine in medicines and. Most of the naphthalene derivatives described herein are not readily accessible under classical conditions.

This strategy based on the xanthates for the synthesis of regioselectively substituted naphthylamides complements existing methods. The final structures of the substituted naphthylamides are predictable from the simple structure of their aniline precursor.

Tetralones **3.9** can also be transformed into *N*-acetylnaphthylamines. For example, exposure of **3.9d** to $NaBH_4$, in methanol at room temperature reduces the ketone into an alcohol.[14]Treatment of this compound with PTSA in refluxing toluene gave rise to the deprotected naphthylamine in 72% yield. As naphthylamines arepotentially carcinogenic, we repeated the reaction using a mixture of acetic acid and acetic anhydride as the solvent instead of toluene to prevent the

deacetylation. Indeed, tetralone **3.9d** could beconverted into *N*-acetyl-4-trifluoromethyl-1-napthylamine **3.11d**in 71% yield (**Scheme II-B12**).



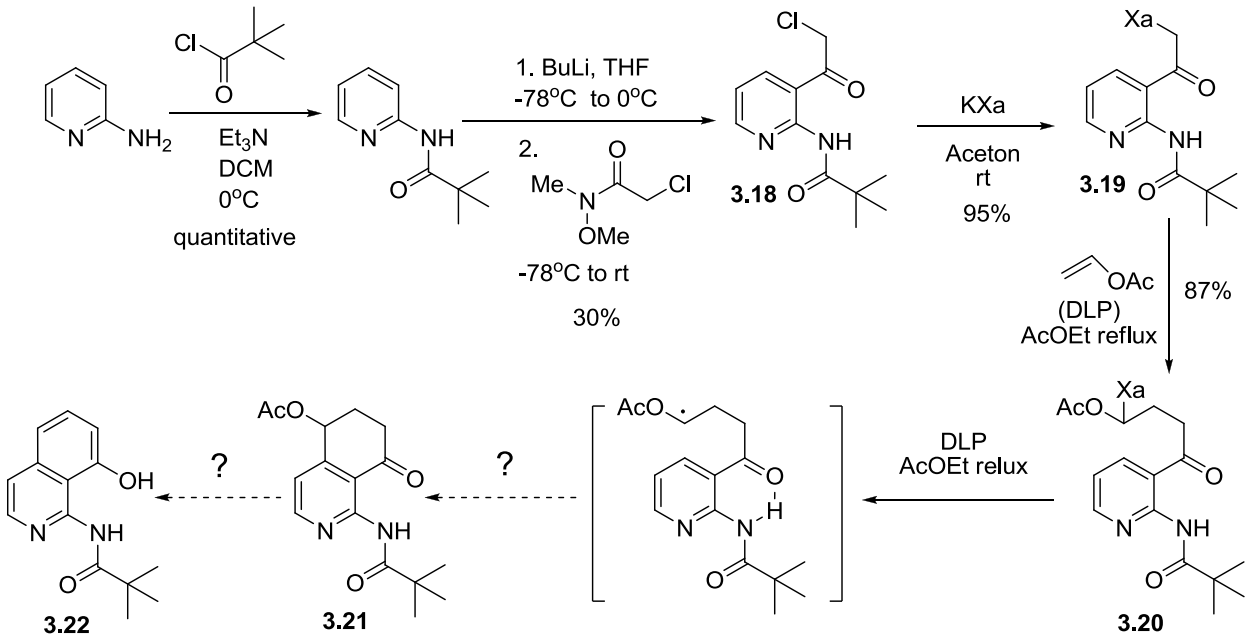
3.9d **3.11d**

Scheme II-B12

5. An attempt to extend the scope

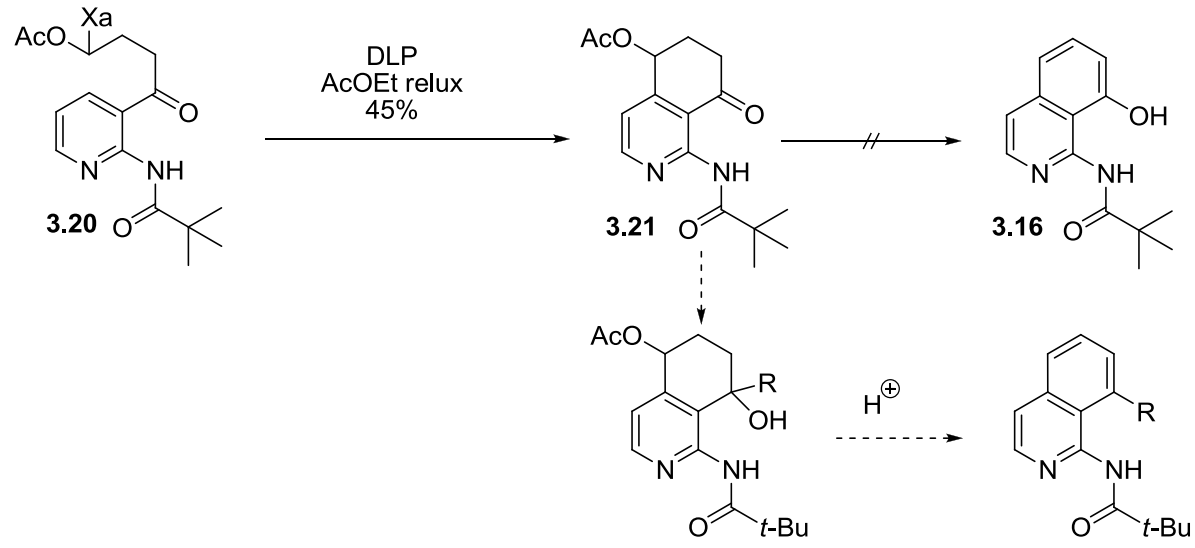
We attempted to extend the scope of our study by using heteroaromatic derivatives instead of anilines. The obvious example that came to our mind was the synthesis of bicycle system **3.21** with the fused pyridine ring because the family of isoquinoline derivatives has many applications in medicinal chemistry. As shown in the **Scheme II-B13**. The sequence started with the protection of amine function with pivaloyl chloride, followed by direct ortho metalation and reaction with the chloro-acetyl Weinreb amide to give compound **3.18.**[132] Subsequently, the substitution of the chlorine by a xanthate generated the xanthate precursor **3.19** which underwent the addition reaction to furnish the corresponding addition adduct **3.20** in 87% yield.

[132]Fang, Y.-Q.; Yuen, J.; Lautens, M. *J. Org. Chem.***2007**,*72*, 5152.



Scheme II-B13

It is reasonable to believe that the cyclisation onto the pyridine nucleus of the xanthate **3.20** would be achieved. As in the preparation of 1-naphthylamide, the intramolecular hydrogen bond in the molecule **3.20** should promote the cyclisation of the intermediate radical onto the pyridine ring. Indeed, the result was in accord with our hypothesis; the cyclisation took placed smoothly under the mild condition to generate the bicycle **3.21** in acceptable yield (45%) (**Scheme II-B14**).



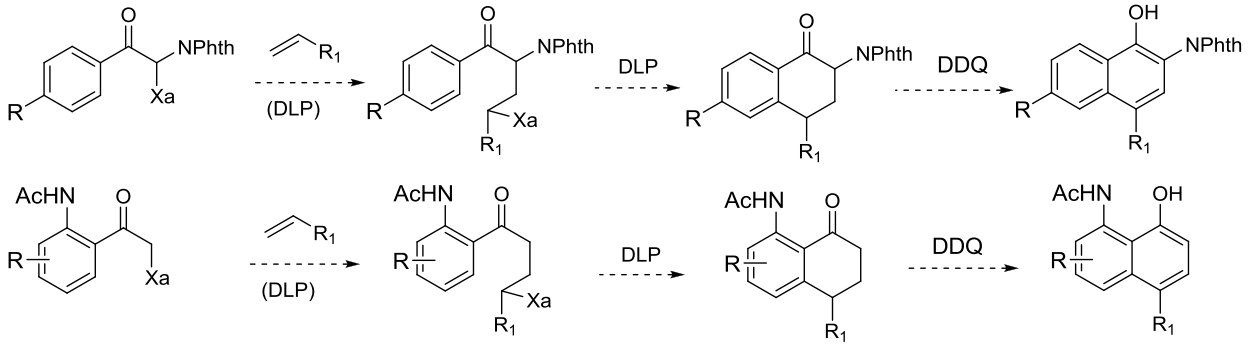
Scheme II-B14

Unfortunately, however several attempts at aromatisation of compound **3.21** proved fruitless. The exposure of **3.21** to various acidic conditions such as $MeSO_3H$, AcOH, PTSA/ toluene, H_2SO_4 at high temperature furnished only deprotected product, and no sign of the aromatic compound was found. Clearly, the electron-withdrawing nature of the pyridine ring disfavors the elimination reaction. Modification of the ketone (reduction or formation of a carbinol by addition of an organometallic reagent) could simplify the aromatization process.

III. Conclusion and perspective

In summary, a practical approach to the synthesis of protected 1- and 2-naphthylamines has been established. Various functional groups can be incorporated in a regioselective manner into the structure. This xanthate radical method allows the access to naphthylamides substituted by either electron-withdrawing (Cl, Br, F, CF_3) or electron-donating (CH_3, OCH_2O)groups.

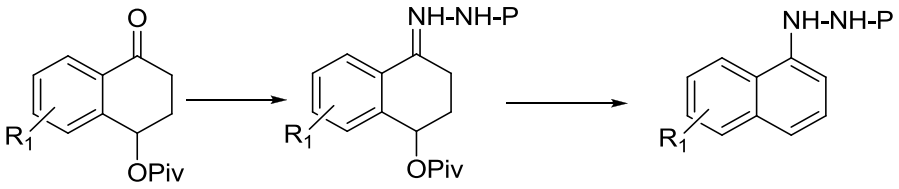
One way to extend the scope is replacing vinyl pivalate by other olefins in the addition step. In this manner,highly functionalised naphthalylamides could be obtained by using an oxidant such as DDQ to aromatise the amino-tetralones (**Scheme III-1**).



Scheme III-1

Another way to exploit this chemistry is to convertα-tetralones obtained through the addition-cyclisation process into the corresponding hydrazones. Subsequent elimination of pivalic acid

could furnish valuable naphthylhydrazines. This modification will constitute the subject matter of the next chapter (**Scheme III-2**).



Scheme III-2

Chapter 4 Synthesis of substituted naphthylhydrazides

I. Introduction

1. Applications of aryl hydrazides
2. Recent syntheses of aryl hydrazides

II. Synthesis of substituted naphthylhydrazides using xanthate chemistry

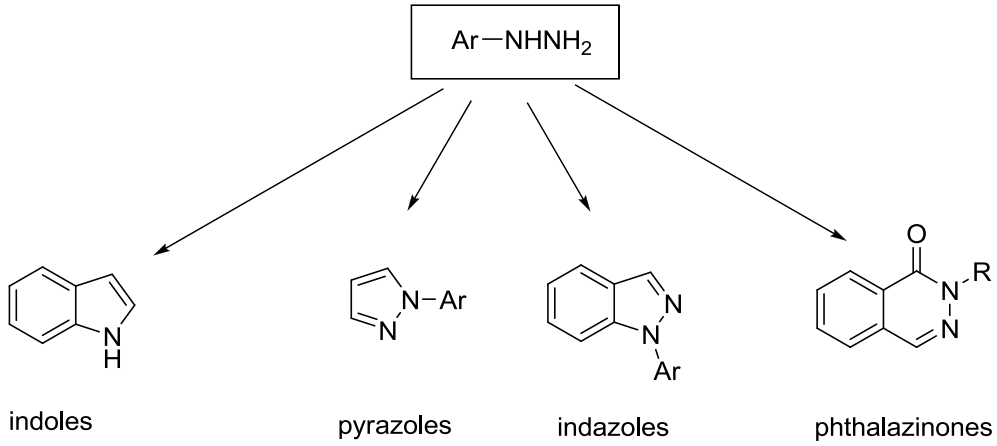
1. Previous work and our strategy
2. Optimization
3. Application to the synthesis of naphthylhydrazides

III. Conclusion

I. Introduction

1. Applications of aryl hydrazides

N-Aryl hydrazines constitute an interesting chemical class found in numerous applications in organic synthesis and in the pharmaceutical and agrochemical industries. They can be easily converted into aryl hydrazides by protection. Aryl hydrazines are versatile intermediates in the synthesis of a broad variety of important nitrogen-containing heterocyclic building blocks such as indoles, indazoles, pyrazoles, etc. many of which are known to be biologically active. These scaffolds represent important sub-structural units used for the discovery of novel drugs. Except for indoles, the N-N linkage in these compounds has acted as a privilege structural motif for their pharmaceutical activities.



For example, Indometacin and Celecoxib are anti-inflammatory drugs which are commonly used to reduce pain and swelling while phthalazinone derivative **1** is an antimicrobial agent which can be used as a potent inhibitor of poly(-ADP-ribose)polymerase-1. Frovatriptan (trade name Frova) works for the treatment of severe headache accompanied by nausea, and Graisetron is used to treat nausea and vomiting (**Figure I-1**).

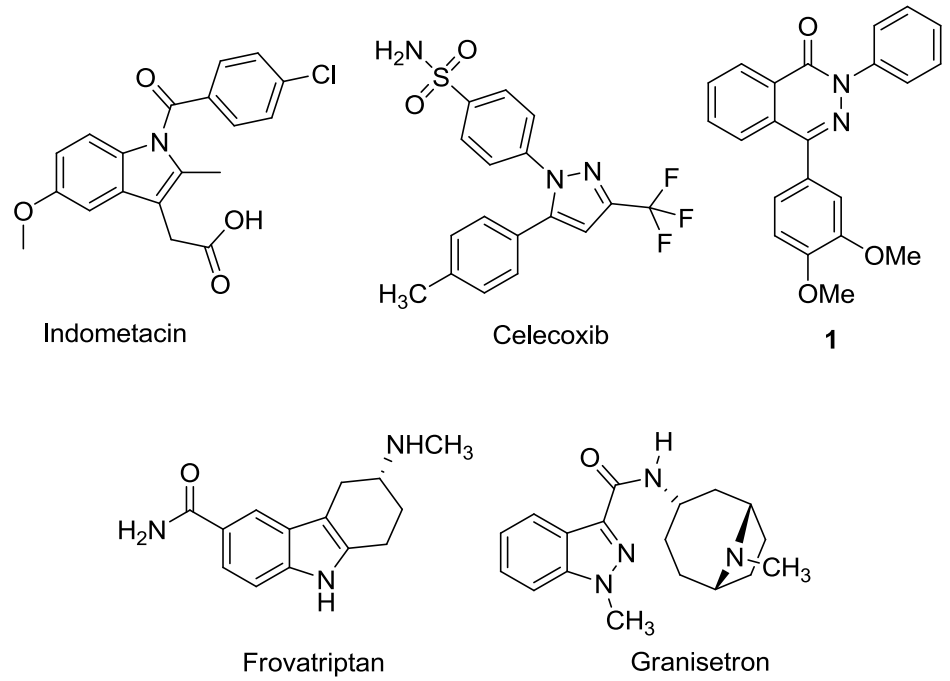


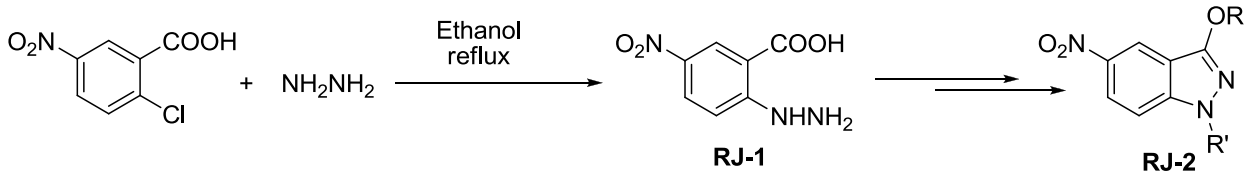
Figure I-1

2. Recent syntheses of aryl hydrazides

Since hydrazine derivatives are the important intermediaries for several important classes of products, various methods to access such structures have been developped. There are numerous approaches to synthesize the aryl hydrazines, traditional as well as modern. Some are listed hereafter.

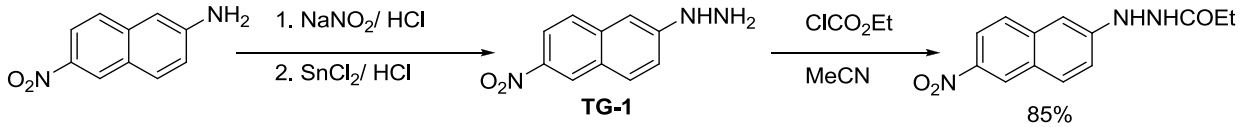
Even though it is not popular to produce aryl hydrazines by substitution, in some special cases where strong electron-withdrawing groups are present on the aromatic ring, the substitution of aryl chloride by hydrazines can occur efficiently. For instance, in their approach to 5-nitroindazole derivatives **RJ-2**, Rodiguez and coworkers applied this strategy to obtain the starting hydrazine **RJ-1 (Scheme I-1)**. The chloride group of the starting material is substituted by hydrazine in refluxing ethanol to give rise to product **RJ-1**.[133]

[133]Rodríguez, J; Arán, V. J.; Boiani, L.; Olea-Azar, C.; Lavaggi, L. M.; González, M.; Cerecetto, H.; Maya, J. D.; Carrasco-Pozo, C.; Cosoy, H. S. *Bioorg. Med. Chem.***2009**, *17*, 8186.



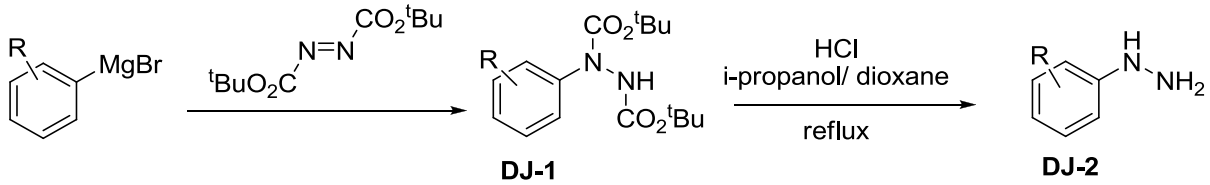
Scheme I-1

One of the classic methods to prepare aryl hydrazine derivatives is from the corresponding aryl amines. This method described in **Scheme I-2** involves the diazotation of a naphthylamine precursor to the diazonium salt by $NaNO_2$, followed by reduction by $SnCl_2$ in acidic medium. It is crucial to control the temperature during diazotation and reduction; the desired product **TG-1** could only be obtained when the reaction temperature was kept below 0°C.[134] As the availability of naphthylamines is not as broad as for anilines, the scope of this method is limited in the naphthyl series.



Scheme I-2

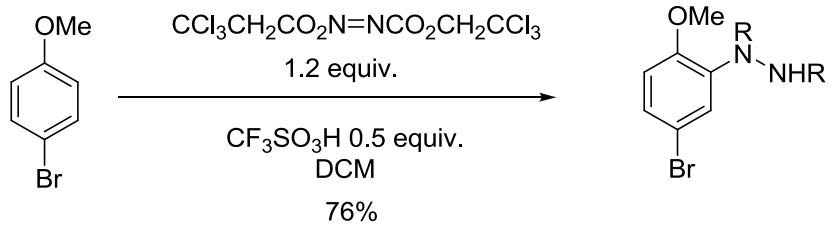
Another traditional route to aryl hydrazines is through the addition of between aryllithiums or aryl Grinard reagent to azodicarboxylates. Discovered by the Klaubert group in 1987, the reaction described in **Scheme I-3** was carried out in THF in a dry ice bath, using di-*t*-butyl azodicarboxylate as the reagent. The deprotection of Boc group could be accomplished by heating with HCl in refluxing mixture of isopropanol and dioxane to give the corresponding benzylhydrazines **DJ-2**.[135]



Scheme I-3

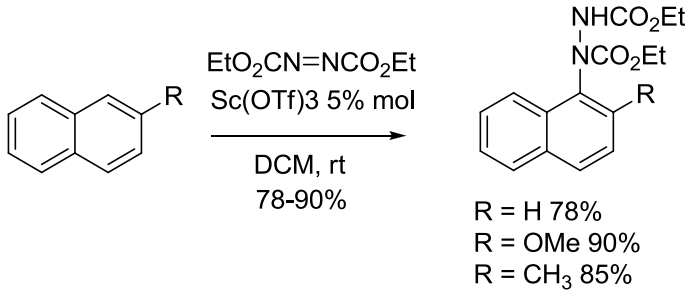
[134] Tschirret-Guth R. A.; de Montellano, P. R. O. *J. Org. Chem.* **1998,** *63,* 9711
[135]Demers, J. P.; Klaubert, D. H. *Tetrahedron Lett.*,**1987**, *28*, 4933.

Alternatively, the Leblanc group exploited the electrophilic amination of arenes with bis(2,2,2-trichloroethyl) azodicarboxylate (BTCEAD) under acidic conditions. The limitation of this strategy is that the arenes must be electron rich and the BTCEAD reagent is expensive (**Scheme I-4**).[136]



Scheme I-4

Later, the Yadav group found that diethyl azodicarboxylate (DEAD) was also a suitable reagent for this transformation in the presence of strong Lewis acid $Sc(OTf)_2$ as a catalyst, as shown in **Scheme I-5**. This procedure presents an improvement because the Lewis acid is used in a catalytic manner and provides better yields. However, as in the case of BTCEAD, the reaction requires electron rich arenes as the precursors.[137]

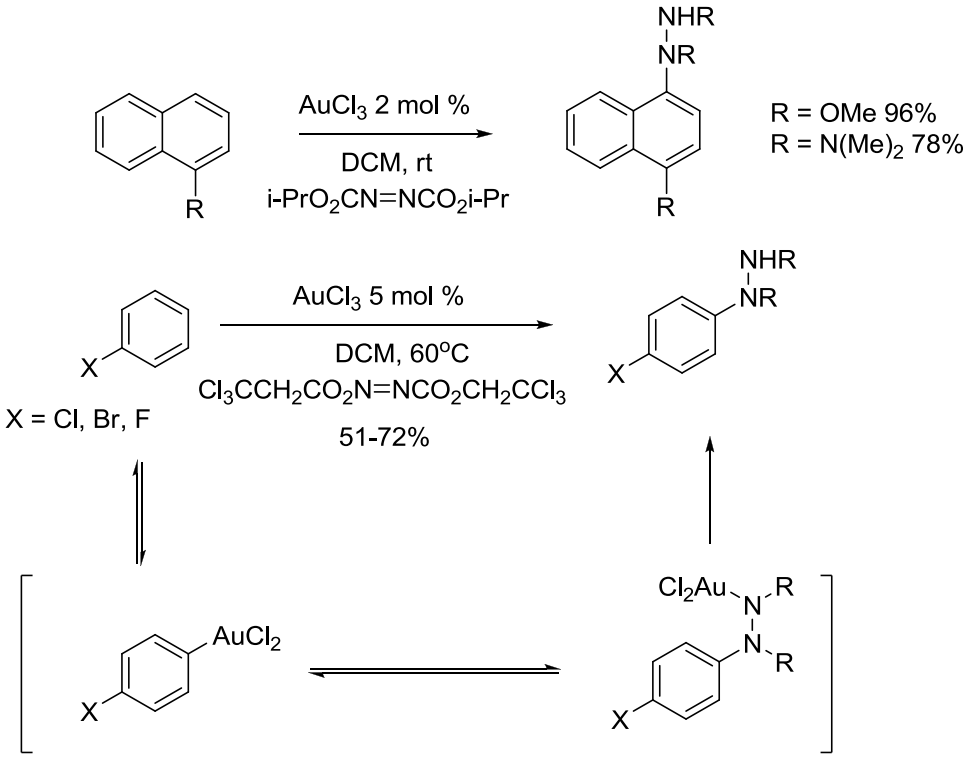


Scheme I-5

Great improvements are observed when a gold catalyst is applied to this transformation. Gu and co-workers reported that the direct amination of arenes with azodicarboxylate can be achieved with not only electron-donnating groups but also with electron-withdrawing groups on the arene

[136]Leblanc, Y.; Boudreault, N. *J. Org. Chem.* **1995**, *60*, 4268.
[137] Yadav, J. S..; Reddy, B. V. S.; Veerendhar, G.; Srinivasa Rao, R. S.; Nagaiah, K. *Chem. Lett.***2002**, 318.

precursors. The reaction described in **Scheme I-6** took place smoothly with electron-rich naphthalenes. By increasing the temperature to 60°C and using bis(2,2,2-trichloroethyl) azodicarboxylate (BTCEAD) in place of isopropyl azodicarboxylate, the unactivated arenes such as halo benzenes could also be converted into the corresponding substituted benzylhydrazides. This gold catalysed-system allows access to a broad range of benzene and naphthalene hydrazides with various other functional groups.[138]

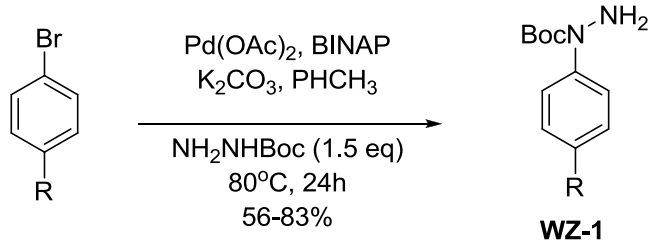


Scheme I-6

As for " Recent syntheses of substituted naphthylamides " , the Buchwald-Hartwig reaction proved to be an efficient method for the synthesis of arylamines via the palladium-catalysed direct amination of aryl halides, based on this results, it is not surprising that the transition metal-catalysed coupling of aryl halides and protected hydrazines should emerge as a promising extension of the process. Indeed, Wang and co-coworkers decided to apply this strategy for the preparation of aryl hydrazines as outlined in **Scheme I-7**.[139] Aryl bromides were reacted with

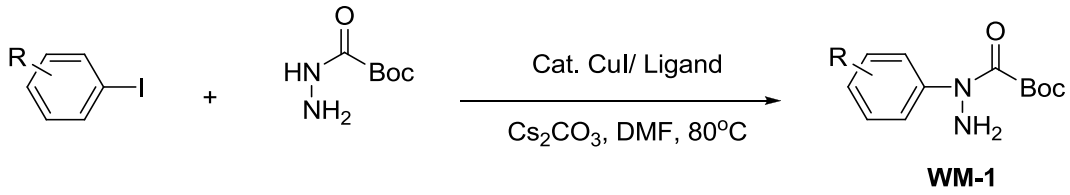
[138]Gu, L.; Neo, B. S.; Zhang, Y. *Org. Lett.***2011**, *13*, 1872.
[139]Wang, Z.; Skerlj, R. T.; Bridger, G. J. *Tetrahedron Lett.***1999**, *40*, 3543.

NH_2NHBoc in the presence of a palladium catalyst and K_2CO_3 to furnish the corresponding protected aryl hydrazines. The yields were good, varying from 65 to 83%, when aryl bromides bearing electron-withdrawing substituents at the para position were employed. Many para substituents such as nitro, cyano, trifluoromethyl, ketones and esters are tolerated. In the case of *m*-substituted analogs, the desired products were obtained in low yields.



Scheme I-7

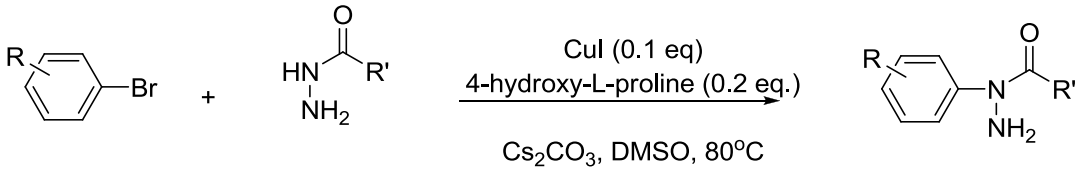
Later, the Buchwald group developed further this amination by using the cheaper catalyst copper in place of the palladium catalyst. As displayed in **Scheme I-8**, The iodide arenes reacted with NH_2NHBoc in the presence of a catalytic amount of copper (I) iodide, 1,10-phenanthroline ligand and Cs_2CO_3. This method provides a more general approach to aryl hydrazines since the aryl iodides bearing subtituents in *para* as well as *meta* position underwent the coupling with NH_2NHBoc to give rise to products **WM-1** in high yields (up to 97%). This work exploited successfully electron-rich as well as electron-deficient substituted-aryl iodides. (R = *p*-OH, *p*-Br, *p*-NH_2, *p*-CN, *m*-OMe, *m*-CH_2OH, *m*-COOEt, *m*-CN).[140]



Scheme I-8

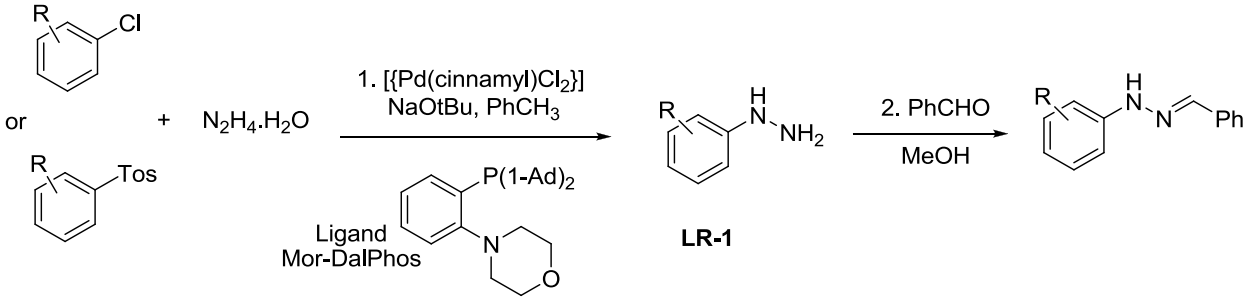
[140]Wolter, M.; Klapars, A.; Buchwald, S. L. *Org. Lett.***2001**, *3*, 3803.

In pursuit of a more efficient catalytic system, this method was extended to aryl bromide by Jiang and coworkers. The conditions were quite similar to the ones in Buchwald's work, except that the ligand in this case was 4-hydroxy-L-proline. Both meta and para-substituted aryl hydrazides with various functional groups could be produced in good yield (substituents = OH, NH_2, F, CF_3, CO_2Me) (**Scheme I-9**).[141]



Scheme I-9

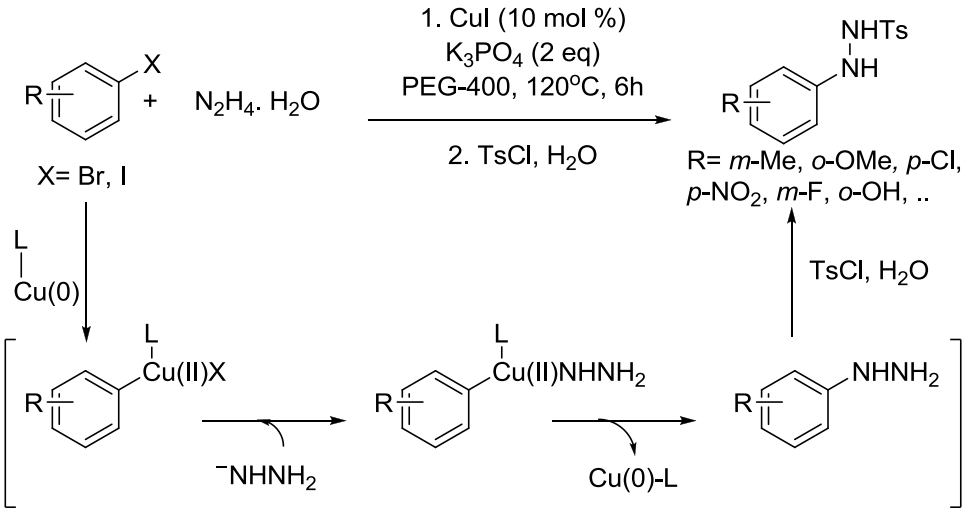
So far a wide range of substituted-aryl hydrazides have been accessed directly and easily by amination. Further investigations found that the amination by metal transition catalyst was not only limited to protected hydrazides, it could also be employed with the unprotected hydrazine as the precursors. The first examples were accomplished by Stradiotto and co-workers.[142] As shown in S**chemeI-10**, the reaction between substituted-chlorobenzenes and hydrazine hydrate in the presence of palladium catalyst furnished aryl hydrazines **LR-1,** which reacted with benzaldehyde to give rise to the corresponding hydrazones. The second step was used to facilitate the product isolation. The key to success of this approach is the special ligand: Mor-DalPhos. The yields varied from good to excellent (up 97%) with a broad variety of functionalized groups. However, the experimented conditions required the use of a glovebox and this method cannot produce chloroarylhydrazine.



SchemeI-10

[141] Jiang, L.; Lu. X.; Zhang, H.; Jiang, Y.; Ma, D. *J. Org. Chem.***2009**, *74*, 4542.
[142]Lundgren, R. J.; Stradiotto, M. *Angew.Chem. Int. Ed.***2010**, *49*, 8686.

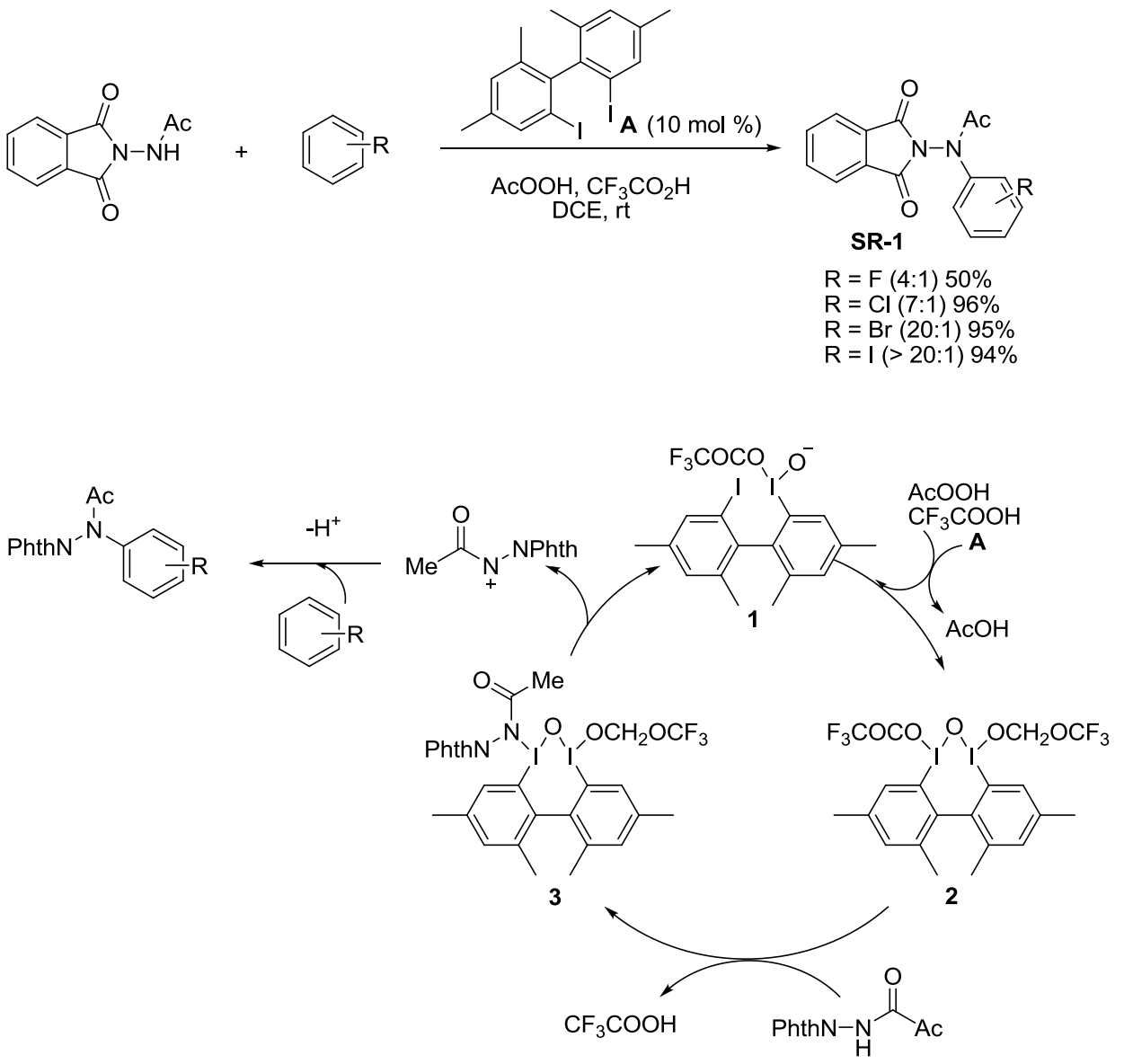
Recently, the Chen group performed the same transformation but used a copper catalyst. The aryl halides (bromides or iodides) underwent the CuI-catalysed coupling with hydrazine hydrate in poly(ethylene glycol) 400 (PEG-400) to furnish the corresponding aryl hydrazines (**Scheme I-11**). The method proved to be a significant advancement towards the preparation of aryl hydrazines.[143]



Scheme I-11

The catalytic methods reported above hinged predominantly on transition-metal process. Recently, the Antonchick group developed the new strategy for the catalytic amination based on organocatalysis.[144] As shown in **Scheme I-12**, arenes underwent cross coupling with *N*-(1,3-dioxoisoindoline-2-yl)acetamide mediated by a hypervalent iodine reagent to form the aryl hydrazines **SR-1**. The products were obtained with good selectivity at ambient temperature. The monosubstituted benzenes furnished a mixture of products with para and ortho-hydrazination in good yield. The bulkier the substitutents were, the more para isomers were formed. For example, the yield and regioselectivity of para-hydrazinated products were increased from fluorobenzene to iodobenzene, and for more hindered structures such as *N*-phenyl succinimides, the reaction produced exclusively one product.

[143]Chen, J.; Zhang, Y.; Hao, W.; Zhang, R.; Yi, F. *Tetrahedron***2013**, *69*, 613.
[144]Samanta, R.; Bauer, J. O.; Strohmann, C.; Antonchick, A. P. *Org Lett.***2012**, *14*, 5518.



Scheme I-12

As shown in **Scheme I-12**, initially, iodoarene **1** is oxidized to hypervalent **2**, which undergoes a ligand substitution to give rise to **3**. The oxidative fragmentation leads to the formation of nitrenium ion which is later transformed into the desired product **SR-1**. This method sheds light on the oxidative process to introduce the hydrazide motif into the structures. The limitation of this process is that for electron deficient arenes, the yields were modest.

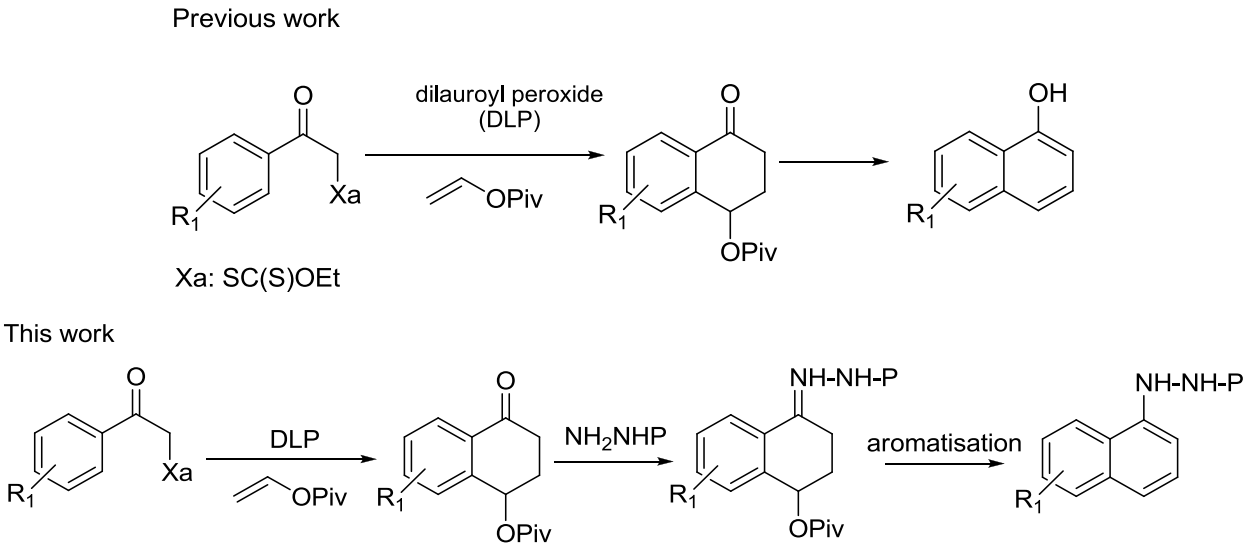
Essentially, all reported methods employ the strategy at introducing the hydrazide motif onto substrates containing already the aromatic nucleus. None has relied on the aromatisation of bicyclic systems. As the availability of naphthalene derivatives is limited, only a few methods have allowed the preparation of naphthylhydrazides. In this chapter, we shall present a new methodology involving the aromatisation of hydrazones derived from α-tetralones to generate naphthylhydrazides.

II. Synthesis of substituted naphthylhydrazides using xanthate chemistry

1. Previous work and our strategy

As described in the previous section, a convenient approach to regioselectively substituted naphthalenes using a xanthate radical sequence was established in our group[145].

We believed that the scope could be extended to access to naphthylhydrazides by reacting a protected hydrazine with the ketone function of α-tetralones. In this manner, regioselectively substituted naphthylhydrazides would be obtained after the aromatisation of the corresponding hydrazones. The key factor of this strategy is the aromatisation step (**Scheme II-1**).

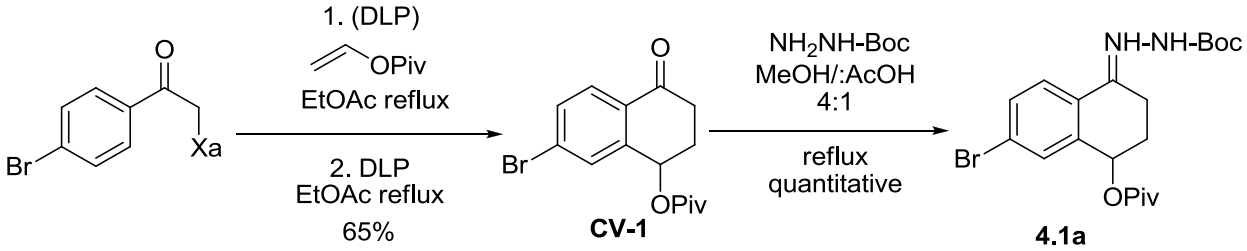


Scheme II-1

[145]Cordero-Vargas, A.; Pérez-Martin, I.; Quiclet-Sire, B.; Zard, S. Z.*Org. Biomol.Chem.***2004**, *2*, 3018.

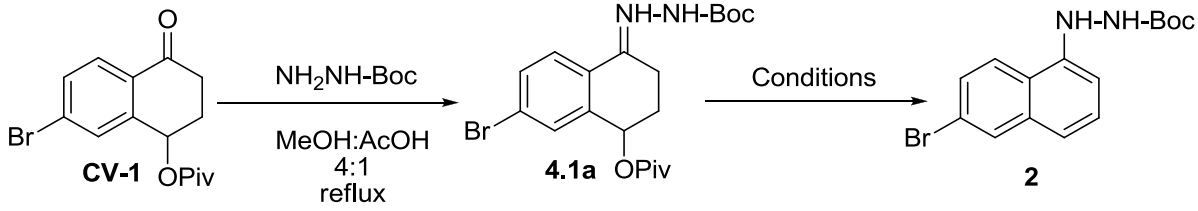
2. Optimization

We decided to optimize the aromatisation with the *p*-bromo derivative. Initially, the *p*-bromo tetralone **CV-1** was synthesized in 65% yield as in the literature. The attack of NH_2NHBoc on the ketone function of tetralone **CV-1**in a refluxing mixture of methanol and acetic acid provided hydrazones in quantitative yield (**Scheme V-3.2**).



Scheme II-2

With hydrazone**4.1a** in hand, we started to optimize the aromatisation of this structure. These attempts were carried out with 0.2 mmol of starting hydrazone**4.1a** heating with under various conditions in five hours.



The results are summarized in **Table II-1** below.

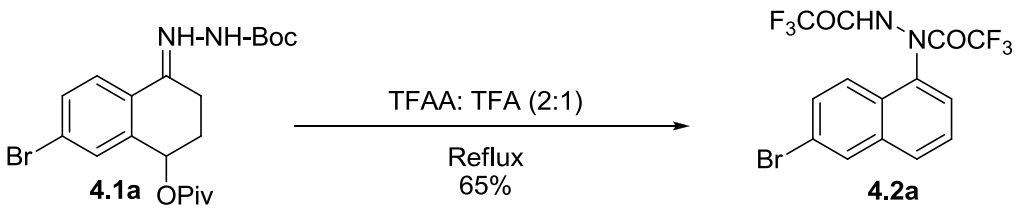
Attemps	Conditions	Results
1	Refluxing toluene (2mL) + *p*-TSA (3 eq)	No desired product
2	Refluxing PhCl (2 mL) + *p*-TSA (3eq)	No desired product
3	Refluxing AcOH : Ac_2O (1.5 mL : 0.5 mL)	No desired product

4	Refluxing AcOH (2mL)	No desired product
5	Refluxing CF_3COOH (2 mL)	No desired product
6	Refluxing $(CF_3CO)_2O$: CF_3COOH (1.5 mL : 0.5 mL)	Precipitate product (after 7h)

Table II-1

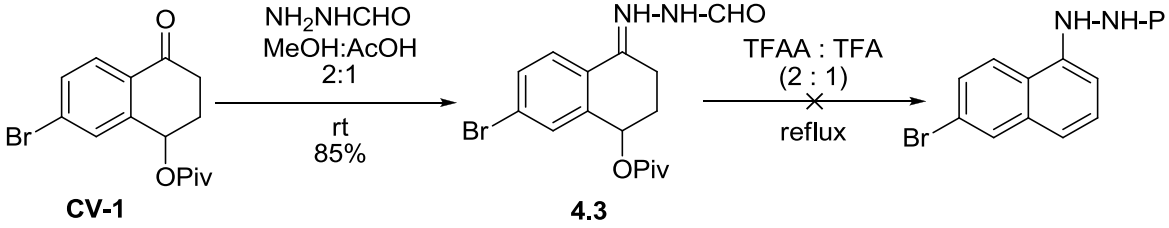
Firstly, we performed the reaction under classical conditions: heating the hydrazone with 3 equivalents of *p*-TSA in toluene using a Dean-Stark apparatus. After 4 hours, the NMR of the crude product provided no signals for aromatised product **2**. According to TLC and NMR, the starting hydrazone was partially cleaved back to its ketone precursor **CV-1**. Heating thereaction mixture overnight did not improve the outcome.

Increasing of the reaction temperature by replacing toluene with chlorobenzene furnished the same disappointing result. Heat hydrazone**4.1a** in a mixture of AcOH: Ac_2O (3: 1) or in AcOH alone or in a more acidic solvent such as CF_3COOH was also unsuccessful. In all cases the hydrazone **4.1a** was partially hydrolysed into the starting ketone **CV-1** andpartially Boc-deprotected. In order to avoid the transformation of hydrazone **4.1a** back to the ketone, it is necessary to eliminate the water present in the solution, therefore a mixture of $(CF_3CO_2)_2O$: CF_3COOH (2: 1) was chosen since $(CF_3CO_2)_2O$ would react with the water to give rise to CF_3COOH. To our delight, after 3 hours heating, a white precipitate appeared in the reaction mixture. We continued heating the mixture for four more hours until there was no more starting material. After cooling the reaction mixture to room temperature, the precipitate was filtered and washed with dichloromethane to furnish the aromatised product **4.2** in 65% yield. Indeed, under these conditions, the Boc-deprotection occurred followed by diprotection to afford naphthylhydrazide **4.2a** (**Scheme II-3**).



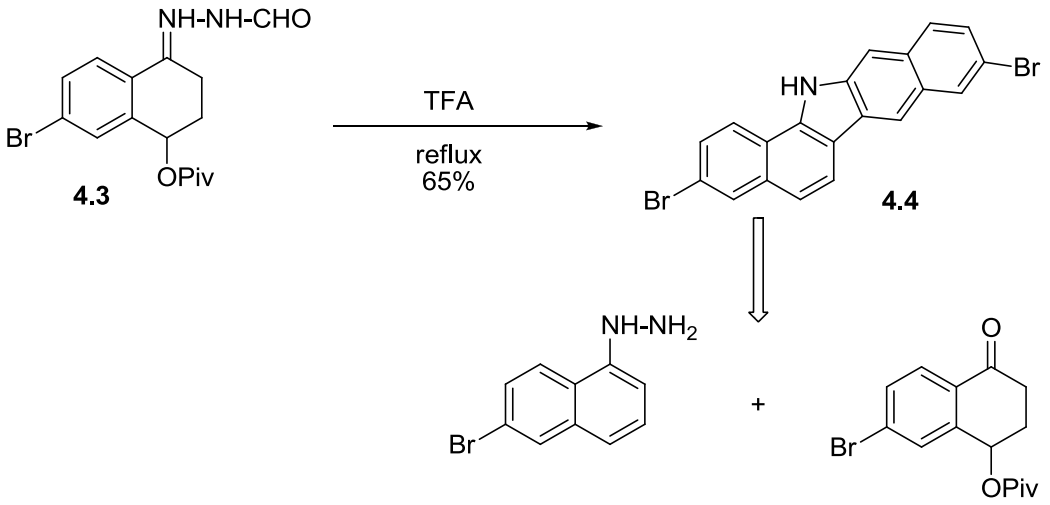
Scheme II-3

Even though we were pleased with this result, we tried to change the protecting group on the hydrazine by using NH_2NHCHO in place of NH_2NHBoc to investigate whether the reaction would proceed better. As in the case with NH_2NHBoc, the reaction of tetralone **CV-1** with NH_2NHCHO furnished the corresponding hydrazone **4.3** in 85% yield. However hydrazone **4.3** bearing CHO-protected group did not aromatise under the optimized conditions. We obtained only the ketone precursor **CV-1** and the starting hydrazone **4.3 (Scheme II-4)**.



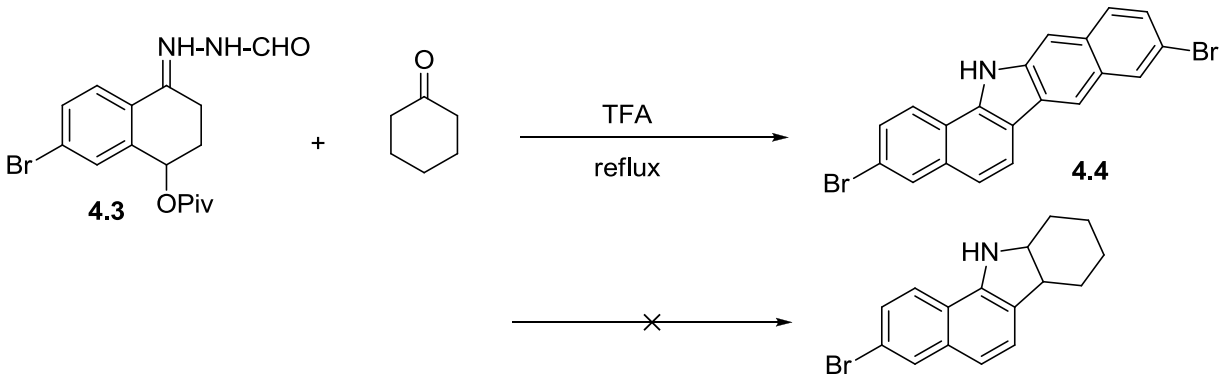
Scheme II-4

We decided to use only the acid (TFA), the results turned out to be quite unexpected. There was also the formation of a precipitate in the reaction mixture; however this precipitate was not the expected naphthylhydrazide but the Fisher indole product **4.4** derived from reaction of the desired naphthylhydrazine with its ketone precursor (**Scheme II-5**).



Scheme II-5

It is important to notice that the self-indolization product **4.4** is totally flat and therefore very crystalline. Indeed, the driving force of this process is the precipitation of this compound. In any case, this result was quite interesting since it perhaps provided a slight chance to obtain the indole product directly if there was another ketone present in the reaction mixture. To test this possibility, we added cyclohexone (1 equivalent) to the solution of hydrazone **4.3** in TFA and heated the mixture to reflux for 7 hours. Unfortunately, as shown in **Scheme II-6**, the resulting precipitate in this case was identified as the self-indolized product **4.4**; there was no formation of indole derived from cyclohexanone.



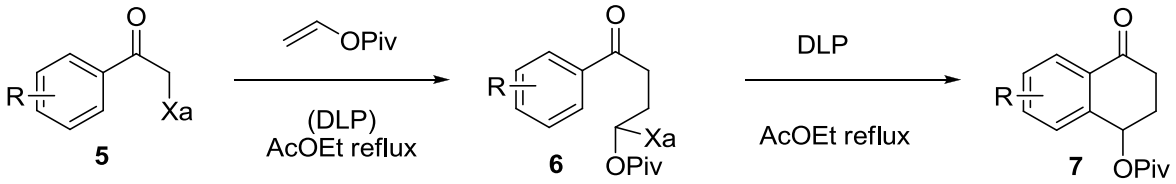
Scheme II-6

In conclusion, after the optimization, the best conditions for the aromatisation appear to be: heating the Boc-protected hydrazone in the mixture of TFAA: TFA (2: 1) at 75^{o}C.

As unprotected naphthylhydrazines are known for their carcinogenicity, no attempts at deprotection were performed.

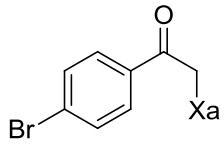
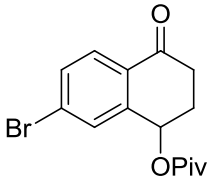
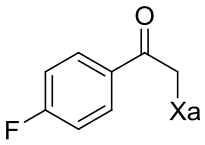
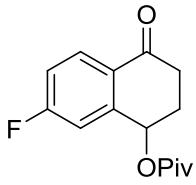
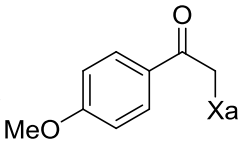
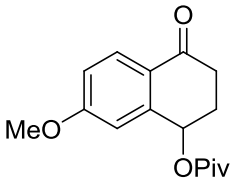
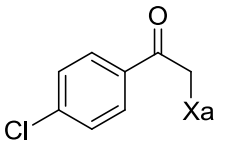
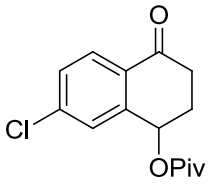
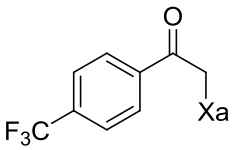
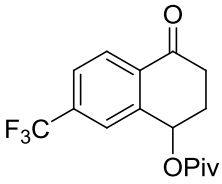
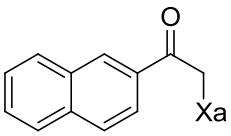
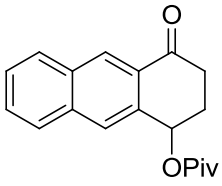
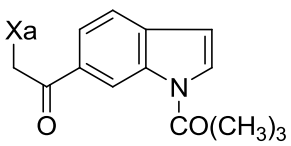
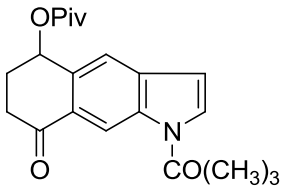
3. Application to the synthesis of naphthylhydrazides

Having defined the conditions for aromatisation, we explored the scope of this strategy. As illustrated in S**cheme II-7**, the xanthate radical sequence started with the addition of xanthate precursors **5** to the vinyl pivalate, followed by the cylization onto the aromatic ring to furnish product **7.**



Scheme II-7

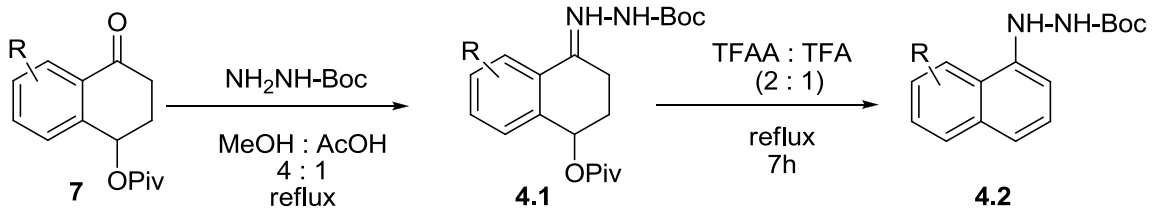
The choice of these precursors is based on the commercial availability of the substituted α-bromoacetophenone and their usefulness in further transformations. By placing different substituents on the aromatic ring, a broad diversity can be introduced into the molecular structures, as portrayed by the examples collected in **Table II-2**.

Xanthates 4	Tetralones 6	Yields (%)
5a 	**7a** 	65
5b 	**7b** 	49[a]
5c 	**7c** 	26[a]
5d 	**7d** 	81[a]
5e 	**7e** 	45
5f 	**7f** 	35[a]
5g 	**7g** 	40

a. The products were reported by Alejandro Cordero-Vargas

Tableau II-2

The optimized conditions for aromatisation were applied to these cyclic compounds **7a-7g**. First the ketone was converted into the hydrazone by heating with NH_2NHBoc in a mixture of methanol and acetic acid. Then, the resulting hydrazones **4.1** were heated in refluxing mixture of TFAA and TFA to furnish the naphthylhyrazides **4.2** (**Scheme II-8).**



Scheme II-8

The results of this transformation are summarized in the **Table II-3**. The reaction proceeded smoothly in most of the cases to give rise to the regioselective substituted naphthylhydrazide products in moderate yield varying from 53 to 65% over 2 steps. Unfortunately, in the case of the tricylic compound containing indole motif **7g**, the reaction produced a mixture of products which could not be identified. The indole ring presumably did not withstand the reaction conditions.

Depending on the nature of the substitutents on the aromatic ring, the resulting products varied from mono-trifluoroacetylate to di-trifluoroacetylate after 7 hours of heating. For example, *p*-bromo and *p*-chloro naphthylhydrazides are di-acylated and precipitated from the reaction mixture; whereas the others; namely *p*-fluoro-, *p*-methoxy-, *p*-trifluoromethyl-substituted and benzo-fused naphthylhydrazides were monoacylated. One of the most attractive aspects of this synthetic route is that it allows the regioselective substitution of the hydrazides, since the position of substituent is determined in the substrate and remains the same during the reaction. It is possible to access naphthylhydrazides bearing electron-donating (OMe) as well as electron withdrawing (CF_3, Br, Cl, F) groups. Among these examples, and to our best knowledge, the regioselective introduction of halide groups (Br, Cl) into naphthylhydrazines has not been reported in the literature. Such product would represent very useful substrate for subsequent transition-metal-catalysed transformations. In addition, the fluorinated products such as *p*-fluoro or *p*-trifluoromethyl naphthylhydrazides could be highly valuable in medicinal chemistry and

agrochemistry. The example of benzo-fused naphthylhydrazide **4.2f** shows that this approach could be used to generate polycyclic aryl hydrazides.

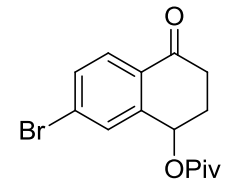
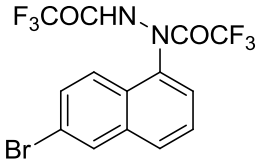
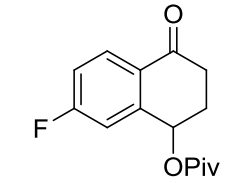
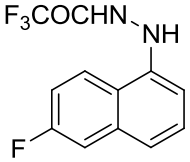
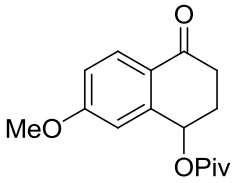
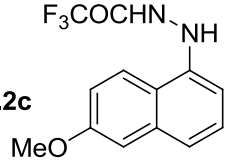
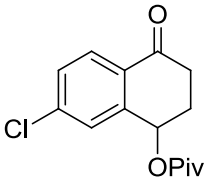
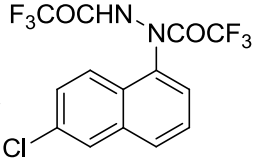
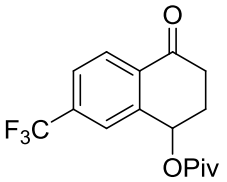
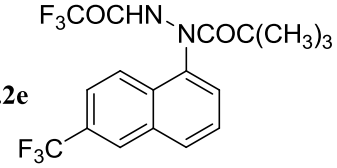
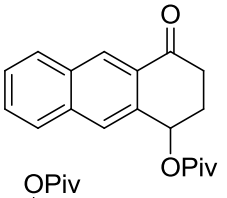
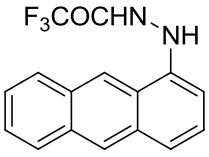
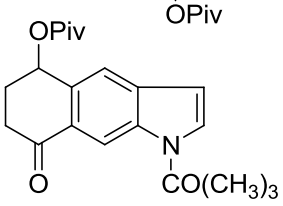
Tetralones **7**	Naphthylhydrazides 4.2	Yield (%)
7a 	**4.2a** 	65
7b 	**4.2b** 	57
7c 	**4.2c** 	60
7d 	**4.2d** 	60
7e 	**4.2e** 	43
7f 	**4.2f** 	50
7g 	Mixture	

Table II-3

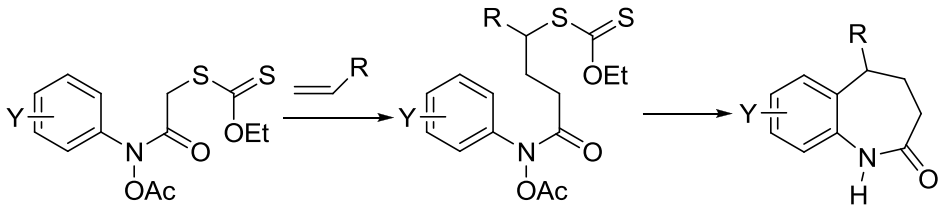
III. Conclusion

In this chapter, a new route was established for the preparation of naphthylhydrazine derivatives. This method based on the formation of intermediate α-tetralones by using xanthate chemistry. Subsequently, these tetralones are transformed into the corresponding hydrazones, followed by aromatisation to furnish the desired products. This strategy allows the synthesis of regioselectively substituted naphthylhydrazides. The corresponding hydrazines may then be used in the synthesis of novel pyrazones and indoles, which are privileged motifs in medicinal chemistry and material sciences. It is interesting to note that all of the examples summarized in this section have not yet been reported in the literature.

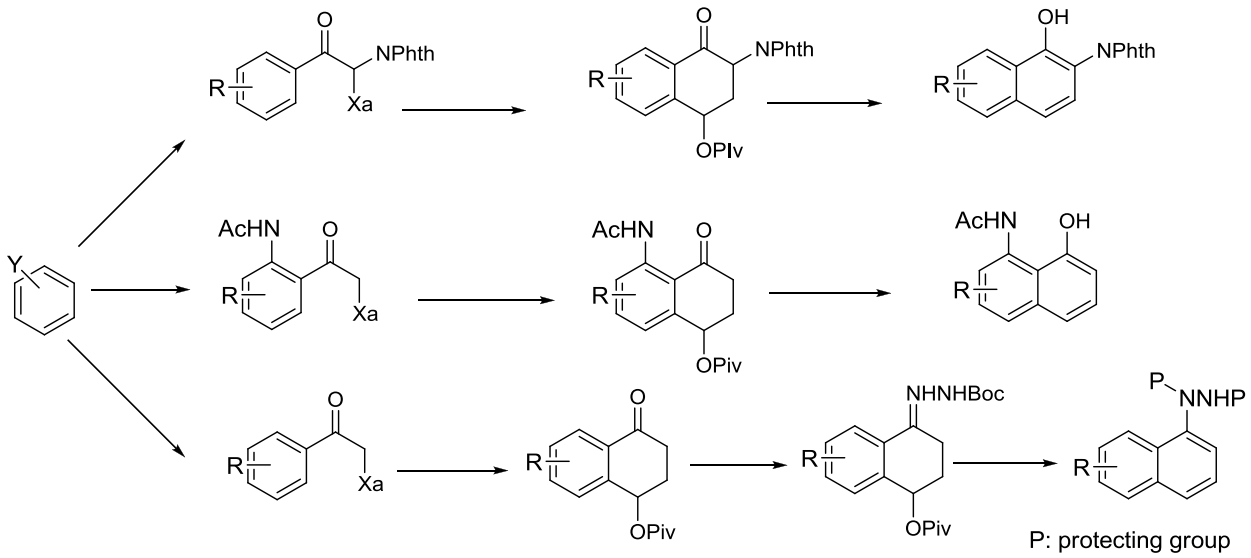
General conclusion

The work presented in this manuscript highlights some further sometimes unusual aspects of the radical chemistry of xanthates.

The study of the cyclisations onto the aromatic ring of hydroxamates has revealed an unexpected fragmentation and a brief investigation provided solid evidence for the homolytic rupture of the N-O bond. Consequently, a new methodology to access the family of *N*-unsubstituted benzazepinones based on the xanthate chemistry was developed. Benzazepinones with various substituents including sugar and boronate could be readily prepared by this route. The process is flexible, convergent and very suitable for the construction of libraries.



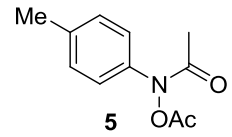
α-Tetralones are readily prepared by the xanthate-based addition/cyclisation sequence and are important intermediates for the synthesis of various aromatic structures. We developed an efficient and general methodology to access regioselectively substituted naphthylamides by aromatisation of the corresponding α-tetralones. Naphthylhydrazides were synthesized in the same fashion, but in this case, the α-tetralones were reacted with Boc-protected hydrazines before undergoing the aromatisation.



In all of these transformations, the tolerance for numerous functional groups is noteworthy. Most of the products obtained are novel and would not be easily obtained by other more conventional routes. Further work is needed to better optimize the yield and to extend the reaction described in this thesis to heteroaromatic substrates.

Molecules cited in the experimental part

Molecules of chapter 2



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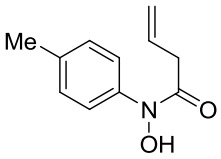

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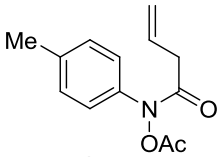

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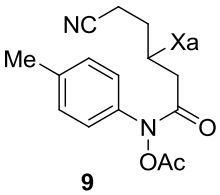

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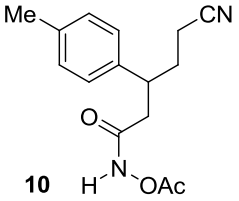

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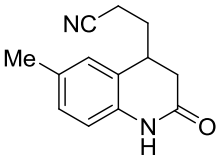

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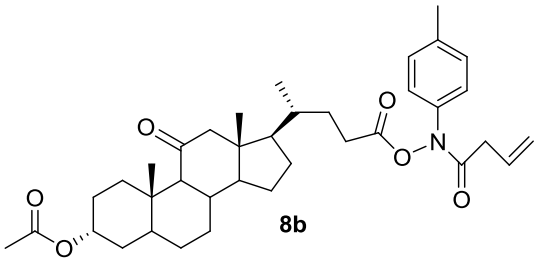

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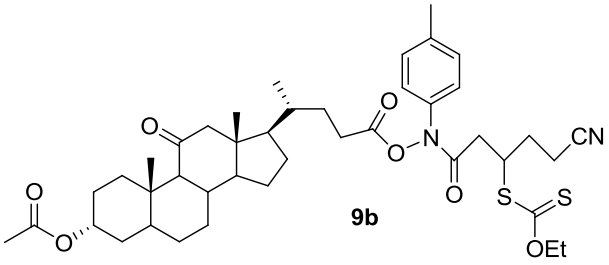

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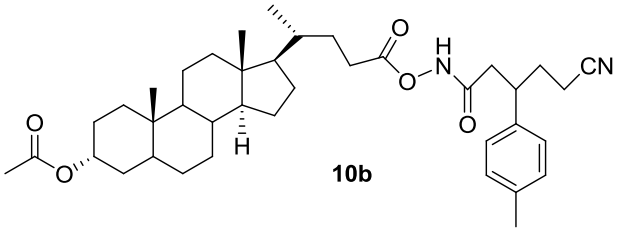

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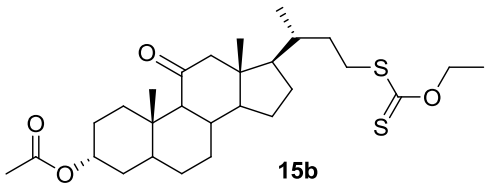

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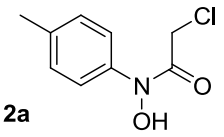

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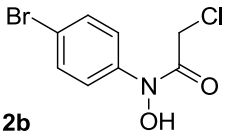

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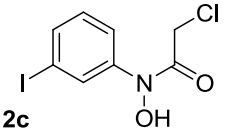

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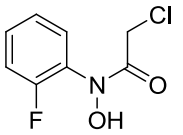

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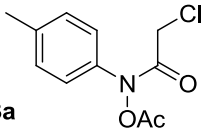

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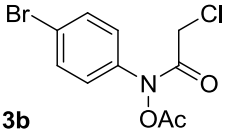

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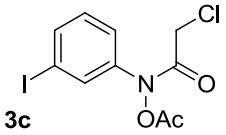

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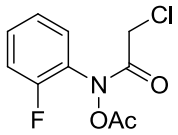

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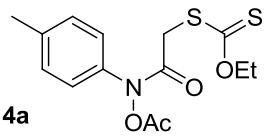

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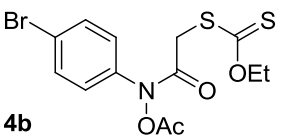

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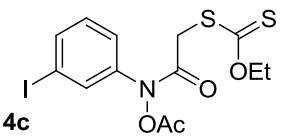

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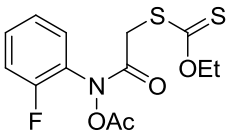

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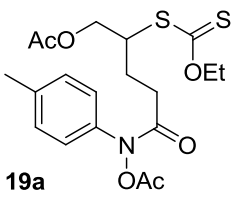

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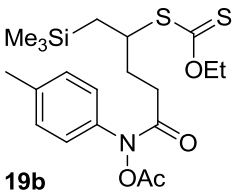

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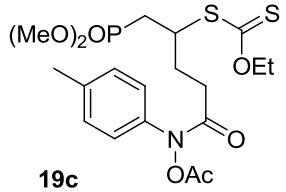

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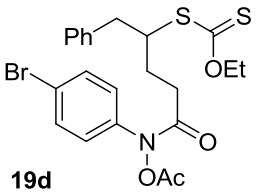

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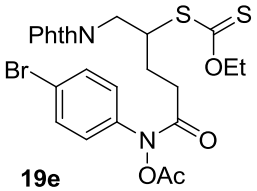

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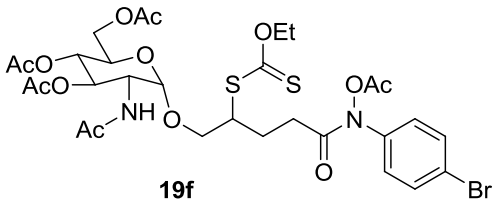

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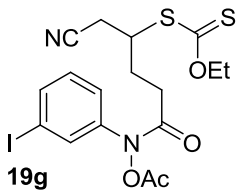

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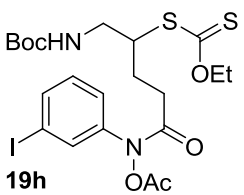

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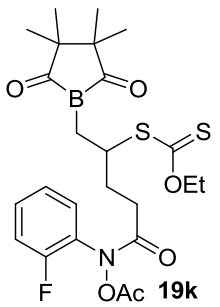

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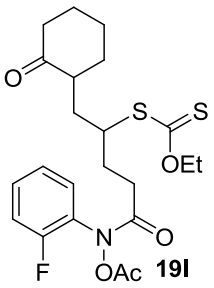

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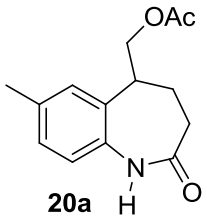

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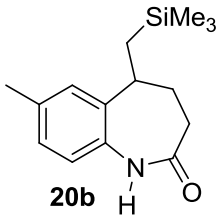

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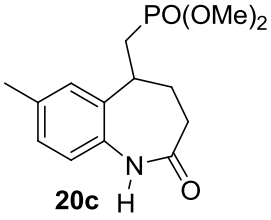

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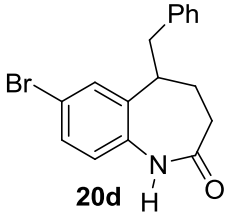

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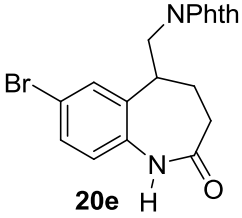

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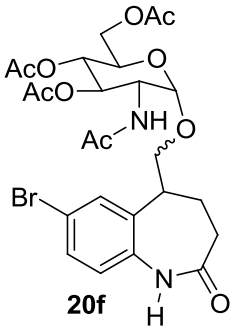

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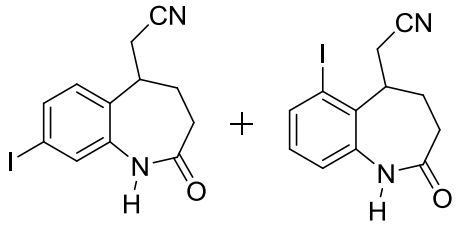

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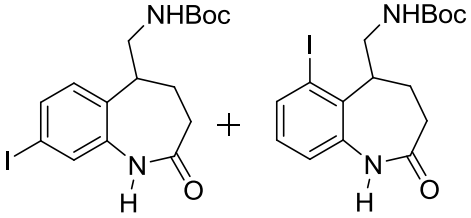

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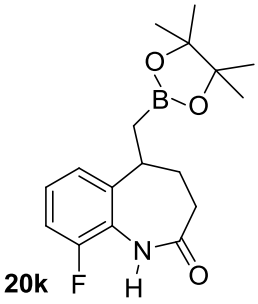

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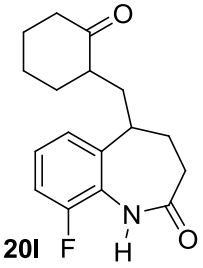

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Molecules of chapter 3

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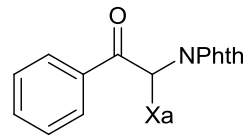

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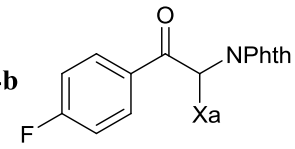

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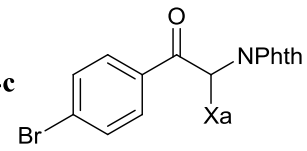

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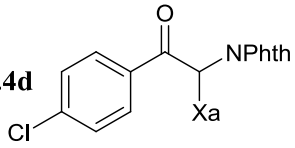

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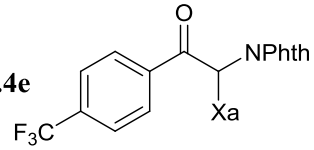

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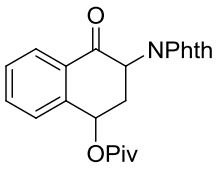

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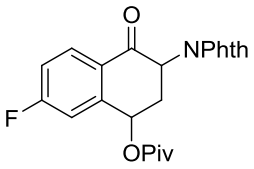

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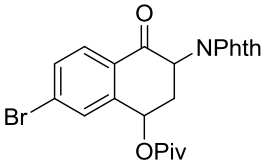

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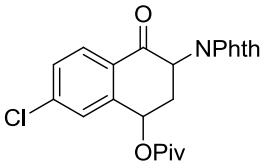

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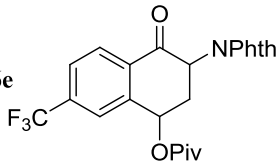

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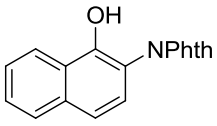

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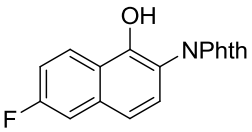

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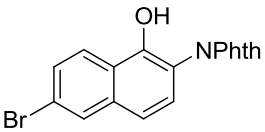

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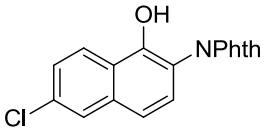

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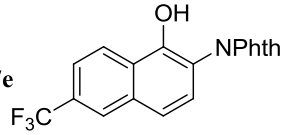

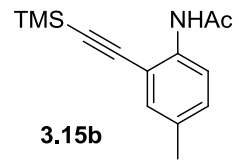

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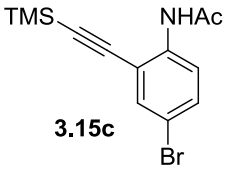

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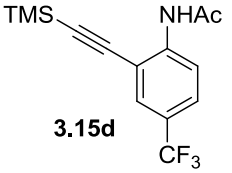

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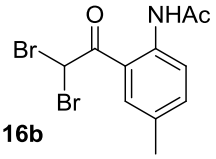

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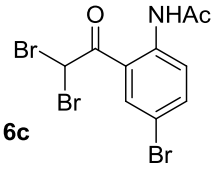

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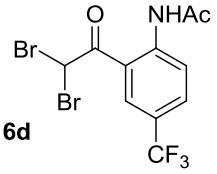

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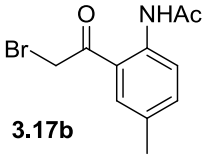

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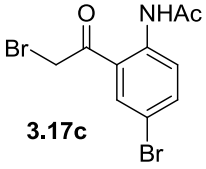

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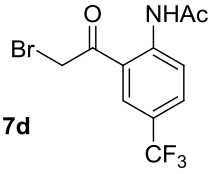

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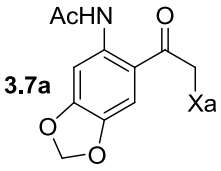

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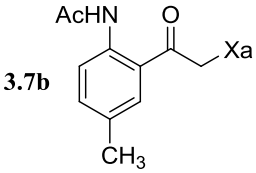

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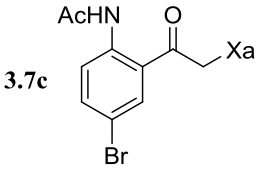

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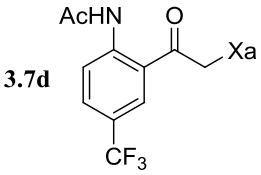

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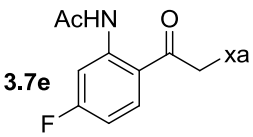

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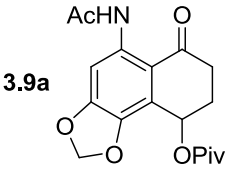

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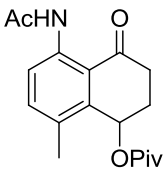

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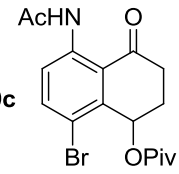

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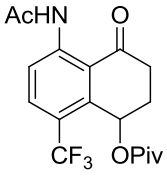

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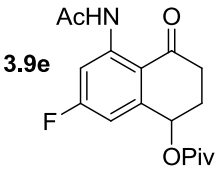

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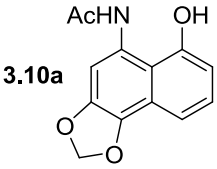

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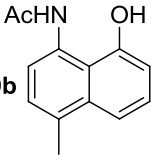

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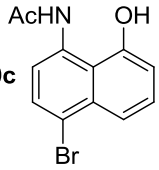

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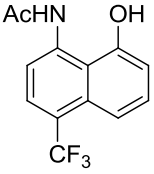

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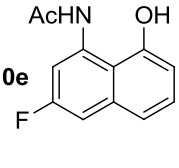

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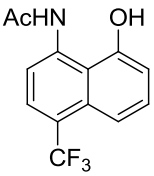

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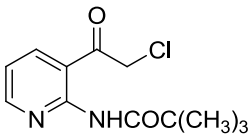

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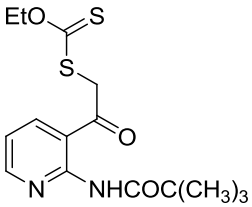

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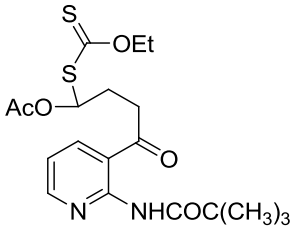

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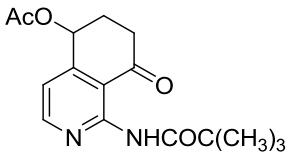

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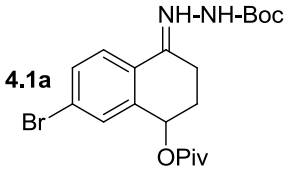
Molecules of chapter 4



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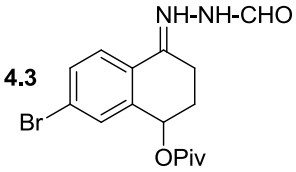

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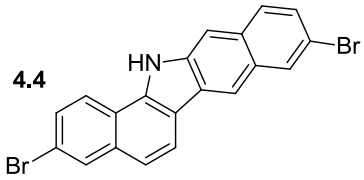

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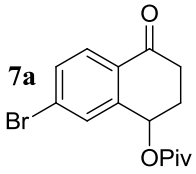

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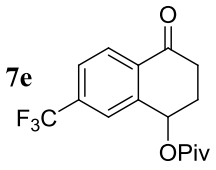

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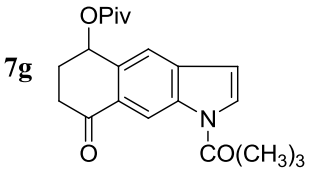

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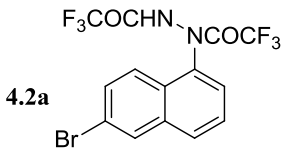

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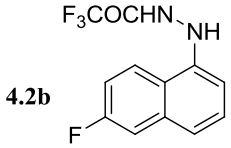

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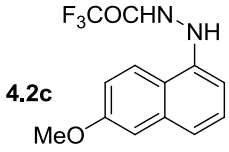

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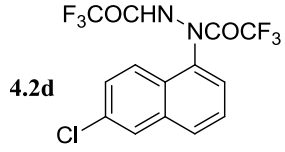

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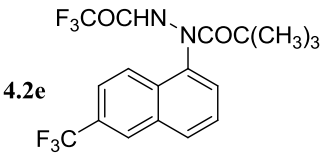

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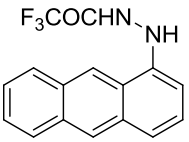


4.2f

General Experimental Methods

Purification procedures were in accordance with the instructions in D. D. Perrin and W. L.F. Armarego, "Purification of Laboratory Chemicals", Fourth Edition, The Bath Press, Bath,2002. All reactions were carried out under dry, oxygen free nitrogen. Flash chromatographywas performed on silica gel (SDS, 60 Å C. C. 40-63 mm) as the stationary phase. ThinLayer Chromatography (TLC) was performed on alumina plates pre-coated with silica gel(Merck silica gel, 60 F254), which were visualized by the quenching of UV fluorescencewhen applicable (λmax = 254 nm and/or 366 nm) and/or by staining with vanillin oranisadehyde in acidic ethanol followed by heating. Infrared spectra were recorded assolutions in $CH2Cl_2$ using NaCl cells, on a Perkin-Elmer FT 2000. Absorption maxima(nmax) are reported in wavenumbers (cm^{-1}) and only selected peaks are reported. Magneticresonance spectra were recorded at room temperature on a Bruker Avance DPX 400instrument.

Proton magnetic resonance spectra (^{1}H NMR) were recorded at 400 MHz and couplingconstants (J) are reported to ± 0.5 Hz. The following abbreviations were utilized to describepeak patterns when appropriate: br = broad, s = singlet, d = doublet, t = triplet, bs = broad singlet, bd = broad doublet, bt = broad triplet, q = quartet, quint = quintuplet, hex = hexuplet, hept = heptuplet, oct = octuplet and m = multiplet.

Due to the presence of rotamers, some quatenary carbons were not observed in the ^{13}C NMR.

Carbon magnetic resonance spectra (^{13}C NMR) were recorded in the same instrument at100.6 MHz. Chemical shifts (δH, δC) are quoted in parts per million (ppm) and arereferenced to TMS (0 ppm). Low-resolution mass spectra (m/z) were recorded by chemicalionization (CI/NH_3) on a Hewlett-Packard HP 5989B and only report molecular species($[M+H]^+$, $[M+NH_4]^+$) and other major fragments. High-resolution mass spectra wererecorded by positive electron impact ionization (EI+) at 70 e.V. on a JEOL JMS-GCmate IImass spectrometer. The quoted masses are accurate to ± 5 ppm.

The names of the molecules that appear in the following pages were generated using eitherBeilstein AutoNom 2000 (CAS) or ChemBioDraw Ultra 10.0.

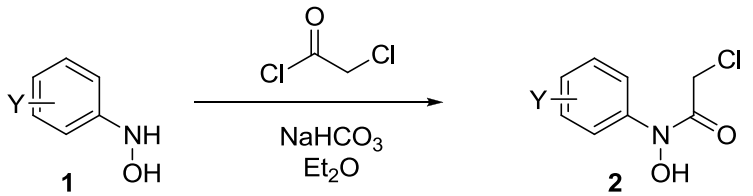
Chapter 2

General procedure I for the reduction of nitroaren

Nitroarene(50 mmol, 1eq) was dissolved in a mixture of NH_4Cl (52.5mmol, 1.05 eq), 60 mL of H_2O, and 60 mL of ethanol. Zinc powder (150 mmol, 3eq)was added to the mixture in small portions while the temperature waskept below 10 °C by cooling with an ice bath. After the addition ofzinc was complete the mixture was stirred for 4 h and filtered. Theprecipitate was washed with ethanol, and the combined solvents were evaporated under reduced pressure. The resulting yellow solids were dissolved in diethyl ether. The organic phase then was washed with water, brine and dried with $MgSO_4$, then filtered. The ether was removed under reduced pressure. The resulting yellow residue waswashed with pentane to yield the desired product. These compounds could be stored for several days at -10°Cwith little decomposition (Beissel, T.; Powers, R. E.; Parac, T. N.; Raymond K. N. *J. Am. Chem. Soc.***1999**, *121*, 4200).

***N*-(4-Methylphenyl)hydroxylamine**4-nitrotoluene (6.9 g, 50 mmol) to form 4.18 g (68%) of a white flaky product.
***N*-(4-Bromophenyl)hydroxylamine**4-bromonitrobenzene (10g, 50 mmol) to form 6.73 g (72%) of a white shiny product.
***N*-(3-Iodophenyl)hydroxylamine**3-Iodonitrobenzene (12.45 g, 50mmol) to form 9.4 g (80%) of a yellow solid.
***N*-(2-Fluorophenyl)hydroxylamine**2-fluoronitrobenzene (7.05 g, 50mmol) to form 4.95 g (78%) of a white solid.

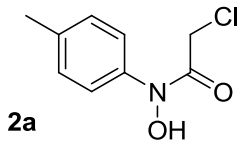
General procedure II for *N*-acylation of hydroxylamine derivatives



Following the method of N-acylation of ring activated phenylhydroxyamines of Edward E.Smissman and Michael D.Corbett (*J.Org. Chem.* **1972**, *37*, 1847-1849), *substituted*-phenylhydroxylamine(30 mmol) dissolved in 50 mL of Et_2O was placed in a flask with $NaHCO_3$ (2.8 g, 34 mmol) in 6 mL of H_2O. The mixture was cooled to -5°C by means of an ice-salt bath and stirred vigorously while chloroacetyl chloride (2.4 mL, 30 mmol) in 10 ml of Et_2O was added dropwise in the course of 15 min. The suspension was stirred until the complete comsumption of the starting marterial while the temperature is up to room temperature. The

mixture was combined with 25 mL of Et_2O and washedtwice with H_2O, then brine and dried with $MgSO_4$, then filtered.The ether was removed under reduced pressure. The residue was triturated in pentane to form a solid, and then after removing the pentane, the solid was washed quickly with dichloromethane to eliminate all of the impurities.

N-(4-methylphenyl)-2-chloro-*N*-hydroxyacetamide 2a



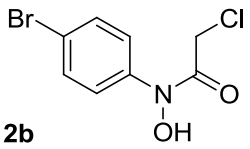
2a

$C_9H_{10}ClNO_2$
M= 199,0400 g.mol^{-1}

Following general procedure **II**for *N*-acylation, the reaction was carried out with a solution of *N*-(4-methylphenyl)hydroxylamine (3.7 g, 30 mmol)in 50 mL Et_2O, $NaHCO_3$ (2.8 g, 34 mmol) in 6 mL water and chloroacetyl chloride (2.4 mL, 30 mol) in 10 mL Et_2O. The product was recrystallized from pentane to form a pink solid. The product was washed with dichloromethane to givethedesired hydroxyacetamide**2a** (4.66 g, 78%) as a white solid.

^{1}H-NMR(δ, ppm) (DMSO-d6, 400 MHz)	10.8 (bs, 1H), 7.51 (bd, *J*= 7.8 Hz, 2H), 7.20 (bd, *J*= 8.2Hz, 2H), 4.61 (bs, 2H), 2.29 (s, 3H).
^{13}C-NMR(δ, ppm) (DMSO-d6, 100 MHz)	165.0 (C=O), 138.7 (Cq), 134.5 (br, Cq), 128.9 (bs, 2CH), 120.2 (br, 2CH), 43.4 (CH_2), 20.4(CH_3).
IR (ν, cm^{-1})	3152, 1636, 1395, 1075.
HRMS (EI)	Calcd. for $C_9H_{10}ClNO_2$: 199.0400 Found: 199.0396
Mp	125° C

N-(4-bromophenyl)-2-chloro-*N*-hydroxyacetamide 2b



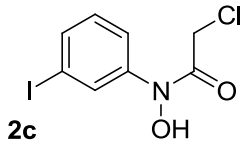
2b

$C_8H_7BrClNO_2$
M= 262.9349 $g.mol^{-1}$

Following general procedure **II**for *N*-acylation, the reaction was carried out with a solution of *N*-(4-bromophenyl)hydroxylamine (5.61g, 30 mmol)in 50 mL Et_2O, $NaHCO_3$ (2.8 g, 34 mmol) in 6 mL water and chloroacetyl chloride (2.4 mL, 30 mmol) in 10 mL Et_2O. The product was recrystallized from pentane to form a solid. The product was washed with dicholoromethane to givethe desired hydroxyacetamide**2b** (6.01 g, 76%) as a white solid.

^{1}H-NMR(δ, ppm) (DMSO-d6, 400 MHz)	11.00 (s, 1H), 7.61 (m, 4H), 4.45 (s, 2H).
^{13}C-NMR(δ, ppm) (DMSO-d6, 100 MHz)	165.5 (C=O), 140.4 (Cq), 131.4 (2CH), 121.5 (bs, 2CH), 117.0 (bs, Cq), 43.5 (CH_2).
IR (ν, cm^{-1})	3420, 3159, 2946, 1660, 1635, 1487, 1375, 1260, 1076.
HRMS (EI)	Calcd. for $C_8H_7BrClNO_2$: 262.9349Found: 262.9346
Mp	152° C

N-(3-iodophenyl)-2-chloro-*N*-hydroxyacetamide 2c



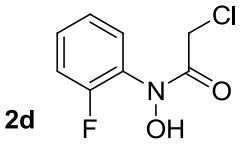
2c

$C_8H_7ClINO_2$
M= 310.09215 $g.mol^{-1}$

Following general procedure **II**for *N*-acylation, the reaction was carried out with a solution of *N*-(3-iodophenyl)hydroxylamine (7.05 g, 30 mmol)in 50 mL Et_2O, $NaHCO_3$ (2.8 g, 34 mmol) in 6 mL water and chloroacetyl chloride (2.4 mL, 30 mmol) in 10 mL Et_2O. The product was recrystallized from pentane to form a solid. The product was washed with dichloromethane to givethe desired hydroxyacetamide**2c**(7.65 g, 82%) as a white solid.

^{1}H-NMR(δ, ppm) (DMSO-D_6, 400 MHz)	11.00 (s, 1H), 8.04 (s, 1H), 7.56 (bd, 1H), 7.34 (bd, 1H), 7.2 (t, *J*= 8.1 Hz, 1H), 4.64 (bs, 2H).
^{13}C-NMR(δ, ppm) (DMSO-D_6, 100 MHz)	165.5 (C=O), 142.1 (Cq), 133.6 (CH), 130.6 (CH), 127.7 (bs, CH), 118.8 (bs, CH), 94.2 (Cq), 43.5 (CH_2).
IR (ν, cm^{-1})	3174, 2859, 1644, 1580, 1468, 1375, 1252, 1081.
HRMS (EI)	Calcd. for $C_8H_7ClINO_2$: 310.9210Found: 310.9215
Mp	157° C

N-(2-fluorophenyl)-2-chloro-*N*-hydroxyacetamide **2d**



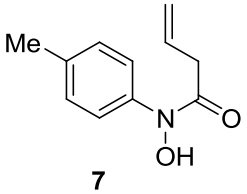
2d

$C_8H_7ClFNO_2$
M= 203.0149 $g.mol^{-1}$

Following general procedure **II**for *N*-acylation, the reaction was carried out with a solution of *N*-(2-Fluorophenyl)hydroxylamine (3.81 g, 30 mmol)in 50 mL Et_2O, $NaHCO_3$ (2.8 g, 34 mmol) in 6 mL water and chloroacetyl chloride (2.4 mL, 30 mol) in 10 mL Et_2O. The product was recrystallized from pentane to form a pink solid. The product was washed with dichloromethane to give the desired hydroxyacetamide**2d**(4.32 g, 71%) as a white solid.

^{1}H-NMR(δ, ppm) (Acetone-D_6, 400 MHz)	9.98 (bs, 1H), 7.53 (t, *J*= 7.0 Hz, 1H), 7.44 (m, 1H), 7.26 (m, 2H), 4.57 (bs, 2H).
^{13}C-NMR(δ, ppm)(Acetone-D_6, 100 MHz)	167.2 (C=O), 158.0 (d, *J*= 251 Hz, Cq-F), 131.2 (br, CH), 129.7 (br, Cq), 129.2 (br, CH), 125.6 (br, CH), 117.1 (d, *J*= 19 Hz, CH), 42.8 (CH_2).
IR (ν, cm^{-1})	3292, 1638, 1503, 1070.
HRMS (EI)	Calcd. for $C_8H_7ClFNO_2$: 203.0149 Found: 203.0149
Mp	130° C

N-hydroxy-*N*-p-tolylbut-3-enamide 7



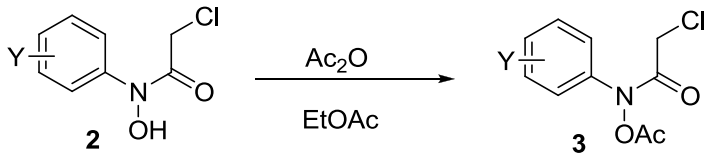
7

$C_{11}H_{13}NO_2$
M= 191.0946 g.mol^{-1}

To a solution of vinylacetic acid (5.1 mL, 60 mmol, 1 eq) in 24 mL dichloromethane and 1 drop of DMF was added oxalyl chloride (5.15 mL, 60 mmol, 1 eq) dropwise at 0°C. After the complete consumption of the starting material (20 minutes), the mixture was concentrated at 20°C under 350 mbar and then the resulting solution was added dropwise to a solution of *N*-(4-methylphenyl)hydroxylamine) (7.4 g, 60 mmol, 1 eq) in 120 mL Et_2O and $NaHCO_3$ (5.54 g, 66 mmol, 1.1 eq) in 12 mL H_2O at -5°C. The suspension was stirred until the complete consumption of the starting material while the temperature is up to room temperature. The mixture was washedtwice with H_2O, then brine and dried with $MgSO_4$, then filtered.The ether was removed under reduced pressure. The residue was purified by silica gel column chromatography with a gradient of ethyl acetate in petroleum ether (10:90 to 20:80) to afford *N*-hydroxy-*N*-p-tolylbut-3-enamide**7**(7.45 g, 65 %) as a brown oil.

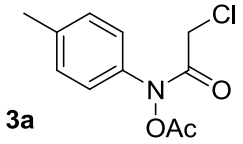
^{1}H-NMR(δ, ppm) ($CDCl_3$, 400 MHz)	8.94 (br, 1H), 7.25 (m, 4H), 5.90 (m, 1H), 5.12 (m, 2H), 3.06 (m, 2H), 2.39 (s, 3H).
^{13}C-NMR(δ, ppm) ($CDCl_3$, 100 MHz)	166.1 (C=O), 139.7 (br, Cq), 135.6 (br, Cq), 130.6 (CH), 130.0 (bs, 2CH), 126.7 (bs, 2CH), 118.7 (CH_2), 37.2 (CH_2), 21.2 (CH_3).
IR (ν, cm^{-1})	3186, 2923, 2857, 1793, 1645, 1651, 1508, 1383, 1275, 1081.
HRMS (EI)	Calcd. for $C_{11}H_{13}NO_2$: 191.0946 Found: 191.0943

General procedure III for acetylation of hydroxylamine derivatives



To a solution of *N*-(*substituted*-phenyl)-2-chloro-*N*-hydroxyacetamide (1 mmol) in ethyl acetate or aceton (2.0 mL) at room temperature, acetic anhydride (2.0 mL) was added and the reaction was stirred overnight at r.t. It was then evaporated to dryness under reduced pressure and diluted with ethyl acetate. The organic phase then was washed with a saturated $NaHCO_3$ solution, brine, water (pH= 7) and dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was pure enough to be used in the following step.

N-acetoxy-*N*-(4-methylphenyl)-2-chloroacetamide 3a

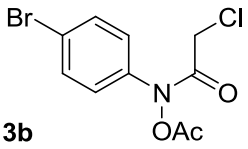


$C_{11}H_{12}ClNO_3$
M= 241.0506 g.mol^{-1}

Following the general procedure for acetylation, the reaction was carried out with *N*-(4-methylphenyl)-2-chloro-*N*-hydroxyacetamide**2a** (4 g, 20 mmol) in ethyl acetate (40 mL) and acetic anhydride (4 mL). The chloro derivative was obtained as a white solid **3a**(4.72 g, 98 %).

^{1}H-NMR(δ, ppm) ($CDCl_3$, 400 MHz) rotamers	7.39 (bd, *J*= 7.5 Hz, 2H), 7.26 (bd, *J*= 7.3 Hz, 2H), 3.96 (bs, 2H), 2.39 (s, 3H), 2.18 (s, 3H).
^{13}C-NMR(δ, ppm) ($CDCl_3$, 100 MHz) rotamers	166.0 (C=O), 160.8 (C=O), 139.9 (bs, Cq), 134.2 (Cq), 128.9 (br, 2CH), 127.1 (br, 2CH), 39.4 (CH_2), 19.9 (CH_3), 16.8(CH_3).
IR (ν, cm^{-1})	2965, 2331, 1788, 1698, 1670, 1176, 1166, 1044.
HRMS (EI)	Calcd. for $C_{11}H_{12}ClNO_3$: 241.0506 Found: 241.0510
Mp	84°C

N-acetoxy-*N*-(4-bromophenyl)-2-chloroacetamide **3b**



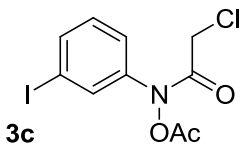
3b

$C_{10}H_9BrClNO_3$
M= 304.9454 g.mol^{-1}

Following the general procedure for acetylation, the reaction was carried out with *N*-(4-bromophenyl)-2-chloro-*N*-hydroxyacetamide**2b** (5.26 g, 20 mmol) in ethyl acetate (40 mL) and acetic anhydride (4 mL). The chloro derivative was obtained as a white solid **3b**(6.00 g, 98 %).

^{1}H-NMR(δ, ppm) ($CDCl_3$, 400 MHz) rotamers	7.54 (bd, 2H), 7.36 (bd, 2H), 4.04 (bs, 2H), 2.19 (s, 3H).
^{13}C-NMR(δ, ppm) ($CDCl_3$, 100 MHz) rotamers	167.5 (C=O), 164.0 (br, C=O), 137.4 (Cq), 132.8 (bs, 2CH), 130.1 (br, 2CH), 125.1 (br, Cq), 41.1 (CH_2), 18.3 (CH_3).
IR (ν, cm^{-1})	2314, 1787, 1693, 1486, 1388, 1364, 1274, 1175, 1160, 1042, 1010.
HRMS (EI)	Calcd. for $C_{10}H_9BrClNO_3$: 304.9454Found: 304.9460
Mp	83° C

N-acetoxy-*N*-(3-iodophenyl)-2-chloroacetamide **3c**



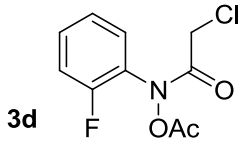
3c

$C_{10}H_9ClINO_3$
M= 352.9316 g.mol^{-1}

Following the general procedure for acetylation, the reaction was carried out with *N*-(3-iodophenyl)-2-chloro-*N*-hydroxyacetamide**2c** (6.22 g, 20 mmol) in ethyl acetate (40 mL) and acetic anhydride (4 mL). The chloro derivative was obtained as a white solid**3c** (7.06 g, 100 %).

^{1}H-NMR(δ, ppm) (DMSO-d6, 400 MHz) rotamers	7.91 (s, 1H), 7.75 (m, 1H), 7.51 (bd, *J*= 7.7 Hz, 1H), 7.27 (t, *J*= 8.0 Hz, 1H), 4.52 (bs, 2H), 2.29 (s, 3H).
^{13}C-NMR(δ, ppm) (DMSO-d6, 100 MHz) rotamers	168.1 (C=O), 164.9 (br, C=O), 139.7 (Cq), 137.3 (br, CH), 131.2 (bs, 3CH), 94.6 (Cq), 42.2 (CH_2), 18.2 (CH_3).
IR (ν, cm^{-1})	2952, 1800, 1704, 1581, 1471, 1428, 1366, 1169, 1057.
HRMS (EI)	Calcd. for $C_{10}H_9ClINO_3$: 352.9316 Found: 352.9309
Mp	157°C

N-acetoxy-*N*-(2-fluorophenyl)-2-chloroacetamide **3d**



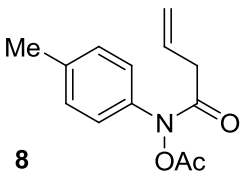
3d

$C_{10}H_9ClFNO_3$
M= 245,0255 g.mol^{-1}

Following the general procedure for acetylation, the reaction was carried out with *N*-(2-fluorophenyl)-2-chloro-*N*-hydroxyacetamide**2d**(4.06 g, 20 mmol) in ethyl acetate (40 mL) and acetic anhydride (4 mL). The chloro derivative was obtained as a yellow oil**3d** (4.89 g, 100 %).

^{1}H-NMR(δ, ppm) ($CDCl_3$, 400 MHz) rotamers	7.54 (m, 1H), 7.43 (m, 1H), 7.19 (m, 2H), 4.01 (br, 2H), 2.14 (s, 3H).
^{13}C-NMR(δ, ppm) ($CDCl_3$, 100 MHz) rotamers	167.4 (C=O), 162.8 (C=O), 158.1 (d, *J*= 252.4 Hz, Cq-F), 132.8 (br, CH), 130.8 (br, CH), 125.9 (Cq), 125.6 (br, CH), 117.0 (d, *J*= 19 Hz, CH), 40.7 (CH_2), 18.2 (CH_3).
IR (ν, cm^{-1})	2924, 1799, 1709, 1499, 1368, 1268, 1171, 1009.
HRMS (EI)	Calcd. for $C_{10}H_9ClFNO_3$: 245,0255 Found: 245.0255

N-acetoxy-*N*-p-tolylbut-3-enamide **8**



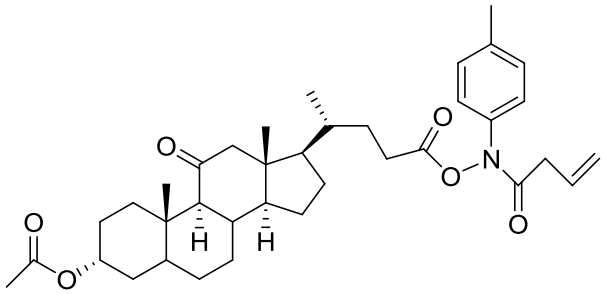
8

$C_{13}H_{15}NO_3$
M= 233.1052 g.mol^{-1}

Following the general procedure for acetylation, the reaction was carried out with *N*-hydroxy-*N*-p-tolylbut-3-enamide**7**(3.8 g, 20 mmol) in ethyl acetate (40 mL) and acetic anhydride (4 mL). After evaporating to dryness, the residue was purified by silica gel column chromatography with a gradient of ethyl acetate in petroleum ether (5:95 to 20:80) to afford the desired product **8** (4 g, 86 %) as a brown oil.

^{1}H-NMR(δ, ppm) ($CDCl_3$, 400 MHz) rotamers	7.31 (bd, 2H), 7.19 (bd, 2H), 5.85 (m, 1H), 5.06 (m, 2H), 2.89 (m, 2H), 2.34 (s, 3H), 2.11 (s, 3H).
^{13}C-NMR(δ, ppm) ($CDCl_3$, 100 MHz) rotamers	167.7 (C=O), 166.5 (br, C=O), 140.4 (br, Cq), 136.5 (Cq), 130.3 (CH), 130.1 (br, 2CH), 128.7 (br, 2CH), 118.7 (CH_2), 38.5 (CH_2), 21.2 (CH_3), 18.3(CH_3).
IR (ν, cm^{-1})	1795, 1693, 1509, 1367, 1275, 1181, 1109, 1009.
HRMS (EI)	Calcd. for $C_{13}H_{15}NO_3$: 233.1052 Found: 233.1051

Compound 8b



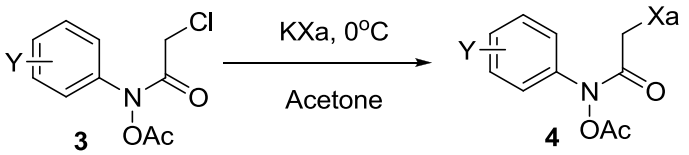
8b

$C_{37}H_{51}NO_6$
M= 605.3716
$g.mol^{-1}$

To a solution of 3α-acetoxy-11-oxo-5β-cholanic acid (2.6 g, 6 mmol, 1.5 eq) in dichloromethane (12 mL) and 1 drop of DMF was added oxalyl chloride (1.55 mL, 4.5 eq) in dichloromethane (3 mL) dropwise at 0°C. After the complete consumption of the starting material (20 minutes), the mixture was evaporated to dryness under reduced pressure then was added dichloromethane (1 mL). This solution was added dropwise to the solution of **7**(810 mg, 4.2 mmol, 1 eq), pyridine (0.37 mL, 4.6 mmol, 1.1 eq) and DMAP (51.3 mg, 0.42 mmol, 0.1 eq)in dichloromethane (5 mL). When the starting hydroxylamine was totally consumed, the mixture reaction was evaporated and diluted with ethyl acetate. The organic phase then was washed with a saturated $NaHCO_3$ solution, brine, water (pH= 7) and dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography with a gradient of ethyl acetate in petroleum ether (10:90 to 25:75) to afford **8b** (990 mg, 39%).

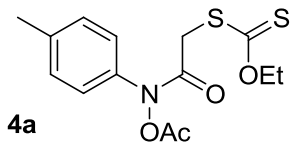
^{1}H-NMR(δ, ppm) ($CDCl_3$, 400 MHz) rotamers	7.17 (bd, 2H), 7.05 (bd, 2H), 5.71 (m, 1H), 4.95 (m, 2H), 4.51 (m, 1H), 2.84 (m, 2H), 2.42-2.10 (m, 6H), 2.19 (s, 3H), 1.86-1.36 (m, 10H), 1.81 (s, 3H), 1.19-0.80 (m, 10H), 0.99 (s, 3H), 0.68 (m, 3H), 0.39 (bs, 3H).
^{13}C-NMR(δ, ppm) ($CDCl_3$, 100 MHz) rotamers	210.8 (C=O), 170.7 (C=O), 170.1 (C=O), 166.0 (C=O), 140.3 (Cq), 136.5 (Cq), 130.4 (CH), 130.0 (br, 2CH), 128.6 (br, 2CH), 118.4 (CH_2), 73.7 (CH), 58.1 (CH_2), 55.4 (CH), 54.8 (CH), 51.2 (CH), 46.6 (Cq), 42.6 (CH), 38.3 (CH_2), 36.8 (CH), 34.8 (CH), 34.2 (CH_2), 33.9 (Cq), 32.4 (CH_2), 30.4 (CH_2), 28.4 (CH_2), 28.2 (CH_2), 27.2 (CH_2), 26.8 (CH_2), 26.4 (CH_2), 23.6 (CH_2), 23.1 (CH_3), 21.3 (CH_3), 21.2 (CH_3), 17.8 (CH_3), 12.7 (CH_3).
IR (ν, cm^{-1})	2929, 2870, 2251, 1789, 1730, 1698, 1509, 1379, 1362, 1244, 1077, 1028.
HRMS (EI)	Calcd. for $C_{37}H_{51}NO_6$: 605.3716 Found:Not found

General procedure IV for the formation of Xanthate:



To a stirred solution of *N*-acetoxy-*N*-(*substituted*-phenyl)-2-chloroacetamide (1 mmol) in acetone (2 mL) at 0°C was added portionwise potassium ethyl xanthate (1.1 mmol). The reaction was stirred until the complete comsumption of the starting marterial. The mixture was filtered and the filtrate was evaporated, and then diluted with ethyl acetate. The organic phase was washed with brine, and then the combined organic extracts were washed with water, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography or recrystallised to afford the desired xanthate.

S-2-(acetoxy(p-tolyl)amino)-2-oxoethyl *O*-ethyl carbonodithioate 4a

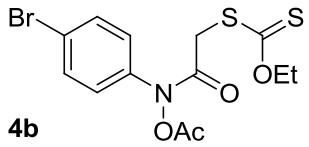


$C_{14}H_{17}NO_4S_2$
M= 327.0599 g.mol^{-1}

Following the general procedure IV, the reaction was carried out with *N*-acetoxy-*N*-(4-methylphenyl)-2-chloroacetamide**3a**(4.4 g, 18 mmol) in acetone (36 mL) and potassium ethyl xanthate (3.2 g, 19.8 mmol) during 6h. The residue was purified by silica gel column chromatography with a gradient of ethyl acetate in petroleum ether (5:95 to 30:70) to afford xanthate **4a** (4.24 g, 72 %) as a light yellow solid.

^{1}H-NMR(δ, ppm) ($CDCl_3$, 400 MHz) rotamers	7.42 (m, 2H), 7.26 (m, 2H), 4.62 (q, *J*= 7.1 Hz, 2H), 3.87 (bs, 2H), 2.39 (s, 3H), 2.18 (s, 3H), 1.40 (t, *J*= 7.1 Hz, 3H).
^{13}C-NMR(δ, ppm) ($CDCl_3$, 100 MHz) rotamers	212.7 (C=S), 167.6 (br, C=O), 162.4 (br, C=O), 141.2 (Cq), 136.0 (br, Cq), 130.5 (br, 2CH), 129.0 (br, 2CH), 70.7 (CH_2), 38.5 (CH_2), 21.4 (CH_3), 18.3 (CH_3), 13.8 (CH_3).
IR (ν, cm^{-1})	2983, 2925, 1797, 1694, 1509, 1366, 1230, 1169, 1112, 1050, 1005.
HRMS (EI)	Calcd. for $C_{14}H_{17}NO_4S_2$: 327.0599 Found: 327.0591
Mp	80° C

S-2-(acetoxy(4-bromophenyl)amino)-2-oxoethyl *O*-ethyl carbonodithioate **4b**



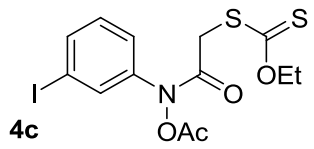
4b

$C_{13}H_{14}BrNO_4S_2$
M= 390.9548g.mol^{-1}

Following the general procedure IV, the reaction was carried out with *N*-acetoxy-*N*-(4-bromophenyl)-2-chloroacetamide**3b**(5.49 g, 18 mmol) in acetone (36 mL) and potassium ethyl xanthate (3.2 g, 19.8 mmol) during 6h. The residue was washed with petroleum ether and then recrystallized from ethanol to afford a pink solid **4b** (4.92 g, 70%).

^{1}H-NMR(δ, ppm) ($CDCl_3$, 400 MHz) rotamers	7.58 (m, 2H), 7.40 (bd, *J*= 7.8 Hz, 2H), 4.61 (q, *J*= 7.1 Hz, 2H), 3.95 (bs, 2H), 2.21 (s, 3H), 1.39 (t, *J*= 7.1 Hz, 3H).
^{13}C-NMR(δ, ppm) ($CDCl_3$, 100 MHz) rotamers	212.6 (C=S), 167.6 (C=O), 137.7 (Cq), 132.8 (br, 2CH), 130.7 (br, 2CH), 125.2 (br, Cq), 70.9 (CH_2), 38.6 (CH_2), 18.4 (CH_3), 13.8 (CH_3).
IR (ν, cm^{-1})	2789, 1787, 1695, 1448, 1159, 1043.
HRMS (EI)	Calcd. for $C_{13}H_{14}BrNO_4S_2$: 390.9548 Found: 390.9554
Mp	81° C

_S_-2-(acetoxy(3-iodophenyl)amino)-2-oxoethyl _O_-ethyl carbonodithioate 4c



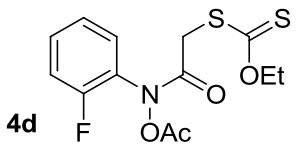
4c

$C_{13}H_{14}INO_4S_2$
M= 438.9409 g.mol^{-1}

Following the general procedure IV, the reaction was carried out with *N*-acetoxy-*N*-(3-iodophenyl)-2-chloroacetamide**3c** (6.35 g, 18mmol) in acetone (36 mL) and potassium ethyl xanthate (3.2 g, 19.8 mmol) during 6h. The residue was purified by silica gel column chromatography with a gradient of ethyl acetate in petroleum ether (10:90 to 30:70)to afford **4c** as a brown oil (5.92 g, 75%).

^{1}H-NMR(δ, ppm) ($CDCl_3$, 400 MHz) rotamers	7.84 (bs, 1H), 7.65 (m, 1H), 7.45 (m, 1H), 7.12 (m, 1H), 4.56 (q, *J*= 6.8 Hz, 2H), 3.95 (bs, 2H), 2.18 (s, 3H), 1.35 (t, *J*= 7.0 Hz, 3H).
^{13}C-NMR(δ, ppm) ($CDCl_3$, 100 MHz) rotamers	212.3 (C=S), 167.6 (C=O), 139.6 (Cq), 137.5 (br, 2CH), 131.0 (CH), 127.8 (br, CH), 94.2 (Cq-I), 71.0 (CH_2), 38.5 (CH_2), 18.4 (CH_3), 13.9 (CH_3).
IR (ν, cm^{-1})	2982, 2935, 1800, 1698, 1580, 1471, 1365, 1347, 1230, 1172, 1047.
HRMS (EI)	Calcd. for $C_{13}H_{14}INO_4S_2$:438.9409 Found: 438.9400

S-2-(acetoxy(2-iodophenyl)amino)-2-oxoethyl *O*-ethyl carbonodithioate **4d**



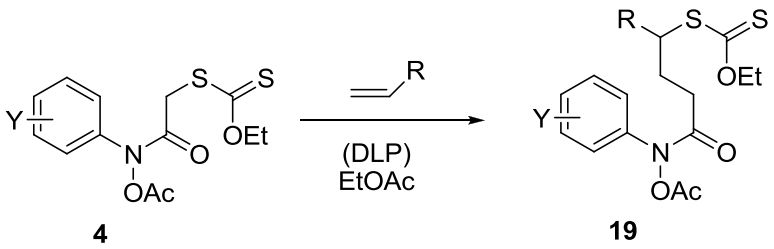
4d

$C_{13}H_{14}FNO_4S_2$
M= 331.3830 g.mol^{-1}

Following the general procedure IV, the reaction was carried out with *N*-acetoxy-*N*-(2-fluorophenyl)-2-chloroacetamide**3d**(4.41 g, 18mmol) in aceton (36 mL) and potassium ethyl xanthate (3.2g, 19.8 mmol) in 6h. The residue was purified by silica gel column chromatography with a gradient of ethyl acetate in petroleum ether (15:85 to 25:75)to afford **4d** as a brown oil (4.60 g, 77%).

^{1}H-NMR(δ, ppm) ($CDCl_3$, 400 MHz) rotamers	7.59 (m, 1H), 7.44 (m, 1H), 7.22 (m, 2H), 4.58 (q, *J*= 7.0 Hz, 2H), 3.85 (bs, 2H), 2.15 (s, 3H), 1.36 (t, *J*= 7.0 Hz, 3H).
^{13}C-NMR(δ, ppm) ($CDCl_3$, 100 MHz) rotamers	212.1 (C=S), 167.5 (br, C=O), 163.0 (br, C=O), 158.2 (d, *J*= 252 Hz, Cq-F), 133.0 (br, CH), 131.3 (br, CH), 126.2 (d, *J*= 12 Hz, Cq), 125.3 (br, CH), 117.0 (d, *J*= 19 Hz, CH), 70.8 (CH_2), 37.8 (CH_2), 18.2 (CH_3), 13.7 (CH_3).
IR (ν, cm^{-1})	2985, 2937, 1800, 1704, 1699, 1499, 1459, 1366, 1234, 1173, 1112, 1049.
HRMS (EI)	Calcd. for $C_{13}H_{14}FNO_4S_2$: 331.3830
	Calcd. for M-$C_3H_5S_2O$: $C_{10}H_9FNO_3$: 210.0566 Found: 210.0574

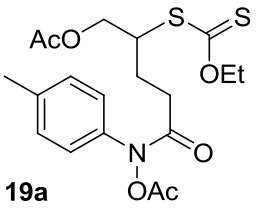
General procedure V for the radical addition:



4 **19**

A magnetically stirred solution of xanthate (1 mmol) and olefin (2 mmol) in ethyl acetate (1 mL) was refluxed for 15 min under a nitrogen flow. Dilauroyl peroxide (DLP) (5 mol %) was then added and additional DLP (2.5 mol %) was added every 60 min until total consumption of the starting material or until no evolution could be detected by TLC analysis. The reaction mixture was then cooled to 20°C and evaporated to dryness under reduced pressure. The residue was purified by silica gel column chromatography to yield the desired compounds.

5-(acetoxy(p-tolyl)amino)-2-(ethoxycarbonothioylthio)-5-oxopentyl acetate **19a**



19a

$C_{19}H_{25}NO_6S_2$
M= 427.1123 g.mol^{-1}

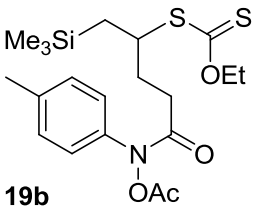
Following general procedure V for the radical addition, the reaction was carried out using xanthate **4a** (655 mg, 2 mmol, 1 eq) and allyl acetate (650 µL, 6.0 mmol, 3 eq) and needed 10 mol% DLP to go to the completion (3 h). The residue was purified by silica gel column chromatography with a gradient of ethyl acetate in petroleum ether (10:90 to 30:70) to afford radical adduct **19a** (521 mg, 61 %) as a light yellow oil.

^{1}H-NMR(δ, ppm) ($CDCl_3$, 400 MHz) rotamers	7.36 (bd, 2H), 7.27 (bd, 2H), 4.76 (m, 2H), 4.27 (m, 2H), 3.97 (m, 1H), 2.49(m+s, 5H), 2.26 (m+s, 4H), 2.03 (s, 3H), 1.90 (m, 1H), 1.40 (t, *J*= 7.1 Hz, 3H).
^{13}C-NMR(δ, ppm) ($CDCl_3$, 100 MHz) rotamers	212.6 (C=S), 170.6 (C=O), 167.8(br, C=O),140.7 (br, Cq), 136.3 (Cq), 130.3 (br, 2CH), 128.7 (br, 2CH), 70.3 (CH_2), 65.6 (CH_2), 48.6 (CH), 30.7 (CH_2), 26.0 (CH_2), 21.3(CH_3), 20.8 (CH_3), 18.4(CH_3), 13.7 (CH_3).

IR (ν, cm^{-1}) 2982, 2938, 1794, 1743, 1689, 1509, 1382, 1366, 1228,1180, 1047.

HRMS (EI) Calcd. for $C_{19}H_{25}NO_6S_2$: 427.1123 Found: 427.1147

S-5-(acetoxy(p-tolyl)amino)-5-oxo-1-(trimethylsilyl)pentan-2-yl *O*-ethyl carbonodithioate **19b**



19b

$C_{20}H_{31}NO_4S_2Si$
M= 441.1464 $g.mol^{-1}$

Following general procedure V for the radical addition, the reaction was carried out using xanthate **4a** (655 mg, 2.0 mmol) and allyl trimethylsilane (640 µL, 2 eq) and needed 15 mol% DLP to go to the completion (5 h). The residue was purified by silica gel column chromatography with a gradient of ethyl acetate in petroleum ether (5:95 to 70:30) to afford radical adduct **19b** (0.50 g, 57 %) as a light yellow oil.

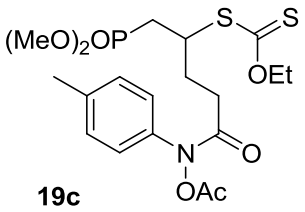
^{1}H-NMR(δ, ppm) ($CDCl_3$, 400 MHz) rotamers: 7.30 (bd, 2H), 7.20 (bd, 2H), 4.59 (m, 2H), 3.82 (m, 1H), 2.36 (m+s, 5H), 2.1(m+s, 4H), 1.89 (m, 1H), 1.38 (t, *J*= 7.0 Hz, 3H), 1.06 (m, 1H), 0.92 (m, 1H), 0.00 (s, 9H).

^{13}C-NMR(δ, ppm) ($CDCl_3$, 100 MHz) rotamers: 214.8 (C=S), 168.6 (C=O), 141.3 (br, Cq), 137.3 (Cq), 131.0 (br, 2CH), 129.5 (br, 2CH), 70.3 (CH_2), 48.8 (CH), 32.9 (CH_2), 31.6 (CH_2), 24.1 (CH_2), 22.0 (CH_3), 19.1 (CH_3), 14.5 (CH_3), 0.0 ($3CH_3$).

IR (ν, cm^{-1}) 2953, 1796, 1693, 1509, 1379, 1368, 1248, 1213, 1181, 1111, 1050.

HRMS (EI) Calcd. for $C_{20}H_{31}NO_4S_2Si$: 441.1464 Found: 441.1473

Compound 19c



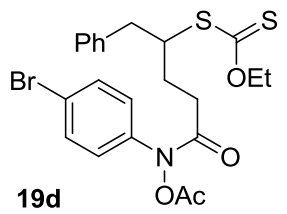
19c

$C_{19}H_{28}NO_7PS_2$
M= 477.1045 g.mol^{-1}

Following general procedure V for the radical addition, the reaction was carried out using xanthate **4a** (655 mg, 2.0 mmol) and dimethylallyl phosphonate (420 µL, 2 eq) and needed 15 mol% DLP to go to the completion (5h). The residue was purified by silica gel column chromatography with a gradient of methanol in dichloromethane (0:100 to 4:96) to afford radical adduct **19c** (610 mg, 64%) as a light yellow oil.

^{1}H-NMR(δ, ppm) ($CDCl_3$, 400 MHz) rotamers	7.26 (br, 2H), 7.17 (br, 2H), 4.55 (m, 2H), 3.90 (m, 1H), 3.75 (d, *J*= 2.9 Hz, 3H), 3.73 (d, *J*= 2.9 Hz, 3H), 2.60-2.25 (m, 4H), 2.37 (s, 3H), 2.01 (m+s, 4H), 1.95 (m, 1H), 1.34 (t, *J*= 7.1 Hz, 3H).
^{13}C-NMR(δ, ppm) ($CDCl_3$, 100 MHz) rotamers	212.4 (C=S), 167.7 (br, C=O), 167.2 (br, C=O), 140.6 (br, Cq), 136.3 (Cq), 130.2 (bs, 2CH), 128.7 (bs, 2CH), 70.1 (CH_2), 52.6 (d, *J*= 7Hz, CH_3), 52.5 (d, *J*= 7Hz, CH_3),44.7 (CH), 30.8 (CH_2), 30.7 (d, *J*= 138 Hz, CH_2), 29.0 (CH_2), 21.2 (CH_3), 18.3 (CH_3), 13.7 (CH_3).
IR (ν, cm^{-1})	2955, 2924, 2953, 1793, 1683, 1509, 1455, 1379, 1226, 1180, 1047.
HRMS (EI)	Calcd. for $C_{19}H_{28}NO_7PS_2$: 477.1045 Found: 477.1038

S-5-(acetoxy(4-bromophenyl)amino)-5-oxo-1-phenylpentan-2-yl *O*-ethyl carbonodithioate **19d**



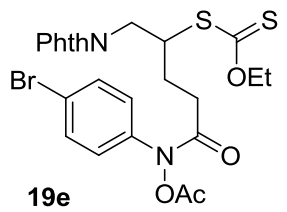
19d

$C_{22}H_{24}BrNO_4S_2$
M= 509,0330 g.mol^{-1}

Following general procedure Vfor the radical addition, the reaction was carried out using xanthate **4b** (785 mg, 2.0 mmol) and allyl benzene (530 µL, 2 eq) and needed 12.5 mol% DLP to go to the completion (4h). The residue was purified by silica gel column chromatography with a gradient of ethyl acetate in petroleum ether (10:90 to 25:75) to afford radical adduct **19d** (710 mg, 70%) as a light yellow oil.

^{1}H-NMR(δ, ppm) ($CDCl_3$, 400 MHz) rotamers	7.51(d, *J*= 8.4 Hz, 2H), 7.25 (m, 7H), 4.60 (q, *J*= 7.1 Hz, 2H), 3.96 (m, 1H), 3.14 (dd, *J*= 5.8 Hz, *J*= 13.8 Hz, 1H), 2.85 (dd, *J*= 8.6 Hz, *J*= 13.0 Hz, 1H), 2.39 (m, 2H), 2.17 (m+s, 4H), 1.86 (m, 1H), 1.39 (t, *J*= 7.1 Hz, 3H).
^{13}C-NMR(δ, ppm) ($CDCl_3$, 100 MHz) rotamers	213.7 (C=S), 167.8 (br, C=O), 138.2 (br, Cq), 138.1 (Cq), 132.6 (br, 2CH), 132.4-125.7 (br, Cq+ 2CH), 129.3 (2CH), 128.5 (2CH), 126.8 (CH), 70.0 (CH_2), 51.6 (CH), 41.5 (CH_2), 31.0 (CH_2), 27.9 (CH_2), 18.4 (CH_3), 13.7 (CH_3).
IR (ν, cm^{-1})	2925, 1798, 1693, 1485, 1368, 1215, 1177, 1111, 1049.
HRMS (EI)	Calcd. for $C_{22}H_{24}BrNO_4S_2$: 509.0330 Calcd. for M-$C_3H_5S_2O$-$OCOCH_3$: $C_{17}H_{16}BrNO$: 329.0415 Found: 329.0410

_S_-5-(acetoxy(4-bromophenyl)amino)-1-(1,3-dioxoisoindolin-2-yl)-5-oxo pentan-2-yl_O_-ethyl carbonodithioate **19e**



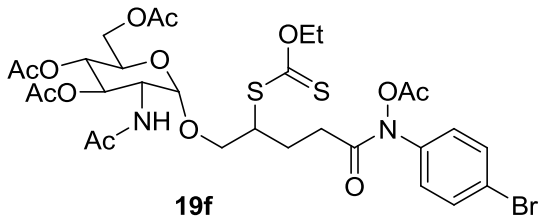
19e

$C_{24}H_{23}BrN_2O_6S_2$
M= 578.0181 g.mol^{-1}

Following general procedure Vfor the radical addition, the reaction was carried out using xanthate **4b**(785 mg, 2 mmol) and allyl phthalimide (750 mg, 4mmol) and needed 15 mol% DLP to go to the completion (5h). The residue was purified by silica gel column chromatography with a gradient of ethyl acetate in petroleum ether (10:90 to 35:65) to afford radical adduct **19e** (671 mg, 58 %) as a light yellow oil.

^{1}H-NMR(δ, ppm) ($CDCl_3$, 400 MHz) rotamers	7.83 (m, 2H), 7.71 (m, 2H), 7.50 (m, 2H), 7.30 (d, *J*= 8.5 Hz, 2H), 4.75 (q, *J*= 7.1 Hz, 2H), 4.12 (m, 1H), 3.93 (m, 2H), 2.48 (m, 2H), 2.18 (bs, 4H), 1.92 (m, 1H), 1.39 (t, *J*= 7.1 Hz, 3H).
^{13}C-NMR(δ, ppm) ($CDCl_3$, 100 MHz) rotamers	212.1 (C=S), 168.0 (2C=O), 167.8 (C=O), 138.0 (Cq), 134.2 (2CH), 132.7 (bs, 2CH), 131.8 (2Cq), 130.5 (br, 2CH), 125.3 (br, Cq), 123.5 (2CH), 70.4 (CH_2), 48.8 (CH), 41.5 (CH_2), 31.5 (CH_2), 26.6 (CH_2), 18.4 (CH_3), 13.7 (CH_3).
IR (ν, cm^{-1})	2958, 2925, 1797, 1772, 1705, 1434, 1260, 1160, 1043.
HRMS (EI)	Calcd. for $C_{24}H_{23}BrN_2O_6S_2$: 578.0181
	Calcd. for M-$C_3H_5S_2O$-$OCOCH_3$: $C_{19}H_{15}BrN_2O_3$: 398.0266 Found: 398.0258

(2S,3R,4R,5S,6R)-5-acetamido-2-(acetoxymethyl)-6-((7-bromo-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepin-5-yl)methoxy)tetrahydro-2H-pyran-3,4-diyldiacetate **19f**



19f

$C_{30}H_{39}BrN_2O_{13}S_2$
M= 778.1077 g.mol^{-1}

Following general procedure Vfor the radical addition, the reaction was carried out using xanthate **4b** (1.56 g, 4 mmol) and olefine **22j**(800 mg, 2mmol) and needed 15 mol% DLP to go to the completion (5h). The residue was purified by silica gel column chromatography with a gradient of ethyl acetate in diethyl ether (30:70 to 60:40) to afford the mixture of two diastereoisomers **19f**(918 mg, 59 %) as a light yellow oil.

^{1}H-NMR(δ, ppm) ($CDCl_3$, 400 MHz) rotamers mixture of diastereoisomers

7.54 (m, 2H), 7.32 (m, 2H), 6.15 (d, *J*= 9.4 Hz, 0.5 NH), 6.07 (bs, 0.5 NH), 5.18 (m, 1H), 5.11 (td, *J*= 9.6 Hz, 1H), 4.87 (d, *J*= 3.6 Hz, 0.5H), 4.83 (d, *J*= 3.6 Hz, 0.5 H), 4.66 (m, 2H), 4.36 (m 1H), 4.23 (m, 1H), 4.07 (m, 1H), 3.97 (m, 2.5H), 3.81 (m, 0.5H), 3.67 (m, 0.5H), 3.53 (m, 0.5H), 2.43 (m, 2H), 2.21 (m+s, 4H), 2.08 (s, 1.5H), 2.07 (s, 1.5H), 2.02 (s, 3H), 2.01 (s, 1.5H), 2.00 (s, 1.5H), 1.93 (m+s, 4H), 1.42 (dt, *J*= 7.1Hz, 3H).

^{13}C-NMR(δ, ppm) ($CDCl_3$, 100 MHz) rotamers mixture of diastereoisomers

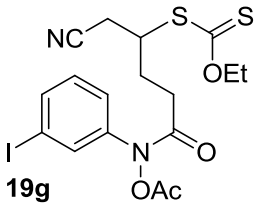
212.9 (C=S); 171.1 (C=O); 170.7 (C=O); 170.6 (C=O); 170.4 (C=O); 169.3 (C=O); 167.9 (C=O); 137.9 (Cq); 132.9 (br, 2CH);130.2 (br, 2CH); 125.5 (br, Cq); 97.9, 97.7 (CH); 71.4, 71.3 (CH); 70.6, 70.5 (CH_2); 70.3 (br, CH), 70.0 (br, CH); 68.2, 68.1 (CH), 61.9 (CH_2); 51.8, 51.7 (CH); 49.8, 49.6 (br, CH_2); 30.6 (br, CH_2); 25.8, 25.4 (br, CH_2); 23.0, 22.9 (CH_3); 20.8 ($2CH_3$); 20.7 (CH_3); 18.3 (CH_3); 13.8, 13.7 (CH_3).

IR (ν, cm^{-1}) 3362, 2954, 2936, 1798, 1748, 1683, 1486, 1368, 1230, 1170, 1113, 1046.

HRMS (EI) Calcd. for $C_{30}H_{39}BrN_2O_{13}S_2$: 778.1077

Calcd. for M-$C_3H_5S_2O$: $C_{27}H_{34}BrN_2O_{12}$: 657.1295
Found: 657.1289

_S_-5-(acetoxy(3-iodophenyl)amino)-1-cyano-5-oxopentan-2-yl _O_-ethyl Carbonodithioate **19g**



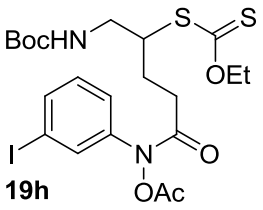
19g

$C_{17}H_{19}IN_2O_4S_2$
M= 505.9831 g.mol^{-1}

Following general procedure Vfor the radical addition, the reaction was carried out using xanthate **4c** (880 mg, 2 mmol) and allyl cyanide (508 µL, 4mmol) and needed 15 mol% DLP to go to the completion (5h). The residue was purified by silica gel column chromatography with a gradient of ethyl acetate in petroleum ether (10:90 to 35:65) to afford radical adduct **19g** (587 mg, 58 %) as a light yellow oil.

^{1}H-NMR(δ, ppm) ($CDCl_3$, 400 MHz) rotamers	7.85 (s, 1H), 7.75 (m, 1H), 7.48 (d, *J*= 7.9 Hz, 1H), 7.20 (br, 1H), 4.71 (m, 2H), 4.03 (m, 1H), 2.95 (m, 2H), 2.54 (m, 2H), 2.27 (m, 4H), 2.10 (m, 1H), 1.48 (t, *J*= 7.1 Hz, 3H).
^{13}C-NMR(δ, ppm) ($CDCl_3$, 100 MHz) rotamers	211.7 (C=S), 167.8 (C=O), 139.7 (Cq), 137.3 (br, CH), 130.8 (bs, 3CH), 116.9 (CN), 94.0 (Cq-I), 70.7 (CH_2), 45.7 (CH), 30.4 (CH_2), 27.5 (CH_2), 24.3 (CH_2), 18.4 (CH_3), 13.9 (CH_3).
IR (ν, cm^{-1})	2982, 2957, 2927, 2249, 1798, 1693, 1581, 1568, 1471, 1367, 1224, 1174, 1048.
HRMS (EI)	Calcd. for $C_{17}H_{19}IN_2O_4S_2$:505.9831
	Calcd. for M-$C_3H_5S_2O$: $C_{14}H_{14}IN_2O_3$: 385.0049 Found: 385.0052

tert-butyl 5-(acetoxy(3-iodophenyl)amino)-2-(ethoxycarbonothioylthio)-5-oxopentylcarbamate **19h**



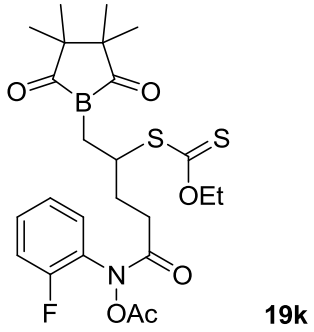
19h

$C_{21}H_{29}IN_2O_6S_2$
M= 596.0512 g.mol^{-1}

Following general procedure Vfor the radical addition, the reaction was carried out using xanthate **4c** (880 mg, 2 mmol) and *N*-Boc-allylamine (560 mg, 4 mmol) and needed 15 mol% DLP to go to the completion (5h). The residue was purified by silica gel column chromatography with a gradient of ethyl acetate in petroleum ether (20:80 to 35:65) to afford radical adduct **19h** (905 mg, 76 %) as a light yellow oil.

^{1}H-NMR(δ, ppm) (CDCl3, 400 MHz) rotamers	7.79 (s, 1H), 7.68 (m, 1H), 7.42 (m, 1H), 7.14 (bt, *J*= 7.8 Hz, 1H), 4.86 (bs, 1H), 4.62 (q, *J*= 7.1 Hz, 2H), 3.84 (m, 1H), 3.43 (m, 2H), 2.47 (m, 2H), 2.21 (m+s, 4H), 1.90 (m, 1H), 1.41 (m, 12H).
^{13}C-NMR(δ, ppm) (CDCl3, 100 MHz) rotamers	213.1 (C=S), 167.8 (C=O), 155.9 (C=O), 140.0 (Cq), 136.9 (br, CH), 130.7 (bs, 3CH), 94.0 (Cq-I), 79.7 (Cq), 70.7 (CH_2), 50.9 (CH), 43.7(CH_2), 30.5 (br, CH_2), 28.4 (3CH_3), 26.2 (br, CH_2), 18.4 (CH_3), 13.8 (CH_3).
IR (ν, cm^{-1})	2978, 2932, 2251, 1799, 1698, 1511, 1471, 1366, 1220, 1171, 1048.
HRMS (EI)	Calcd. for $C_{21}H_{29}IN_2O_6S_2$: 596.0512
	Calcd. for M- $C_3H_5S_2O$: $C_{18}H_{24}IN_2O_5$: 475.0730 Found: 475.0733

_S_-5-(acetoxy(2-fluorophenyl)amino)-5-oxo-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentan-2-yl _O_-ethyl carbonodithioate **19k**



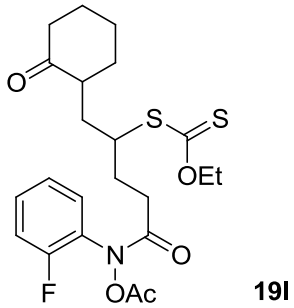
19k

$C_{22}H_{31}BFNO_6S_2$
M= 499.1670 g.mol^{-1}

Following general procedure Vfor the radical addition, the reaction was carried out using xanthate **4d**(660 mg, 2 mmol) and allylboronic acid pinacolester (750 µL, 4mmol) and needed 15 mol% DLP to go to the completion (5h). The residue was purified by silica gel column chromatography with a gradient of ethyl acetate in petroleum ether (10:90 to 25:75) to afford radical adduct **19k** (669 mg, 67 %) as a light yellow oil.

^{1}H-NMR(δ, ppm) ($CDCl_3$, 400 MHz) rotamers	7.52 (bt, *J*= 7.0 Hz, 1H), 7.42 (bs, 1H), 7.19 (m, 2H), 4.58 (m, 2H), 3.88 (m, 1H), 2.32 (m, 2H), 2.16 (m+s, 4H), 2.05 (m, 1H), 1.38 (t,*J*= 7.0 Hz, 3H), 1.30-1.20 (m, 2H), 1.21 (s, 6H), 1.22 (s, 6H).
^{13}C-NMR(δ, ppm) ($CDCl_3$, 100 MHz) rotamers	214.0 (br, C=S), 167.8 (br, C=O), 158.3 (d, *J*= 259 Hz, Cq-F), 132.1 (br, CH), 131.3 (br, CH), 126.9 (d, *J*= 12 Hz, Cq), 125.1 (br, CH), 117.0 (d, *J*= 19 Hz, CH), 83.6 (2Cq), 69.6 (CH_2), 46.9 (CH), 31.2 (CH_2), 30.3 (CH_2), 24.8 (d, 4CH_3), 18.3 (CH_3), 17.8 (br, CH_2) 13.7 (CH_3).
IR (ν, cm^{-1})	2979, 2928, 1798, 1699, 1499, 1371, 1331, 1215, 1176, 1144, 1049.
HRMS (EI)	Calcd. for $C_{22}H_{31}BFNO_6S_2$: 499.1670
	Calcd. for M-$C_3H_5S_2O$: $C_{19}H_{26}BFNO_5$: 378.1888 Found: 378.1897

_S_-5-(acetoxy(2-fluorophenyl)amino)-5-oxo-1-(2-oxocyclohexyl)pentan -2-yl _O_-ethyl carbonodithioate **19l**



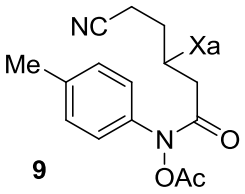
19l

$C_{22}H_{28}FNO_5S_2$
M= 469.1393 g.mol^{-1}

Following general procedure Vfor the radical addition, the reaction was carried out using xanthate **4d** (660 mg, 2 mmol) and 2-allyl cyclohexanone (600 µL, 4 mmol) and needed 12.5 mol% DLP to go to the completion (4h). The residue was purified by silica gel column chromatography with a gradient of ethyl acetate in petroleum ether (10:90 to 30:70) to afford the mixture of two diastereoisomers**19l** (704 mg, 75 %) as a light yellow oil.

^{1}H-NMR(δ, ppm) ($CDCl_3$, 400 MHz) rotamers	7.53 (m,1H), 7.42 (bs, 1H), 7.20 (m, 2H), 4.58 (m, 2H), 3.76 (m, 1H), 2.55-1.34 (m+s, 21H).
^{13}C-NMR(δ, ppm) ($CDCl_3$, 100 MHz) rotamers mixture of two diastereoisomers	213.8 (C=S); 212.1, 211.9 (C=O); 167.7 (br, C=O); 158.3 (d, *J*= 259 Hz, Cq-F); 132.3 (br, CH); 131.1 (br, CH); 126.7 (d, *J*= 12 Hz, Cq); 125.0 (br, CH); 116.9 (d, *J*= 19 Hz, CH); 70.1, 70.0 (CH_2): 49.3, 48.1(CH); 48.1, 47.9 (CH); 40.3, 40.0 (CH_2); 34.4, 34.9 (CH_2); 33.8, 33.3 (CH_2); 30.5, 30.1 (CH_2); 29.9 (CH_2); 28.2, 27.8 (CH_2); 25.3, 25.0 (CH_2); 18.2 (CH_3), 13.7 (CH_3).
IR (ν, cm^{-1})	2934, 2861, 1797, 1704, 1498, 1368, 1216, 1176, 1110, 1046.
HRMS (EI)	Calcd. for $C_{22}H_{28}FNO_5S_2$: 469.1393
	Calcd. for M- $C_3H_5S_2O$: $C_{19}H_{23}FNO_4$: 348.1611 Found: 348.1614

S-1-(acetoxy(p-tolyl)amino)-5-cyano-1-oxopentan-3-yl *O*-ethyl carbonodithioate **9**



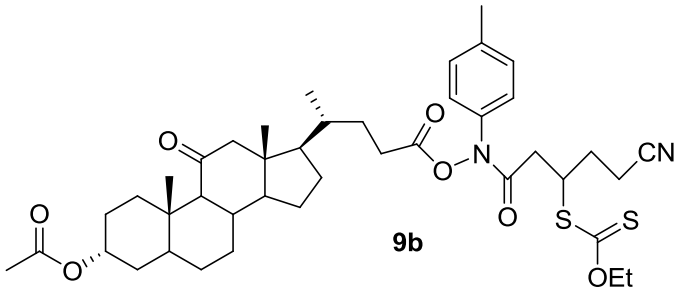
9

$C_{18}H_{22}N_2O_4S_2$
M= 394.1021 g.mol^{-1}

The reaction was carried out as the general procedure V (radical addition), except that S-cyanomethyl O-ethyl xanthate (724mg, 4.5mmol, 1.5 eq) is used in excess to olefin **8**(700mg, 3mmol, 1eq). The residue was purified by silica gel column chromatography with a gradient of ethyl acetate in petroleum ether (2:8 to 6:4) to afford radical adduct **9**(827 mg, 70 %) as a light yellow oil.

^{1}H-NMR(δ, ppm) ($CDCl_3$, 400 MHz) rotamers	7.33 (bd, *J*= 8.3Hz, 2H), 7.26 (m, 2H), 4.60 (m, 2H), 4.14 (m, 1H), 2.80-2.12 (m, 6H), 2.4 (s, 3H), 2.17 (s, 3H), 1.39 (t, *J*= 7.1 Hz, 3H).
^{13}C-NMR(δ, ppm) ($CDCl_3$, 100 MHz) rotamers	212.3 (C=S), 167.5 (C=O), 165.1 (C=O), 141.1 (Cq), 135.8 (Cq), 130.7 (2CH), 128.9 (2CH), 118.9 (CN), 70.4 (CH_2), 45.8 (CH), 38.1 (CH_2), 29.6 (CH_2), 21.3 (CH_3), 18.3 (CH_3), 15.3 (CH_2), 13.8 (CH_3).
IR (ν, cm^{-1})	2927, 2248, 1795, 1683, 1509, 1384, 1224, 1179, 1112, 1048, 1003.
HRMS (EI)	Calcd. for $C_{18}H_{22}N_2O_4S_2$: 394.1021
	Calcd. for M-$C_3H_5S_2O$: $C_{15}H_{17}N_2O_3$: 273.1239 Found: 273.1234

Compound 9b



$C_{42}H_{58}N_2O_7S_2$
M= 766.3685 g.mol^{-1}

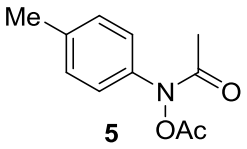
The reaction was carried out as the general procedure V, except that S-cyanomethyl O-ethyl xanthate (485 mg, 3 mmol, 2 eq)is used in excess to olefin **8b** (910 mg, 1.5 mmol, 1eq). The residue was purified by silica gel column chromatography with a gradient of ethyl acetate in petroleum ether (1:9 to 7:3) to afford radical adduct **9b** (723 mg, 63 %) as a light yellow oil.

^{1}H-NMR(δ, ppm) ($CDCl_3$, 400 MHz) rotamers	7.26 (bd, 2H, *J*= 7.8 Hz), 7.21 (m, 2H), 4.63 (m, 3H), 4.01 (m, 1H), 2.73-2.37 (m, 10H), 2.37 (s, 3H), 2.05-1.51 (m, 11H), 1.99 (s, 3H), 1.50-1.00 (m, 14H), 1.12 (s, 3H), 0.80 (s, 3H), 0.51 (s, 3H).
^{13}C-NMR(δ, ppm) ($CDCl_3$, 100 MHz) rotamers	212.3 (C=S), 211.4 (C=O), 170.8 (C=O), 170.7 (C=O), 170.5 (C=O), 141.1 (Cq), 135.7 (Cq), 130.6 (2CH), 128.9 (2CH), 118.9 (CN), 74.0 (CH), 70.4 (CH_2), 58.3 (CH_2), 55.7 (CH), 55.0 (CH), 51.4 (CH), 46.8 (Cq), 45.8 (CH), 42.7 (CH), 38.1 (CH_2), 37.0 (CH), 34.9 (CH), 34.3 (CH_2), 34.0 (Cq), 32.5 (CH_2), 30.4 (CH_2), 29.5 (CH_2), 28.4 ($2CH_2$), 27.3 (CH_2), 26.9 (CH_2), 26.4 (CH_2), 23.7 (CH_2), 23.1 (CH_3), 21.5 (CH_3), 21.4 (CH_3), 17.9 (CH_3), 15.3 (CH_2), 13.7 (CH_3), 12.7 (CH_3).
IR (ν, cm^{-1})	2928, 2870, 2251, 1789, 1728, 1699, 1509, 1451, 1381, 1363, 1243, 1111, 1050.
HRMS (EI)	Calcd. for $C_{42}H_{58}N_2O_7S_2$: 766.3685
	Calcd. for M-$C_3H_5S_2O$: $C_{39}H_{53}N_2O_6$: 645.3904 Found:645.3902

General procedure VI for the radical cyclisation:

A magnetically stirred solution of xanthate (1 mmol) in ethyl acetate(AcOEt) (1 mL) was refluxed for 15 min under a nitrogen flow. Dilauroylperoxide (DLP) (5 mol %) was then added and additional DLP (20 mol %) was added every 60 min until total consumption of the starting material or until no evolution could bedetected by TLC analysis. The reaction mixture was then cooled to 20°C and evaporated. The lauric acid was recrystallized from acetonitrile and filtered (except when the product is not soluble in acetonitrile), then the organic phase was evaporated.The mixture was purified by silica gel column chromatography or recrystallized from an appropriate solvent to yield the desired compounds.

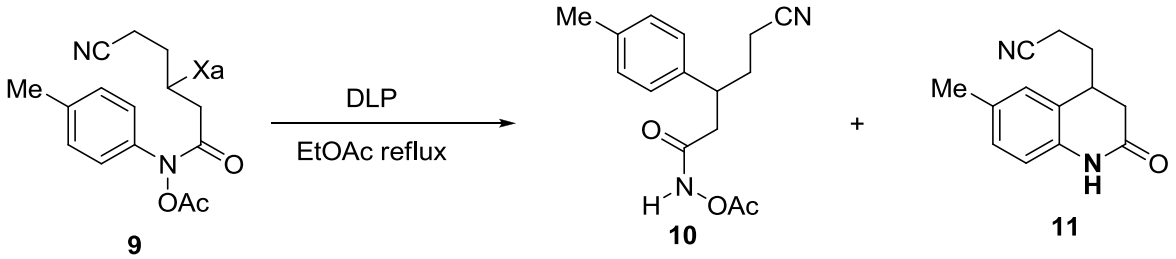
N-acetoxy-N-(tolyl)-acetamide **5**



5

$C_{11}H_{13}NO_3$
M= 207,0895 g.mol^{-1}

Following general procedure VIfor the radicalcyclisation, the reaction was carried out using xanthate **4a**(330 mg, 1 mmol, 1 eq) in refluxing ethyl acetate and needed 1 eq. of DLP to go to the completion (5 h). After elimination of lauric acid, the residue was purified by silica gel column chromatography with a gradient of ethyl acetate in petroleum ether (10:90 to 20:80) to afford **5** (195 mg, 95%) as a yellow oil. The NMR data of compound **5** are in accordance with the literature data.



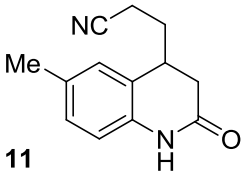
9 **10** **11**

Following general procedure VI for the radical cyclisation, the reaction was carried out using xanthate **9** (400 mg, 1 mmol, 1 eq) in refluxing ethyl acetate and needed 1 eq. of DLP to go to the completion (5 h). After elimination of lauric acid, the residue was purified by silica gel

column chromatography with a gradient of methanol in dichloromethane (2:98 to 5:95) to afford the cyclised product **11** 75 mg (35% isolated yield) and 123 mg of a mixture of rearrangement product **10** (40% NMR yield) and cyclised product **11** (60 % NMR yield).

Problem: The two compounds have nearly the same polarity; it is very difficult to separate them completely.

3-(6-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-4-yl)propanenitrile **11**

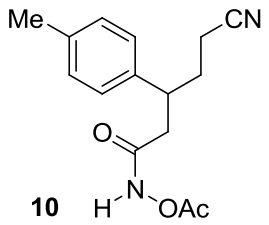


11

$C_{13}H_{14}N_2O$
M= 214.1106 g.mol^{-1}

^{1}H-NMR(δ, ppm) ($CDCl_3$, 400 MHz)	9.18 (bs, 1H), 7.03 (d, *J*= 8.0 Hz, 1H), 7.00 (s, 1H), 6.78 (d, *J*= 8.0 Hz, 1H), 3.08 (m, 1H), 2.85 (dd, *J*= 6.2 Hz, *J*= 16.4 Hz, 1H), 2.54 (dd, *J*= 2.3 Hz, *J*= 16.4 Hz, 1H), 2.33 (m+s, 5H), 1.89 (dd, *J*= 7.4 Hz, *J*= 14.5 Hz, 2H).
^{13}C-NMR(δ, ppm) ($CDCl_3$, 100 MHz)	169.5 (C=O), 132.9 (Cq), 132.1 (Cq), 128.0 (CH), 127.6 (CH), 123.6 (Cq), 118.0 (CN), 115.2 (CH), 35.0 (CH_2), 34.1 (CH), 28.4 (CH_2), 19.8 (CH_3), 14.0 (CH_2)
IR (ν, cm^{-1})	3395, 2894, 2243, 1792, 1667, 1648, 1383, 1148, 1072.
HRMS (EI)	Calcd. for $C_{13}H_{14}N_2O$: 214.1106 Found: 214.1106
Mp	169° C

N-acetoxy-5-cyano-3-p-tolylpentanamide **10**

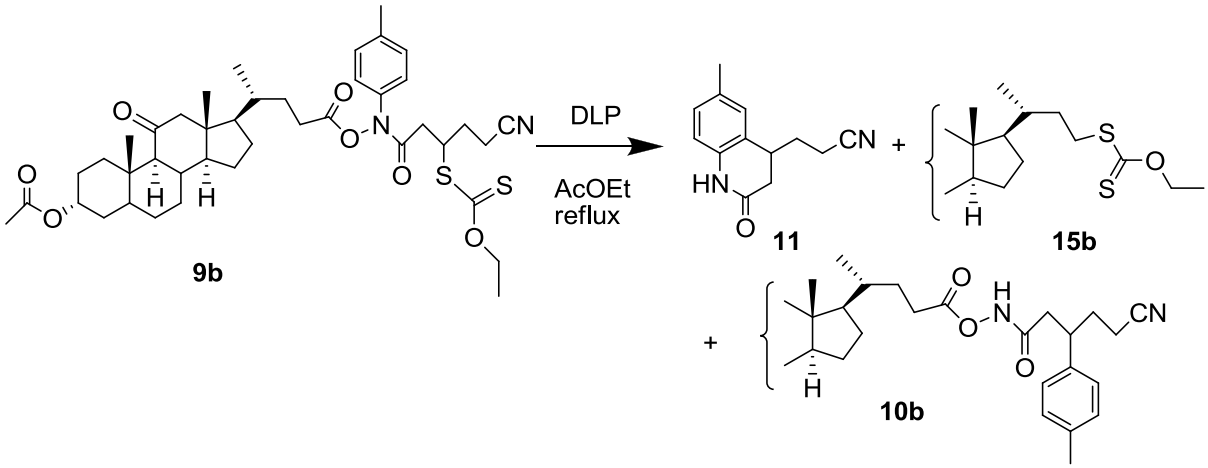


10

$C_{15}H_{18}N_2O_3$
M= 274.1317g.mol^{-1}

^{1}H-NMR(δ, ppm) ($CDCl_3$, 400 MHz)	9.63 (bd, 1H), 7.11 (d, *J*= 7.9 Hz, 2H), 7.05 (d, *J*= 8.1 Hz, 2H), 3.19 (m, 1H), 2.53 (bd, 2H), 2.30 (s, 3H), 2.11 (m+s, 6H), 1.89 (m, 1H).
^{13}C-NMR(δ, ppm) ($CDCl_3$, 100 MHz)	168.9 (C=O), 168.8 (C=O), 137.9 (Cq), 137.2 (Cq), 129.8 (2CH), 127.3 (2CH), 119.5 (CN), 40.8 (CH), 39.8 (CH_2), 31.2 (CH_2), 21.1 (CH_3), 18.3 (CH_3), 15.0 (CH_2).
IR (ν, cm^{-1})	3208, 2931, 2248, 1791, 1668, 1515, 1423, 1182.
HRMS (EI)	Calcd. for $C_{15}H_{18}N_2O_3$: 274.1317Found: 274.1319

Compounds 11 + 15b +10b

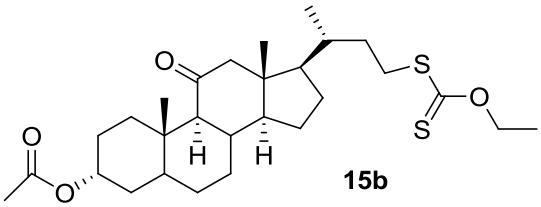


9b **11** **15b** **10b**

Following general procedure VI for the radical cyclisation, the reaction was carried out using xanthate **9b** (770 mg, 1 mmol, 1 eq) in refluxing ethyl acetate and needed 1 eq. of DLP to go to

the completion (5h). After elimination of lauric acid, the residue was purified by silica gel column chromatography with a gradient of ethyl acetate in petroleum ether (10:90 to 20:80) to afford the xanthate of steroid**15b** (152 mg, 30 %) as a as a white foam, then with a gradient of ethyl acetate in diethyl ether (40:60 to (50:50) to afford the product of rearrangement **10b** (252 mg, 39%) as a yellow oil and the cyclised product**20** (86 mg, 40%) as a white solid.

Compound 15b

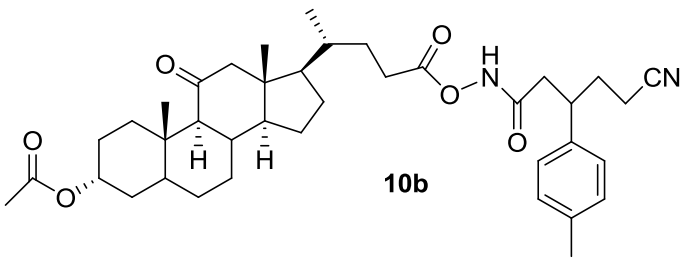


15b

$C_{28}H_{44}O_4S_2$
M= 508,2681 g.mol^{-1}

^{1}H-NMR(δ, ppm) ($CDCl_3$, 400 MHz)	4.70 (m, 1H), 4.64 (q, *J*= 7.1Hz, 2H), 3.19 (ddd, *J*= 4.5Hz, *J*= 10.3Hz, *J*= 13.2Hz, 1H), 2.98 (ddd, *J*= 6.6Hz, *J*= 9.8Hz, *J*= 13.2Hz, 1H), 2.62 (td, *J*=3.3Hz, *J*=14.5Hz, 1H), 2.57 (d, *J*=12.2Hz, 1H), 2.41 (d, *J*= 10.2Hz, 1H), 2.28 (d, *J*= 12.2Hz, 1H), 2.09-1.72 (m, 7H), 2.06 (s, 3H), 1.69-1.25 (m, 11H), 1.46 (t, *J*= 7.1 Hz, 3H), 1.09 (m+s, 5H), 0.95 (d, *J*=6.3Hz, 3H), 0.62 (s, 3H).
^{13}C-NMR(δ, ppm) ($CDCl_3$, 100 MHz)	215.1 (C=S), 211.4 (C=O), 170.6 (C=O), 74.0 (CH), 69.8 (CH_2), 58.4 (CH_2), 55.7 (CH), 55.1 (CH), 51.4 (CH), 46.9 (Cq), 42.7 (CH), 37.0 (CH), 35.5 (CH), 34.5 (CH_2), 34.3 (CH_2), 33.2 (CH_2), 33.5 (CH_2), 28.5 (CH_2), 28.4 (CH), 27.3 (CH_2), 26.9 (CH_2), 26.5 (CH_2), 23.7 (CH_2), 23.1 (CH_3), 21.4 (CH_3), 18.2 (CH_3), 13.9 (CH_3), 12.9 (CH_3).
IR (ν, cm^{-1})	2933, 2869, 2253, 1731, 1704, 1454, 1380, 1362, 1244, 1213, 1112, 1049, 1029.
HRMS (EI)	Calcd. for $C_{28}H_{44}O_4S_2$: 508,2681 Found: 508,2695

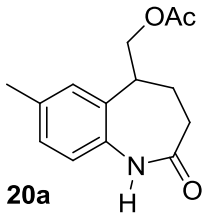
Compound 10b



$C_{39}H_{54}N_2O_6$
M= 646.3982 g.mol^{-1}

^{1}H-NMR(δ, ppm) ($CDCl_3$, 400 MHz)	8.85 (bs, 1H), 7.14 (d, *J*= 8.0Hz, 2H), 7.07 (d, *J*= 8.0Hz, 2H), 4.70 (m, 1H), 3.21 (m, 1H), 2.64-1.86 (m, 14H), 2.37 (s, 3H), 2.06 (s, 3H), 1.83-1.59 (m, 7H), 1.47-1.07 (m, 11H), 1.20 (s, 3H), 0.87 (d, *J*= 5.9Hz, 3H), 0.61 (s, 3H).
^{13}C-NMR(δ, ppm) ($CDCl_3$, 100 MHz)	211.4 (C=O), 171.9 (C=O), 170.6 (C=O), 168.8 (C=O), 137.7 (Cq), 137.3 (Cq), 129.9 (2CH), 127.2 (2CH), 119.3 (CN), 74.1 (CH), 58.3 (CH_2), 55.7 (CH), 55.0 (CH), 51.5 (CH), 46.9 (Cq), 42.7 (CH), 40.8 (CH), 40.1 (CH_2), 37.0 (CH), 35.0 (CH), 34.3 (CH_2), 34.1 (Cq), 32.5 (CH_2), 31.2 (CH_2), 30.4 (CH_2), 28.6 (CH_2), 28.4 (CH_2), 27.3 (CH_2), 26.9 (CH_2), 26.5 (CH_2), 23.7 (CH_2), 23.1 (CH_3), 21.5 (CH_3), 21.1 (CH_3), 17.9 (CH_3), 15.2 (CH_2), 12.9 (CH_3).
IR (ν, cm^{-1})	3230, 2936, 2870, 2250, 1789, 1726, 2704, 1699, 1515, 1454, 1381, 1363, 1245, 1081.
HRMS (EI)	Calcd. for $C_{39}H_{54}N_2O_6$: 646.3982 Found: 646.3992

(7-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepin-5-yl)methyl acetate 20a



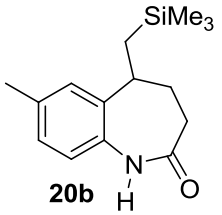
20a

$C_{14}H_{17}NO_3$
M= 247.1208 g.mol^{-1}

Following general procedure VI for the radical cyclisation, the reaction was carried out using xanthate **19a** (430 mg, 1 mmol, 1 eq) in refluxingethyl acetate and needed 1 eq. of DLP to go to the completion (5h). After elimination of lauric acid, the residue was washed with petroleum ether and recrystallized from a mixture of ethyl acetate and diethyl ether (60:40) to afford a white solid **20a** (99 mg, 40 %).

^{1}H-NMR(δ, ppm) ($CDCl_3$, 400 MHz)	7.96 (s, 1H), 7.06 (dd, *J*= 1.3 Hz, *J*= 7.9 Hz, 1H), 7.00 (s, 1H), 6.91 (d, *J*= 7.9 Hz, 1H), 4.50 (dd, *J*= 6.8 Hz, *J*= 11.1 Hz, 1H), 4.35 (dd, *J*= 7.1Hz, *J*= 11.1 Hz , 1H), 3.32 (m, 1H), 2.45 (m, 1H), 2.34 (m+s, 5H), 2.05 (s, 3H), 1.84 (m, 1H).
^{13}C-NMR(δ, ppm) ($CDCl_3$, 100 MHz)	174.9 (C=O), 171.1 (C=O), 135.8 (Cq), 135.0 (Cq), 133.4 (Cq), 128.2 (CH), 127.2 (CH), 122.3 (CH), 65.3 (CH_2), 37.9 (CH), 32.2 (CH_2), 31.6 (CH_2), 21.2 (CH_3), 20.9 (CH_3).
IR (ν, cm^{-1})	3307, 3205, 3087, 2924, 2860, 1731, 1690, 16667, 1505, 1438, 1398, 1371, 1262, 1039.
HRMS (EI)	Calcd. for $C_{14}H_{17}NO_3$: 247.1208 Found: 247.1211
Mp	171° C

7-methyl-5-((trimethylsilyl)methyl)-4,5-dihydro-1H-benzo[b]azepin-2(3H)-one 20b



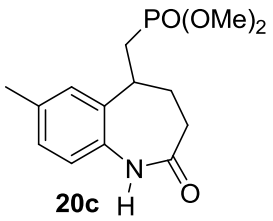
20b

$C_{15}H_{23}NOSi$
M= 261.1548 g.mol^{-1}

Following general procedure VI for the radical cyclisation, the reaction was carried out using xanthate **19b** (440 mg, 1 mmol, 1 eq) in refluxing ethyl acetate and needed 1 eq. of DLP to go to the completion (5h). After the elimination of lauric acid, the residue was purified by silica gel column chromatography with a gradient of ethyl acetate in petroleum ether (10:90 to 30:70) to afford product **20b** (154 mg, 59 %) as a white solid.

^{1}H-NMR(δ, ppm) ($CDCl_3$, 400 MHz)	8.91 (bs, 1H), 7.10 (s, 1H), 6.97(d, *J*= 7.9 Hz, 1H), 6.89 (d, *J*= 7.9 Hz, 1H), 3.10 (m, 1H), 2.37 (m, 4H), 2.25 (m, 2H), 1.69 (m, 1H), 1.12 (dd, *J*= 6.4 Hz, *J*= 14.5 Hz, 1H), 0.91 (dd, *J*= 8.6 Hz, *J*= 14.5 Hz, 1H), 0.00 (s, 9Hz).
^{13}C-NMR(δ, ppm) ($CDCl_3$, 100 MHz)	176.7 (C=O), 138.9 (Cq), 135.9 (Cq), 135.6 (Cq), 128.3 (CH), 128.0 (CH), 122.6 (CH), 38.9 (CH_2), 35.9 (CH), 33.8 (CH_2), 21.9 (CH_2), 21.7(CH_3), 0.00 ($3CH_3$).
IR (ν, cm^{-1})	3193, 3087, 2949, 2911, 1664, 1479, 1385, 1249, 1180.
HRMS (EI)	Calcd. for $C_{15}H_{23}NOSi$: 261,1549 Found: 261.1548
Mp	123° C

Compound 20c



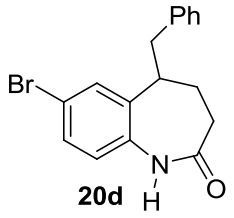
20c

$C_{14}H_{20}NO_4P$
M= 297.1130 g.mol^{-1}

Following general procedure VI for the radical cyclisation, the reaction was carried out using xanthate **19c**(480 mg, 1 mmol, 1 eq) in refluxing ethyl acetate and needed 1 eq. of DLP to go to the completion (5h). After the elimination of lauric acid, the residue was washed with petroleum ether and dichloromethane to afford a white solid **20c** (185 mg, 62%).

^{1}H-NMR(δ, ppm) ($CDCl_3$, 400 MHz)	7.36 (bs, 1H), 7.04 (m, 2H), 6.87 (d, *J*= 7.8 Hz, 1H), 3.75 (dd, *J*= 1.1 Hz, *J*= 10.9 Hz, 3H), 3.71 (dd, *J*= 1.1 Hz, *J*= 10.9 Hz, 3H), 3.43(m, 1H), 2.66 (m, 1H), 2.35 (s, 3H), 2.30 (m, 3H), 2.16 (m, 1H), 1.83 (m, 1H).
^{13}C-NMR(δ, ppm) ($CDCl_3$, 100 MHz)	174.7 (C=O), 135.7 (Cq), 135.6 (Cq), 134.8 (Cq), 128.2 (CH), 127.3 (CH), 122.3 (CH), 52.5 (d, *J*= 7 Hz, CH_3), 52.4 (d, *J*= 7 Hz, CH_3), 35.5 (d, *J*= 7 Hz, CH_2), 33.8 (CH), 32.5 (CH_2), 28.9 (d, *J*= 142 Hz, CH_2), 21.2 (CH_3).
IR (ν, cm^{-1})	3195, 2947, 1662, 1499, 1377, 1230, 1177, 1053, 1025.
HRMS (EI)	Calcd. for $C_{14}H_{20}NO_4P$: 297.1130 Found: 297.1130
Mp	144° C

5-benzyl-7-bromo-4,5-dihydro-1H-benzo[b]azepin-2(3H)-one **20d**



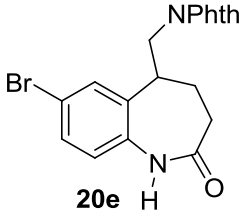
20d

$C_{17}H_{16}BrNO$
M= 329.0415g.mol^{-1}

Following general procedure VI for the radical cyclisation, the reaction was carried out using xanthate **23d** (510 mg, 1 mmol, 1 eq) in refluxing ethyl acetate and needed 1 eq. of DLP to go to the completion (5h). After the elimination of lauric acid, the residue was washed with petroleum ether and dichloromethane, and then the mixture was centrifuged to afford **24d** as a white solid (168 mg, 51 %).

^{1}H-NMR(δ, ppm) (DMSO-d6, 400 MHz)	9.60 (bs, 1H), 7.46 (m, 1H), 7.40 (dd, *J*= 2.0 Hz, *J*= 8.4 Hz, 1H), 7.23 (m, 5H), 6.93 (d, *J*= 8.4 Hz, 1H), 3.09 (m, 2H), 2.93 (m, 1H), 2.08 (m, 3H), 1.74 (m, 1H).
^{13}C-NMR(δ, ppm) (DMSO-d6, 100 MHz)	178.3 (C=O), 145.2 (Cq), 143.7 (Cq), 143.4 (Cq), 134.9 (2CH), 134.2 (2CH), 133.5 (2CH), 131.3 (CH), 129.1 (CH), 122.2 (Cq), 45.4 (CH), 43.1 (CH_2), 38.9 (CH_2), 37.8 (CH_2).
IR (ν, cm^{-1})	3351, 2924, 1692, 1484, 1383, 1239, 1174, 1071.
HRMS (EI)	Calcd. for $C_{17}H_{16}BrNO$: 329.0415Found: 329.0419
Mp	206° C

2-((7-bromo-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepin-5-yl)methyl) isoindoline-1,3-dione **20e**



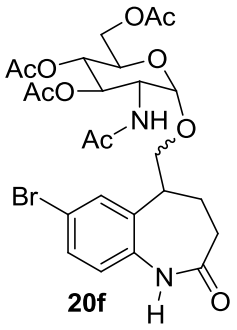
20e

$C_{19}H_{15}BrN_2O_3$
M= 398.0266 g.mol^{-1}

Following general procedure VI for the radical cyclisation, the reaction was carried out using xanthate **23e** (580 mg, 1 mmol, 1 eq) in refluxing ethyl acetate and needed 1 eq. of DLP to go to the completion (5h). The cyclised product precipitated in the flask. After filtering and washing with cold ethyl acetate, the cyclised product was isolated by centrifugation of dichloromethane as a white solid **24e** (239 mg, 60 %).

^{1}H-NMR(δ, ppm) (DMSO-d6, 400 MHz)	9.63 (bs, 1H), 7.85 (m, 4H), 7.50 (d, *J*= 2.1 Hz, 1H), 7.43 (dd, *J*= 2.2 Hz, *J*= 8.4 Hz, 1H), 6.94 (d, *J*= 8.4 Hz, 1H), 3.97 (m, 2H), 3.38 (m, 1H), 2.33 (m, 1H), 2.14 (m, 2H), 1.83 (m, 1H).
^{13}C-NMR(δ, ppm) (DMSO-d6, 100 MHz)	172.8 (C=O), 167.9 (2C=O), 138.2 (Cq), 135.7 (Cq), 134.4 (2CH), 131.4 (2Cq), 130.1(CH), 129.3 (CH), 123.9 (CH), 123.1 (2CH), 116.9 (Cq), 40.1 (CH_2), 37.6 (CH), 32.3 (CH_2), 31.8 (CH_2).
IR (ν, cm^{-1})	3192, 3089, 2977, 2963, 1774, 1715, 1662, 1484, 1443, 1376, 1163.
HRMS (EI)	Calcd. for $C_{19}H_{15}BrN_2O_3$: 398.0266Found: 398.0269
Mp	260° C

(2S,3R,4R,5S,6R)-5-acetamido-6-(5-(acetoxy(4-bromophenyl)amino)-2-(ethoxycarbonothioylthio)-5-oxopentyloxy)-2-(acetoxymethyl)tetrahydro-2H-pyran-3,4-diyl diacetate **20f**



20f

$C_{25}H_{31}BrN_2O_{10}$
M= 598.1162g.mol^{-1}

Following general procedure VI for the radical cyclisation, the reaction was carried out using xanthate **19f** (780 mg, 1 mmol, 1 eq) in refluxing ethyl acetate and needed 1 eq. of DLP to go to the completion (5h). After evaporation to dryness, the residue was purified by silica gel column chromatography with a gradient of methanol in dichloromethane (2:98 to 4:96) to afford two diastereoisomers **20f** (**20f**: 305 mg, 51% and **20f'**: 167 mg, 28 %) as a white solid.

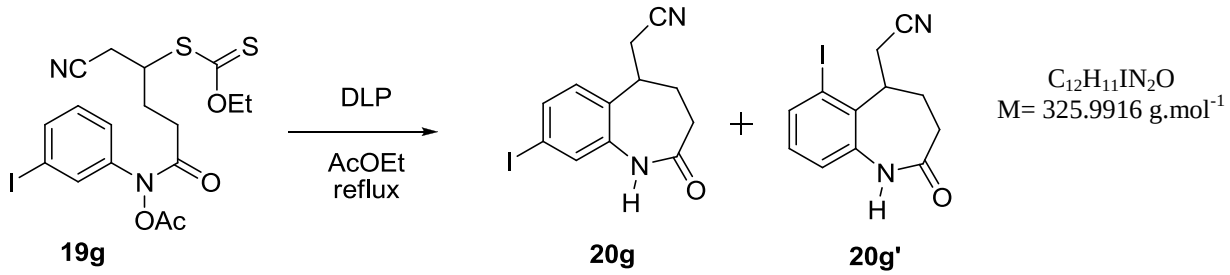
Compound 20f

^{1}H-NMR(δ, ppm) ($CDCl_3$, 400 MHz)	8.52 (bs, 1H), 7.39 (dd, *J*= 2.2 Hz, *J*= 8.4 Hz, 1H), 7.28 (d, *J*= 2.2 Hz, 1H), 6.95 (d, *J*= 8.4 Hz, 1H), 5.70 (d, *J*= 9.5 Hz, 1H), 5.06 (m, 2H), 4.87 (d, *J*= 3.6 Hz, 1H), 4.33 (dt, *J*=3.8Hz, *J*=9.5Hz, 1H), 4.16 (dd, *J*=4.5Hz, *J*=12.3Hz, 1H), 4.03 (dd, *J*=2.4Hz, *J*=12.3Hz, 1H), 3.90 (dd, *J*=5.5Hz, *J*=9.9Hz, 1H), 3.72 (m, 2H), 3.30 (m, 1H), 2.38 (m, 3H), 2.06 (s, 3H), 1.98 (s, 6H), 1.90 (s, 3H), 1.85 (m, 1H).
^{13}C-NMR(δ, ppm) ($CDCl_3$, 100 MHz)	175.0 (C=O), 171.4 (C=O), 170.6 (C=O), 170.3 (C=O), 169.3 (C=O), 137.2 (Cq), 135.7 (Cq), 130.8 (CH), 130.4 (CH), 124.3 (CH), 118.7 (Cq), 97.5 (CH), 71.1 (CH), 69.2 (CH_2), 68.1 (2CH), 61.9 (CH_2), 51.6 (CH_2), 39.4 (CH), 32.3 (CH_2), 31.2 (CH_2), 23.2 (CH_3), 20.8 (CH_3), 20.7 (CH_3), 20.6 (CH_3).
IR (ν, cm^{-1})	3300, 2929, 1745, 1669, 1367, 1230.
HRMS (EI)	Calcd. for $C_{25}H_{31}BrN_2O_{10}$: 598.1162Found: 598.1152
Mp	125° C

Compound 20f'

^{1}H-NMR(δ, ppm) ($CDCl_3$, 400 MHz)	8.29 (bs, 1H), 7.35 (m, 2H), 6.68 (d, *J*= 8.7 Hz, 1H), 6.22 (bd, 1H), 5.13 (m, 2H), 4.93 (d, *J*= 3.7 Hz, 1H), 4.37 (dt, *J*= 3.7Hz, *J*= 10.3Hz, 1H), 4.22 (dd, *J*= 4.4Hz, *J*= 12.4Hz, 1H), 4.14 (m, 2H), 3.81 (ddd, *J*= 2.4Hz, *J*= 4.2Hz, *J*= 9.5Hz, 1H), 3.71 (dd, *J*= 5.6Hz, *J*= 9.9Hz, 1H), 3.34 (m, 1H), 2.52 (m, 1H), 2.35 (m, 2H), 2.09 (s, 3H), 2.01 (s, 3H), 2.00 (s, 3H), 1.92 (s, 3H), 1.90 (m,1H).
^{13}C-NMR(δ, ppm) ($CDCl_3$, 100 MHz)	174.8 (C=O), 171.4 (C=O), 170.7 (C=O), 170.4 (C=O), 169.3 (C=O), 137.0 (Cq), 136.0 (Cq), 130.8 (CH), 130.0 (CH), 123.9 (CH), 118.9 (Cq), 97.4 (CH), 71.1 (CH), 69.2 (CH_2), 68.2 (CH), 68.0 (CH), 62.0 (CH_2), 51.7 (CH_2), 38.6 (CH), 32.2 (CH_2), 31.3 (CH_2), 23.1 (CH_3), 20.8 ($2CH_3$), 20.6 (CH_3).
IR (ν, cm^{-1})	3350, 2930, 2319, 1742, 1654, 1363, 1223.
HRMS (EI)	Calcd. for $C_{25}H_{31}BrN_2O_{10}$: 598.1162 Found: 598.1164
Mp	112° C

Compound 20g + 20g'



$C_{12}H_{11}IN_2O$
M= 325.9916 $g.mol^{-1}$

Following general procedure VI for the radical cyclisation, the reaction was carried out using xanthate **19f** (510 mg, 1 mmol, 1 eq) in refluxing ethyl acetate and needed 1 eq. of DLP to go to the completion (5h). The residue was purified by silica gel column chromatography with a gradient of ethyl acetate in petroleum ether (10:90 to 25:75) to afford a mixture of two regioisomers (**20g: 20g'**) (2:1) (186 mg, 57 %) as a yellow oil. Dichloromehane was added to the oil to precipitate partly the major isomer as a white solide **20g**.

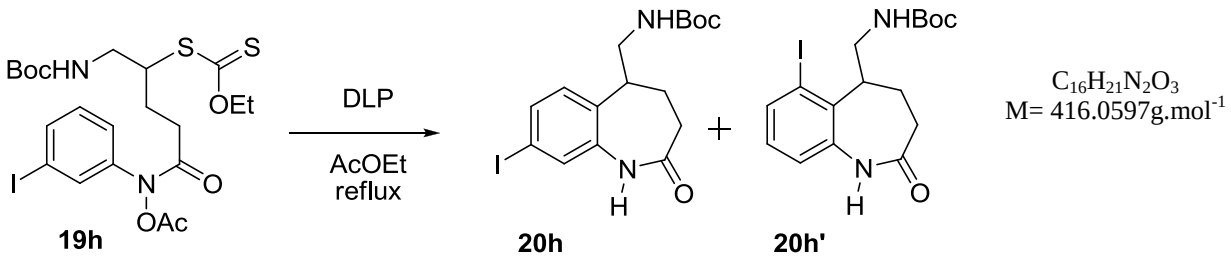
2-(8-iodo-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepin-5-yl)acetonitrile 20g

^{1}H-NMR(δ, ppm) (DMSO-d6, 400 MHz)	9.66 (s, 1H), 7.55 (dd, *J*=1.7Hz, *J*=8.1Hz, 1H), 7.35 (d, *J*=1.7Hz, 1H), 7.09 (d, *J*=8.2Hz, 1H), 3.17 (m, 1H), 3.00 (m, 2H), 2.35 (m, 1H), 2.14 (m, 2H), 1.76 (m, 1H).
^{13}C-NMR(δ, ppm) (DMSO-d6, 100 MHz)	172.6 (C=O), 140.1 (Cq), 133.3 (CH), 132.8 (Cq), 130.1 (CH), 128.1 (CH), 119.5 (CN), 92.7 (Cq), 35.5 (CH), 33.4 (CH_2), 32.4 (CH_2), 19.5 (CH_2).
IR (ν, cm^{-1})	3174, 2834, 2243, 1658, 1385, 1074.
HRMS (EI)	Calcd. for $C_{12}H_{11}IN_2O$: 325.9916 Found : 325.9918
Mp	235° C

2-(6-iodo-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepin-5-yl)acetonitrile 20g'

^{1}H-NMR(δ, ppm) ($CDCl_3$, 400 MHz)	9.7 (s, 1H), 7.72 (dd, *J*= 3.0 Hz, *J*= 6.1 Hz, 1H), 7.04 (m, 2H), 3.84 (m, 1H), 2.94 (m, 2H), 2.21 (m, 4H).
^{13}C-NMR(δ, ppm) ($CDCl_3$, 100 MHz)	173.0 (C=O), 138.5 (Cq), 136.0 (CH), 134.7 (Cq), 130.0 (CH), 123.7 (CH), 118.5 (CN), 92.7 (Cq), 43.3 (CH), 31.6 (CH_2), 31.1 (CH_2), 20.6 (CH_2).
IR (ν, cm^{-1})	3174, 2834, 2243, 1658, 1385, 1074.
HRMS (EI)	Calcd. for $C_{12}H_{11}IN_2O$: 325.9916 Found: 325.9918

Compound 20h



$C_{16}H_{21}N_2O_3$
M= 416.0597g.mol^{-1}

Following general procedure VI for the radical cyclisation, the reaction was carried out using xanthate **19h** (600 mg, 1 mmol, 1 eq) in refluxing ethyl acetate and needed 1 eq. of DLP to go to the completion (5h). The residue was purified by silica gel column chromatography with a gradient of ethyl acetate in petroleum ether (20:80 to 60:40) to afford two regioisomers, the ma*J*or isomer **20h** (182 mg, 44 %) as a white solid and the minor isomer **20h'** (90 mg, 21 %) as a yellow oil.

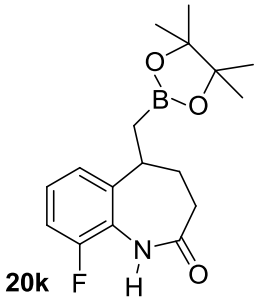
***tert*-butyl (8-iodo-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepin-5-yl) methylcarbamate** **20h**

^{1}H-NMR(δ, ppm) ($CDCl_3$, 400 MHz)	9.12 (bs, 1H), 7.51 (dd, *J*= 1.7 Hz, *J*= 8.1 Hz, 1H), 7.38 (d, *J*= 1.7 Hz, 1H), 7.02 (d, *J*= 8.1 Hz, 1H), 5.20 (bs, 1H), 3.63 (m, 1H), 3.34 (m, 1H), 3.01 (m, 1H), 2.28 (m, 2H), 1.95 (m, 1H), 1.66 (m, 1H), 1.39 (s, 9H).
^{13}C-NMR(δ, ppm) ($CDCl_3$, 100 MHz)	175.8 (C=O), 155.9 (C=O), 139.4 (Cq), 135.0 (CH), 133.9 (Cq), 130.9 (CH), 128.8 (CH), 92.0 (Cq), 79.5 (Cq), 41.9(CH_2), 39.4 (CH), 32.3 (CH_2), 32.1 (CH_2), 28.4 ($3CH_3$).
IR (ν, cm^{-1})	3250, 2974, 2254, 1705, 1660, 1515, 1366, 1277, 1162.
HRMS (EI)	Calcd. for $C_{16}H_{21}N_2O_3$: 416.0597 Found: 416.0608
Mp	100°C

tert-butyl (6-iodo-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepin-5-yl) methylcarbamate **20h'**

^{1}H-NMR(δ, ppm) ($CDCl_3$, 400 MHz)	8.71 (bs, 1H), 7.70 (d, *J*= 7.9 Hz, 1H), 6.99 (d, *J*= 7.8 Hz, 1H), 6.89 (dt, *J*= 1.8 Hz, *J*= 7.9 Hz, 1H), 4.53 (bs, 1H), 3.77 (m, 1H), 3.57 (m, 1H), 3.38 (m, 1H), 2.38 (m, 2H), 2.26 (m, 1H), 2.12 (m, 1H), 1.32 (s, 9H).
^{13}C-NMR(δ, ppm) ($CDCl_3$, 100 MHz)	175.5 (C=O), 155.7 (C=O), 137.8 (Cq), 137.3 (Cq), 136.6 (CH), 129.4 (CH), 123.9 (CH), 104.7 (Cq), 79.2 (Cq), 47.8 (CH_2), 43.5 (CH), 32.0 (CH_2), 30.1 (CH_2), 28.4 ($3CH_3$).
IR (ν, cm^{-1})	3307, 2976, 2929, 2247, 1710, 1674, 1564, 1454, 1391, 1366, 1252.
HRMS (EI)	Calcd. for $C_{16}H_{21}N_2O_3$: 416.0597 Found : 416.0597

9-fluoro-5-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)-4,5-dihydro-1H-benzo[b]azepin-2(3H)-one **20k**



20k

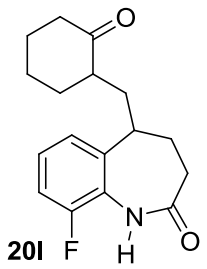
$C_{17}H_{23}BFNO_3$
M= 319.1755 $g.mol^{-1}$

Following general procedure VI for the radical cyclisation, the reaction was carried out using xanthate **19k** (500 mg, 1 mmol, 1 eq) in refluxing ethyl acetate and needed 1 eq. of DLP to go to the completion (5h). After evaporation to dryness, the residue was washed with petroleum ether, then with mixture of ethyl acetate : petroleum ether (10:90), then with petroleum ether again. The washing was repeated three times to afford **20k** as a white solid (172 mg, 54 %).

^{1}H-NMR(δ, ppm) ($CDCl_3$, 400 MHz)	7.25 (bs, 1H), 7.10 (m, 2H), 6.99 (m, 1H), 3.31 (m, 1H), 2.50 (m, 1H), 2.32 (m, 2H), 1.73 (m, 1H), 1.27 (m, 2H), 1.19 (s, 6H), 1.14 (s, 6H).

^{13}C-NMR(δ, ppm) ($CDCl_3$, 100 MHz)	174.1 (C=O), 153.8 (d, *J*= 245 Hz, Cq-F), 140.7 (Cq), 126.0 (d, *J*= 8 Hz, CH), 125.6 (d, *J*= 12 Hz, Cq), 121.7 (d, *J*= 3 Hz, CH), 113.6 (d, *J*= 19 Hz, CH), 83.4 (Cq), 37.2 (CH_2), 34.9 (CH), 33.1 (CH_2), 24.7 ($4CH_3$), 16.0 (CH_2).
IR (ν, cm^{-1})	3402, 3207, 3081, 2979, 2929, 2891, 2248, 1679, 1372, 1326, 1144.
HRMS (EI)	Calcd. for $C_{17}H_{23}BFNO_3$: 319.1755 Found: 319.1755
Mp	130°C

9-fluoro-5-((2-oxocyclohexyl)methyl)-4,5-dihydro-1H-benzo[b]azepin-2(3H)-one 20l



20l

$C_{17}H_{20}FNO_2$
M= 289.1478g.mol^{-1}

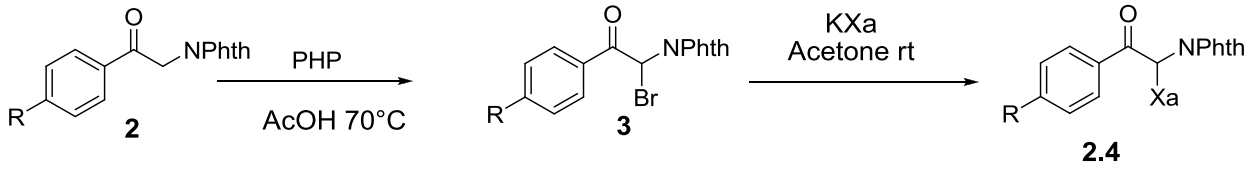
Following general procedure VI for the radical cyclisation, the reaction was carried out using xanthate **19l** (470 mg, 1 mmol, 1 eq) in refluxing ethyl acetate and needed 1 eq. of DLP to go to the completion (5h). After evaporation to dryness, the residue was washed with petroleum ether, then mixture of ethyl acetate : petroleum ether (10:90), then petroleum ether again. The washing was repeated three times to afford a white solid **20l**as a mixture of diastereoisomers (153 mg, 53 %).

^{1}H-NMR(δ, ppm) ($CDCl_3$, 400 MHz)	7.39 (bs, 1H), 7.14 (m, 1H), 7.01 (m, 2H), 3.08 (m, 1H), 2.57-1.32 (m, 15H).
^{13}C-NMR(δ, ppm) ($CDCl_3$, 100 MHz) (mixture of diastereoisomers)	212.5, 212.4 (C=O); 174.2 (d, C=O); 154.2, 154.1 (d, *J*= 246 Hz, Cq); 139.1, 138.6 (Cq); 126.4, 126.2 (d, *J*= 8 Hz, CH); 126.1, 125.9 (d, *J*= 3 Hz, Cq); 122.1, 121.7 (d, *J*= 3Hz, CH); 113.9, 113.7 (CH); 48.3, 48.1 (CH); 42.3, 42.1 (CH_2); 36.4, 35.8 (d, *J*= 2.2 Hz, CH); 35.5, 34.7, 34.6, 34.4, 32.9, 32.8, 32.4, 31.8 ($4CH_2$); 28.1, 27.8 (CH_2); 25.3, 25.1 (CH_2).

IR (ν, cm^{-1})	3210, 2918, 1706, 1673, 1440, 1379, 1244.
HRMS (EI)	Calcd. for $C_{17}H_{20}FNO_2$: 289.1478Found: 289.1478
Mp	175°C

Chapter 3

General procedure I for the formation of xanthates (2.4)

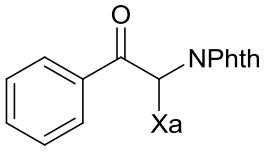


Step 1: Bromination of substituted acetophenones **2**: A solution of the 2-phthalimido-acetophenone (**2**) (5 mmol) in acetic acid (15 mL) at rt was added pyridinium hydrobromide perbromide (880 mg, 5.5 mmol). The reaction mixture was heated at 70 °C for 4 hours, cooled and diluted with dichloromethane (15 mL). The resulting solution was then washed with water, then with a saturated aqueous solution of $NaHCO_3$ (2 times) and then with brine. The organic phase was dried with $MgSO_4$ and evaporated to dryness under reduced pressure. The crude residue contained the mixture of the desired product (around 60% by NMR) and the starting material.

Step 2: Formation of xanthate (**2.4**): To a stirred solution of the crude product of step 1 in acetone (10 mL) at rt was added portion-wise potassium O-ethyl xanthate (885 mg, 5.5 mmol). The reaction was stirred until the complete consumption of the starting material. The acetone was evaporated and the reaction mixture was diluted with ethyl acetate. The organic phase was washed with water and brine, dried over $MgSO_4$, filtered and evaporated to dryness under reduced pressure. The residue was purified by silica gel column chromatography or recrystallised to afford the desired xanthate.

S-1-(1,3-Dioxoisoindolin-2-yl)-2-oxo-2-phenylethyl *O*-ethyl carbonodithioate 2.4a

2.4a



$C_{19}H_{15}NO_4S$
M= 385.0442 g.mol $^{-1}$

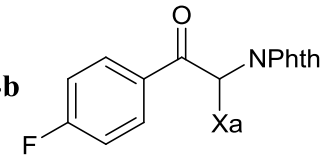
Following general procedure I, after workup, the residue was washed with hot ethanol several times to eliminate the starting un-brominated acetophenone (**2a**) and afford the desired xanthate (**2.4a**) as a white solid (1.1 g, 57%)

^{1}H-NMR (δ, ppm) (CDCl$_3$, 400 MHz) 7.95 (d, *J* = 8.0 Hz, 2H), 7.89 (m, 2H), 7.86 (s, 1H), 7.58 (t, 7.4 Hz, 1H), 7.75 (m, 2H), 7.45 (t, *J* = 7.4 Hz, 2H), 4.72 (m, 2H), 1.46 (t,

	J= 7.1 Hz, 3H)
^{13}C-NMR (δ, ppm) ($CDCl_3$, 100 MHz)	210.2 (CS), 189.4 (CO), 166.4 (2CO), 134.5 (2CH), 133.9 (2CH), 133.6 (Cq), 131.7 (2Cq), 128.8 (2CH), 128.6 (2CH), 123.9 (2CH), 71.8 (CH), 62.0 (CH_2), 13.8 (CH_3).
IR (ν, cm^{-1})	1704, 1653, 1558, 1231, 1113, 1053.
HRMS (EI)	Calcd. for $C_{19}H_{15}NO_4S_2$: 385.0442Found: 385.0442
Mp	149-150°C

_S_-1-(1,3-Dioxoisoindolin-2-yl)-2-(4-fluorophenyl)-2-oxoethyl _O_-ethyl carbonodithioate2.4b

2.4b

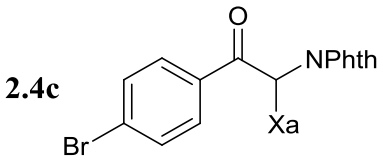


$C_{19}H_{14}FNO_4S_2$
M= 403.0348 $g.mol^{-1}$

Following general procedure I, after workup, the residue was purified by silica gel column chromatography with a gradient of dichloromethane in petroleum ether (30 : 70 to 50 : 50) to afford xanthate (**2.4b**) (1.09 g, 54%) as a white solid.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz)	7.99 (m, 2H), 7.89 (m, 2H), 7.83 (m, 1H), 7.75 (m, 2H), 7.13 (t, *J*= 8.6 Hz, 2H), 4.72 (m, 2H), 1.44 (t, *J*= 7.1 Hz, 3H).
^{13}C-NMR (δ, ppm) ($CDCl_3$, 100 MHz)	210.2 (CS), 187.9 (CO), 166.4 (2CO), 166.2 (d, *J*= 256 Hz, Cq), 134.6 (2CH), 131.7 (2Cq), 131.5 (d, *J*= 9 Hz, CH), 129.9 (d, *J*= 3 Hz, Cq), 123.9 (2CH), 116.1 (d, *J*= 22 Hz, 2CH), 71.9 (CH), 62.0 (CH_2), 13.8 (CH_3).
IR (ν, cm^{-1})	1777, 1731, 1703, 1601, 1377, 1240, 1103, 1048.
HRMS (EI)	Calcd. for $C_{19}H_{14}FNO_4S_2$: 403.0348 Found: 403.0350
Mp	131-132°C

S-2-(4-Bromophenyl)-1-(1,3-dioxoisoindolin-2-yl)-2-oxoethyl *O*-ethyl carbonodithioate 2.4c



$C_{19}H_{14}BrNO_4S_2$
M= 462.9548 g.mol $^{-1}$

Following general procedure I, after workup, the residue was purified by silica gel column chromatography with a gradient of dichloromethane in petroleum ether (30 : 70 to 50 : 50) to afford xanthate (**2.4c**) (1.25 g, 54%) as a white solid.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.90 (m, 2H), 7.81 (m, 3H), 7.76 (m, 2H), 7.60 (m, 2H), 4.73 (m, 2H), 1.44 (t, *J*= 7.1 Hz, 3H).

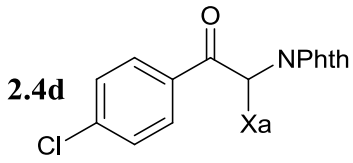
^{13}C-NMR (δ, ppm) ($CDCl_3$, 100 MHz): 210.2 (CS), 188.6 (CO), 166.4 (2CO), 134.6 (2CH), 132.4 (Cq), 132.2 (2CH), 131.7 (2Cq), 130. (2CH), 129.3 (Cq), 124.0 (2CH), 72.0 (CH), 62.0 (CH_2), 13.8 (CH_3).

IR (ν, cm^{-1}): 1731, 1703, 1588, 1377, 1242, 1048.

HRMS (EI): Calcd. for $C_{19}H_{14}BrNO_4S_2$: 462.9548 Found: 462.9548

Mp: 102-103°C

S-2-(4-Chlorophenyl)-1-(1,3-dioxoisoindolin-2-yl)-2-oxoethyl *O*-ethyl carbonodithioate 2.4d



$C_{19}H_{14}ClNO_4S_2$
M= 419.0053 g.mol $^{-1}$

Following general procedure I, after workup, the residue was purified by silica gel column chromatography with a gradient of dichloromethane in toluene (30 : 70 to 50 : 50) to afford xanthate (**2.4d**) (1.15 g, 55%) as a light yellow solid.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.90 (m, 4H), 7.83 (s, 1H), 7.76 (m, 2H), 7.43 (m, 2H), 4.72 (m, 2H), 1.45 (t, *J*= 7.1 Hz, 3H).

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100 MHz): 210.2 (CS), 188.4 (CO), 166.4 (2CO), 140.5 (Cq), 134.6 (2CH), 131.9 (Cq), 131.7 (2Cq), 130.0 (2CH), 129.2 (2CH), 123.9 (2CH),

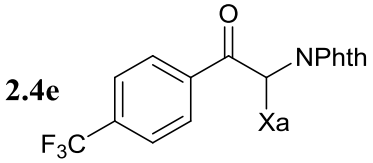
72.0 (CH), 62.0 (CH_2), 13.8 (CH_3).

IR (ν, cm^{-1}) 1731, 1703, 1596? 1376, 1243, 1094, 1048.

HRMS (EI) Calcd. for $C_{19}H_{14}ClNO_4S_2$: 419.0053 Found: 419.0045

Mp 84-85°C

_S_-1-(1,3-Dioxoisoindolin-2-yl)-2-oxo-2-(4-(trifluoromethyl)-phenyl)ethyl _O_-ethyl carbonodithioate 2.4e



$C_{20}H_{14}F_3NO_4S_2$
M= 453.0316 $g.mol^{-1}$

Following general procedure I, after workup, the residue was purified by silica gel column chromatography with a gradient of ethyl acetate in petroleum ether (5 : 95 to 15 : 85) to afford xanthate (**2.4e**) (1.2 g, 53%) as a light yellow solid.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 8.05 (m, 2H), 7.87 (m, 3H), 7.70–7.76 (m, 4H), 4.73 (m, 2H), 1.42 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100 MHz) 210.0 (CS), 188.9 (CO), 166.3 (2CO), 136.7 (Cq), 135.0 (q, *J* = 33 Hz, Cq), 134.7 (2CH), 131.6 (2Cq), 128.9 (2CH), 125.9 (2CH), 124.0 (2CH), 123.4 (q, *J* = 272 Hz, CF_3), 72.2 (CH), 62.2 (CH_2), 13.8 (CH_3)

IR (ν, cm^{-1}) 1777, 1731, 1708, 1615, 1410, 1376, 1324? 1242, 1175, 1140, 1048.

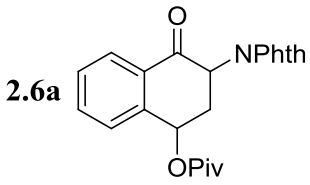
HRMS (EI) Calcd. for $C_{20}H_{14}F_3NO_4S_2$: 453.0316 Found: 453.0321

Mp 57-58°C

General procedure II for the synthesis of tetralones (2.6) by radical addition and cyclisation

A magnetically stirred solution of xanthate (1 mmol) and olefin (2.5 mmol) in 1,2-dichloroethane (1 mL) was refluxed for 15 min under a nitrogen flow. Dilauroyl peroxide (DLP) (5 mol%) was then added and additional DLP (2.5 mol%) was added every 60 min until total consumption of the starting material or until no evolution could be detected by TLC analysis. The reaction mixture was then cooled to 20 °C and evaporated to dryness under reduced pressure. The residue was then dissolved in 10 mL ethyl acetate or chlorobenzene. The mixture was refluxed for 15 min under a nitrogen flow. Dilauroyl peroxide (DLP) (20 mol%) was then added and additional DLP (20 mol%) was added every 60 min until total consumption of the starting material or until no evolution could be detected by TLC analysis. The reaction mixture was then cooled to 20 °C and evaporated to dryness under reduced pressure. The residue was purified by silica gel column chromatography to yield the desired compound.

3-(1,3-Dioxoisoindolin-2-yl)-4-oxo-1,2,3,4-tetrahydronaphthalen-1-yl pivalate **2.6a**



2.6a

$C_{23}H_{21}NO_5$
M= 391.1420 g.mol $^{-1}$

Following general procedure II, the reaction was carried out using xanthate (**2.4a**) (385 mg, 1 mmol, 1 equiv.) and vinyl pivalate (0.37 mL, 2.5 mmol, 2.5 equiv.) in refluxing 1,2-dichloroethane (1 mL); it needed 25 mol% DLP to go to completion. After the reaction mixture was evaporated to dryness under reduced pressure, the residue was dissolved in chlorobenzene (10 mL), heated to reflux and treated with 1.2 equiv. of DLP. After evaporation, the residue was purified by silica gel column chromatography using a gradient of dichloromethane in petroleum ether (30 : 70 to 50 : 50) to afford 187 mg mixture of (**2.6a**) contaminated with (**2a**) ((**2.6a**) : (**2a**) = 1 : 0.2) as a yellow oil. The calculated NMR yield of (**2.6a**) is 42%.

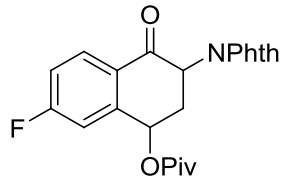
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz)

8.16 (m, 1H), 7.90 (m, 2H), 7.78 (m, 2H), 7.69 (m, 1H), (7.41–7.57, m, 2H), 6.35 (dd, *J* = 11.5 Hz, *J* = 5.0 Hz, 1H maj), 6.25 (m, 1H min), 5.54 (dd, *J* = 13.3 Hz, *J* = 4.8 Hz, 1H min), 5.18 (dd, *J* = 14.2 Hz, *J* = 4.6 Hz, 1H maj), 3.28 (dt, *J* = 13.3 Hz, *J* = 2.9 Hz, 1H min), 3.11 (td, *J* = 14.2 Hz, *J* = 11.6 Hz, 1H maj), 2.66 (td, *J* = 11.6 Hz, *J* = 4.6 Hz, 1H maj), 2.54 (m, 1H min), 1.31 (s, 9H maj), 1.22 (s, 9H min).

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100 MHz)	191.1 (CO min), 190.3 (CO maj), 177.8 (CO maj + min), 167.7 (2CO maj), 167.6 (2CO min), 142.4 (Cq maj), 139.2 (Cq min), 134.7 (CH min), 134.5 (CH maj), 134.3 (2CH maj + min), 132.9 (2Cq maj), 132.0 (2Cq min), 131.4 (Cq min), 130.3 (Cq maj), 130.1 (CH maj), 129.8 (CH min), 128.5 (CH min), 128.2 (CH maj), 128.1 (CH min), 125.6 (CH maj), 123.6 (2CH maj + min), 68.6 (CH maj), 68.3 (CH min), 53.1 (CH maj), 50.7 (CH min), 39.1 (Cq maj + min), 33.8 (CH_2 maj), 32.9 (CH_2 min), 27.2 ($3CH_3$ maj), 27.1 ($3CH_3$ min).
IR (ν, cm^{-1})	2974, 2909, 1725, 1605, 1390, 1230, 1145, 1003.
HRMS (EI)	Calcd. for $C_{23}H_{20}BrNO_5$: 391.1420 Found: 391.1436

3-(1,3-Dioxoisoindolin-2-yl)-7-fluoro-4-oxo-1,2,3,4-tetrahydronaphthalen-1-yl pivalate 2.6b

2.6b



$C_{23}H_{20}FNO_5$
M= 409.1326 g.mol $^{-1}$

Following general procedure II, the reaction was carried out using xanthate (**2.4b**) (403 mg, 1 mmol, 1 equiv.) and vinyl pivalate (0.37 mL, 2.5 mmol, 2.5 equiv.) in refluxing 1,2-dichloroethane (1 mL); it needed 25 mol% DLP to go to completion. The reaction mixture was then evaporated to dryness under reduced pressure and the residue was dissolved in chlorobenzene (10 mL), heated to reflux and treated with 1.2 equiv. DLP. After evaporation, the residue was purified by silica gel column chromatography with a gradient of dichloromethane in petroleum ether (30 : 70 to 50 : 50) to afford (**2.6b**) (184 mg, 45%) as a yellow oil.

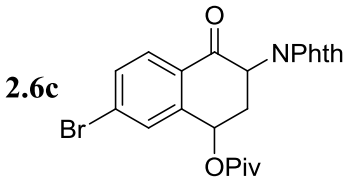
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz)	8.16 (m, 1H), 7.85 (m, 2H), 7.73 (m, 2H), 7.03–7.23 (m, 2H), 6.28 (dd, *J* = 11.6 Hz, *J* = 5.0 Hz, 1H maj), 6.19 (m, 1H min), 5.50 (dd, *J* = 13.2 Hz, *J* = 4.8 Hz, 1H min), 5.17 (dd, *J* = 14.2 Hz, *J* = 4.6 Hz, 1H maj), 3.26 (dt, *J* = 13.6 Hz, *J* = 2.9 Hz, 1H min), 3.08 (m, 1H maj), 2.65 (td, *J* = 11.5 Hz, *J* = 4.8 Hz, 1H maj), 2.48 (m, 1H min), 1.30 (s, 9H maj), 1.22 (s, 9H min).
^{13}C-NMR (δ, ppm) ($CDCl_3$, 100 MHz)	189.7 (CO min), 189.0 (CO maj), 177.6 (CO maj), 177.5 (CO min), 167.7 (2CO maj), 167.5 (2CO min), 166.6 (d, *J* = 256 Hz, Cq maj), 166.2 (d, *J* = 256 Hz, Cq min), 145.7 (d, *J* = 9 Hz, Cq maj), 142.2 (d, *J* = 9 Hz, Cq min), 134.3 (d, *J* = 3 Hz, 2CH maj + min), 132.0 (2Cq maj + min), 131.6 (d, *J* = 10 Hz, CH maj), 131.4 (d, *J* = 10

Hz, CH min), 128.1 (d, *J* = 3 Hz, Cq min), 126.9 (d, *J* = 3 Hz, Cq maj), 123.6 (2CH maj + min), 117.5 (d, *J* = 22 Hz, CH min), 116.8 (d, *J* = 22 Hz, CH min), 116.3 (d, *J* = 22 Hz, CH maj), 112.6 (d, *J* = 23 Hz, CH maj), 68.0 (CH maj), 67.9 (CH min), 52.9 (CH maj), 50.4 (CH min), 39.0 (Cq maj + min), 33.8 (CH_2 maj), 32.8 (CH_2 min), 27.1 ($3CH_3$ maj + min).

IR (ν, cm^{-1}) 3412, 1783, 1724, 1612, 1551, 1389, 1264, 1142.

HRMS (EI) Calcd. for $C_{23}H_{20}FNO_5$: 409.1326 Found: 409.1327

7-Bromo-3-(1,3-dioxoisoindolin-2-yl)-4-oxo-1,2,3,4-tetrahydronaphthalen-1-yl pivalate 2.6c



$C_{23}H_{20}BrNO_5$
M= 469.0525 $g.mol^{-1}$

Following general procedure II, the reaction was carried out using xanthate (**2.4c**) (464 mg, 1 mmol, 1 equiv.) and vinyl pivalate (0.37 mL, 2.5 mmol, 2.5 equiv.) in refluxing 1,2-dichloroethane (1 mL); it needed 25 mol% DLP to go to completion. The reaction mixture was then evaporated to dryness under reduced pressure, and the residue was dissolved in chlorobenzene (10 mL), heated to reflux and treated with 1.2 equiv. of DLP. After evaporation, the residue was purified by silica gel column chromatography with a gradient of dichloromethane in petroleum ether (30 : 70 to 50 : 50) to afford **2.6c** (187 mg, 40%) as a yellow oil.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 7.79 (m, 1H), 7.86 (m, 2H), 7.52–7.75 (m, 4H), 6.29 (dd, *J* = 11.6 Hz, *J* = 5.0 Hz, 1H maj), 6.17 (m, 1H min), 5.49 (dd, *J* = 13.3 Hz, *J* = 4.8 Hz, 1H min), 5.16 (dd, *J* = 14.2 Hz, *J* = 4.6 Hz, 1H maj), 3.23 (dt, *J* = 2.9 Hz, *J* = 13.6 Hz, 1H min), 3.07 (td, *J* = 11.6 Hz, *J* = 14.2 Hz, 1H maj), 2.64 (td, *J* = 4.8 Hz, *J* = 11.6 Hz, 1H maj), 2.48 (m, 1H min), 1.31 (s, 9H maj), 1.22 (s, 9H min).

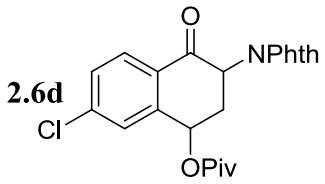
^{13}C-NMR (δ, ppm) ($CDCl_3$, 100 MHz) 190.4 (CO min), 189.6 (CO maj), 177.6 (CO maj), 177.5 (CO min), 167.6 (2CO maj), 167.5 (2CO min), 144.0 (Cq maj), 140.7 (Cq min), 134.3 (2CH maj + min), 133.3 (CH min), 133.0 (CH min), 132.0 (CH maj), 131.9 (2Cq maj), 131.8 (2Cq min), 130.1 (Cq maj + min), 130.0 (Cq min), 129.9 (CH maj), 129.8 (CH min), 129.1 (Cq maj), 129.0 (CH maj), 123.7 (2CH maj + min), 67.9 (CH min),

67.7 (CH maj), 52.9 (CH maj), 50.5 (CH min), 39.0 (Cq maj + min), 33.7 (CH_2 maj), 32.8 (CH_2 min), 27.2 ($3CH_3$ maj), 27.1 ($3CH_3$ min).

IR (ν, cm^{-1}) 3481, 1726, 171à, 1589, 1470, 1389, 1142.

HRMS (EI) Calcd. for $C_{23}H_{20}BrNO_5$: 469.0525 Found: 469.0520

7-Chloro-3-(1,3-dioxoisoindolin-2-yl)-4-oxo-1,2,3,4-tetrahydronaphthalen-1-yl pivalate 2.6d



$C_{23}H_{20}ClNO_5$
M= 425.1030 $g.mol^{-1}$

Following general procedure II, the reaction was carried out using xanthate (**2.4d**) (420 mg, 1 mmol, 1 equiv.) and vinyl pivalate (0.37 mL, 2.5 mmol, 2.5 equiv.) in refluxing 1,2-dichloroethane (1 mL); it needed 30 mol% DLP to go to completion. The reaction mixture was evaporated to dryness under reduced pressure and the residue was dissolved in chlorobenzene (10 mL), heated to reflux and treated with 1.2 equiv. of DLP. After evaporation, the residue was purified by silica gel column chromatography with a gradient of dichloromethane in petroleum ether (30 : 70 to 50 : 50) to afford **2.6d** (157 mg, 37%) as a yellow oil.

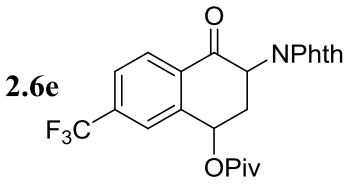
^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz) 8.07 (m, 1H), 7.87 (m, 2H), 7.75 (m, 2H), 7.36–7.54 (m, 2H), 6.28 (dd, *J* = 11.6 Hz, *J* = 4.9 Hz, 1H maj), 6.16 (m, 1H min), 5.50 (dd, *J* = 13.2 Hz, *J* = 4.8 Hz, 1H min), 5.16 (dd, *J* = 14.2 Hz, *J* = 4.7 Hz, 1H maj), 3.24 (dt, *J* = 13.7 Hz, *J* = 2.9 Hz, 1H min), 3.08 (m, 1H maj), 2.65 (m, 1H maj), 2.49 (m, 1H min), 1.31 (s, 9H).

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100 MHz) 190.2 (CO min), 189.4 (CO maj), 177.6 (CO maj + min), 167.6 (2CO maj), 167.5 (2CO min), 144.0 (Cq maj), 141.3 (Cq maj), 141.1 (Cq min), 140.7 (Cq min), 134.3 (2CH maj + min), 132.0 (2Cq min), 131.9 (2Cq maj), 130.3 (CH min), 130.0 (CH min), 129.9 (CH maj), 129.8 (CH min), 129.1 (CH maj), 128.7 (Cq maj + min), 125.8 (CH maj), 123.6 (2CH maj + min), 68.0 (CH min), 67.8 (CH maj), 52.9 (CH maj), 50.5 (CH min), 39.0 (Cq maj + min), 33.7 (CH_2 maj), 33.5 (CH_2 min), 27.1 ($3CH_3$).

IR (ν, cm^{-1}) 3486, 1782, 1727, 1595, 1470, 1389, 1230, 1142.

HRMS (EI) Calcd. for $C_{23}H_{20}ClNO_5$: 425.1030 Found: 425.1036

3-(1,3-Dioxoisoindolin-2-yl)-4-oxo-7-(trifluoromethyl)-1,2,3,4-tetrahydronaphthalen-1-yl pivalate 2.6e



$C_{24}H_{20}F_3NO_5$
M= 459.1294 g.mol $^{-1}$

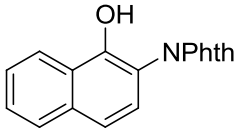
Following general procedure II, the reaction was carried out using xanthate (**2.4e**) (455 mg, 1 mmol, 1 equiv.) and vinyl pivalate (0.37 mL, 2.5 mmol, 2.5 equiv.) in refluxing 1,2-dichloroethane (1 mL); it needed 25 mol% DLP to go to completion. The reaction mixture was evaporated to dryness under reduced pressure and the residue was dissolved in chlorobenzene (10 mL), heated to reflux and treated with 1.2 equiv. DLP. After evaporation, the residue was purified by silica gel column chromatography with a gradient of dichloromethane in petroleum ether (30 : 70 to 50 : 50) to afford (**2.6e**) (188 mg, 41%) as a white solid. The product consisted of a 33 : 67 mixture of two diastereoisomers of (**2.6e**) and a pure sample of the major diastereoisomer could be obtained by chromatography.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz)	8.25 (d, *J*= 8.1 Hz, 1H), 7.67 – 7.89 (m, 6H), 6.36 (dd, *J*= 11.4 Hz, *J*= 4.9 Hz, 1H), 5.22 (dd, *J*= 14.2 Hz, *J*= 4.7 Hz, 1H), 3.11 (m, 1H), 2.70 (m, 1H), 1.33 (s, 9H).
^{13}C-NMR (δ, ppm) ($CDCl_3$, 100 MHz)	189.5 (CO), 177.6 (CO), 167.4 (2CO), 143.2 (Cq), 135.8 (q, *J*= 33 Hz, Cq), 134.4 (2CH), 132.7 (Cq), 131.9 (2Cq), 129.1 (CH), 125.3 (q, *J*= 3.5 Hz, CH), 123.7 (2CH),123.3 (q, *J*= 272 Hz, CF_3), 123.0 (q, *J*= 3.9 Hz, CH), 67.8 (CH), 53.0 (CH_2), 39.1 (Cq), 33.7 (CH_3), 27.1 ($3CH_3$).
IR (ν, cm^{-1})	3615, 1726, 1549, 1389, 1142.
HRMS (EI)	Calcd. for $C_{24}H_{20}F_3NO_5$: 459.1294 Found: 459.1283
Mp	185-186°C

General procedure III for the aromatisation into naphthylamine derivatives (2.7)

To a solution of tetralone (**2.6**) (1 mmol) in toluene (3 mL), p-toluenesulfonic acid (PTSA; 3 mmol) was added and the reaction mixture was heated to reflux using a Dean–Stark apparatus for 3 h. The reaction mixture was allowed to cool to rt, diluted with saturated sodium carbonate solution, and extracted with ethyl acetate. The combined organic layers were dried and concentrated. The residue was washed with pentane or dichloromethane, and then filtered to afford the desired product.

2-(1-Hydroxynaphthalen-2-yl)isoindoline-1,3-dione **2.7a**

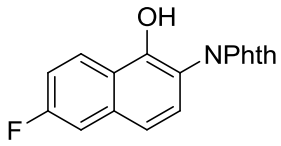
2.7a 

$C_{18}H_{11}NO_3$
M= 289.0739 g.mol $^{-1}$

Following general procedure III, the reaction was carried out using (**2.6a**) (78 mg, 0.2 mmol, 1 equiv.) and PTSA (105 mg, 0.6 mmol, 3 equiv.) in refluxing toluene (3 mL). The residue was washed with dichloromethane to afford (**2.7a**) (48 mg, 83%).

^{1}H-NMR (δ, ppm) (DMSO-D_6, 400 MHz)	10.20 (bs, 1H), 8.23 (d, *J*= 8.0 Hz, 1H), 7.90-7.99 (m, 5H), 7.55 (m, 2H), 7.45 (d, *J*= 8.6 Hz, 1H), 7.33 (d, *J*= 8.6 Hz, 1H).
^{13}C-NMR (δ, ppm) (DMSO-D_6, 100 MHz)	167.6 (2CO), 150.1 (Cq), 134.3 (2CH), 132.5 (2Cq), 132.4 (Cq), 127.5 (CH), 127.4 (CH), 127.1 (CH), 125.3 (CH), 125.2 (Cq), 123.2 (2CH), 122.5 (CH), 118.7 (CH), 112.4 (Cq).
IR (ν, cm^{-1})	3377, 1696, 1541, 1399, 1229, 1083.
HRMS (EI)	Calcd. for $C_{18}H_{11}NO_3$: 289.0739 Found: 289.0737
Mp	287–288°C

2-(6-Fluoro-1-hydroxynaphthalen-2-yl)isoindoline-1,3-dione **2.7b**

2.7b 

$C_{18}H_{10}FNO_3$
M= 307.0645 g.mol $^{-1}$

Following general procedure III, the reaction was carried out using (**2.6b**) (82 mg, 0.2 mmol, 1 equiv.) and PTSA (105 mg, 0.6 mmol, 3 equiv.) in refluxing toluene (3 mL). The residue was washed with dichloromethane to afford (**2.7b**) as a yellow solid (48 mg, 78%).

^{1}H-NMR (δ, ppm) (DMSO-D_6, 400 MHz): 10.32 (bs, 1H), 8.30 (dd, *J* = 9.2 Hz, *J* = 5.9 Hz, 1H), 7.90–7.99 (m, 4H), 7.70 (dd, *J* = 10.4 Hz, *J* = 2.6 Hz, 1H), 7.37–7.46 (m, 3H).

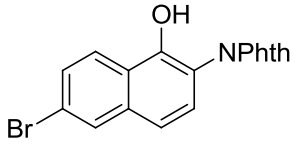
^{13}C-NMR (δ, ppm) (DMSO-D_6, 100 MHz): 167.6 (2CO), 160.9 (d, *J* = 245 Hz, Cq), 150.4 (Cq), 135.4 (d, *J* = 10 Hz, Cq), 134.3 (2CH), 132.5 (2Cq), 128.9 (CH), 125.8 (d, *J* = 9 Hz, CH), 123.2 (2CH), 122.4 (Cq), 118.2 (d, *J* = 5 Hz, CH), 115.2 (d, *J* = 25 Hz, CH), 112.1 (d, *J* = 2 Hz, Cq), 110.6 (d, *J* = 21 Hz, Cq).

IR (ν, cm^{-1}): 3313, 1721, 1551, 1398, 1244.

HRMS (EI): Calcd. for $C_{18}H_{10}FNO_3$: 307.0645 Found: 307.0644

Mp: 265–267 °C

2-(6-Bromo-1-hydroxynaphthalen-2-yl)isoindoline-1,3-dione **2.7c**

2.7c 

$C_{18}H_{10}BrNO_3$
M= 366.9844 g.mol $^{-1}$

Following general procedure III, the reaction was carried out using (**2.6c**) (95 mg, 0.2 mmol, 1 equiv.) and PTSA (105 mg, 0.6 mmol, 3 equiv.) in refluxing toluene (3 mL). The residue was washed with dichloromethane to afford a yellow solid (**2.7c**) (53 mg, 72%).

^{1}H-NMR (δ, ppm) (DMSO-D_6, 400 MHz): 10.40 (bs, 1H), 8.18 (m, 2H), 7.97–7.99 (m, 4H), 7.66 (m, 1H), 7.43 (m, 2H).

^{13}C-NMR (δ, ppm) (DMSO-D_6, 100 MHz): 167.5 (2CO), 150.4 (Cq), 135.5 (Cq), 134.3 (2CH), 132.5 (2Cq), 129.3 (CH), 128.9 (CH), 128.2 (CH), 125.0 (CH), 123.8 (Cq),

123.2 (2CH), 120.6 (Cq), 117.9 (CH), 113.0 (Cq).

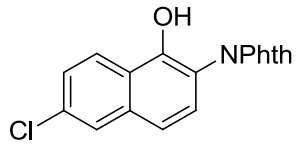
IR (ν, cm^{-1}) 3301, 1701, 1550, 1398, 1103.

HRMS (EI) Calcd. for $C_{18}H_{10}BrNO_3$: 366.9844Found: 366.9845

Mp 294–295 °C

2-(6-Chloro-1-hydroxynaphthalen-2-yl)isoindoline-1,3-dione 2.7d

2.7d



$C_{18}H_{10}ClNO_3$
M= 323.0349 $g.mol^{-1}$

Following general procedure III, the reaction was carried out using (**2.6d**) (85 mg, 0.2 mmol, 1 equiv.) and PTSA (105 mg, 0.6 mmol, 3 equiv.) in refluxing toluene (3 mL). The residue was washed with dichloromethane to afford a yellow solid (**2.7d**) (52 mg, 80%).

^{1}H-NMR (δ, ppm) (DMSO-D_6, 400 MHz) 10.40 (bs, 1H), 8.25 (m, 2H), 7.91–8.05 (m, 4H), 7.40–7.56 (m, 3H).

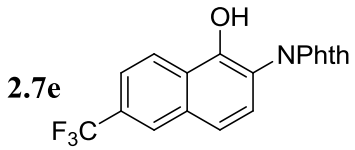
^{13}C-NMR (δ, ppm) (DMSO-D_6, 100 MHz) 167.5 (2CO), 150.4 (Cq), 135.5 (Cq), 134.3 (2CH), 132.5 (2Cq), 131.9 (CH), 128.9 (Cq), 126.1 (Cq), 125.7 (CH), 125.0 (CH), 123.7 (2CH), 123.2 (Cq), 118.0 (CH), 113.0 (Cq).

IR (ν, cm^{-1}) 3302, 1708, 1152, 1396, 1265, 1082.

HRMS (EI) Calcd. for $C_{18}H_{10}ClNO_3$: 323.0349Found: 323.0349

Mp 283-284°C

2-(1-Hydroxy-6-(trifluoromethyl)naphthalen-2-yl)isoindoline-1,3-dione 2.7e



2.7e

$C_{19}H_{10}F_3NO_3$
M= 357.0613 g.mol $^{-1}$

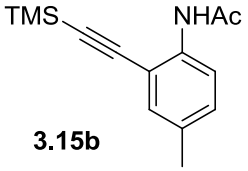
Following general procedure III, the reaction was carried out using (**2.6e**) (92 mg, 0.2 mmol, 1 equiv.) and PTSA (105 mg, 0.6 mmol, 3 equiv.) in refluxing toluene (3 mL). The residue was washed with dichloromethane to afford (**2.7e**) as a yellow solid (56 mg, 79%).

^{1}H-NMR (δ, ppm) (DMSO-D_6, 400 MHz)	10.58 (bs, 1H), 8.43 (m, 2H), 7.91–8.00 (m, 4H), 7.78 (d, *J* = 8.9 Hz, 1H), 7.69 (d, *J* = 8.7 Hz, 1H), 7.52 (d,*J* = 8.7 Hz, 1H).
^{13}C-NMR (δ, ppm) (DMSO-D_6, 100 MHz)	167.4 (2CO), 150.2 (Cq), 134.4 (2CH), 133.1 (Cq), 132.4 (2Cq), 129.1 (CH), 127.3 (q, *J* = 32 Hz, Cq), 126.7 (Cq), 125.4 (q, *J* = 5 Hz, CH), 124.4 (q, *J* = 272 Hz, CF_3), 124.3 (CH), 123.3 (2CH), 120.5 (d, *J* = 3 Hz, CH), 119.7 (CH), 114.7 (Cq).
IR (ν, cm^{-1})	3333, 1713, 1554, 1264, 1102.
HRMS (EI)	Calcd. for $C_{19}H_{10}F_3NO_3$: 357.0613Found: 357.0615
Mp	307-309°C

General procedure IV for the Sonogashira reaction

A suspension of 2-iodoaniline (1.0 mmol), $PdCl_2(PPh_3)_2$ (14.0 mg, 0.02 mmol, 2.0 mol%) and CuI (2.0 mg, 0.01 mmol, 1.0 mol%) in 2 mL triethylamine and 2 mL THF was degassed with argon and evacuated/backfilled with argon (3 cycles). The reaction mixture was stirred at rt for 10 minutes. After addition of the alkyne (1.2 mmol) the suspension was stirred for 24 hours at rt under an argon atmosphere. The reaction mixture was evaporated to dryness under reduced pressure, then diluted with 2.0 mL water and extracted with EtOAc (2 × 2.0 mL). The combined organic phases were washed with brine and dried over $MgSO_4$. Removal of the solvent under reduced pressure afforded the desired product. To a solution of the Sonogashira product (1 mmol) in dichloromethane (2 mL) was added Ac_2O (1.25 mmol) and the resulting solution was stirred at rt until complete consumption of the starting material. It was then diluted with dichloromethane, extracted with saturated solution of $NaHCO_3$, brine, dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by silica gel column chromatography with a gradient of ethyl acetate in petroleum ether (5/95 to 35/65) to afford the product as a solid.

N-(4-Methyl-2-((trimethylsilyl)ethynyl)phenyl)acetamide 3.15b



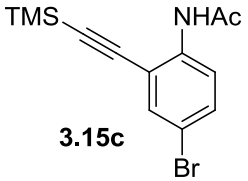
3.15b

$C_{14}H_{19}NOSi$
M= 245.1236 g.mol $^{-1}$

Following general procedure IV, to a solution of 2-iodo-4-methylaniline (20 mmol, 4.66 g, 1.0 equiv.), $PdCl_2(PPh_3)_2$ (280 mg, 0.4 mmol, 2.0 mol%) and CuI (40 mg, 0.2 mmol, 1.0 mol%) in 40 mL triethylamine in 40 mL THF, trimethylsilylacetylene (24 mmol, 3.42 mL, 1.2 equiv.) was added. After workup, the product was dissolved in DCM (40 mL) and then Ac_2O (25 mmol, 2.36 mL, 1.25 equiv.) was added. Upon complete acetylation, the residue was purified by silica gel column chromatography with a gradient of ethyl acetate in petroleum ether (5/95 to 25/75) to afford the product (**3.15b**) as a pinkish solid (4.6 g, 95%).

^{1}H-NMR(δ, ppm) ($CDCl_3$, 400 MHz)	8.25 (d, *J*= 8.4 Hz, 1H), 7.90 (bs, 1H), 7.22 (d, *J*= 1.3 Hz, 1H), 7.13 (dd, *J*= 8.4 Hz, *J*= 1.3 Hz, 1H), 2.27 (s, 3H), 2.09 (s, 3H), 0.00 (s, 9H).
^{13}C-NMR(δ, ppm) ($CDCl_3$, 100 MHz)	167.9 (CO), 137.2 (Cq), 132.8 (Cq), 131.7 (CH), 130.8 (CH), 118.9 (CH), 111.5 (Cq), 101.8 (C≡C), 100.6 (C≡C), 24.8 (CH_3), 20.7 (CH_3), 0.0 ($3CH_3$).
IR (ν, cm^{-1})	3334, 2956, 2155, 1669, 1507, 1121.
HRMS (EI)	Calcd. for $C_{14}H_{19}NOSi$: 245,1236Found: 245.1240
Mp	82-83°C

N-(4-Bromo-2-((trimethylsilyl)ethynyl)phenyl)acetamide 3.15c



3.15c

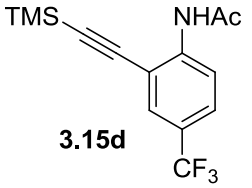
$C_{13}H_{16}BrNOSi$
M= 309.0185 g.mol $^{-1}$

Following general procedure IV, to a solution of 2-iodo-4-bromoaniline (20 mmol, 5.96 g), $PdCl_2(PPh_3)_2$ (280 mg, 0.4 mmol, 2.0 mol%) and CuI (40 mg, 0.2 mmol, 1.0 mol%) in 40 mL triethylamine in 40 mL THF, trimethylsilylacetylene (24 mmol, 3.42 mL, 1.2 equiv.) was added. After workup, the product was dissolved in DCM (40 mL) and Ac_2O (25 mmol, 2.36 mL, 1.25

equiv.) was added. Upon complete acetylation, the residue was purified by silica gel column chromatography with a gradient of ethyl acetate in petroleum ether (5/95 to 25/75) to afford the product (**3.15c**) as a white solid (5.90 g, 92%).

^{1}H-NMR(δ, ppm) ($CDCl_3$, 400 MHz)	8.31 (d, *J*= 8.9 Hz, 1H), 7.92 (bs, 1H), 7.53 (d, *J*= 2.3 Hz, 1H), 7.42 (dd, *J*= 8.9 Hz, *J*= 2.3 Hz, 1H), 2.20 (s, 3H), 0.00 (s, 9H).
^{13}C-NMR(δ, ppm) ($CDCl_3$, 100 MHz)	168.2 (CO), 138.7 (Cq), 134.0 (CH), 133.0 (CH), 120.5 (CH), 115.4 (Cq), 113.6 (Cq), 104.0 (CH), 98.8 (CH), 25.0 (CH_3), 0.0 ($3CH_3$).
IR (ν, cm^{-1})	3304, 2925, 2162, 1673, 1519, 1393, 1297.
HRMS (EI)	Calcd. for$C_{13}H_{16}BrNOSi$: 309,0185Found: 309.0185
Mp	88-100°C

N-(4-(Trifluoromethyl)-2-((trimethylsilyl)ethynyl)-phenyl)acetamide 3.15d



3.15d

$C_{14}H_{16}F_3NOSi$
M= 299.0953g.mol $^{-1}$

Following general procedure IV, the reaction was carried out with a solution of 2-iodo-4-methylaniline (20 mmol, 5.74 g), $PdCl_2(PPh_3)_2$ (280 mg, 0.4 mmol, 2.0 mol%) and CuI (40 mg, 0.2 mmol, 1.0 mol%) in 40 mL triethylamine in 40 mL THF, to which trimethylsilylacetylene (24 mmol, 3.42 mL, 1.2 equiv.) was added. After workup, the product was dissolved in DCM (40 mL) and then Ac_2O (25 mmol, 2.36 mL, 1.25 equiv.) was added. Upon complete acetylation, the residue was purified by silica gel column chromatography with a gradient of ethyl acetate in petroleum ether (5/95 to 35/65) to afford the product (**3.15d**) as a rose solid (5.45 g, 91%).

^{1}H-NMR(δ, ppm) ($CDCl_3$, 400 MHz)	8.55 (d, *J*= 8.7 Hz, 1H), 8.10 (bs, 1H), 7.67 (d, *J*= 1.9 Hz, 1H), 7.55 (dd, *J*= 8.7 Hz, *J*= 1.9 Hz, 1H), 2.29 (s, 3H), 0.00 (s, 9H).
^{13}C-NMR(δ, ppm) ($CDCl_3$, 100 MHz)	168.5 (CO), 142.0 (Cq), 128.7 (q, *J*= 4 Hz, CH), 127.0 (q, *J*= 4 Hz, CH), 125.3 (q, *J*= 33 Hz, Cq), 123.8 (q, *J*= 272 Hz, CF_3), 118.9 (CH), 112.0 (Cq), 104.3 (C≡C), 98.8 (C≡C), 25.1 (CH_3), 0.0 ($3CH_3$).

IR (ν, cm^{-1}) 3307, 2972, 2161, 1681, 1520, 1416, 1331.

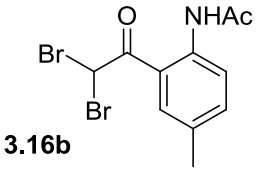
HRMS (EI) Calcd. for$C_{14}H_{16}F_3NOSi$: 299.0953Found: 229.0955

Mp 65-66°C

General procedure V for the preparation of dibromoacetylphenylacetamides (3.16)

To a solution of phenylacetamide (**3.15**) (1 mmol) in methanol (2.5 mL), potassium carbonate was added (5 mol%). After 30 minutes, the solvent was evaporated and to the residue, N-bromosuccinimide (2 mmol), $FeCl_3 \cdot 6H_2O$ (0.05 mmol), water (2.0 mL) and tetrahydrofuran (2.0 mL) were added under nitrogen at rt. The reaction temperature was raised to 80 °C for several hours. After the complete consumption of the starting material, the reaction mixture was cooled to rt and quenched with 2.0 mL of saturated $NaHCO_3$ and then extracted with 3 × 15 mL of ether. The combined extracts were dried over $MgSO_4$ and the solvent was evaporated in vacuo to afford the crude product, which was purified by silica gel column chromatography with a gradient of ethyl acetate in toluene (0/100 to 8/92) to afford the product as a solid.

N-(2-(2,2-Dibromoacetyl)-4-methylphenyl)acetamide 3.16b



3.16b

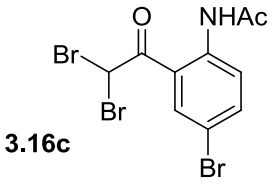
$C_{11}H_{11}Br_2NO_2$
M= 346.9157g.mol $^{-1}$

Following general procedure V, the reaction was carried out with a solution of compound (**3.15b**) (2.45 g, 10 mmol) in MeOH (25 mL) and potassium carbonate (70 mg). After removing the methanol, N-bromosuccinimide (20 mmol, 3.56 g), $FeCl_3 \cdot 6H_2O$ (0.5 mmol, 135 mg), water (20 mL) and tetrahydrofuran (20 mL) were added under nitrogen at rt. The reaction temperature was raised to 80 °C and kept for 3 h. After workup, the crude product was purified by silica gel column chromatography with a gradient of ethyl acetate in toluene (0/100 to 8/92) to afford the product (**3.16b**) as a brown solid (1.98 g, 57%).

^{1}H-NMR(δ, ppm) ($CDCl_3$, 400 MHz) 11.00 (bs, 1H), 8.67 (d, *J*= 8.7 Hz, 1H), 7.67 (s, 1H), 7.45 (d, *J*= 8.7 Hz, 1H), 6.92 (s, 1H), 2.37 (s, 3H), 2.24 (s, 3H).

^{13}C-NMR(δ, ppm) ($CDCl_3$, 100 MHz)	189.4 (CO), 169.3 (CO), 140.5 (Cq), 137.7 (CH), 132.1 (Cq), 130.5 (CH), 121.6 (CH), 116.0 (Cq), 40.1 (CH), 25.6 (CH_3), 20.9 (CH_3).
IR (ν, cm^{-1})	3371, 1678, 1579, 1505, 1462, 1249
HRMS (EI)	Calcd. for$C_{11}H_{11}Br_2NO_2$: 346.9157Found: 346.9162
Mp	144-146°C

N-(4-Bromo-2-(2,2-dibromoacetyl)phenyl)acetamide 3.16c



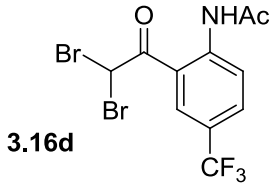
3.16c

$C_{10}H_8Br_3NO_2$
M= 410.8105g.mol $^{-1}$

Following general procedure V, the reaction was carried out with a solution of compound (**3.15c**) (3.1 g, 10 mmol) in MeOH (25 mL) and potassium carbonate (70 mg). After removing the methanol, N-bromosuccinimide (20 mmol, 3.56 g), $FeCl_3 \cdot 6H_2O$ (0.5 mmol, 135 mg), water (20 mL) and tetrahydrofuran (20 mL) were added under nitrogen at rt. The reaction temperature was raised to 80 °C and kept for 3 h. After workup, the crude product was purified by silica gel column chromatography with a gradient of ethyl acetate in toluene (0/100 to 8/92) to afford the product (**3.16c**) as a brown solid (2.69 g, 65%).

^{1}H-NMR(δ, ppm) ($CDCl_3$, 400 MHz)	11.00 (bs, 1H), 8.74 (d, *J*= 9.1 Hz, 1H), 8.03 (d, *J*= 2.3 Hz, 1H), 7.72 (d, *J*= 9.1 Hz, J= 2.3 Hz, 1H), 6.80 (s, 1H), 2.27 (s, 3H).
^{13}C-NMR(δ, ppm) ($CDCl_3$, 100 MHz)	194.3 (CO), 169.5 (CO), 140.9 (Cq), 138.8 (CH), 133.6 (CH), 122.9 (CH), 120.2 (Cq), 114.7 (Cq), 32.0 (CH), 25.6 (CH_3).
IR (ν, cm^{-1})	3330, 1682, 1564, 149(, 1393, 1295, 1195.
HRMS (EI)	Calcd. for$C_{10}H_8Br_3NO_2$: 410.8105Found: 410.8105
Mp	140-141°C

N-(2-(2,2-Dibromoacetyl)-4-(trifluoromethyl)-phenyl)acetamide 3.16d



3.16d

$C_{11}H_8Br_2F_3NO_2$
M= 400.8874g.mol $^{-1}$

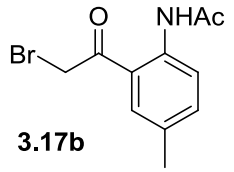
Following general procedure V, the reaction was carried out with a solution of compound (**3.15d**) (3 g, 10 mmol, 3.0 g, 1 equiv.) in MeOH (25 mL) and potassium carbonate (0.5 mmol, 70 mg, 5 mol%). After removing the methanol, N-bromosuccinimide (20 mmol, 3.56 g, 2 equiv.), $FeCl_3 \cdot 6H_2O$ (0.5 mmol, 135 mg, 5 mol%), water (20 mL) and tetrahydrofuran (20 mL) were added under nitrogen at rt. The reaction temperature was raised to 80 °C and kept for 3 h. After workup, the crude product was purified by silica gel column chromatography with a gradient of ethyl acetate in toluene (0/100 to 8/92) to afford the product (**3.16d**) as a brown solid (2.40 g, 60%).

^{1}H-NMR(δ, ppm) ($CDCl_3$, 400 MHz)	11.26 (bs, 1H), 8.98 (d, *J*= 9.0 Hz, 1H), 8.22 (d, *J*= 1.4 Hz, 1H), 7.85 (dd, *J*= 9.0 Hz, *J*= 1.4 Hz, 1H), 6.85 (s, 1H), 2.31 (s, 3H).
^{13}C-NMR(δ, ppm) ($CDCl_3$, 100 MHz)	187.8 (CO), 168.7 (CO), 144.3 (Cq), 131.9 (q, *J* = 4 Hz, CH), 126.9 (q, *J* = 4 Hz, CH), 123.18 (q, *J* = 33.8 Hz, Cq), 122.2 (q, *J* = 272.0 Hz, CF_3), 120.7 (CH), 114.2 (Cq), 38.4 (CH), 24.7 (CH_3).
IR (ν, cm^{-1})	3296, 1693, 1586? 1515, 1421, 1299, 1131.
HRMS (EI)	Calcd. for$C_{11}H_{11}Br_2NO_2$: 400.8874Found: 400.8883
Mp	133-134°C

General procedure VI for the preparation of monobromo-ketones (3.17)

To a mixture of dibromoketone (**3.16**) (1 mmol) and Et_3N (1.05 mmol) in THF (4 mL), $(EtO)_2POH$ (1.05 mmol) was added at rt. After 30 min, the resulting reaction solution was quenched with 2 mL of saturated $NaHCO_3$ and extracted with 3 × 15 mL of ethyl acetate. The combined extracts were dried over $MgSO_4$ and the solvent was evaporated in vacuo to afford the crude bromoketone (**3.17**), which was sufficiently pure for the next step.

N-(2-(2-Bromoacetyl)-4-methylphenyl)acetamide 3.17b



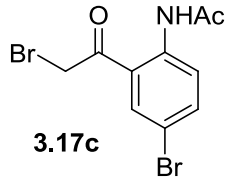
3.17b

$C_{11}H_{12}BrNO_2$
M= 269.0051g.mol $^{-1}$

Following general procedure VI, the reaction was carried out with a solution of compound (**3.16b**) (1.74 g, 5 mmol, 1 equiv.), Et_3N (0.73 mL, 5.25 mmol, 1.05 equiv.) and $(EtO)_2POH$ (0.67 mL, 5.25 mmol, 1.05 equiv.) in THF (20 mL) at rt. The product (**3.17b**) was obtained as a white solid (1.27 g, 95%).

^{1}H-NMR(δ, ppm) ($CDCl_3$, 400 MHz)	11.25 (bs, 1H), 8.65 (d, *J*= 8.7 Hz, 1H), 7.64 (s, 1H), 7.41 (d, *J*= 8.7 Hz, 1H), 4.53 (s, 2H), 2.37 (s, 3H), 2.22 (s, 3H).
^{13}C-NMR(δ, ppm) ($CDCl_3$, 100 MHz)	195.1 (CO), 169.4 (CO), 139.6 (Cq), 137.0 (CH), 132.0 (Cq), 131.2 (CH), 121.2 (CH), 118.9 (Cq), 32.6 (CH_2), 25.6 (CH_3), 20.9 (CH_3).
IR (ν, cm^{-1})	3244, 1682, 1659, 1597, 1506, 1366, 1300, 1173.
HRMS (EI)	Calcd. for$C_{11}H_{12}BrNO_2$: 269.0051Found: 269.0056
Mp	139-141°C

N-(4-Bromo-2-(2-bromoacetyl)phenyl)acetamide 3.17c



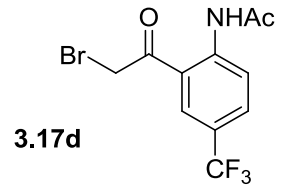
3.17c

$C_{10}H_9Br_2NO_2$
M= 332.9000g.mol $^{-1}$

Following general procedure VI, the reaction was carried out with a solution of compound (**3.16c**) (2.07 g, 5 mmol, 1 equiv.), Et_3N (0.73 mL, 5.25 mmol, 1.05 equiv.) and $(EtO)_2POH$ (0.67 mL, 5.25 mmol, 1.05 equiv.) in THF (20 mL) at rt. The product (**3.17c**) was obtained as a white solid (1.6 g, 96%).

^{1}H-NMR(δ, ppm) ($CDCl_3$, 400 MHz)	11.26 (bs, 1H), 8.72 (d, *J* = 9.1 Hz, 1H), 7.97 (d, *J* = 2.3 Hz, 1H), 7.68 (dd, *J* = 9.1 Hz, *J* = 2.3 Hz, 1H), 4.49 (s, 2H), 2.24 (s, 3H)
^{13}C-NMR(δ, ppm) ($CDCl_3$, 100 MHz)	194.3 (CO), 169.5 (CO), 140.9 (Cq), 138.8 (CH), 133.6 (CH), 123.0 (CH), 120.3 (Cq), 114.7 (Cq), 32.6 (CH_2), 25.6 (CH_3).
IR (ν, cm^{-1})	3234, 1668, 1599, 1580, 1505, 1372, 1290, 1178.
HRMS (EI)	Calcd. for$C_{10}H_9Br_2NO_2$: 332.9000Found: 332.8994
Mp	188-190°C

N-(2-(2-Bromoacetyl)-4-(trifluoromethyl)phenyl)acetamide **3.17d**



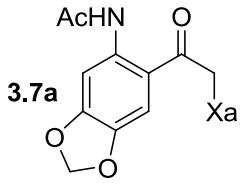
3.17d

$C_{11}H_9BrF_3NO_2$
M= 322.9769 g.mol $^{-1}$

Following general procedure VI, the reaction was carried out with a solution of compound (**3.16d**) (2.0 g, 5 mmol, 1 equiv.), Et_3N (0.73 mL, 5.25 mmol, 1.05 equiv.) and $(EtO)_2POH$ (0.67 mL, 5.25 mmol, 1.05 equiv.) in THF (20 mL) at rt. The product (**3.17d**) was obtained as a white solid (1.55 g, 96%).

^{1}H-NMR(δ, ppm) ($CDCl_3$, 400 MHz)	11.50 (bs, 1H), 8.96 (d, *J*= 8.9 Hz, 1H), 8.12 (d, *J*= 2.0 Hz, 1H), 7.82 (dd, *J*= 8.9 Hz, *J*= 2.0 Hz, 1H), 4.54 (s, 2H), 2.29 (s, 3H).
^{13}C-NMR(δ, ppm) ($CDCl_3$, 100 MHz)	194.7 (CO), 169.7 (CO), 144.6 (Cq), 132.5 (q, *J*= 4 Hz, CH), 128.3 (q, *J*= 4 Hz, CH), 124.2 (q, *J*= 33 Hz, Cq), 123.4 (q, *J*= 272 Hz, CF_3), 121.4 (CH), 118.2 (Cq), 31.8 (CH_2), 25.7 (CH_3).
IR (ν, cm^{-1})	3282, 1719, 1660, 1590, 1525, 1292, 1135.
HRMS (EI)	Calcd. for$C_{11}H_9BrF_3NO_2$: 322.9769Found: 322.9764
Mp	110–112°C

S-2-(6-Acetamidobenzo[d][1,3]dioxol-5-yl)-2-oxoethyl *O*-ethyl carbonodithioate 3.7a



$C_{14}H_{15}NO_5S_2$
M= 341.0392 g.mol $^{-1}$

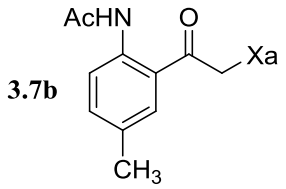
To a refluxing solution of $CuBr_2$ (2.25 g, 10.1 mmol, 2.01 equiv.) in 11 mL AcOEt was added dropwise a solution of N-(6-acetylbenzo[d][1,3]dioxol-5-yl)acetamide **5** (1.1 g, 5 mmol, 1 equiv.) in 11 mL $CHCl_3$. Reflux was continued for 8 hours (or until a white precipitate was formed). Then, the solvent was evaporated and the remaining solid was boiled in the 1 : 1 mixture of ethanol and chloroform and filtered off while hot. The filtrate was left to cool down and the resulting solid was collected. The crude solid was dissolved in acetone (10 mL) and potassium *O*-ethyl xanthate (805 mg, 5 mmol) was added at rt. After completion of the reaction, the acetone was evaporated and the mixture was diluted with ethyl acetate. The organic layer was washed with water, brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography with a gradient of dichloromethane in petroleum ether (50/50 to 90/10) to afford the desired xanthate (**3.7a**) as a white solid (684 mg, 40%).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz)	11.57 (bs, 1H), 8.41 (s, 1H), 7.39 (s, 1H), 6.06 (s, 2H), 4.66 (q, *J* = 7.1 Hz, 2H), 4.63 (s, 2H), 2.20 (s, 3H), 1.42 (t, *J* = 7.1 Hz, 3H).
^{13}C-NMR (δ, ppm) ($CDCl_3$, 100 MHz)	213.0 (CS), 193.9 (CO), 169.5 (CO), 153.7 (Cq), 142.7 (Cq), 140.9 (Cq), 113.9 (Cq), 108.6 (CH), 102.4 (CH), 101.8 (CH_2), 71.0 (CH_2), 44.9 (CH_2), 25.6 (CH_3), 13.8 (CH_3).
IR (ν, cm^{-1})	3124, 1704, 1614, 1541, 1435, 1354, 1274, 1051.
HRMS (EI)	Calcd. for $C_{14}H_{15}NO_5S_2$: 341.0392 Found: 341.0395
Mp	132°C

General procedure VII for the formation of xanthates (3.7)

To a stirred solution of 2-bromoacetylphenylacetamide (1 mmol) (**3.17**) in acetone (2 mL) at rt was added portion-wise potassium ethyl xanthate (1.1 mmol). The reaction was stirred until complete consumption of the starting material. The solvent was evaporated, and the residue was diluted with ethyl acetate. The organic phase was washed with brine, and the organic layer was washed with water, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was recrystallised from ethanol to afford the desired xanthate (**3.7**).

S-2-(2-Acetamido-5-methylphenyl)-2-oxoethyl *O*-ethyl carbonodithioate 3.7b



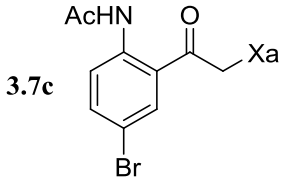
3.7b

$C_{14}H_{17}NO_3S_2$
M= 311.0650g.mol $^{-1}$

Following general procedure VII, the reaction was carried out with a solution of compound (**3.17b**) (1.08 g, 4 mmol, 1 equiv.) in acetone (8 mL) and potassium ethyl xanthate (705 mg, 4.4 mmol, 1.1 equiv.) at rt for 1 h. Xanthate (**3.7b**) was obtained as a white solid (1.18 g, 95%).

^{1}H-NMR(δ, ppm) ($CDCl_3$, 400 MHz)	11.22 (bs, 1H), 8.65 (d, *J* = 8.7 Hz, 1H), 7.79 (s, 1H), 7.42 (d, *J* = 8.7 Hz, 1H), 4.74 (s, 2H), 4.66 (q, *J* = 7.1 Hz, 2H), 2.40 (s, 3H), 2.20 (s, 3H), 1.42 (t, *J* = 7.1 Hz, 3H).
^{13}C-NMR(δ, ppm) ($CDCl_3$, 100 MHz)	213.1 (CS), 196.1 (CO), 169.4 (CO), 138.9 (Cq), 136.7 (CH), 132.1 (Cq), 130.8 (CH), 121.1 (Cq), 120.8 (CH), 71.0 (CH_2), 45.0 (CH_2), 25.6 (CH), 20.9 (CH_3), 13.8 (CH_3).
IR (ν, cm^{-1})	2989, 1698, 1667, 1587, 1505, 1356, 1295, 1234, 1111, 1049.
HRMS (EI)	Calcd. for$C_{14}H_{17}NO_3S_2$: 311.0650Found: 311.0653
Mp	149–150 °C (from EtOH)

S-2-(2-Acetamido-5-bromophenyl)-2-oxoethyl *O*-ethyl carbonodithioate 3.7c



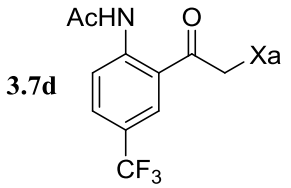
3.7c

$C_{13}H_{14}BrNO_3S_2$
M= 374.9598g.mol $^{-1}$

Following general procedure VII, the reaction was carried out with a solution of compound (**3.17c**) (1.34 g, 4 mmol, 1 equiv.) in acetone (8 mL) and potassium ethyl xanthate (705 mg, 4.4 mmol, 1 equiv.) at rt for 1 h. Xanthate (**3.7c**) was obtained as a pinkish solid (1.4 g, 93%).

^{1}H-NMR(δ, ppm) ($CDCl_3$, 400 MHz)	11.20 (bs, 1H), 8.68 (d, *J* = 9.1 Hz, 1H), 8.10 (d, *J* = 2.3 Hz, 1H), 7.66 (dd, *J* = 9.1 Hz, *J* = 2.3 Hz, 1H), 4.67 (s, 2H), 4.64 (q, *J* = 7.1 Hz, 2H), 2.19 (s, 3H), 1.41 (t, *J* = 7.1 Hz, 3H).
^{13}C-NMR(δ, ppm) ($CDCl_3$, 100 MHz)	212.8 (CS), 195.3 (CO), 169.5 (CO), 140.2 (Cq), 138.4 (CH), 133.1 (CH), 122.8 (CH), 122.3 (Cq), 114.8 (Cq), 71.2 (CH_2), 44.7 (CH_2), 25.6 (CH), 13.8 (CH_3).
IR (ν, cm^{-1})	3290, 1673, 1574, 1496, 1394, 1288, 1229, 1113, 1048.
HRMS (EI)	Calcd. for$C_{13}H_{14}BrNO_3S_2$: 374.9598Found: 374.9600
Mp	144–145 °C (from EtOH)

S-2-(2-Acetamido-5-(trifluoromethyl)phenyl)-2-oxoethyl *O*-ethyl carbonodithioate 3.7d



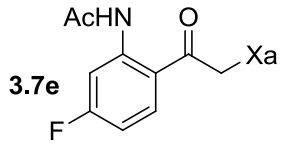
3.7d

$C_{14}H_{14}F_3NO_3S_2$
M= 365.0367 g.mol $^{-1}$

Following general procedure VII, the reaction was carried out with a solution of compound (**3.17d**) (1.30 g, 4 mmol, 1 equiv.) in acetone (8 mL) and potassium ethyl xanthate (705 mg, 4.4 mmol, 1.1 equiv.) at rt. The reaction finished in one hour. Xanthate (**3.7d**) was obtained as a pinkish solid (1.34 g, 92%).

^{1}H-NMR(δ, ppm) ($CDCl_3$, 400 MHz)	11.50 (bs, 1H), 8.94 (d, *J* = 8.9 Hz, 1H), 8.25 (m, 1H), 7.82 (dd, *J* = 9.0 Hz, *J* = 1.9 Hz, 1H), 4.74 (s, 2H), 4.66 (q, *J* = 7.1 Hz, 2H), 2.25 (s, 3H), 1.42 (t, *J* = 7.1 Hz, 3H).
^{13}C-NMR(δ, ppm) ($CDCl_3$, 100 MHz)	212.7 (CS), 195.8 (CO), 169.8 (CO), 143.9 (Cq), 132.2 (q, *J* = 3 Hz, CH), 127.7 (q, *J* = 4 Hz, CH), 124.4 (q, *J* = 33 Hz, Cq), 123.5 (q, *J* = 272 Hz, CF_3), 121.4 (CH), 120.3 (Cq), 71.3 (CH_2), 44.5 (CH_2), 25.7 (CH), 13.8 (CH_3).
IR (ν, cm^{-1})	3279, 1714, 1660, 1591, 1524, 1419, 1340, 1293, 1230, 1134, 1053.
HRMS (EI)	Calcd. for$C_{14}H_{14}F_3NO_3S_2$: 365.0367Found: 365.0369
Mp	85–86 °C (from EtOH).

S-2-(2-Acetamido-4-fluorophenyl)-2-oxoethyl *O*-ethyl carbonodithioate **3.7e**

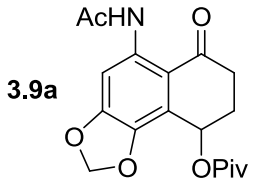


$C_{13}H_{14}FNO_3S_2$
M= 315.0399 g.mol $^{-1}$

Starting with *N*-(2-acetyl-5-fluorophenyl)acetamide (976 mg, 5 mmol) and pyridinium hydrobromide perbromide (880 g, 5.5 mmol) in 15 mL acetic acid at rt, general procedure I was followed, but the reaction mixture was heated to only 50 °C in the first step. After the substitution of bromine by potassium O-ethyl xanthate, the residue was purified by silica gel column chromatography with a gradient of ethyl acetate in toluene (0 : 100 to 5 : 95) to afford xanthate (**3.7e**) (995 g, 63%) as a white solid.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz)	11.57 (bs, 1H), 8.59 (dd, *J* = 2.6 Hz, *J* = 12.0 Hz, 1H), 8.04 (dd, *J* = 9.0 Hz, *J* = 6.2 Hz, 1H), 6.84 (ddd, *J* = 9.1 Hz, *J* = 7.3 Hz, *J* = 2.6 Hz, 1H), 4.69 (s, 2H), 4.66 (q, *J* = 7.1 Hz, 2H), 2.21 (s, 3H), 1.41 (t, *J* = 7.1 Hz, 3H).
^{13}C-NMR (δ, ppm) ($CDCl_3$, 100 MHz)	213.0 (CS), 195.1 (CO), 169.7 (CO), 166.8 (d, *J* = 256 Hz, Cq), 144.1 (d, *J* = 13 Hz, Cq), 133.3 (d, *J* = 11 Hz, CH), 117.2 (d, *J* = 3 Hz, Cq), 109.9 (d, *J* = 23 Hz, CH), 108.0 (d, *J* = 28 Hz, CH), 71.0 (CH_2), 44.8 (CH_2), 25.6 (CH_3), 13.8 (CH_3).
IR (ν, cm^{-1})	3271, 1711, 1652, 1592, 1554, 1431, 1234, 1113, 1052.
HRMS (EI)	Calcd. for $C_{20}H_{14}F_3NO_4S_2$: 315.0399 Found: 315.0413
Mp	98–100 °C

5-Acetamido-6-oxo-6,7,8,9-tetrahydronaphtho[2,1-d][1,3]dioxol-9-yl pivalate 3.9a

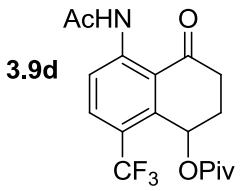


$C_{18}H_{21}FNO_6$
M= 347.1369 g.mol $^{-1}$

Following general procedure II, the reaction was carried out using xanthate (**3.7a**) (341 mg, 1 mmol, 1 equiv.) and vinyl pivalate (0.37 mL, 2.5 mmol, 2.5 equiv.) in refluxing dichloromethane (1 mL) and needed 10 mol% DLP to go to completion. The reaction mixture was evaporated to dryness under reduced pressure and the residue was dissolved in ethyl acetate (10 mL), heated to reflux and treated with 1.0 equiv. DLP to go to completion. After evaporation, the residue was purified by silica gel column chromatography with a gradient of ethyl acetate in petroleum ether (5 : 95 to 30 : 70) to afford (**3.9a**) (198 mg, 57%) as a white solid.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz)	12.36 (bs, 1H), 8.39 (s, 1H), 6.19 (s, 1H), 6.02 (d, *J* = 8.4 Hz, 2H) 2.85 (m, 1H), 2.57 (m, 1H), 2.20 (s + m, 5H), 1.17 (s, 9H).
^{13}C-NMR (δ, ppm) ($CDCl_3$, 100 MHz)	200.0 (CO), 177.5 (CO), 169.7 (CO), 153.2 (Cq), 140.6 (Cq), 140.1 (Cq), 120.0 (CH), 111.1 (Cq), 102.5 (CH_2), 101.5 (CH), 63.8 (CH), 39.0 (Cq), 34.8 (CH_2), 27.1 ($3CH_3$ + CH_2), 25.6 (CH_3).
IR (ν, cm^{-1})	3124, 1733, 1703, 1653, 1625, 1503, 1503, 1470, 1367, 1257, 1142.
HRMS (EI)	Calcd. for $C_{17}H_{21}FNO_4$: 347.1369Found: 347.1373
Mp	120–121 °C

5-Acetamido-4-oxo-8-(trifluoromethyl)-1,2,3,4-tetrahydronaphthalen-1-ylpivalate 3.9d

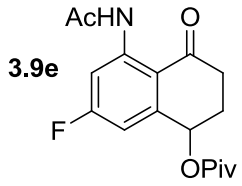


$C_{18}H_{20}F_3NO_4$
M= 371.1344 g.mol $^{-1}$

Following general procedure II, the reaction was carried out using xanthate (**3.7d**) (365 mg, 1 mmol, 1 equiv.) and vinyl pivalate (0.37 mL, 2.5 mmol, 2.5 equiv.) in refluxing dichloromethane (1 mL) and needed 10 mol% DLP to go to completion. Then the reaction mixture was evaporated to dryness under reduced pressure. The residue was dissolved in ethyl acetate (10 mL), heated to reflux, and needed 1 equiv. DLP to go to completion. After evaporation, the residue was purified by silica gel column chromatography with a gradient of petroleum ether in dichloromethane (40 : 60 to 100 : 0) to afford (**3.9d**) (222 mg, 60%) as a white solid.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz)	12.28 (bs, 1H), 8.94 (d, *J* = 9.1 Hz, 1H), 7.87 (d, *J* = 9.1 Hz, 1H), 6.35 (m, 1H), 2.934 (m, 1H), 2.70 (m, 1H), 2.54 (m, 1H), 2.28 (s, 3H), 2.21 (m, 1H), 1.15 (s, 9H).
^{13}C-NMR (δ, ppm) ($CDCl_3$, 100 MHz)	202.3 (CO), 177.0 (CO), 170.0 (CO), 144.7 (Cq), 139.8 (Cq), 132.8 (q, *J* = 5.7 Hz, CH), 123.5 (q, *J* = 272 Hz, CF_3), 122.8 (q, *J* = 31.2 Hz, Cq), 121.0 (CH), 118.7 (Cq), 64.9 (CH_2), 39.0 (Cq), 33.7 (CH_2), 27.0 ($3CH_3$), 26.1 (CH_2), 25.8 (CH_3).
IR (ν, cm^{-1})	3215, 1737, 1713, 166é, 1595, 1398, 1286, 1135.
HRMS (EI)	Calcd. for $C_{17}H_{20}F_3NO_4$: 371.1344Found: 371.1339
Mp	150–151 °C

5-Acetamido-7-fluoro-4-oxo-1,2,3,4-tetrahydronaphthalen-1-yl pivalate **3.9e**



$C_{17}H_{20}FNO_4$
M= 321.1376 g.mol $^{-1}$

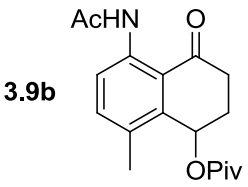
Following general procedure II, the reaction was carried out using xanthate (**3.7e**) (315 mg, 1 mmol, 1 equiv.) and vinyl pivalate (0.37 mL, 2.5 mmol, 2.5 equiv.) in refluxing dichloromethane (1 mL) and needed 10 mol% DLP to go to completion. The reaction mixture was evaporated to dryness under reduced pressure and the residue was dissolved in ethyl acetate (10 mL), heated to reflux and treated with 1.0 equiv. DLP. After evaporation, the residue was purified by silica gel column chromatography with a gradient of ethyl acetate in petroleum ether (5 : 95 to 15 : 85) to afford (**3.9e**) (208 mg, 65%) as a white solid.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz)	12.24 (bs, 1H), 8.55 (dd, *J* = 11.8 Hz, *J* = 2.5 Hz, 1H), 6.78 (dd, *J* = 8.4 Hz, *J* = 2.5 Hz, 1H), 5.99 (dd, *J* = 7.0 Hz, *J* = 3.7 Hz, 1H), 2.91 (m, 1H), 2.70 (m, 1H), 2.33 (m, 1H), 2.19 (s + m, 4H), 1.12 (s, 9H).
^{13}C-NMR (δ, ppm) ($CDCl_3$, 100 MHz)	200.5 (CO), 177.5 (CO), 169.8 (CO), 166.4 (d, *J* = 256 Hz, Cq), 145.5 (d, *J* = 10 Hz, Cq), 144.7 (d, *J* = 14 Hz, Cq), 113.9 (d, *J* = 3 Hz, Cq), 109.3 (d, *J* = 23 Hz, CH), 107.4 (d, *J* = 28 Hz, CH), 69.1 (CH_2), 39.0 (Cq), 35.8 (CH_2), 27.7 (CH_2), 27.1 ($3CH_3$), 25.6 (CH_3).
IR (ν, cm^{-1})	3217, 1734, 1654, 1542, 1445, 1142.
HRMS (EI)	Calcd. for $C_{17}H_{20}FNO_4$: 321.1376Found: 321.1374
Mp	119–120 °C.

General procedure VIII for the synthesis of tetralones (3.9) by radical addition and cyclisation

A magnetically stirred solution of xanthate (1 mmol) and vinyl pivalate (2.5 mmol) in 1,2-dichloroethane (2 mL) was refluxed for 15 min under a slightly positive nitrogen pressure. Dilauroyl peroxide (DLP) (10 mol%) was then added and additional DLP (10 mol%) was added every 60 min until total consumption of the starting material or until no evolution could be detected by TLC analysis. The reaction mixture was then cooled to 20 °C and evaporated to dryness under reduced pressure. The residue was purified by silica gel column chromatography to yield the desired compound.

5-Acetamido-8-methyl-4-oxo-1,2,3,4-tetrahydronaphthalen-1-ylpivalate 3.9b



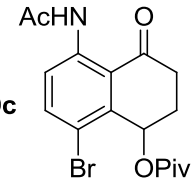
3.9b

$C_{18}H_{23}NO_4$
M= 317.1627 g.mol $^{-1}$

Following general procedure VIII, the reaction was carried out using xanthate (**3.7b**) (310 mg, 1 mmol, 1 equiv.) with vinyl pivalate (0.37 mL, 2.5 mmol, 2.5 equiv.) in refluxing dichloroethane and needed 1.2 equiv. of DLP (478 mg) to go to completion (7 h). The residue after evaporation of the solvent was purified by silica gel column chromatography with a gradient of ethyl acetate in petroleum ether (5 : 95 to 15 : 85) to afford (**3.9b**) (152 mg, 48%) as a white solid.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz)	12.03 (bs, 1H), 8.68 (d, *J* = 8.7 Hz, 1H), 7.41 (d, *J* = 8.7 Hz, 1H), 6.18 (m, 1H), 2.92 (m, 1H), 2.61 (m, 1H), 2.37 (m, 1H), 2.31 (s, 3H), 2.23 (s + m, 4H), 1.18 (s, 9H).
^{13}C-NMR (δ, ppm) ($CDCl_3$, 100 MHz)	203.1 (CO), 177.8 (CO), 169.6 (CO), 140.0 (Cq), 138.3 (Cq), 137.9 (CH), 131.5 (Cq), 121.1 (CH), 118.2 (Cq), 66.2 (CH_2), 39.2 (Cq), 34.4 (CH_2), 27.2 ($3CH_3$), 26.7 (CH_2), 25.7 (CH_3), 18.6 (CH_3).
IR (ν, cm^{-1})	3228, 1730, 1703, 1655, 1541, 1256, 1143.
HRMS (EI)	Calcd. for $C_{18}H_{23}NO_4$: 317.1627Found: 317.1627
Mp	104–105 °C

5-Acetamido-8-bromo-4-oxo-1,2,3,4-tetrahydronaphthalen-1-yl pivalate 3.9c



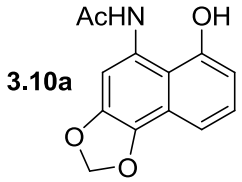
3.9c

$C_{17}H_{20}BrNO_4$
M= 381.0576 g.mol $^{-1}$

Following general procedure VIII, the reaction was carried out using xanthate (**3.7c**) (375 mg, 1 mmol, 1 equiv.) and vinyl pivalate (0.37 mL, 2.5 mmol, 2.5 equiv.) in refluxing dichloroethane and needed 1.1 equiv. of DLP (438 mg) to go to completion (6 h). After evaporation of the solvent, the residue was purified by silica gel column chromatography with dichloromethane to afford (**3.9c**) (195 mg, 51%) as a white solid.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz)	12.08 (bs, 1H), 8.74 (d, *J* = 9.1 Hz, 1H), 7.77 (d, *J* = 9.2 Hz, 1H), 6.27 (m, 1H), 2.94 (m, 1H), 2.65 (m, 1H), 2.43 (m, 1H), 2.31 (s + m, 4H), 1.21 (s, 9H).
^{13}C-NMR (δ, ppm) ($CDCl_3$, 100 MHz)	202.3 (CO), 177.3 (CO), 169.7 (CO), 141.3 (Cq), 139.7 (CH), 139.2 (Cq), 122.6 (CH), 119.6 (Cq), 118.1 (Cq), 68.9 (CH_2), 39.2 (Cq), 34.3 (CH_2), 27.2 ($3CH_3$), 26.3 (CH_2), 25.7 (CH_3).
IR (ν, cm^{-1})	3227, 1734, 1709, 1660, 1541, 1507, 1138, 1037.
HRMS (EI)	Calcd. for $C_{17}H_{20}BrNO_4$: 381.0576Found: 381.0595
Mp	202–203 °C

N-(6-Hydroxynaphtho[2,1-d][1,3]dioxol-5-yl)acetamide **3.10a**

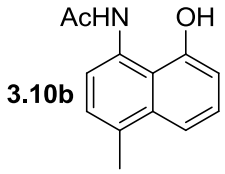


$C_{13}H_{11}NO_4$
M= 245.0688 $g.mol^{-1}$

Following general procedure III, the reaction was carried out using (**3.9a**) (70 mg, 0.2 mmol, 1 equiv.) and PTSA (105 mg, 0.6 mmol, 3 equiv.) in refluxing toluene (3 mL) and needed 3 hours to go to completion. The residue was washed with pentane to afford a white solid (**3.10a**) (34.3 mg, 70%).

^{1}H-NMR (δ, ppm) (DMSO-D_6, 400 MHz)	11.3 (bs, 2H), 8.26 (s, 1H), 7.27 (m, 1H), 7.13 (d, *J* = 8.3 Hz, 1H), 6.74 (d, *J* = 7.5 Hz, 1H), 6.14 (s, 2H), 2.12 (s, 3H).
^{13}C-NMR (δ, ppm) (DMSO-D_6, 100 MHz)	167.0 (CO), 154.6 (Cq), 142.2 (CH), 136.0 (Cq), 131.1 (Cq), 127.2 (CH), 121.2 (CH), 11.1 (Cq), 110.4 (Cq), 108.1 (CH), 101.3 (CH_2), 100.1 (Cq), 25.1 (CH_3).
IR (ν, cm^{-1})	2918, 1550, 1264.
HRMS (EI)	Calcd. for $C_{13}H_{11}NO_4$: 245.0688 Found: 245.0688
Mp	189–190 °C

N-(8-Hydroxy-4-methylnaphthalen-1-yl)acetamide 3.10b

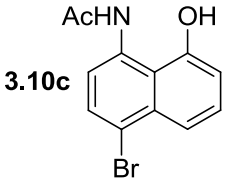


$C_{13}H_{13}NO_2$
M= 215.0946 g.mol $^{-1}$

Following general procedure III, the reaction was carried out using (**3.9b**) (64 mg, 0.2 mmol, 1 equiv.) and PTSA (105 mg, 0.6 mmol, 3 equiv.) in refluxing toluene (3 mL) and needed 3 hours to go to completion. The product was recrystallised from dichloromethane to afford a pinkish solid (**3.10b**) (32 mg, 74%).

^{1}H-NMR (δ, ppm) (Acetone-D_6, 400 MHz)	10.93 (bs, 1H), 10.09 (bs, 1H), 8.43 (d, *J* = 7.9 Hz, 1H), 7.42 (dd, *J* = 1.0 Hz, *J* = 8.5 Hz, 1H), 7.25 (m, 1H), 7.16 (d, *J* = 7.9 Hz, 1H), 6.91 (dd, *J* = 7.6 Hz, *J* = 1.0 Hz, 1H), 2.46 (s, 3H), 2.05 (s, 3H).
^{13}C-NMR (δ, ppm) (Acetone-D_6, 100 MHz)	168.2 (CO), 154.4 (Cq), 136.3 (Cq), 135.5 (Cq), 129.1 (Cq), 127.9 (CH), 126.8 (CH), 117.7 (CH), 116.3 (Cq), 115.6 (CH), 111.2 (CH), 25.6 (CH_3), 20.0 (CH_3).
IR (ν, cm^{-1})	3733, 2359, 1542.
HRMS (EI)	Calcd. for $C_{13}H_{13}NO_2$: 215.0946Found: 215.0947
Mp	143–145 °C

N-(4-Bromo-8-hydroxynaphthalen-1-yl)acetamide 3.10c



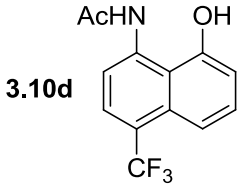
$C_{12}H_{10}BrNO_2$
M= 278.9895 g.mol $^{-1}$

Following general procedure III, the reaction was carried out using (**3.9c**) (77 mg, 0.2 mmol, 1 equiv.) and PTSA (105 mg, 0.6 mmol, 3 equiv.) in refluxing toluene (3 mL) and needed 3 hours to go to completion. The product was washed with dichloromethane to afford a greyish solid (**3.10c**) (40.2 mg, 72%).

^{1}H-NMR (δ, ppm) (Acetone-D_6, 400 MHz)	11.01 (bs, 1H), 10.38 (bs, 1H), 8.45 (d, *J* = 8.5 Hz, 1H), 7.64 (m, 2H), 7.34 (m, 1H), 6.97 (dd, *J* = 0.6 Hz, 7.6 Hz, 1H), 2.05 (s, 3H).

^{13}C-NMR (δ, ppm) (Acetone-D_6, 100 MHz)	168.5 (CO), 154.5 (Cq), 137.5 (Cq), 135.0 (Cq), 131.4 (CH), 128.5 (CH), 120.6 (CH), 117.4 (Cq), 116.1 (Cq), 116.0 (CH), 112.3 (CH), 25.6 (CH_3).
IR (ν, cm^{-1})	2360, 1542, 1258.
HRMS (EI)	Calcd. for $C_{12}H_{10}BrNO_2$: 278.9895 Found: 278.9899
Mp	149–150 °C

N-(8-Hydroxy-4-(trifluoromethyl)naphthalen-1-yl)acetamide **3.10d**



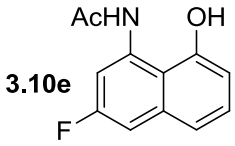
3.10d

$C_{13}H_{10}F_3NO_2$
M= 269.0664 $g.mol^{-1}$

Following general procedure III, the reaction was carried out using (**3.9d**) (74 mg, 0.2 mmol, 1 equiv.) and PTSA (105 mg, 0.6 mmol, 3 equiv.) in refluxing toluene (3 mL) and needed 3 hours to go to completion. The product was washed with pentane to afford a light pinkish solid (**3.10d**) (40 mg, 74%).

^{1}H-NMR (δ, ppm) (Acetone-D_6, 400 MHz)	11.22 (bs, 1H), 10.42 (bs, 1H), 8.59 (d, *J* = 8.5 Hz, 1H), 7.71 (d, *J* = 8.5 Hz, 1H), 7.51 (m, 1H), 7.35 (m, 1H), 6.97 (d, *J* = 7.6 Hz, 1H), 1.89 (s, 3H).
^{13}C-NMR (δ, ppm) (Acetone-D_6, 100 MHz)	168.9 (CO), 154.7 (Cq), 141.5 (Cq), 133.0 (Cq), 129.0 (CH), 127.1 (q, *J* = 6 Hz, CH), 126.1 (q, *J* = 272 Hz, CF_3), 120.0 (q, *J* = 30 Hz, Cq), 117.3 (q, *J* = 3 Hz, CH), 116.3 (Cq), 113.2 (CH), 112.2 (CH), 25.7 (CH_3).
IR (ν, cm^{-1})	2592, 1549, 1291.
HRMS (EI)	Calcd. for $C_{13}H_{10}F_3NO_2$: 269.0664 Calcd. for $C_{13}H_{10}F_3NO_2$ - H_2O = 251.0558 Found: 251.0555
Mp	177–178 °C

N-(3-Fluoro-8-hydroxynaphthalen-1-yl)acetamide 3.10e



$C_{12}H_{10}FNO_2$
M= 219.0696 g.mol $^{-1}$

Following general procedure III, the reaction was carried out using (**3.9e**) (65 mg, 0.2 mmol, 1 equiv.) and PTSA (105 mg, 0.6 mmol, 3 equiv.) in refluxing toluene (3 mL) and needed 3 hours to go to completion. After evaporation of the solvent, the residue was purified by silica gel column chromatography with a gradient of ethyl acetate in toluene (10 : 90 to 30 : 70) to afford (**3.10e**) as a pinkish solid (26.5 mg, 60%).

^{1}H-NMR (δ, ppm) (DMSO-D_6, 400 MHz): 11.49 (bs, 1H), 11.31 (bs, 1H), 8.37 (dd, *J* = 12.2 Hz, *J* = 2.7 Hz, 1H), 7.32 (m, 1H), 7.31 (m, 1H), 7.27 (dd, *J* = 9.6 Hz, *J* = 2.7 Hz, 1H), 6.86 (m, 1H), 2.18 (s, 3H).

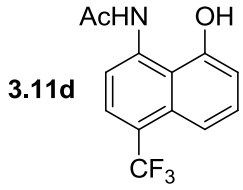
^{13}C-NMR (δ, ppm) (DMSO-D_6, 100 MHz): 168.2 (CO), 159.5 (d, *J* = 240 Hz, Cq), 153.6 (Cq), 138.0 (d, *J* = 13 Hz, Cq), 136.5 (d, *J* = 11 Hz, Cq), 127.5 (CH), 119.5 (d, *J* = 5 Hz, CH), 112.1 (Cq), 109.6 (d, *J* = 2 Hz, CH), 105.3 (d, *J* = 21 Hz, CH), 103.6 (d, *J* = 31 Hz, CH), 25.3 (s, CH_3).

IR (ν, cm^{-1}): 2500, 1545, 1360.

HRMS (EI): Calcd. for $C_{12}H_{10}FNO_2$: 219.0696
Calcd. for $C_{12}H_{10}FNO_2$ - H_2O = 201.0590 Found: 201.0589

Mp: 193–194 °C

N-(4-(Trifluoromethyl)naphthalen-1-yl)acetamide 3.11d



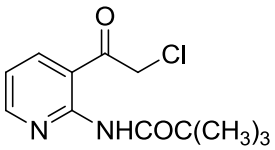
$C_{13}H_{10}F_3NO$
M= 253.0714 g.mol $^{-1}$

To a solution of (**3.10d**) (74 mg, 0.2 mmol, 1 equiv.) in methanol (3 mL), $NaBH_4$ (12 mg, 0.3 mmol, 1.5 equiv.) was added and the mixture was stirred for 1 hour at rt. A saturated solution of NH_4Cl was added to the reaction and the mixture was extracted with ethyl acetate. The organic layer was washed twice with H_2O, brine, dried with $MgSO_4$ and then filtered. The solvent was removed under reduced pressure to provide a brown residue. Following general procedure III, the second step was carried out with the residue and PTSA (105 mg, 0.6 mmol, 3 equiv.) in

refluxing Ac_2O–AcOH (1 mL/2 mL) and needed 3 hours to go to completion. The product was washed with pentane to afford a light pink solid (**3.11d**) (36 mg, 71%).

^{1}H-NMR (δ, ppm) (Acetone-D_6, 400 MHz)	9.20 (bs, 1H), 8.09 (d, *J* = 8.2 Hz, 1H), 7.93 (m, 2H), 7.70 (d, *J* = 8.1 Hz, 1H), 7.48 (ddd, *J* = 8.2 Hz, *J* = 6.9 Hz, *J* = 1.3 Hz, 1H), 7.41 (ddd, *J* = 8.1 Hz, *J* = 6.9 Hz, *J* = 1.3 Hz, 1H), 2.57 (s, 3H).
^{13}C-NMR (δ, ppm) (Acetone-D_6, 100 MHz)	169.8 (CO), 139.3 (Cq), 130.4 (Cq), 128.7 (CH), 128.0 (Cq), 127.4 (CH), 126.1 (q, *J* = 6 Hz, CH), 125.0 (q, *J* = 2 Hz, CH), 126.0 (q, *J* = 272 Hz, CF_3), 123.6 (CH), 122.1 (q, *J* = 30 Hz, Cq), 118 (CH), 24.2 (CH_3).
IR (ν, cm^{-1})	3464, 1714, 1558, 1338, 1125.
HRMS (EI)	Calcd. for $C_{13}H_{10}F_3NO_2$: 253.0714 Found: 253.0713
Mp	185–186 °C

N-(3-(2-chloroacetyl)pyridin-2-yl)pivalamide **3.18**



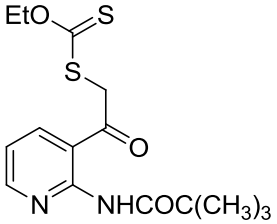
$C_{12}H_{15}ClN_2O_2$
M= 254.0822g.mol $^{-1}$

To a solution of 2-PivNH pyridine (2.82 g, 16 mmol) in THF (40 mL) was added n-BuLi dropwise at -78 ºC. After addition, the mixture was warmed to 0 ºC in an ice bath and stirred for 2 h. The mixture was cooled to -78 ºC, and a solution of 2-chloro-*N*-methoxy-*N*-methylacetamide (2.6 g, 19 mmol) in THF (10 mL) was added. The mixture was stirred for 10 min and warmed to rt for 5h. The reaction was quenched by addition of NH_4Cl (30 mL), extracted with Et_2O (30 mL), washed by NaHCO3, brine, and dried over Na_2SO_4. The crude material was purified by by silica gel column chromatography with a gradient of ethyl acetate in petroleum ether (30:70 to 40:60) to afford **3.18** (1.22 g, 30 %) as a white solid.

^{1}H-NMR(δ, ppm) ($CDCl_3$, 400 MHz)	10.54 (bs, 1H), 8.63 (dd, *J*= 1.8 Hz, J= 4.7 Hz, 1H), 8.09 (dd, *J*= 1.8 Hz, *J*= 7.9 Hz, 1H), 7.13 (dd, *J*= 4.8 Hz, *J*= 7.9 Hz, 1H), 4.71 (s, 2H), 1.39 (bs, 9H).
^{13}C-NMR(δ, ppm)	193.4 (CO), 176.8 (CO), 153.2 (CH), 151.0 (Cq), 138.9 (CH),

($CDCl_3$, 100 MHz)	118.6 (CH), 117.8(Cq), 46.6 (CH_2), 40.3 (Cq), 27.3($3CH_3$).
IR (ν, cm^{-1})	3438, 2967, 1699, 1492, 1435, 1264.
HRMS (EI)	Calcd. for $C_{12}H_{15}ClN_2O_2$: 254.0822Found: 254.0828
Mp	97-98°C

O-ethyl S-2-oxo-2-(2-pivalamidopyridin-3-yl)ethyl carbonodithioate **3.19**

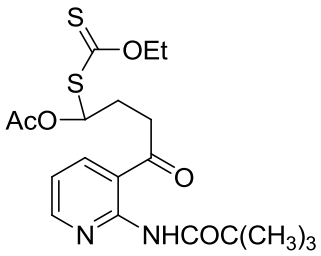


$C_{15}H_{20}N_2O_3S_2$
M= 340.0915g.mol $^{-1}$

Following general procedure VII, the reaction was carried out with a solution of compound (**3.18**) (1.02 g, 4 mmol, 1 equiv.) in acetone (8 mL) and potassium ethyl xanthate (705 mg, 4.4 mmol, 1.1 equiv.) at rt for 1 h. The crude material was purified byflash chromatography (ethyl acetate : petroleum ether 4:6) to afford xanthate **3.19**as a yellow oil (1.30 g, 95%).

^{1}H-NMR(δ, ppm) ($CDCl_3$, 400 MHz)	10.68 (bs, 1H), 8.61 (dd, *J*= 1.8 Hz, *J*= 4.8 Hz, 1H), 8.28 (dd, *J*= 1.8 Hz, *J*= 7.9 Hz, 1H), 7.13 (dd, *J*= 4.8 Hz, *J*= 7.9 Hz, 1H), 4.63 (s, 2H), 4.61 (q, *J*= 7.1 Hz, 2H), 1.38 (t, *J*= 7.1 Hz, 3H), 1.39 (bs, 9H).
^{13}C-NMR(δ, ppm) ($CDCl_3$, 100 MHz)	213.1(CS), 194.8 (CO), 176.8 (CO), 153.4 (CH), 151.2 (Cq), 138.9 (CH), 119.0 (Cq), 118.4 (CH), 71.1 (CH_2), 44.3 (CH_2), 40.5 (Cq), 27.4($3CH_3$), 13.8 (CH_3).
IR (ν, cm^{-1})	3440, 2967, 1701, 1589, 1491, 1434, 1227, 1149, 1053.
HRMS (EI)	Calcd. for $C_{15}H_{20}N_2O_3S_2$: 340.0915 Found: 340.0921

1-(ethoxycarbonothioylthio)-4-oxo-4-(2-pivalamidopyridin-3-yl)butyl acetate 3.20

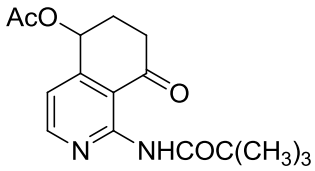


$C_{19}H_{26}N_2O_5S_2$
M= 426.1283g.mol $^{-1}$

A magnetically stirred solution of xanthate **3.19** (1.10 g, 3 mmol) and vinyl acetate (0.7 mL, 7.5 mmol) in ethyl acetate(3 mL) was refluxed for 15 min under a nitrogen flow. Dilauroyl peroxide (DLP) (5 mol %) was then added and additional DLP (2.5 mol %) was added every 60 min until total consumption of the starting material or until no evolution could be detected by TLC analysis. The reaction mixture was then cooled to 20°C and evaporated to dryness under reduced pressure.After evaporation, the residue was purified by silica gel column chromatography with a gradient of ethyl acetate in petroleum ether (30:70 to 50:50) to afford **3.20**as a yellow oil (1.10 g, 87 %).

^{1}H-NMR(δ, ppm) ($CDCl_3$, 400 MHz)	11.23 (bs, 1H), 8.65 (dd, *J*= 1.8 Hz, *J*= 4.8 Hz, 1H), 8.16 (dd, *J*= 1.8 Hz, *J*= 7.9 Hz, 1H), 7.11 (dd, *J*= 4.8 Hz, *J*= 7.9 Hz, 1H), 6.73 (m, 1H), 4.64 (s, 2H), 3.17 (m, 2H), 2.41 (m, 2H), 2.08 (bs, 3H), 1.41 (t, *J*= 7.1 Hz, 3H), 1.36 (bs, 9H).
^{13}C-NMR(δ, ppm) ($CDCl_3$, 100 MHz)	209.8 (CS), 200.5 (CO), 176.7 (CO), 169.4 (CO), 153.5 (CH), 151.7 (Cq), 138.8 (CH), 118.2 (Cq), 118.1 (CH), 80.2 (CH), 70.4 (CH_2), 40.6 (Cq), 35.2 (CH), 28.5 (CH_2), 27.4 ($3CH_3$), 20.9 (CH_3), 13.7 (CH_3).
IR (ν, cm^{-1})	3440, 3285, 2966, 1752, 1706, 1663, 1590, 1575, 1492, 1447, 1434, 1227.
HRMS (EI)	Calcd. for $C_{19}H_{26}N_2O_5S_2$: 426.1283 Calcd. for M – Xa : $C_{16}H_{21}N_2O_4^{\bullet}$: 305.1501Found:305.1489

8-oxo-1-pivalamido-5,6,7,8-tetrahydroisoquinolin-5-yl acetate **3.21**



$C_{16}H_{20}N_2O_4$
M= 304.1423g.mol $^{-1}$

Compound **3.20** (430 mg, 1 mol) was dissolved in 10 mL ethyl acetate. The mixture was refluxed for 15 min under a nitrogen flow. Dilauroyl peroxide (DLP) (20 mol %, mg) was then added and additional DLP (20 mol %) was added every 60 min until total consumption of the starting material or until no evolution could be detected by TLC analysis. The reaction mixture was then cooled to 20°C and evaporated to dryness under reduced pressure. After evaporation, the residue was purified by silica gel column chromatography with a gradient of ethyl acetate in petroleum ether (30:70 to 50:50) to afford **3.21** as a yellow oil (136 mg, 45 %).

^{1}H-NMR(δ, ppm) ($CDCl_3$, 400 MHz)	12.0 (bs, 1H), 8.65 (dd, *J*= 2.4 Hz, J= 5.0 Hz, 1H), 7.05 (dd, *J*= 0.7 Hz, *J*= 5.0 Hz, 1H), 6.04 (dd, *J*= 4.0 Hz, *J*= 7.9 Hz, 1H), 2.95 (m, 2H), 2.77 (m, 1H), 2.42 (m,1H), 2.24 (m, 1H), 2.17 (bs, 3H), 1.37 (bs, 9H).
^{13}C-NMR(δ, ppm) ($CDCl_3$, 100 MHz)	199.9 (CO), 176.7 (CO), 170.0 (CO), 154.4 (CH), 153.0 (Cq), 151.8 (Cq), 116.4 (CH), 112.5 (Cq), 68.3 (CH), 40.8 (Cq), 35.8 (CH_2), 27.7 (CH_2), 27.5 ($3CH_3$), 21.0 (CH_3).
IR (ν, cm^{-1})	3504, 3272, 2967, 1749, 1714, 1660, 1596, 1455, 1370, 1226, 1140.
HRMS (EI)	Calcd. for $C_{16}H_{20}N_2O_4$: 304.1423 Found: 304.1418

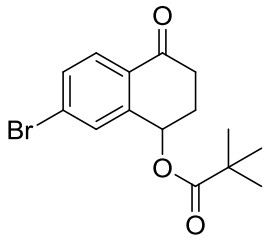
Chapter 4

General procedure I for the radical addition and cyclisation

A magnetically stirred solution of xanthate (1 mmol) and olefin (2.5 mmol) in dichloroethane(1 mL) was refluxed for 15 min under a nitrogen flow. Dilauroyl peroxide (DLP) (5 mol %) was then added and additional DLP (2.5 mol %) was added every 60 min until total consumption of the starting material or until no evolution could be detected by TLC analysis. The reaction mixture was then cooled to 20°C and evaporated to dryness under reduced pressure.

The residue was then dissolved in 10 mL ethyl acetate or chlorobenzene. The mixture was refluxed for 15 min under a nitrogen flow. Dilauroyl peroxide (DLP) (20 mol %) was then added and additional DLP (20 mol %) was added every 60 min until total consumption of the starting material or until no evolution could be detected by TLC analysis.The reaction mixture was then cooled to 20°C and evaporated to dryness under reduced pressure. The residue was purified by silica gel column chromatography to yield the desired compounds.

7-bromo-4-oxo-1,2,3,4-tetrahydronaphthalen-1-yl pivalate **7a**



$C_{15}H_{17}BrO_3$
M= 324.0361g.mol $^{-1}$

Following general procedure **I**, the reaction was carried out using xanthate **5a**(600 mg, 3 mmol, 1 eq) and vinyl pivalate (0.7 mL, 7.5 mmol, 2.5 eq) in refluxing ethyl acetate (3 mL) needed 10 mol % DLP to the completion. After the reaction mixture was evaporate to dryness under reduced pressure. The residue was dissolved ethyl acetate (30 mL), heated to reflux and needed 1 eq DLP to the completion. After evaporation, the residue was purified by silica gel column chromatography with a gradient of ethyl acetate in petroleum ether (2.5:97.5 to 15:85) to afford **7a** (634 mg, 65 %) as a white solid.

^{1}H-NMR(δ, ppm) ($CDCl_3$, 400 MHz): 7.91 (d, *J*= 8.2 Hz, 1H), 7.58 (m, 2H), 6.04 (dd, *J*= 3.8 Hz, *J*= 7.1 Hz, 1H), 2.88 (m, 1H), 2.68 (m, 1H), 2.39 (m, 1H), 2.25 (m, 1H), 1.24 (bs, 9H).

^{13}C-NMR(δ, ppm) ($CDCl_3$, 100 MHz): 195.9 (CO), 177.7 (CO), 142.8 (Cq), 132.3 (CH), 130.8 (CH), 130.6 (Cq), 129.1 (Cq), 129.0 (CH), 68.3 (CH), 39.0 (Cq), 34.6

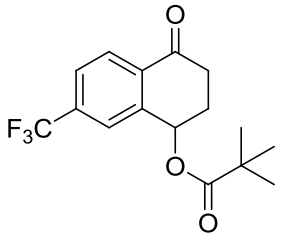
(CH$_2$), 28.5 (CH$_2$), 27.1 (3CH$_3$).

IR (ν, cm^{-1}) 2961, 1733, 1697, 1588, 1476, 1276, 1143.

HRMS (EI) Calcd. for $C_{15}H_{17}BrO_3$: 324.0361 Found: 324.0370

Mp 94-95°C

4-oxo-7-(trifluoromethyl)-1,2,3,4-tetrahydronaphthalen-1-yl pivalate 7e



$C_{16}H_{17}F_3O_3$
M= 314.1130g.mol $^{-1}$

Following general procedure **I**, the reaction was carried out using xanthate **5e**(565 mg, 3 mmol, 1 eq) and vinyl pivalate (0.7 mL, 7.5 mmol, 2.5 eq) in refluxing ethyl acetate (1 mL) needed 10 mol % DLP to the completion. After the reaction mixture was evaporate to dryness under reduced pressure. The residue was dissolved ethyl acetate (30 mL), heated to reflux and needed 1 eq DLP to the completion. After evaporation, the residue was purified by silica gel column chromatography with a gradient of ethyl acetate in petroleum ether (2.5:97.5 to 10:90) to afford **7e** (423 mg, 45 %) as a white solid.

^{1}H-NMR(δ, ppm) (CDCl$_3$, 400 MHz) 8.13 (d,*J*= 8.5 Hz, 1H), 7.66 (m, 2H), 6.10 (m, 1H), 2.90 (m, 1H), 2.71 (m, 1H), 2.41 (m, 1H), 2.26 (m, 1H), 1.26 (bs, 9H).

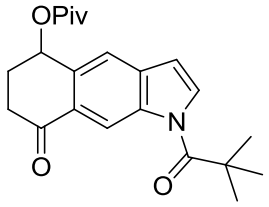
^{13}C-NMR(δ, ppm) (CDCl$_3$, 100 MHz) 195.5 (CO), 177.7 (CO), 142.1 (Cq), 135.1 (q, *J*= 33Hz, Cq), 134.2 (Cq), 128.0 (CH), 125.5 (q, *J*= 3.5 Hz, CH), 124 (q, *J*= 3.8 Hz, CH), 123.4 (q, *J*= 272 Hz, CF$_3$), 68.3 (CH), 39.0 (Cq), 34.7 (CH$_2$), 28.4 (CH$_2$), 27.0 (3CH$_3$).

IR (ν, cm^{-1}) 1735, 1702, 1326, 1175.

HRMS (EI) Calcd. for $C_{16}H_{17}F_3O_3$: 314.1130Found: 314.1138

Mp 54-55°C

8-oxo-1-pivaloyl-5,6,7,8-tetrahydro-1H-benzo[f]indol-5-yl pivalate **7g**

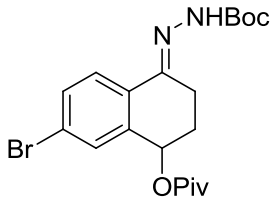


$C_{22}H_{27}NO_4$
M= 369.1940g.mol $^{-1}$

Following general procedure **I**, the reaction was carried out using xanthate **5g**(690 mg, 3 mmol, 1 eq) and vinyl pivalate (0.7 mL, 7.5 mmol, 2.5 eq) in refluxing ethyl acetate (1 mL) needed 10 mol % DLP to the completion. After the reaction mixture was evaporate to dryness under reduced pressure. The residue was dissolved ethyl acetate (30 mL), heated to reflux and needed 1 eq DLP to the completion. After evaporation, the residue was purified by silica gel column chromatography with a gradient of ethyl acetate in petroleum ether (2.5:97.5 to 10:90) to afford **7e** (443 mg, 40 %) as a white solid.

^{1}H-NMR(δ, ppm) ($CDCl_3$, 400 MHz)	8.05 (m, 1H), 7.74 (m, 1H), 7.62 (m, 1H), 6.63 (m, 1H), 6.43 (m, 1H), 2.98 (m, 1H), 2.68 (m, 1H), 2.43 (m, 2H), 1.56 (bs, 9H), 1.05 (bs, 9H).
^{13}C-NMR(δ, ppm) ($CDCl_3$, 100 MHz)	197.9 (CO), 180.1 (CO), 177.5 (CO), 135.9 (Cq), 133.6 (Cq), 130.1 (Cq), 130.0 (CH), 129.3 (Cq), 123.1 (CH), 121.6 (CH), 107.1 (CH), 65.8 (CH), 42.1 (Cq), 38.8 (Cq), 32.6 (CH_2), 29.0 ($3CH_3$), 27.5 (CH_2), 27.1($3CH_3$).
IR (ν, cm^{-1})	2976, 1725, 1683, 1479, 1296, 1274, 1152.
HRMS (EI)	Calcd. for $C_{22}H_{27}NO_4$: 369.1940Found: 369.1936
Mp	159-160°C

(E)-tert-butyl 2-(6-bromo-4-(pivaloyloxy)-3,4-dihydronaphthalen-1(2H)-ylidene) hydrazinecarboxylate 4.1a

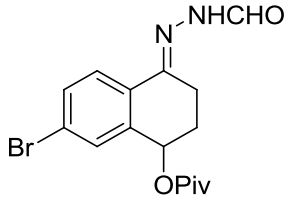


$C_{20}H_{27}BrN_2O_4$
M= 438.1154 g.mol $^{-1}$

To a solution of compound **5a** (325 mg, 1 mmol) in the mixture of methanol/ acetic acid (1 mL/0.25 mL) was added NH_2NHBoc(145 mg, 1.1 mmol). The reaction was refluxed until the complete consumption of the starting material, the solvent was evaporated. The residue was diluted in ethyl acetate, extracted with aqueous $NaHCO_3$solution and dried ($MgSO_4$). The ethyl acetate was removed under reduced pressure. The residue was washed with pentane to afford the product hydrazoneas a white solid (419 mg, 95%).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz)	8.11 (d, *J*= 8.0 Hz, 1H), 7.90 (bs, 1H), 7.48 (bs + d, *J*= 8.0 Hz, 2H), 5.88 (m, 1H), 2.63 (m, 2H), 2.14 (m, 2H), 1.57 (bs, 9H), 1.20 (bs, 9H).
^{13}C-NMR (δ, ppm) ($CDCl_3$, 100 MHz)	177.7 (CO), 144.6 (CN), 137.6 (Cq), 132.0 (CH), 131.2 (Cq), 130.6 (CH), 127.0 (CH), 123.5 (Cq), 81.7 (Cq), 68.4 (CH), 39.0 (Cq), 28.3 ($3CH_3$), 27.1 ($3CH_3$), 26.3 (CH_2), 20.3 (CH_2).
IR (ν, cm^{-1})	2980, 1757, 1731, 1609, 1478, 1369, 1277, 1227.
HRMS (EI)	Calcd. for $C_{20}H_{27}BrN_2O_4$: 438.1154Found: 438.1149
Mp	160-161^{o}C

(E)-7-bromo-4-(2-formylhydrazono)-1,2,3,4-tetrahydronaphthalen-1-yl pivalate 4.3



$C_{16}H_{19}BrN_2O_3$
M= 366.0579g.mol $^{-1}$

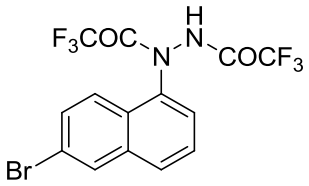
To a solution of compound **5a** (325 mg, 1 mmol) in the mixture of methanol/ acetic acid (1 mL/0.5 mL) was added NH_2NHCHO (66 mg, 1.1 mmol). The reaction was stired overnight at room temperature until the complete consumption of the starting material, the solvent was evaporated. The residue was diluted in ethyl acetate, extracted with aqueous $NaHCO_3$solution and dried ($MgSO_4$). The ethyl acetate was removed under reduced pressure. The residue was washed with methanol to afford the product hydrazoneas a white solid (311 mg, 85%).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz)	10.38 (bs, *J*= 9.8 Hz, 1H), 7.99 (d, *J*= 8.5 Hz, 1H), 7.49 (m, 2H), 5.82 (m, 1H), 2.68 (m, 2H), 2.09 (m, 2H), 1.13 (bs, 9H).
^{13}C-NMR (δ, ppm) ($CDCl_3$, 100 MHz)	177.7 (CO), 166.8 (CO), 147.7 (CN), 138.5 (Cq), 132.0 (CH), 130.9 (CH), 130.7 (Cq), 126.6 (CH), 124.1 (Cq), 68.3 (CH), 39.0 (Cq), 27.1 ($3CH_3$), 26.5 (CH_2), 21.1 (CH_2).
HRMS (EI)	Calcd. for C16H19BrN_2O3: 366.0579Found: 366.0579

General procedure II

To a solution of compound **5** (1 mmol) in the mixture ofmethanol/ acetic acid (1 mL/0.25 mL) was added NH_2NHBoc (145 mg, 1.1 mmol). The reaction was refluxeduntil the complete consumption of the starting material,the solvent was evaporated. The residue wasdiluted in ethyl acetate, extracted with aqueous $NaHCO_3$solution and dried ($MgSO_4$).The ethyl acetate was removed under reduced pressure. The crude product was dissolved in TFAA/ TFA (1.5 mL/ 0.5 mL). The mixture was heated to 70^{o}C for 7 hours, the mixture was cooled to room temperature. In case of no precipitation, the solvent was evaporated under a nitrogen flow, the residue was diluted in ethyl acetate, extracted with aqueous $NaHCO_3$solution and dried ($MgSO_4$). Ethyl acetate was removed under reduced pressure.The residue was purified by silica gel column chromatography to afford the desired compound.

Compound 4.2a

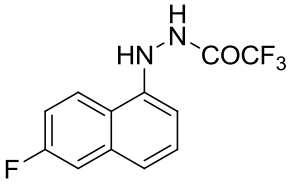


$C_{14}H_7BrF_6N_2O_2$
M= 427.9595g.mol $^{-1}$

Following general procedure **II,** the reaction was carried out with a solution of **7a** (325 mg, 1 mmol) and NH_2NHBoc in the refluxing mixture of MeOH/ AcOH (1 mL/ 0.25 mL). After work up and evaporation, the crude product was dissolved in TFAA/ TFA (1.5 mL/ 0.5 mL). The mixture was heated at 70^{o}C. After heating for 7 hours, the resulting precipitate was filter and washed with dichloromethane several times. The product**4.2a** was obtained as white solids (275 mg, 65%).

^{1}H-NMR(δ, ppm) (DMSO, 400 MHz)	11.0 (bs, 0.4 H), 10.5 (bs, 0.6 H), 7.99-8.25 (m, 3H), 7.74-7.88 (m, 2H), 7.65 (m, 1H).
^{13}C-NMR(δ, ppm) (DMSO, 100 MHz) rotamers	155.6 (q, *J*= 37 Hz, CO), 155.3 (q, *J*= 37 Hz, CO), 135.1, 134.9, 133.5, 130.7, 130.7, 130.2, 129.6, 128.6, 128.2, 126.9, 126.4, 124.2, 120.6, 120.3, 115.6 (q, *J*= 288 Hz, CF_3), 115.5 (q, *J*= 288 Hz, CF_3), 115.2 (q, *J*= 288 Hz, CF_3), 115.0 (q, *J*= 288 Hz, CF_3).
IR (ν, cm^{-1})	2360, 2342, 1776, 1716, 1545, 1171, 1114.
HRMS (EI)	Calcd. for $C_{14}H_7BrF_6N_2O_2$: 427.9595Found: 427.9592
Mp	212-214°C

2,2,2-trifluoro-N'-(6-fluoronaphthalen-1-yl)acetohydrazide **4.2b**

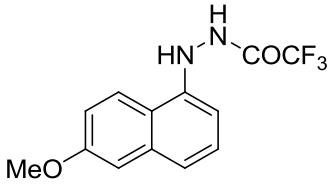


$C_{12}H_8F_4N_2O$
M= 274.0729 g.mol $^{-1}$

Following general procedure **II,** the reaction was carried out with a solution of **7b**(265 mg, 1mmol)and NH_2NHBoc in the refluxing mixture of MeOH/ AcOH (1 mL/ 0.25 mL). After work up and evaporation, the crude product was dissolved in TFAA/ TFA (1.5 mL/ 0.5 mL). The mixture was heated to 70^{o}C in 7 hours. After work up and evaporation, the residue was purified by silica gel column chromatography with a gradient of ethyl acetate in petroleum ether (10:90 to 30:70) to afford the product **4.2b**as a white solid (156mg, 57%).

^{1}H-NMR(δ, ppm) ($CDCl_3$, 400 MHz)	8.24 (bs, 1H), 7.77 (dd, *J*= 9.1 Hz, *J*= 5.3 Hz, 1H), 7.38 (m, 3H), 7.15 (m, 1H), 6.81 (d, *J*= 6.4 Hz, 1H).
^{13}C-NMR(δ, ppm) ($CDCl_3$, 100 MHz)	160.8 (d, *J*= 245 Hz, Cq), 157.3 (q, *J*= 37 Hz, CO-CF_3), 140.6 (Cq), 135.3 (d, *J*= 9 Hz, Cq), 126.9 (CH), 122.5 (d, *J*= 9 Hz, CH), 122.3 (d, *J*= 5 Hz, CH), 120.5 (Cq), 115.9 (d, *J*= 25 Hz, CH), 115.8 (q, *J*= 288 Hz, CF_3), 117 (d, *J*= 20 Hz, CH), 107.1 (CH).
IR (ν, cm^{-1})	3435, 2970, 1750, 1541, 1161.
HRMS (EI)	Calcd. for $C_{12}H_8F_4N_2O$: 272.0573Found: 272.0573
Mp	105-106°C

2,2,2-trifluoro-N'-(6-methoxynaphthalen-1-yl)acetohydrazide **4.2c**

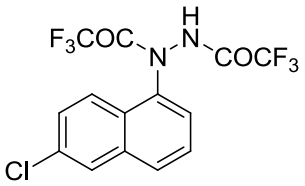


$C_{13}H_{11}F_3N_2O_2$
M= 284.0773g.mol $^{-1}$

Following general procedure **II,** the reaction was carried out with a solution of **7c** (280 mg, 1 mmol) and NH_2NHBoc in the refluxing mixture of MeOH/ AcOH (1 mL/ 0.25 mL). After work up and evaporation, the crude product was dissolved in TFAA/ TFA (1.5 mL/ 0.5 mL). The mixture was heated to 70^{o}C in 7 hours. After work up and evaporation, the residue was purified by silica gel column chromatography with a gradient of ethyl acetate in petroleum ether (10:90 to 30:70) to afford the product **4.2c**as a white solid (170 mg, 60%).

^{1}H-NMR(δ, ppm) ($CDCl_3$, 400 MHz)	8.36 (bs, 1H), 7.62 (d, *J*= 9.2 Hz, 1H), 7.37 (m, 1H), 7.27 (t, *J*= 7.9 Hz, 1H), 7.10 (d, *J*= 2.5 Hz, 1H), 7.04 (dd, *J*= 2.6 Hz, *J*= 9.2 Hz, 1H), 6.67 (d, *J*= 7.4 Hz, 1H), 6.63 (m, 1H).
^{13}C-NMR(δ, ppm) ($CDCl_3$, 100 MHz)	157.8 (Cq), 157.2 (q, *J*= 36 Hz, CO-CF_3), 140.6 (Cq), 135.7 (Cq), 126.4 (CH), 122.0 (CH), 121.6 (CH), 118.8 (Cq), 118.3 (CH), 115.8 (q, *J*= 288 Hz, CF_3), 106.8 (CH), 106.0 (CH), 55.4 (CH_3).
IR (ν, cm^{-1})	3430, 1748, 1544, 1265, 1175.
HRMS (EI)	Calcd. for $C_{13}H_{11}F_3N_2O_2$: 284.0773 Found: 284.0773
Mp	125-126°C

Compound 4.2d

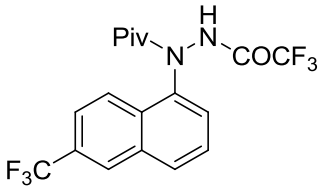


$C_{14}H_7ClF_6N_2O_2$
M= 384.0100 $g.mol^{-1}$

Following general procedure **II,** the reaction was carried out with a solution of **7d** (280 mg, 1 mmol) and NH_2NHBoc in the refluxing mixture of MeOH/ AcOH (1 mL/ 0.25 mL). After work up and evaporation, the crude product was dissolved in TFAA/ TFA (1.5 mL/ 0.5 mL). The mixture was heated at 70°C. After heating for 7 hours, the resulting precipitate was filter and washed with dichloromethane several times. The**4.2d**was obtained as white solids (230mg, 60%).

^{1}H-NMR(δ, ppm) (DMSO, 400 MHz)	13.2-13.6 (bs, 1H), 8.01-8.24 (3H), 7.71-7.87 (3H).
^{13}C-NMR(δ, ppm) (DMSO, 100 MHz) rotamers	155.3 (q, *J*= 37 Hz, CO), 155.1 (q, *J*= 37 Hz, CO), 134.6, 134.5, 133.3, 132.0, 131.6, 130.9, 129.8, 128.7, 128.5, 127.8, 127.3, 127.1, 127.0, 126.8, 126.5, 124.4, 115.6 (q, *J*= 288 Hz, CF_3), 115.5 (q, *J*= 288 Hz, CF_3), 115.3 (q, *J*= 288 Hz, CF_3), 115.2 (q, *J*= 288 Hz, CF_3).
IR (ν, cm^{-1})	3250, 3030, 2360, 1776, 1716, 1705, 1504, 1430, 1211.
HRMS (EI)	Calcd. for $C_{14}H_7ClF_6N_2O_2$: 384.0100Found: 384.0099
Mp	221-222°C

tert-butyl 2-(2,2,2-trifluoroacetyl)-2-(6-(trifluoromethyl)naphthalen-1-yl)hydrazinecarboxylate 4.2e

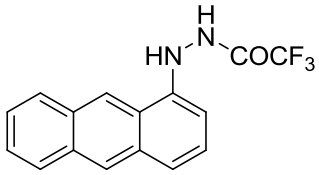


$C_{18}H_{16}F_6N_2O_2$
M= 406.1116g.mol $^{-1}$

Following general procedure **II,** the reaction was carried out with a solution of **7e** (315 mg, 1mmol) and NH_2NHBoc (145 mg, 1.1 mmol) in the refluxing mixture of MeOH/ AcOH (1 mL/ 0.25 mL). After work up and evaporation, the crude product was dissolved in TFAA/ TFA (1.5 mL/ 0.5 mL). The mixture was heated to 80^{o}C in 7 hours. After work up and evaporation, the residue was purified by silica gel column chromatography with a gradient of ethyl acetate in petroleum ether (10:90 to 30:70) to afford the product **4.2e** as a white solid (175 mg, 43%).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz)	8.78 (bs, 1H), 8.25 (m, 1H), 8.15 (m, 1H), 8.06 (d, *J*= 8.5 Hz, 1H), 7.90 (d, *J*= 7.3 Hz, 1H), 7.79 (d, *J*= 8.5 Hz, 1H), 7.63 (t, *J*= 7.3 Hz, 1H), 1.07 (s, 9H).
^{13}C-NMR (δ, ppm) ($CDCl_3$, 100 MHz)	177.7 (CO), 155.4 (q, *J*= 36 Hz, CO-CF_3), 136.7 (Cq), 132.4 (Cq), 130.9 (Cq), 130.4 (CH), 129.1 (CH), 128.0 (q, *J*= 33 Hz, Cq), 125.7 (CH), 125.4 (q, *J*= 4 Hz, CH), 122.9 (q, *J*= 272 Hz, CF_3), 122.8 (CH), 122.6 (q, *J*= 3 Hz, CH), 114.5 (q, *J*= 288 Hz, CF_3), 39.6 (Cq), 27.5 ($3CH_3$).
IR (ν, cm^{-1})	2360, 1766, 1683, 1312, 1175.
HRMS (EI)	Calcd. for $C_{18}H_{16}F_6N_2O_2$: 406.1116Found: 406.1094
Mp	165-167°C

N'-(anthracen-1-yl)-2,2,2-trifluoroacetohydrazide **4.2f**

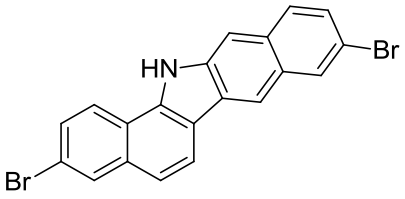


$C_{16}H_{11}F_3N_2O$
M= 304.0823 g.mol $^{-1}$

Following general procedure **II,** the reaction was carried out with a solution of **7f** (295 mg, 1 mmol) and NH_2NHBoc (145 mg, 1.1 mmol) in the refluxing mixture of MeOH/ AcOH (1 mL/ 0.25 mL). After work up and evaporation, the crude product was dissolved in TFAA/ TFA (1.5 mL/ 0.5 mL). The mixture was heated to 70^{o}C in 7 hours. After work up and evaporation, the residue was purified by silica gel column chromatography with a gradient of ethyl acetate in petroleum ether (10:90 to 30:70) to afford the product **4.2f**as a white solid (152 mg, 50%).

^{1}H-NMR(δ, ppm) (CD_3CN, 400 MHz)	9.58 (bs, 1H), 8.73 (d, *J*= 8.0 Hz, 1H), 8.36 (d, *J*= 8.3 Hz, 1H), 7.91 (m, 3H), 7.76 (m, 1H), 7.57 (t, *J*= 8.0 Hz, 1H), 7.29 (s, 1H), 7.06 (d, *J*= 7.6 Hz, 1H).
^{13}C-NMR(δ, ppm) (CD_3CN, 100 MHz)	156.7 (q, *J*= 36 Hz, CO-CF_3), 143.4 (Cq), 132.6 (Cq), 131.9 (Cq), 131.0 (Cq), 129.4 (CH), 127.9 (2CH), 127.8 (CH), 127.4 (CH), 124.1 (CH), 121.2 (Cq), 119.8 (CH), 116.9 (CH), 115.9 (q, *J*= 288 Hz, CF_3), 109.6 (CH).
IR (ν, cm^{-1})	1716, 1159.
HRMS (EI)	Calcd. for $C_{16}H_{11}F_3N_2O$: 304.0823Found: 304.0824
Mp	203-205°C

3,9-dibromo-13H-dibenzo[a,h]carbazole **4.4**

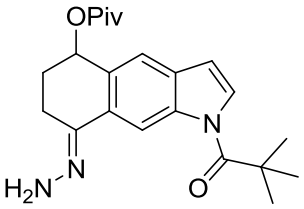


$C_{20}H_{11}Br_2N$
M= 422.9258g.mol $^{-1}$

Following general procedure **II,** the reaction was carried out with a solution of **7a** (325 mg, 1 mmol) and NH_2NHCHO in the refluxing mixture of MeOH/ AcOH (1 mL/ 0.25 mL). After work up and evaporation, the crude product was dissolved in TFAA/ TFA (1.5 mL/ 0.5 mL). The mixture was heated at 70^{o}C. After heating for 7 hours, the resulting precipitate was filter and washed with dichloromethane several times. The product was obtained as a white solid (276mg, 65%).

^{1}H-NMR(δ, ppm) (DMSO, 400 MHz)	13.0 (bs, 1H), 8.68 (d, *J*= 8.8 Hz, 2H), 8.35 (dd, *J*= 3.3 Hz, *J*= 5.3 Hz, 4H), 7.87 (dd, *J*= 2.0 Hz, *J*= 8.8 Hz, 2H), 7.71 (d, *J*= 8.6 Hz, 2H).
^{13}C-NMR(δ, ppm) (DMSO, 100 MHz)	133.8 (2Cq), 132.8 (2Cq), 130.4 (2CH), 128.5 (2CH), 124.1 (2CH), 120.6 (2CH), 120.1 (2Cq), 119.3 (2CH), 118.7 (2Cq), 118.0 (2Cq).
IR (ν, cm^{-1})	3424, 2958, 1550, 1367, 1264, 1069.
HRMS (EI)	Calcd. for $C_{20}H_{11}Br_2N$: 422.9258Found: 422.9267

(E)-*N'*-(5-hydroxy-1-pivaloyl-6,7-dihydro-1H-benzo[f]indol-8(5H)-ylidene)pivalohydrazide



$C_{22}H_{29}N_3O_3$
M= 383.2209g.mol $^{-1}$

To a solution of **5g** (357 mg, 1 mmol) in the mixture of ethanol/ acetic acid (1 mL/ 0.5 mL) was added NH_2NHBoc(145 mg , 1.1 mmol). The reaction was refluxedfor 6 hours,the solvent was evaporated. The residue wasdiluted in ethyl acetate, extracted with aqueous $NaHCO_3$solution and dried ($MgSO_4$).The ethyl acetate was removed under reduced pressure. The residue was purified by silica gel column chromatography with a gradient of ethyl acetate in petroleum ether (5:95 to 10:90) to afford the product hydrazoneas a white solid (230 mg, 60%).

^{1}H-NMR(δ, ppm) ($CDCl_3$, 400 MHz)	8.36 (d, *J*= 8.3 Hz, 1H), 7.62 (m, 2H), 6.61 (d, J= 3.7 Hz, 1H), 6.30 (s, 1H), 2.99 (dd, *J*= 5.0 Hz, *J*= 18.3 Hz, 1H), 2.80 (m, 1H), 2.35 (m, 1H), 2.06 (m, 1H), 1.57 (bs, 9H), 1.43 (s, 1H), 1.10 (bs, 9H).
^{13}C-NMR(δ, ppm) ($CDCl_3$, 100 MHz)	180.4 (CO), 177.6 (CO), 155.6 (Cq), 134.5 (Cq), 132.8 (Cq), 130.5 (Cq), 127.9 (CH), 125.5 (Cq), 122.1 (CH), 121.4 (CH), 107.3 (CH), 66.2 (CH), 42.0 (Cq), 38.8 (Cq), 29.1 ($3CH_3$), 27.2 ($3CH_3$), 26.3 (CH_2), 21.7 (CH_2).
IR (ν, cm^{-1})	3391, 2979, 2935, 1755, 1723, 1479, 1369, 1286, 1224, 1159.
HRMS (EI)	Calcd. for $C_{22}H_{29}N_3O_3$: 383.2209Found: 383.2177
Mp	110-111^{o}C