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Applications of radical reactions for the synthesis of β -amino acids and carbonyl compounds

Xuan Chen

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Applications of radical reactions for the synthesis of β -amino acids and carbonyl compounds

Thèse de doctorat de l'Institut Polytechnique de Paris
préparée à École Polytechnique

École doctorale n°626 Ecole Doctorale de l'Institut Polytechnique de
Paris (ED IP Paris)
Spécialité de doctorat: Chimie

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Abbreviations

Ac	acetyl
AIBN	azobisisobutyronitrile
Ar	aryl
Boc	<i>tert</i> -butyloxycarbonyl
Bu	butyl
<i>t</i> -Bu	<i>tert</i> -butyl
Bn	benzyl
Bz	benzoyl
Cbz	carboxybenzyl
Cat.	catalyst
DCE	1,2-dichloroethane
DCM	dichloromethane
DLP	dilauroyl peroxide
DMF	N, N-dimethylformamide
dppm	bis(diphenylphosphino)methane
DTBP	di- <i>tert</i> -butyl peroxide
EA	ethyl acetate
EP	petroleum ether
Et	ethyl
HMDS	bis(trimethylsilyl)amine
LDA	lithium diisopropylamide
Me	methyl
Ms	methanesulfonyl
NBS	N-bromosuccinimide
NMP	N-methyl-2-pyrrolidone
NPhth	phthalimide
Piv	pivalate
Ph	phenyl
PhCl	chlorobenzene
Pr	propyl
<i>i</i> -Pr	<i>iso</i> -propyl
PTSA	<i>p</i> -toluenesulfonic acid
Py	pyridine
TEA	triethylamine
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TMS	trimethylsilyl
Ts	<i>p</i> -toluenesulfonyl
Xa	<i>O</i> -ethyl xanthate
Stoich.	stoichiometric

DNA	deoxyribonucleic acid
ESR	electron spin resonance
HOMO	highest occupied molecular orbital
IR	infrared
LUMO	lowest unoccupied molecular orbital
NMR	nuclear magnetic resonance
Nu	nucleophile
RNA	ribonucleic acid
SOMO	singly occupied molecular orbital
°C	degree Celsius
eq.	equivalent
Hz	hertz
h	hour
min	minute
M	mole per liter
ppm	parts per million
hν	photochemical irradiation

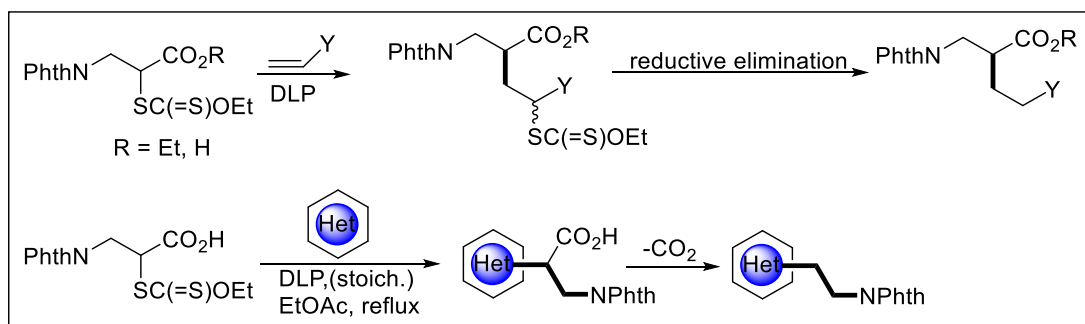
Avant-Propos

Dans cette thèse, nous nous concentrons sur l'application de la chimie des radicaux issus des xanthates pour la synthèse de cétones, d'esters et de dérivés d'acides aminés β^2 . Cette recherche surmonte de nombreux inconvénients associés à l'alkylation des cétones et des esters lors de l'utilisation de méthodes basées sur l'énolate, et complète la dialkylation des cétones insaturées. Le processus de transfert de xanthate offre également une voie convergente vers des acides aminés potentiellement bioactifs. Ces études ont été réalisées sous la direction du Prof. Samir Z. Zard au Laboratoire de Synthèse Organique de l'Ecole Polytechnique. Ce manuscrit comprend quatre chapitres et une partie expérimentale.

Dans le chapitre 1, les aspects généraux de la chimie radicalaire sont brièvement présentés, y compris les propriétés physiques et chimiques des radicaux, les méthodes de génération de radicaux et les types de réactions radicalaires, ainsi que les mécanismes des réactions radicalaires.

Dans le chapitre 2, le mécanisme général et le développement de la désoxygénation de Barton-McCombie sont discutés, suivis de la découverte du transfert dégénératif du xanthate et de ses applications dans la synthèse de divers composés hautement fonctionnalisés ; le groupe fonctionnel pouvant être présent dans le xanthate ou dans l'alcène.

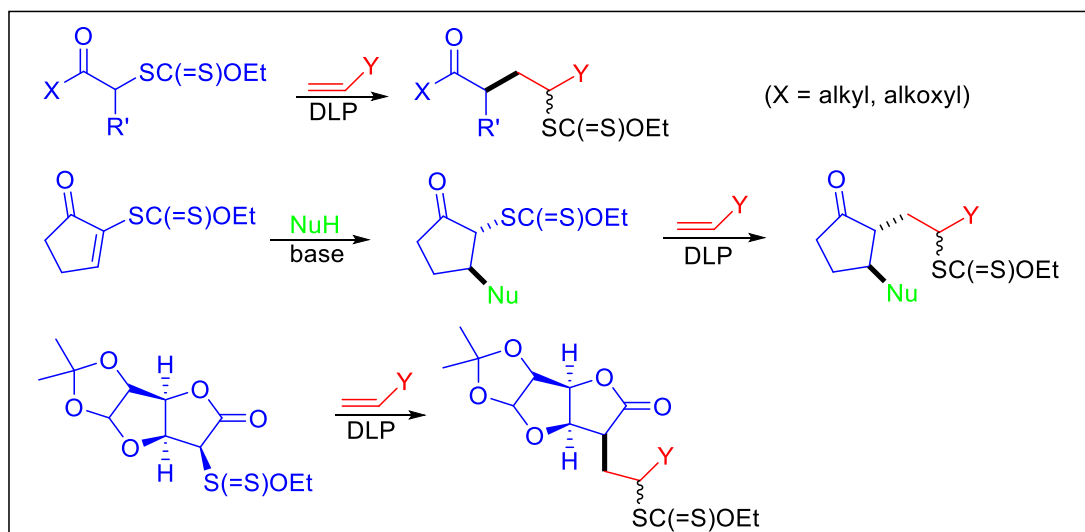
Dans le chapitre 3, nous résumons tout d'abord l'utilité et les stratégies de synthèse vis-à-vis des acides aminés, puis nous décrivons une voie convergente vers les dérivés d'acides aminés β^2 en adoptant le processus de transfert du xanthate. Le xanthate peut porter soit un ester, soit un groupe acide carboxylique libre. Lorsque l' α -xanthyl- β -amino ester est utilisé comme xanthate de départ, presque toutes les réactions ont été effectuées sans solvant et ont fourni les produits d'addition souhaités avec un rendement bon à excellent. Lorsque le xanthate portait un groupe acide libre, l'addition sur des hétérocycles était accompagnée d'une décarboxylation spontanée pour donner des hétéroaryléthylamines N-protégées. Dans certains cas, des produits vinyliques inattendus se sont formés et un mécanisme plausible est discuté.



Une voie convergente vers les acides aminés β^2 et les hétéroaryléthylamines N-protégées

Dans le chapitre 4, nous présentons brièvement les méthodes précédemment décrites pour l'alkylation des cétones, puis passons à nos propres recherches. En remplaçant les énolates et équivalents d'énolates par des radicaux α -cétonyle, de nombreux inconvénients de l'alkylation des cétones tels que la condensation des aldols, le manque de régiosélectivité, la O-alkylation et la polyalkylation peuvent être minimisés. Ensuite, nous nous concentrons sur la dialkylation

des cétones α , β -insaturées. Contrairement aux méthodes ioniques traditionnelles qui doivent utiliser des organocuprates et des halogénures d'alkyle, notre nouvelle méthode intègre à la fois des processus ioniques et radicalaires qui évitent l'utilisation des agents organométalliques et des halogénures d'alkyle. Il est à noter que l'étape d'addition de Michael a été significativement affectée par l'encombrement stérique tandis que l'étape d'addition radicalaire a été peu affectée. Sur la base de cette méthodologie, diverses cyclopentanones dialkylées ont été rapidement synthétisées, y compris des composés polycycliques qui sont couramment présents dans les produits naturels. Enfin, afin de généraliser l'alkylation des composés carbonyles, l' α -alkylation des esters a également été étudiée. Dans la section d'extension de portée, nous testons les ajouts radicaux à différents alcènes fonctionnalisés. Toutes les réactions se sont déroulées sans difficultés et présentent une large tolérance de groupe fonctionnel. Des réactions utilisant des lactones comme substrats ont également été réalisées dans les mêmes conditions et se sont avérées tout aussi efficaces.



Application de xanthate à la synthèse de composés carbonyles

En résumé, nous avons utilisé ce processus de transfert de xanthate comme un outil puissant pour synthétiser de nombreux cétones, esters et dérivés d'acides aminés utiles. Cette méthode sans métal présente des conditions de réaction douces, une excellente compatibilité des groupes fonctionnels et une bonne diversité de substrats qui, selon nous, seront particulièrement utiles dans la fonctionnalisation à un stade avancé des produits naturels et pharmaceutiques.

Dans la section expérimentale, les synthèses des 79 produits dans les deux chapitres précédents sont décrites ainsi que leur caractérisation par RMN ^1H , RMN ^{13}C , IR, HRMS et points de fusion (lorsque cela est possible).

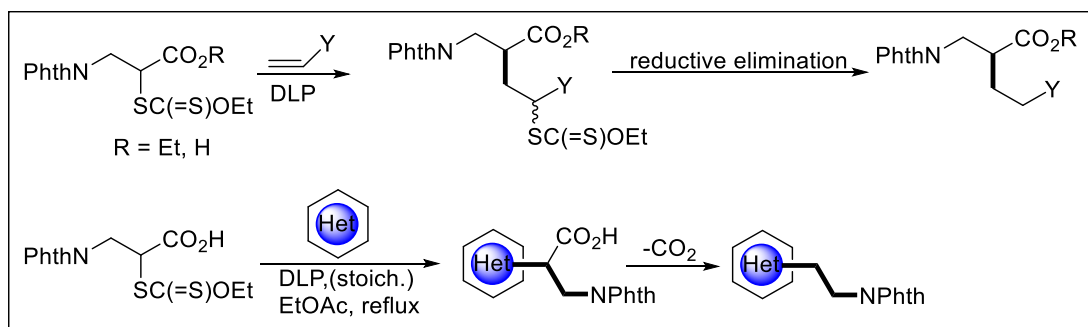
General introduction

In this thesis, we focus on the application of xanthate based radical chemistry for the synthesis of ketones, esters and β^2 -amino acids derivatives. This research overcomes many drawbacks associated with the alkylation of ketones and esters when using enolate based methods, and complements the dialkylation of unsaturated ketones. The xanthate transfer process also offers a convergent route to potential bioactive amino acids. These studies were accomplished under the guidance of Prof. Samir Z. Zard in the Laboratoire de Synthèse Organique in Ecole Polytechnique. This manuscript consists of four chapters and an experimental part.

In chapter 1, general aspects of radical chemistry are briefly presented, including physical and chemical properties of radicals, methods for radical generation and types of radical reactions, as well as mechanisms of radical reactions.

In chapter 2, the general mechanism and development of the Barton-McCombie deoxygenation is discussed, followed by the discovery of degenerative transfer of the xanthate and the applications in the synthesis of various highly functionalized compounds. Functional group can be present in the xanthate or in the alkene.

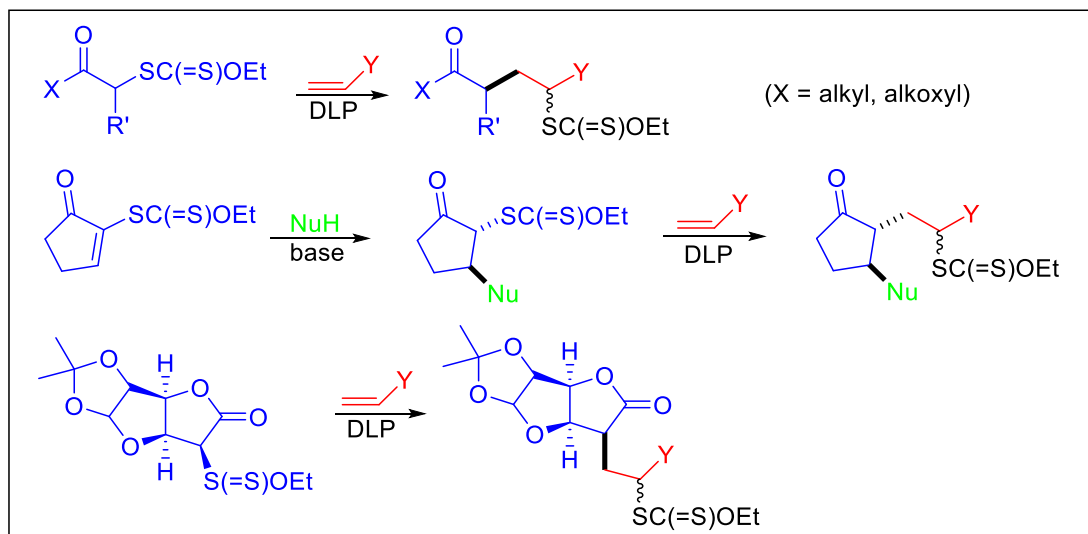
In chapter 3, we firstly summarize the utility and synthetic strategies towards amino acids, then we describe a convergent route to β^2 -amino acids derivatives by adopting the xanthate transfer process. The xanthate can bear either an ester or a free carboxylic acid group. When the α -xanthyl- β -amino ester is used as the starting xanthate, almost all the reactions were performed neat and provided the desired adducts in good to excellent yield. When the xanthate was bearing a free acid group, the addition to hetero-rings was accompanied by spontaneous decarboxylation to afford the N-protected heteroarylethylamines. In some cases, unexpected vinyl products were formed and a plausible mechanism is discussed.



A convergent route to β^2 -amino acids and N-protected heteroarylethylamines

In chapter 4, we briefly introduce the previously reported methods for the alkylation of ketones, and then move on to our own research. By replacing enolates and enolate equivalents with α -ketonyl radicals, many disadvantages of alkylation of ketones such as aldol condensation, lack of regioselectivity, *O*-alkylation and polyalkylation can be minimized. Then we focus on the dialkylation of α , β -unsaturated ketones. In contrast with traditional ionic methods which have to use organocopper and alkyl halides, our new method incorporates both ionic and radical processes which avoids the use of aforementioned organometallic

agents and alkyl halides. It is noteworthy that the Michael addition step was significantly affected by steric hindrance while the radical addition step was little affected. Based on this methodology, various dialkylated cyclopentanones were rapidly synthesized including ring-fused compounds which are commonly present in natural products. Finally, in order to generalize the alkylation of carbonyl compounds, α -alkylation of esters was also investigated. In the scope extension section, we test the radical additions to different functionalized alkenes. All reactions proceeded smoothly and show a broad functional group tolerance. Reactions using lactones as substrates were also performed with the same conditions and were shown to be equally efficient.



Application of xanthate to synthesis of carbonyl compounds

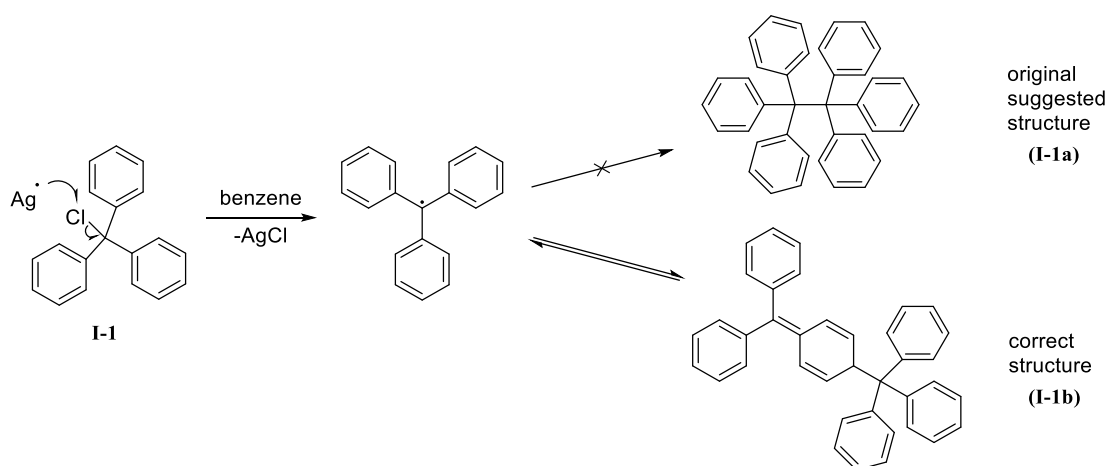
In summary, we used this xanthate transfer process as a powerful tool to synthesize many useful ketones, esters and amino acid derivatives. This metal-free method features mild reaction conditions, excellent functional group compatibility and good substrate scope which we anticipate will be especially useful in the late-stage functionalization of natural products and drugs.

In the experimental section, the syntheses of the 79 products in previous two chapters are described as well as their characterization by ^1H NMR, ^{13}C NMR, IR, HRMS, and melting points, when applicable.

Chapter 1 Introduction to radical chemistry

1.1 Introduction

This section will give an overview of radical properties with respect to both physical and chemical properties in order to understand the processes of radical transformation. A free radical is defined as a specie that contains one unpaired electron. It has been 120 years since the first persistent radical (triphenylmethyl radical) was described in 1900 by Moses Gomberg.¹ Although the original suggested structure (**I-1a**) of triphenylmethyl dimer was proved to be incorrect by NMR in 1970,² it aroused more and more attentions in the context of radical transformations. It is now very clear that steric hindrance of triphenylmethyl radical prevents the formation of structure (**I-1a**). Therefore, the unpaired electron has to delocalize from the tertiary carbon to the benzene carbon and then interact with the original radical to form the dimer (**I-1b**) (Scheme 1.1).



Scheme 1.1 Formation of triphenylmethyl radical and dimerization

1.2 Physical properties of radicals

1.2.1 The geometry: planar or pyramidal?

Carbocations have generally planar structures and unstabilized carbanions have pyramidal structures because of the different molecular orbital hybridizations. Radicals have two extreme options. In the first, the carbon center connects three other atoms in a plane and the unpaired electron occupies an empty p orbital. In the second, the unpaired electron is in an sp^3 orbital. In this case, the structure would be pyramidal. ESR spectra,³ gas-phase infrared spectroscopy,⁴ and complementary matrix isolation studies⁵⁻⁶ indicate that the methyl radical is planar, that is a π radical; the methyl must therefore be sp^2 hybridized with the unpaired electron in a p orbital. The geometry and energy level diagram is depicted below (Figure 1.1).

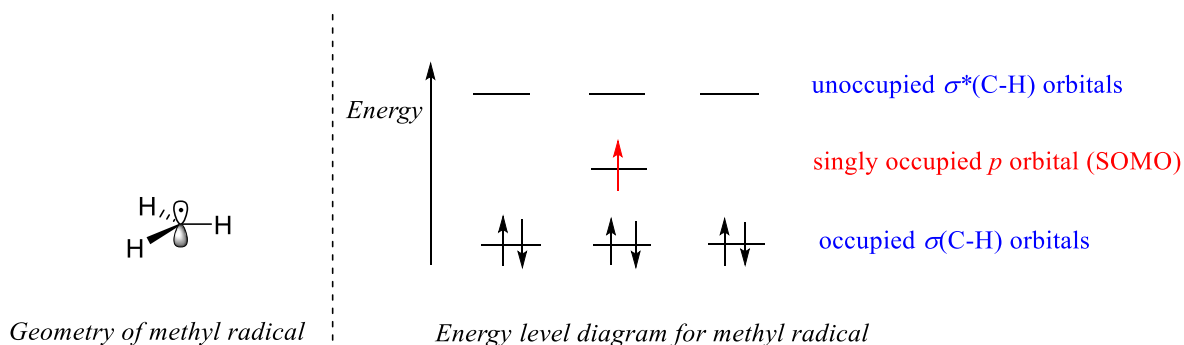


Figure 1.1 Geometry and energy level diagram of methyl radical

Since the barrier of inversion is very small, simple alkyl radicals tend to be slightly pyramidal. The more hindered substituents attached to the radical carbon, the more pyramidal the radical is (*ethyl* < *i-propyl* < *t-butyl*). Note that the degree of pyramidalization of the *t-butyl* radical is approximately 40% that of a perfect tetrahedron, and it has a barrier to inversion on the order of 1 kcal/mol.⁷ There is another situation when the radical carbon is connected to very electronegative atoms (e.g., CF_3). In this case, the radical will prefer a pyramidal shape,⁸ i.e. increasing the electronegativity increases the deviation from planarity.⁹



Figure 1.2 Geometry of substituted alkyl radicals¹⁰

1.2.2 Radical stability

The bond dissociation energy can give a guide to the ease of which kind of radicals can form and also indirectly show their stability (**Table 1.1**).¹¹ A conclusion can be made: the order of stability of radicals is tertiary > secondary > primary, and benzyl radicals, allyl radicals are more stable than alkyl radicals. These observations can be explained by π -delocalization and hyperconjugation.¹² Furthermore, alkyl radicals (even tertiary radicals) are less stable than those radicals which are adjacent to carbonyl or ether groups, or radicals centered on a carbonyl carbon atom.

Table 1.1 Dissociation energy of various C-H bonds

C-H bonds	Dissociation energy, kJ mol^{-1}	C-H bonds	Dissociation energy, kJ mol^{-1}
$\text{CH}_3\text{-H}$ (methyl)	439	$\text{HC}\equiv\text{C-H}$ (alkynyl)	544
$\text{EtOCH}(\text{Me})\text{-H}$	385	$\text{H}_2\text{C}=\text{CH-H}$ (vinyl)	431

MeCH ₂ -H (primary)	423	MeCOCH ₂ -H	385
Me ₂ CH-H (secondary)	410	H ₂ C=CH ₂ CH ₂ -H (allyl)	364
RC(=O)-H (acyl)	364	Me ₃ C-H (tertiary)	397
PhCH ₂ -H (benzyl)	372	Ph-H (phenyl)	464

(i) Radical stabilized by electron-withdrawing groups

The unpaired electron usually occupies a p orbital (SOMO orbital), while electron-withdrawing groups like carbonyl and nitrile have a low-lying empty π^* orbital. By combining the two orbitals (p and π^* orbital), two new orbitals are generated according to *Molecular Orbital Theory*. Now, the unpaired electron occupies the new lower-energy SOMO, which therefore lowers the total energy of the molecule. The unpaired electron decreases in energy and is so-called electrophilic in character (**Figure 1.3**).

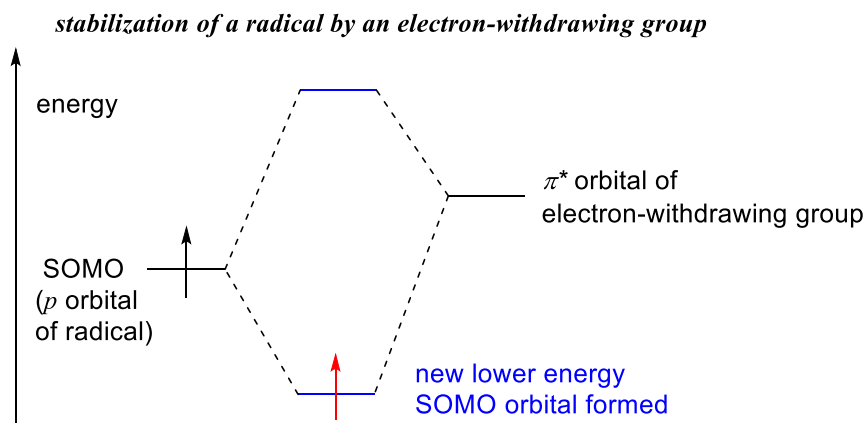


Figure 1.3 Radical stabilized by electron-withdrawing groups

(ii) Radical stabilized by electron-donating groups

Similarly, when combining the relatively high-energy and fully occupied n orbitals of an electron-donating group (taking an alkoxy group as an example) with an occupied p orbital of a radical (radical SOMO orbital), again, two new molecular orbitals are formed. Two paired electrons will fill the newly formed lower-energy orbital and one electron will occupy the newly formed SOMO orbital, which will have a higher energy than the old SOMO. Although the single electron now occupies a higher-energy SOMO orbital, the other paired electrons occupy a lower-energy orbital which has a net effect of lowering the overall energy (**Figure 1.4**).

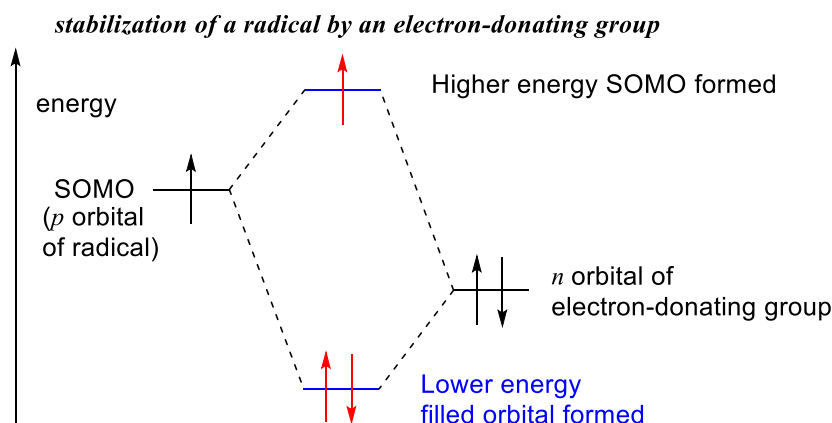


Figure 1.4 Radical stabilized by electron-donating groups

(iii) Radical kinetically stabilized by stereochemistry

Electronic effects and steric hindrance also play a crucial role in the kinetic stability of radicals. The observation that both phenyl and *t*-butyl substituted phenoxy radicals **1** are persistent, which means the steric effects probably dominate. Some crowded alkyl radicals like **2-4** do not dimerize. Thus, while steric effects do not thermodynamically stabilize a radical, they can modify considerably its kinetic stability. (Figure 1.5).¹³

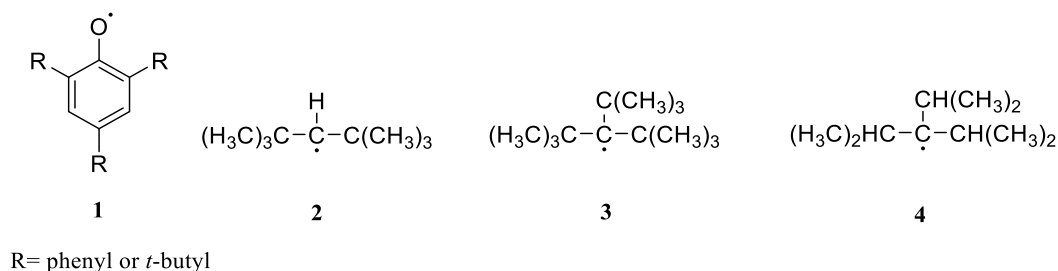


Figure 1.5 Radical stabilized by steric hinderance

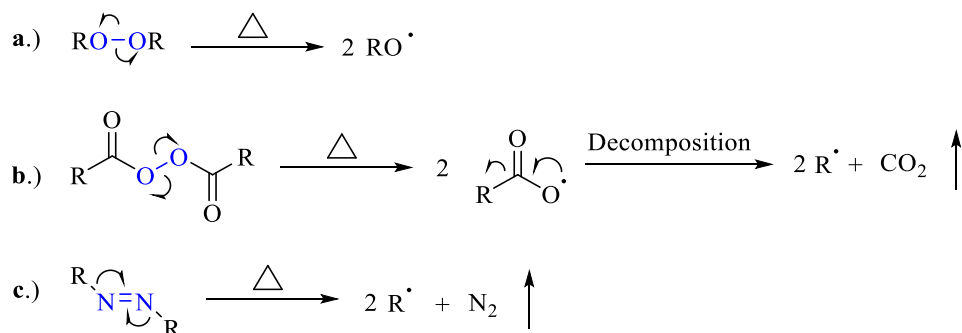
1.3 Chemical properties of radicals

Free radicals arise from the homolytic cleavage of a chemical bond so that each part keeps one electron. Generally speaking, the energy to sever a chemical bond can be supplied by two methods: thermally and photochemically.

1.3.1 Thermal cleavage

Heating organic molecules at a high enough temperature in the gas phase can produce free radicals. Organic peroxides and aliphatic azo compounds are frequently used sources to generate radicals in a by thermal decomposition. Two radicals can be formed by the cleavage of an O-O bond of an organic peroxide (eq **a**. in Scheme 1.2). For diacyl peroxides, the radicals formed will decarboxylate and give alkyl radicals (eq **b**. in Scheme 1.2). Cleavage of two C-N

bonds on an azo compound will release one molecule nitrogen and afford two alkyl radicals (eq c. in **Scheme 1.2**).



Scheme 1.2 Formation of radicals by thermal cleavage of chemical bond

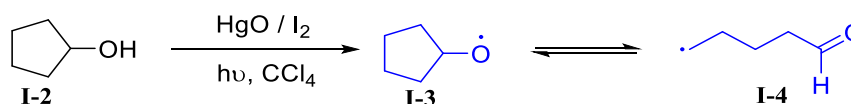
1.3.2 Photochemical cleavage

The energy of visible light energy ranges from 167–293 kJ/mol and the energy of ultraviolet light is approximately 586 kJ/mol. The energies of some covalent single bonds are also known and are of the same order of magnitude (**Table 1.2**).¹⁴⁻¹⁶ Treatment these chemical bonds with visible or UV light will homolytically cleave the covalent bonds when the light has an energy of the same order of magnitude of the covalent bond.

Table 1.2 Energies of some covalent single bonds

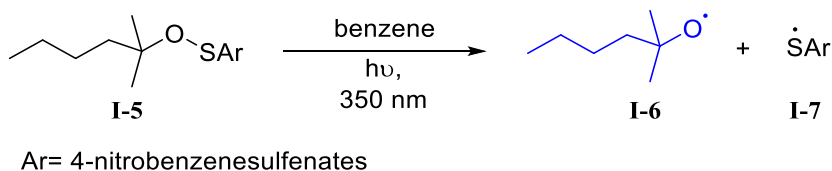
Bond type	Energy (kJ/mol)	Corresponding wavelength (nm)
C-H	397	301
C-O	368	325
C-C	347	345
C-S	255	470
C-Br	275	436
O-O	159	755
Cl-Cl	243	495

In 1992, Courtneidge reported the photo-induced generation of alkoxy radicals upon the irradiation of cyclopentanol in the presence of mercuric oxide and iodine (**Scheme 1.3**).¹⁷

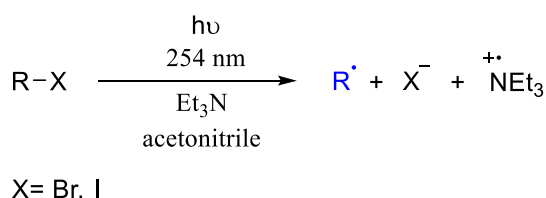


Scheme 1.3 Formation of alkoxy radicals by photolysis

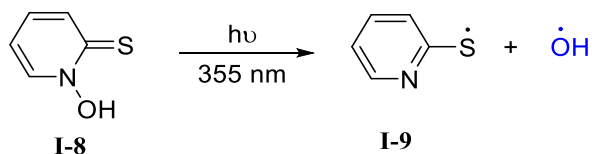
Another efficient and selective approach to generate alkoxy radicals by homolytic dissociation of O-S bond was developed by Pasto and co-workers in 1994. (**Scheme 1.4**).¹⁸

**Scheme 1.4** Photochemical cleavage of O-S bond to form alkyl radicals

In 1994, the Cossy group reported the generation of alkyl radicals by irradiating alkyl halides at 254 nm in the presence of triethylamine (**Scheme 1.5**).¹⁹

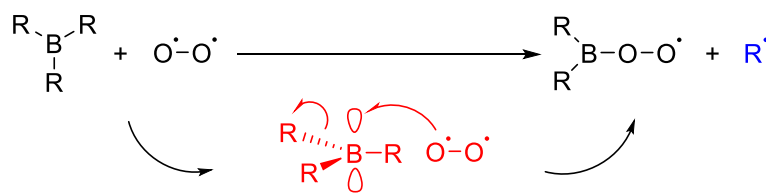
**Scheme 1.5** homolytic cleavage of C-X bond

The hydroxyl radical (HO•) is a widely used oxygen centered reactive intermediate in both biological and environmental processes. Homolysis of N-hydroxypyridin-2-thione (**I-8**) was achieved with a laser flash (Nd:YAG laser, nominal pulse width =10 ns) in acetonitrile, which afforded the hydroxyl radical and the pyrithiyl radical (**I-9**) (**Scheme 1.6**).²⁰

**Scheme 1.6** Hydroxyl radical generated by laser flash

1.3.3 Radicals arising from organoboranes

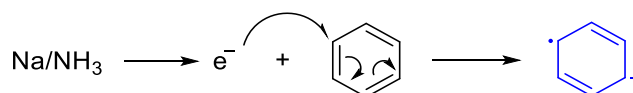
The so-called S_H2 reaction (second-order homolytic displacement) is a substitution of an alkyl group of a trialkyl borane with triplet diradical oxygen. In this process, the oxygen enters the unoccupied *p* orbital of the trigonal borane while displacing one of the alkyl radicals. (**Scheme 1.7**).²¹



Scheme 1.7 Borane as a source of radicals

1.3.4 Radicals generated by single electron transfer process (SET)

Alkali metals such as sodium, lithium or potassium when dissolved in liquid ammonia can serve as reducing reagents in the Birch reduction. In fact, sodium and liquid ammonia exist as the electride salt form ($[\text{Na}(\text{NH}_3)_x]^+ \text{e}^-$), which means the single electron is solvated and standing by to add onto the aromatic ring to give the corresponding radical anion (**Scheme 1.8**).



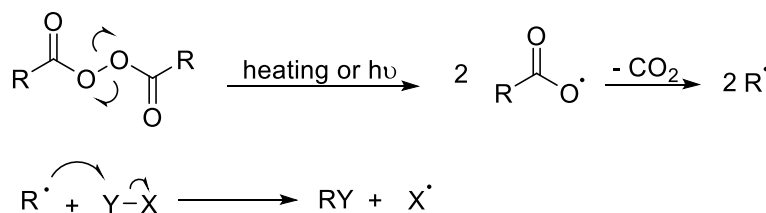
Scheme 1.8 Radical generation by single electron transfer process

1.4 Radical reactions

1.4.1 Radical chain reactions

The radical chain process involves three steps: *initiation*, *propagation* and *termination*.

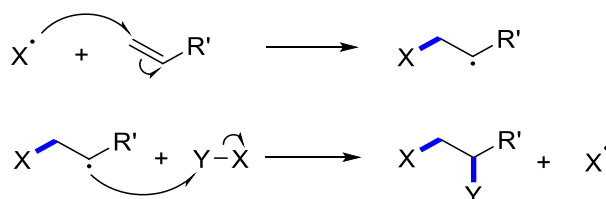
(i) *Initiation*: Organic peroxides or other azo compounds can act as initiators and can be thermally or photochemically cleaved to form two radicals. This is followed by an interaction with one of the starting materials to generate a new radical for the further transformation (**Scheme 1.9**).



Scheme 1.9 Initiation of chain reaction

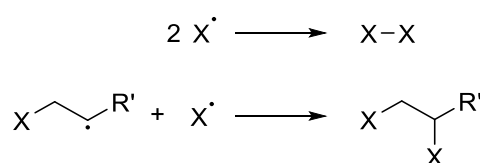
(ii) *Propagation*: in this step, the radical $\text{X}\cdot$ which arises from starting material Y-X will be trapped by an unsaturated bond, for example an alkene, which in turn generates a new carbon-centered radical. This newly formed radical reacts with Y-X to form the final addition product and regenerate $\text{X}\cdot$, and thus propagate the chain. (**Scheme 1.10**) In principle, only one molecule

of initiator is necessary (actually, sub-stoichiometric quantities, about 10 mol% are needed) for the reaction to reach completion.



Scheme 1.10 Propagation of chain reaction

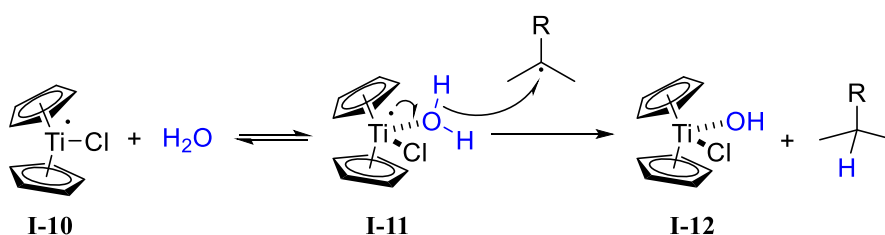
(iii) *Termination*: When two free radicals react with each other, a stable and non-reactive adduct is formed. Although this process decreases the overall energy, it rarely happens because of the low concentration of radical species. Nevertheless, these termination reactions stop the chain and more initiator has to be added (**Scheme 1.11**).



Scheme 1.11 Termination of chain reaction

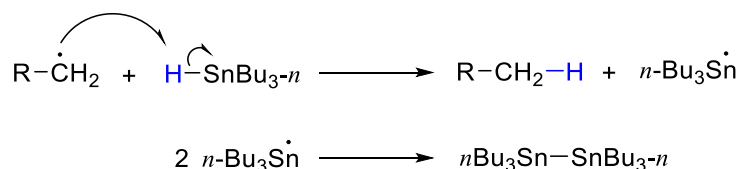
1.4.2 Hydrogen abstraction

The process of abstraction involves a radical reacting with another molecule to abstract a hydrogen atom, or the hydrogen atom is transferred in an intramolecular process. An example of this process is the abstraction of a hydrogen atom from water, mediated by Ti^{III} complexes (**I-10**) (**Scheme 1.12**).²²



Scheme 1.12 Water acts as hydrogen source

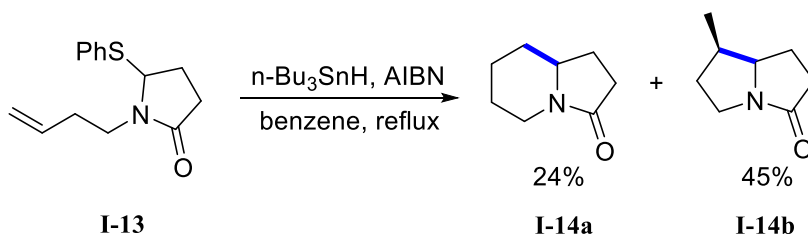
In a radical chain polymerization reaction, there can be hundreds or thousands of propagation steps between initiation and termination steps. However, for the synthesis of small molecules far fewer propagation steps are used and often employ tributyltin hydride to reduce the carbon-centered radical by an atom-transfer reaction. In this process, the alkyl radical can abstract a hydrogen from $n\text{-Bu}_3\text{SnH}$ to provide alkane and a new radical $n\text{-Bu}_3\text{Sn}\cdot$. Tin radicals react with each other tin radical to give $(n\text{-Bu}_3\text{Sn})_2$, which constitutes one of the possible termination steps (**Scheme 1.13**).



Scheme 1.13 Tributyltin hydride as hydrogen source

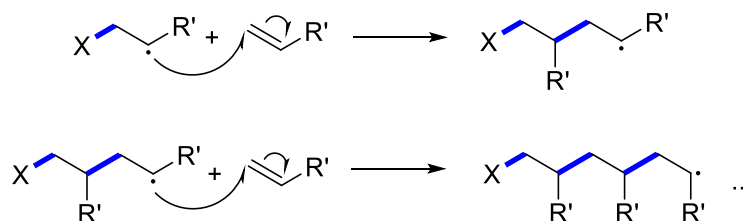
1.4.3 Addition to unsaturated bonds

Addition to alkenes and alkynes can be intra- or intermolecular. The initially formed radical can be trapped by an internal double bond to produce a cyclic product. In the formation of bicyclic rings reaction, the ratio of six-membered ring product **I-14a** and five-membered ring product **I-14b** is approximately 1:2 (Scheme 1.14). This means even if a six-membered ring is more stable, the formation of a five-membered ring is faster. The product distribution depends on the length of the chain connecting the radical and olefinic centers.²³



Scheme 1.14 Radical addition to form cyclic compounds

The propagation in a radical chain reaction we mentioned above involves a radical addition to a double bond. If the newly formed radical adds to another alkene molecule, a dimer is formed, and this second radical can add to the third molecule of alkene, and so on, until the chain process terminated by other methods. This is the mechanism of free radical polymerization (Scheme 1.15).

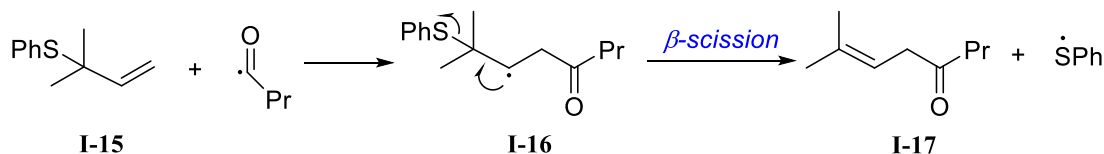


Scheme 1.15 Polymerization of alkene

1.4.4 Fragmentation

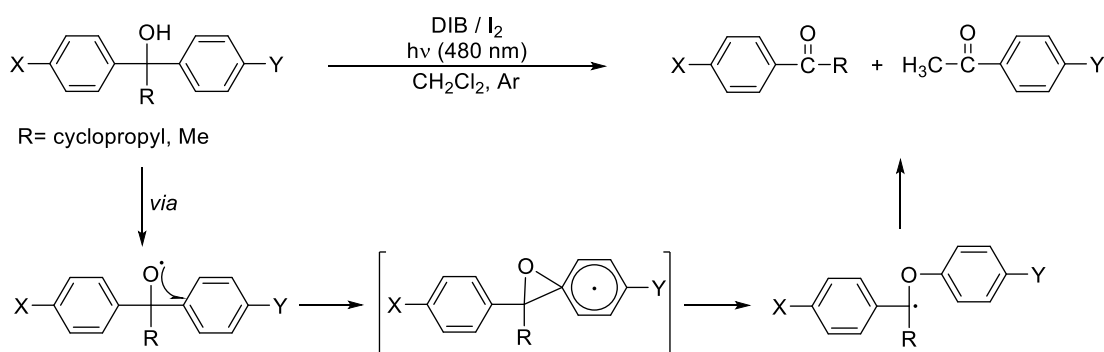
Fragmentation of radicals can generate a new radical and a new molecule. For example, the reaction of a butanoyl radical with α, α -dimethylallyl phenyl sulfides (**I-15**) provides the radical

adduct **I-16**, which undergoes a β -elimination to afford a thiyl radical and 7-methyloct-6-en-4-one **I-17**. This kind of fragmentation is referred to as β -scission (**Scheme 1.16**).²⁴

Scheme 1.16 β -scission of radical

1.4.5 Rearrangement

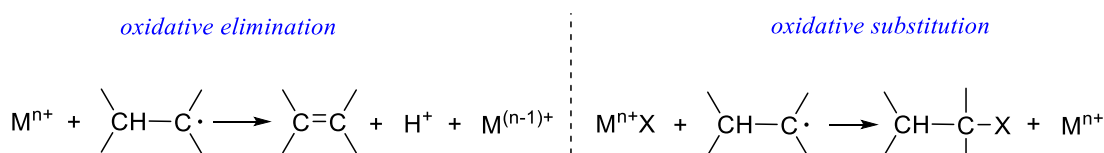
Radical mediated 1,2-rearrangements are much less common than the nucleophilic type rearrangements, but they do occur in a two-step sequence. The neophyl rearrangement for example is a free radical mediated 1,2- migration of an aryl group and the rearrangement occurs via a 1-oxaspiro [2,5] octadienyl radical (**Scheme 1.17**). The substituent on the ring is crucial to this rearrangement's rate constant: electron-withdrawing groups can increase the rate constant whereas the electron-donating groups decrease the rate constant.²⁵



Scheme 1.17 Radical rearrangement

1.4.6 Radical Oxidation

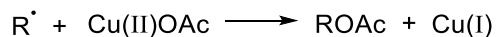
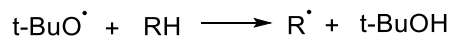
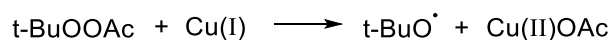
Oxidation takes place when radicals lose one electron to metal ions. Alkyl radicals have two pathways: oxidative elimination and oxidative substitution (**Scheme 1.18**).



Scheme 1.18 Radical oxidation

In some cases, the metal acts as not only oxidant but also as an initiator for a radical process. For example, *t*-butyl peracetate can be cleaved by Cu(I) to form a Cu(II)OAc and a *t*-butoxy

radical which then abstracts a hydrogen from an alkane to generate an alkyl radical which undergoes oxidation by Cu(II) to give Cu(I) species and the corresponding acetoxy alkane (**Scheme 1.19**).²⁶



Scheme 1.19 Copper initiated and oxidized radical reaction

1.5 Conclusion

Interest in free radicals over the past decades has increased as their crucial role in both chemistry and biology has come to light. In this chapter, the physical property of free radicals was briefly discussed both in geometry and stability aspects. Meanwhile, the radical generation methods and some fundamental radical reactions were particularly emphasized not only by general principle description but also some practical examples. However, free radical intermediates are involved in many reactions in organic synthesis - too many to list and therefore this brief introduction is just a glance at free radical chemistry.

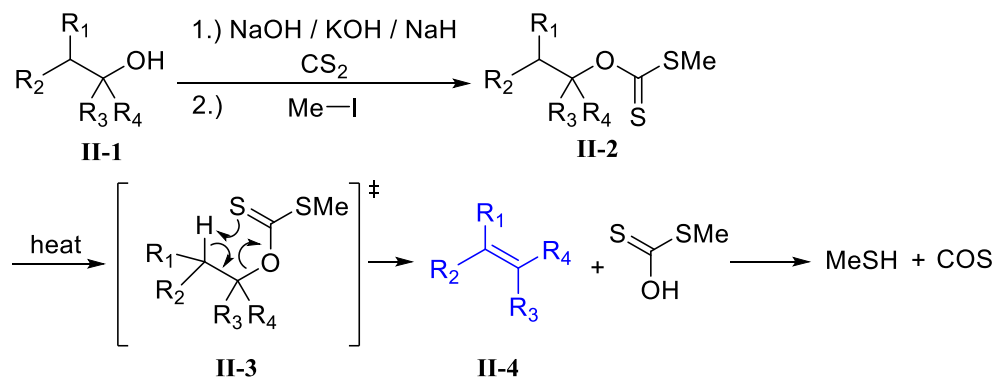
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Chapter 2 Xanthate based radical chemistry

2.1 Introduction

Many xanthate salts are yellow, hence their Greek name 'xanthos' meaning "yellowish, golden. The term xanthate usually refers to a salt with the formula ROCS_2M^+ where R is an alkyl group and the metal ion is potassium or sodium ion. Although it has been 198 years since xanthate salts were discovered by Danish chemist William Christopher Zeise,¹ the utility of xanthate in chemistry remained largely unexplored until 1899, when a xanthate reaction was reported for the first time in a pyrolysis process by L. Chugaev.²⁻³ The xanthate group arises from the corresponding alcohols **II-1** (1°, 2°, and 3°) and then undergoes a unimolecular elimination to afford desired alkene **II-4**. The β -hydrogen atom is removed via cis-elimination through a 6-membered cyclic transition state **II-3**. The reaction is especially valuable for the conversion of sensitive alcohols to the corresponding olefins without rearrangement of the carbon skeleton (**Scheme 2.1**).

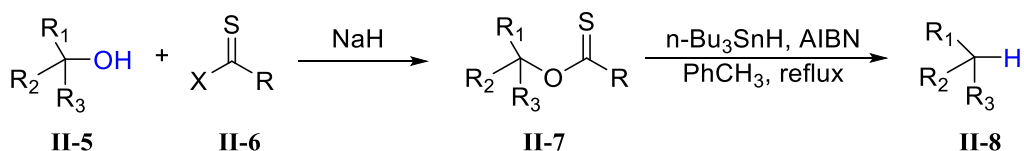


Scheme 2.1 Chugaev elimination

2.2 The Barton-McCombie deoxygenation

2.2.1 An overall view: from alcohol to alkane

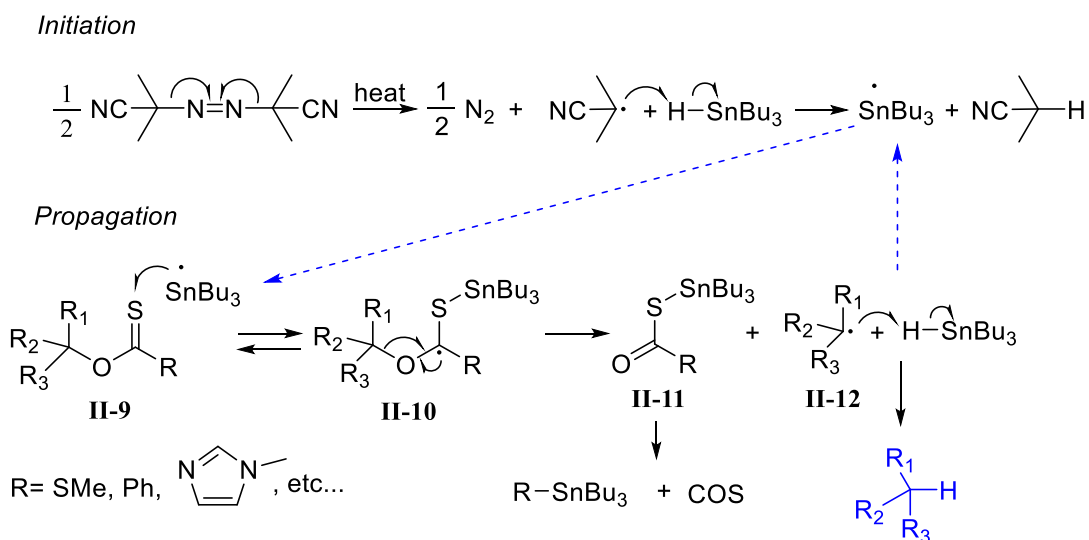
The Chugaev elimination aroused some interest in xanthate chemistry, but was nevertheless very limited in applications. The discovery of the Barton-McCombie radical deoxygenation⁴ had a deep influence in organic synthesis. Traditional methods to reduce alcohol derivatives such as tosylate, mesylate, sulphate, or halides using LiAlH_4 ,⁵ NaBH_4 ,⁶ or metal catalysis⁷ have limitations when sterically hindered -OH groups are involved since the reactants and intermediates cannot get close to each other. The Barton-McCombie deoxygenation uses widely commercialized and easily handled alcohols as the radical source and is less susceptible to steric factors which means even more sterically hindered secondary and certain tertiary alcohols (tertiary xanthates are very susceptible to the Chugaev elimination) may be reduced by this method.⁸ In a typical procedure the alcohol **II-5** is first converted to a xanthate or related derivative **II-7**, which is then exposed to tri-*n*-butyltin hydride in refluxing toluene to afford the desired alkane **II-8** (**Scheme 2.2**).



Scheme 2.2 Barton-McCombie deoxygenation

2.2.2 The mechanism

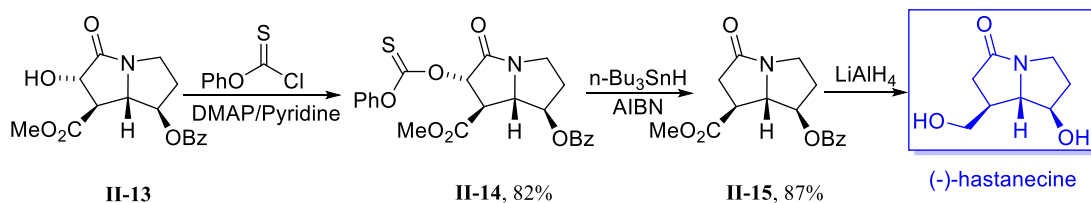
A proposed mechanism of Barton-McCombie deoxygenation is given in **Scheme 2.3**.⁹⁻¹⁰ The initiation step involves the thermal homolysis of 2,2'-azobis(iso-butyronitrile) (AIBN) followed by a hydrogen abstraction from tri-*n*-butyltin hydride. In the propagation step, the formation of a strong tin-sulfur bond drives the tin radical to add reversibly to the carbon-sulfur double bond to form radical **II-10**, which then fragments to radical **II-12** and byproduct **II-11**. Radical **II-12** moves one step forward to abstract hydrogen from tri-*n*-butyltin hydride to complete the overall reaction and regenerate the chain-carrier, tri-*n*-butyltin radical. However, byproduct **II-11** has a different fate. It is unstable and decomposes to yield carbonyl sulphide (COS) and tri-*n*-butylstannane (**Scheme 2.3**).



Scheme 2.3 Proposed mechanism of Barton-McCombie deoxygenation

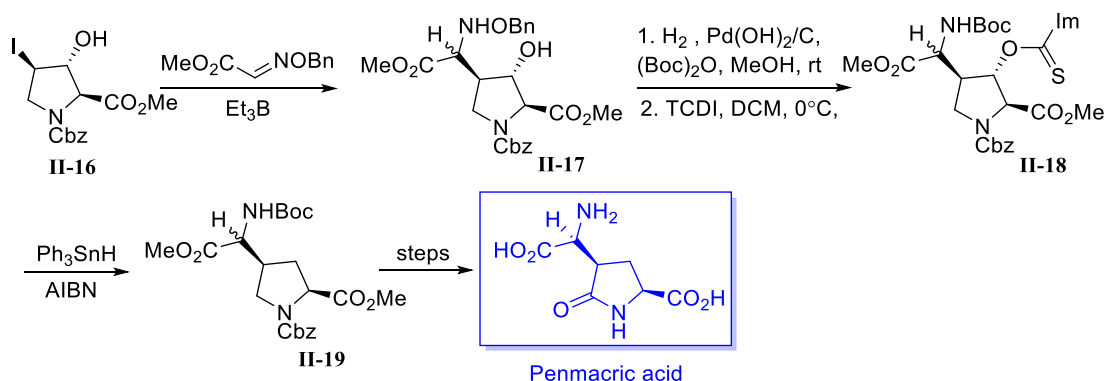
2.2.3 Applications

Denmark and co-workers developed an asymmetric synthetic route to access pyrrolizidine necine base (-)-hastanecine. The key reaction in the transformation is a sequential inter [4+2]/inter [3+2] cycloaddition.¹¹ After rapidly constructing the desired carbon framework, a late-stage removal of the hydroxyl group was accomplished using the Barton-McCombie deoxygenation procedure (**Scheme 2.4**).



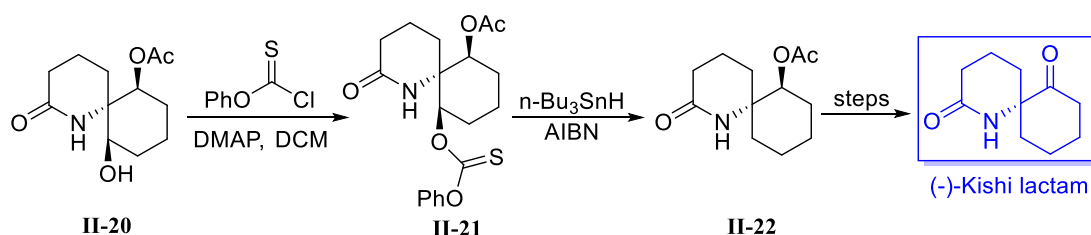
Scheme 2.4 Removal of hydroxyl group in the total synthesis of (-)-Hastaneceine

The first total synthesis of penmacric acid and its stereoisomer was reported by Naito's group.¹² After the crucial Et₃B-induced stereoselectivity step, the unnecessary hydroxyl group was reduced efficiently by the Barton-McCombie procedure (Scheme 2.5).



Scheme 2.5 Hydroxyl group reduction in total synthesis of Penmacric acid

(-)-Kishi lactam, which is a versatile intermediate to construct perhydrohistrionicotoxin (pHTX) alkaloids, was synthesized by Luzzio's and co-workers.¹³ Barton-McCombie process was again employed at a late stage to remove one of the secondary hydroxyl groups (Scheme 2.6).



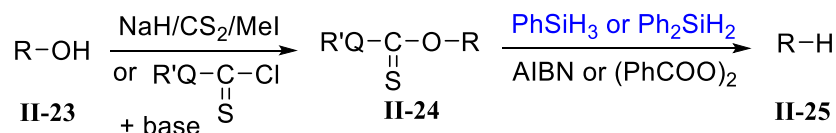
Scheme 2.6 -OH reduction in total synthesis of Penmacric acid

2.3 Development of the Barton-McCombie deoxygenation

Even nowadays, the Barton-McCombie deoxygenation is still a powerful synthetic tool in organic chemistry despite it being more than 40 years since its discovery.¹⁴⁻¹⁶ Tri-*n*-butyltin hydride represents an efficient hydrogen donor in this process because of the relatively weak Sn-H bond strength (74 Kcal/mol),¹⁷ but has several drawbacks including toxicity, complicating purifications and in some cases the need for a syringe pump when low concentrations are

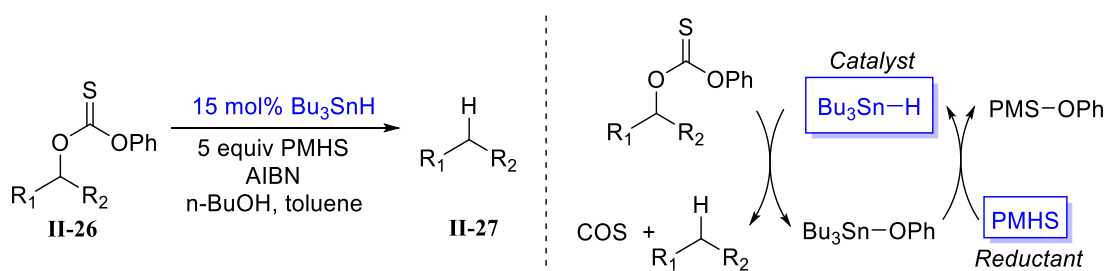
necessary.

To overcome the disadvantages of tin hydride, certain organosilicon hydrides contribute another option in the deoxygenation the process due to the weak Si-H bond strength (79 Kcal/mol). In 1991, Barton's group reported deoxygenation of primary and secondary alcohols with phenylsilane instead of tri-*n*-butyltin hydride as hydrogen donor. The reaction proceeded efficiently in boiling toluene with good to excellent yields (**Scheme 2.7**).¹⁸



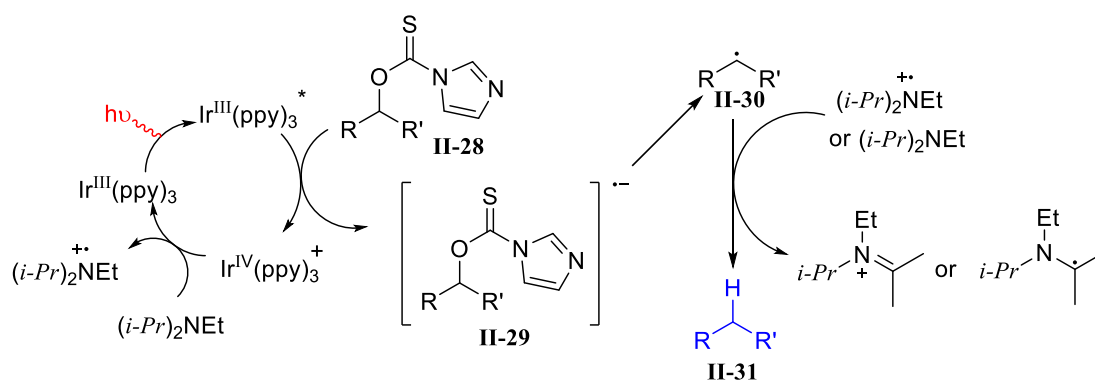
Scheme 2.7 Silanes acting as hydrogen atom donor in deoxygenation

An alternative to the original method of Barton-McCombie deoxygenation was developed by Gregory C. Fu and co-workers which involved a new procedure that can dramatically decrease the amount of tri-*n*-butyltin hydride from 1.5-3 equiv to 15 mol%.¹⁹ In this procedure, the Bu₃SnH is a catalyst and polymethylhydrosiloxane (PMHS; TMSO-(SiHMeO)_n-TMS) is the stoichiometric reductant (**Scheme 2.8**).



Scheme 2.8 Bu₃SnH catalyzed deoxygenation

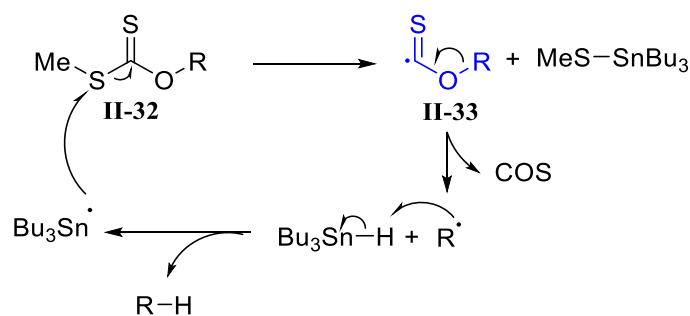
Ollivier and co-workers developed a tin-free photoredox procedure to accomplish deoxygenation.²⁰ Activation of the secondary or tertiary alcohol with thiocarbonyl diimidazole (TCDI) provides intermediate **II-28**, which is followed by a visible light photocatalytic reduction procedure in the presence of iridium complex Ir(ppy)₃ and N,N-diisopropylethylamine (DIPEA), to provide the desired alkanes **II-31**. This tin-free process proceeds by a SET manner to transfer one electron from the iridium complex to the thiocarbamate precursor to form a thiocarbamate radical anion. This radical anion then collapses to generate a carbon-centered radical which can abstract a hydrogen atom either from the amine radical cation coming from the reduction of iridium catalyst or directly from DIPEA (**Scheme 2.9**).



Scheme 2.9 Proposed mechanism for photocatalytic Barton-McCombie deoxygenation

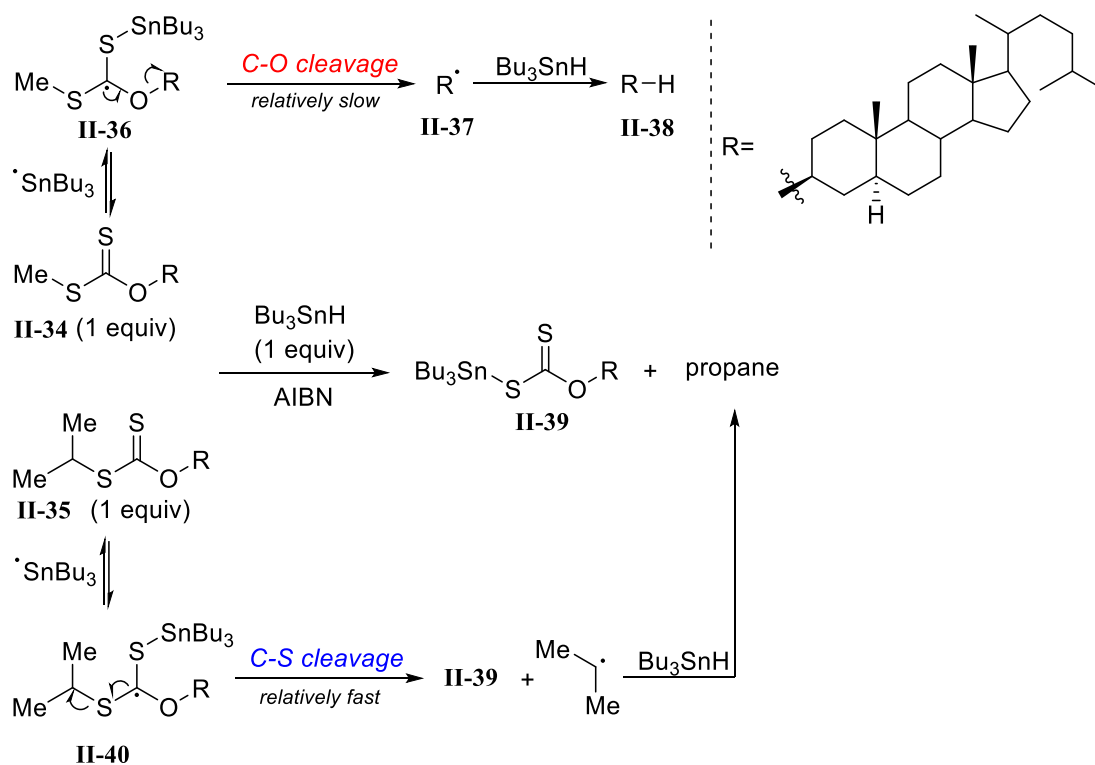
2.4 Radicals generation from carbon-sulfur bond disconnection: *the degenerate transfer of xanthates*

After the explosive growth of deoxygenations with the Barton-McCombie method, chemists uncovered more details about the mechanism. Unlike the originally proposed mechanism, Barker and Beckwith assumed another pathway for the Barton-McCombie deoxygenation,²¹ whereby the tin radical reacts with the sulfide sulfur of the xanthate **II-32** to form an alkoxythiocarbonyl radical **II-33** which releases one molecule carbonyl sulfide to give an R radical. Then the alkyl radical abstracts a hydrogen atom from tri-*n*-butyltin hydride to afford alkane and stannyl radical to accomplish the chain propagation (**Scheme 2.10**).



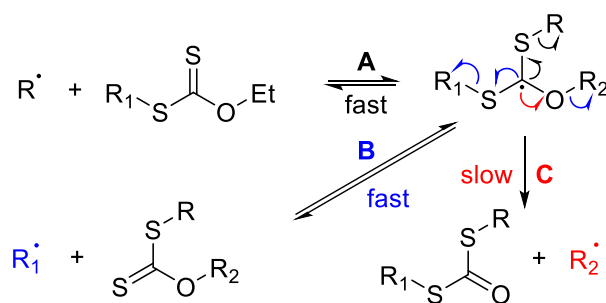
Scheme 2.10 Barker and Beckwith's mechanism of deoxygenation

Barton's group subsequently conducted a series of competition experiments to investigate the mechanistic issues.^{10, 22} Radical S_{H2} reactions are affected by steric hinderance like other bimolecular substitutions. Hence, the idea was to do a comparison between the S-methyl dithiocarbonate **II-34** and the bulkier isopropyl analogue **II-35** (**Scheme 2.11**). If the reduction process was as Barker and Beckwith described, then substrate **II-34** should react faster than **II-35** and afford the desired product. But the outcome was surprising: the more hindered xanthate reacted faster than the less hindered one and the S-stannylated xanthate **II-39** was isolated along with propane as the co-product.



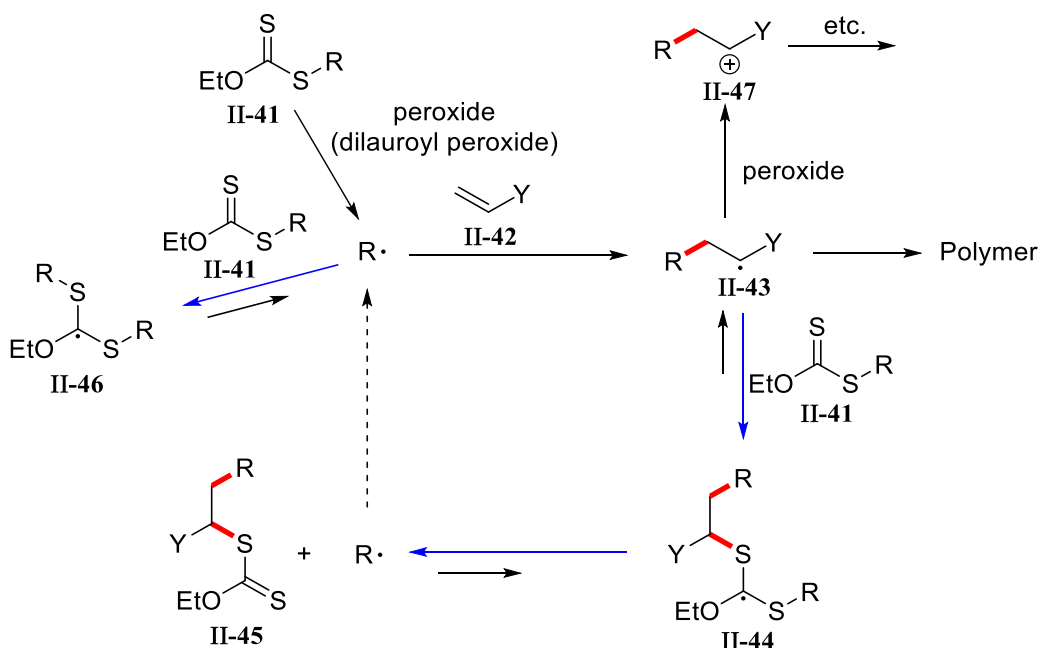
Scheme 2.11 General principle for the competition experiment

Two conclusions could be drawn from these observations, summarized in **Scheme 2.11**: 1. Since carbon radicals also react fast with thiocarbonyl derivatives, it is possible now to write a reaction manifold where an exchange between radicals $\text{R}\cdot$ and $\text{R}_1\cdot$ by an addition-fragmentation (paths A, B in **Scheme 2.12**); 2. when the newly generated carbon radicals have similar stabilities (cholestanyl and isopropyl radicals in the present case), the weaker C-S bond cleavage is favored over the cleavage of the C-O bond (**Scheme 2.12**).



Scheme 2.12 Possible fragmentation of xanthate radical

Based on these facts, a large amount of work has been done in the past three decades in the Zard group²³⁻²⁶ to investigate the disconnection of a carbon-sulfur bond in xanthates to participate in a general radical-chain process. To understand the transformation, a simplified mechanism is shown below (**Scheme 2.13**).



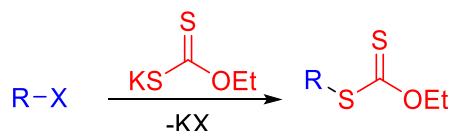
Scheme 2.13 Simplified mechanism for the addition of xanthates to alkenes

1.) The initiation step is the homolytic cleavage of the dilauroyl peroxide (DLP) to generate undecyl radicals, which can attack the starting xanthate to provide radical $R\cdot$. This radical can rapidly react with its precursor, xanthate **II-41**, to form a stabilized radical **II-46**. Radical **II-46** is a hindered but stabilized radical that interacts only slowly with other radicals. Besides, it is unable to disproportionate (no β -hydrogens). Therefore, it has to fragment back to radical $R\cdot$. The equilibrium between radical **II-46** and radical $R\cdot$ ensures the continuous regeneration of $R\cdot$, hence considerably increasing its lifetime in the medium. Radical $R\cdot$ can now be trapped by unactivated alkene **II-42** to provide adduct radical **II-43**, which can react with the starting xanthate **II-41** to form another dormant radical **II-44**. 2.) Because the active radicals $R\cdot$ and **II-43** are mostly in their dormant state **II-46** and **II-44** respectively, their absolute concentration remain very low and unwanted radical-radical interactions are curtailed. 3.) In order to limit oligomerization, $R\cdot$ should be more stable than **II-43**. 4.) If adduct radical **II-43** is particularly electron-rich, it can be oxidized by the peroxide to give cation **II-47**. This process is particularly useful in cyclizations and intermolecular additions to (hetero)aromatics. The only cost is to use stoichiometric quantities of dilauroyl peroxide.

2.5 Preparation of xanthates

2.5.1 By a simple substitution

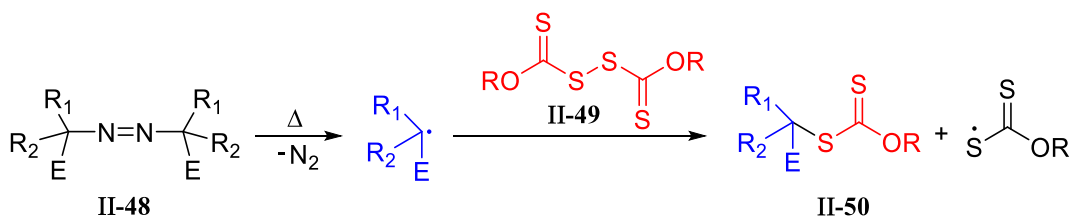
Generally, displacement of a leaving group such as a halide or a tosylate by a xanthate salt furnishes the desired xanthate (**Scheme 2.14**).



Scheme 2.14 General xanthate formation method by substitution

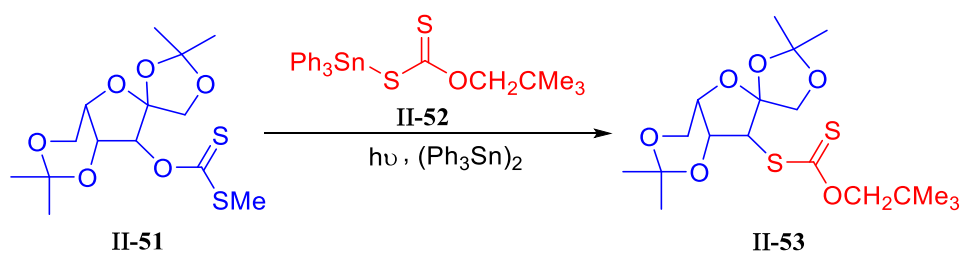
2.5.2 Using a radical procedure

The $\text{S}_{\text{N}}2$ reaction mentioned above to synthesize xanthate is a quite simple approach but is inefficient with hindered substrates (e.g. tertiary). This limitation can be overcome by radical based approaches. Thus, merely heating a mixture of a tertiary diazo derivative **II-48** and a bis-xanthate **II-49** in cyclohexane will give the desired tertiary xanthate **II-50** (Scheme 2.15).²⁷

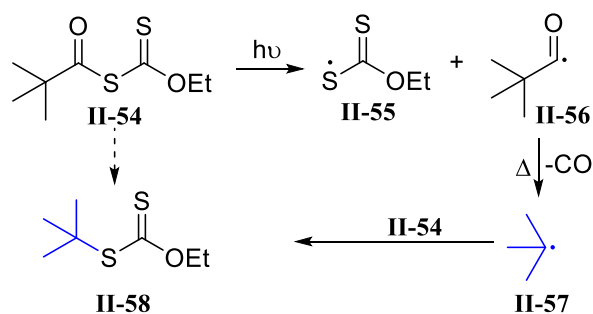


Scheme 2.15 Diazo react with dithionodisulfide to form stereo hindered xanthate

The addition of tin radicals onto a xanthate group is a reversible process. It is therefore possible to use *S*-triphenylstannyl xanthate **II-52** as a tin radical source which can generate an $\text{R}\cdot$ radical from R-X (X represents a group that can be abstracted by tin radicals: bromide, iodide, xanthate). The newly formed alkyl radical can then react with the tin xanthate and by a series of reversible steps give the desired xanthate **II-53** (Scheme 2.16).²⁸

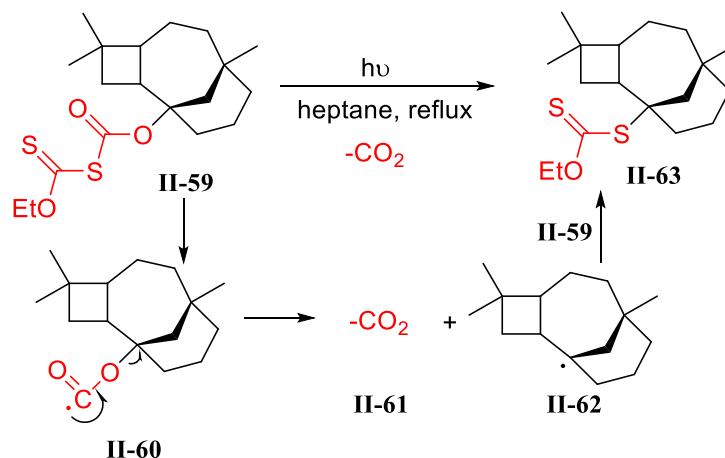
Scheme 2.16 Reaction of R-X with stannyl xanthate

Acyl radicals can be generated by irradiating *S*-acyl xanthate **II-54** with mercury-arc or tungsten lamps. On one hand, the acyl radical **II-56** can be captured by appropriate olefinic traps but on the other hand it can lose carbon monoxide at an appropriate temperature to give an alkyl radical **II-57** which can react with xanthate radical **II-55** to furnish a new *S*-alkyl xanthate **II-58** (Scheme 2.17).²⁹



Scheme 2.17 Generation of *S*-alkyl xanthate from *S*-acyl xanthate

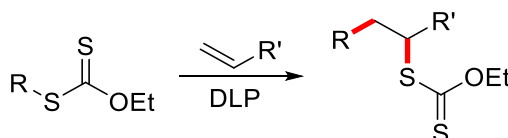
S-Alkoxy carbonyl xanthate **II-59** is also able to generate alkoxy carbonyl radical **II-60**, and tend to lose carbon dioxide to form radical **II-61**. The radical **II-61** could react with alkyl radical **II-62** to give a new xanthate **II-63** (Scheme 2.18).³⁰



Scheme 2.18 Decarboxylation of *S*-alkoxy carbonyl xanthate to form alkyl xanthate

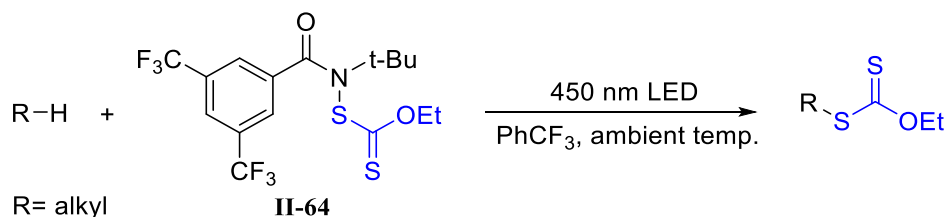
2.5.3 Other radical approaches

During the xanthate radical addition, a new xanthate product is formed (Scheme 2.19), and thus constitutes a powerful synthesis of xanthates.



Scheme 2.19 Radical addition to form a new xanthate

In 2016, Alexanian and co-workers developed another radical method to prepare xanthates through aliphatic C–H xanthylation. *N*-Xanthylamide **II-64** acts as both hydrogen abstractor and xanthate source in this transformation (Scheme 2.20).³¹



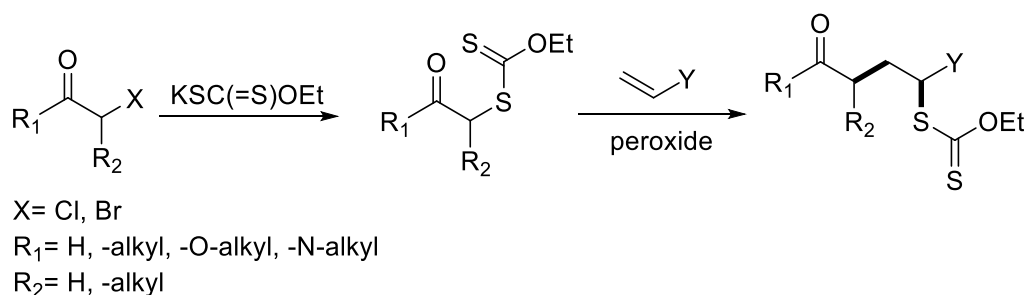
Scheme 2.20 Direct C-H xanthylation

2.6 Applications of xanthate chemistry

The degenerative radical transfer process of xanthate onto unactivated alkenes offers a convenient, efficient, and economical synthetic methodology to rapidly construct richly functionalized compounds. During the past three decades Zard's group has broadly extended the scope of this process in organic synthesis. To date, this transformation not only can be readily applied to access open-chain, cyclic and polycyclic compounds but also it exhibits efficiency in the synthesis or modification of aromatic and heterocyclic compounds.

2.6.1 Applications of radical additions to the synthesis of ketones

The general procedure of regioselective alkylation of carbonyl compounds includes two steps: the first step is the preparation of xanthate from alkyl halides and the second step is a radical addition to alkenes (Scheme 2.21).

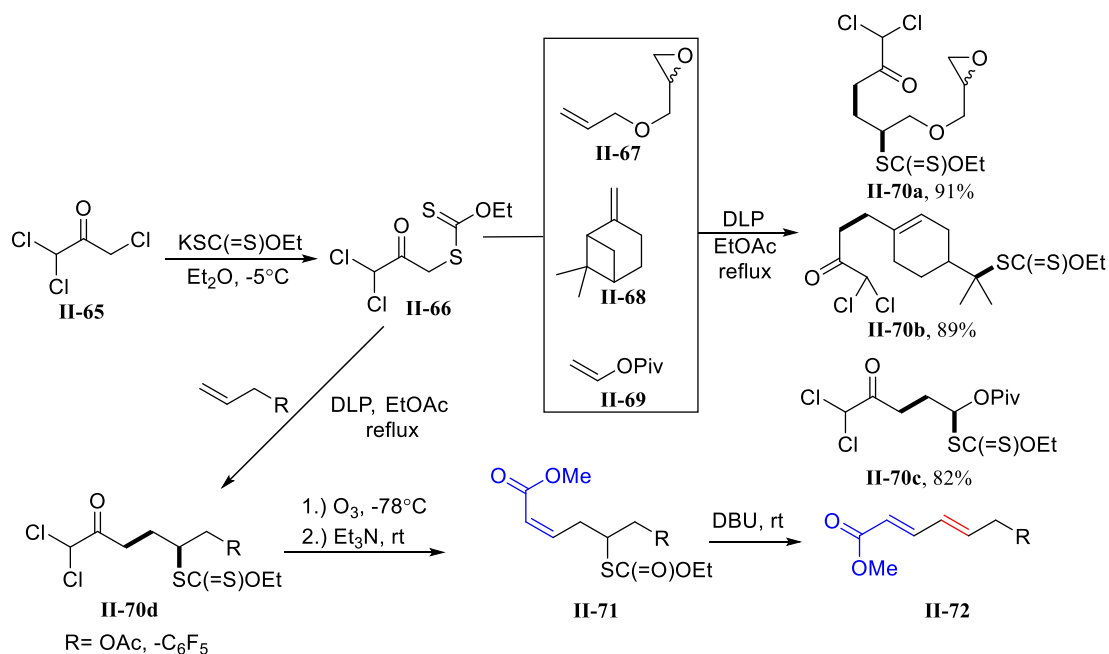


Scheme 2.21 General procedure for the radical alkylation of carbonyl compounds

(i) mono-alkylation of ketone

To functionalize highly base-sensitive α , α -dichloroketones, the 1,1-dichloroacetyl xanthate **II-66** has emerged as the appropriate substrate and its radical addition to several olefins proceeded efficiently (Scheme 2.22). Epoxide bearing alkene **II-67** was well tolerated in this reaction and gave a high yield of adduct **II-70a**. The reaction resulted in an addition-fragmentation product **II-70b** in 89% yield when β -pinene **II-68** was used as the alkene partner. It should be mentioned that adding xanthate **II-66** to vinyl pivalate **II-69** can form a latent aldehyde group **II-70c**. The further transformation of the radical adducts is also synthetically interesting. The xanthate adducts **II-70d** were ozonolyzed, followed by a

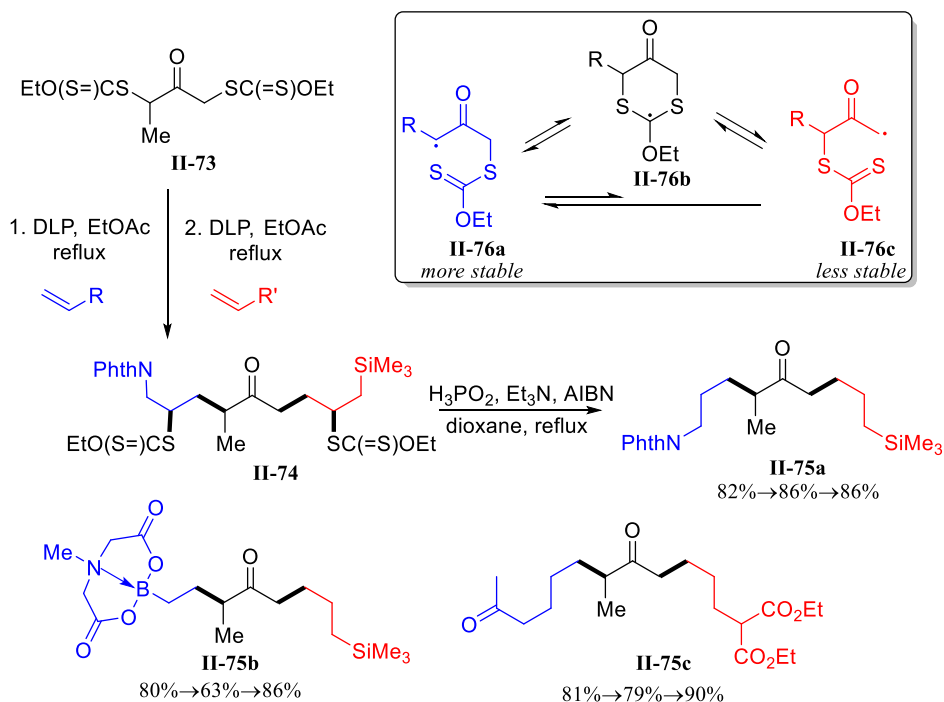
triethylamine-catalyzed Favorskii rearrangement to give complete selectivity in the formation of the corresponding *Z*-alkene **II-71**. The newly formed thiocarbonate enones can be further elaborated into the corresponding dienes **II-72** by exposure to DBU in toluene at ambient temperature.³²



Scheme 2.22 Synthesis of *Z*-alkenoates and *E, E*-dienoates

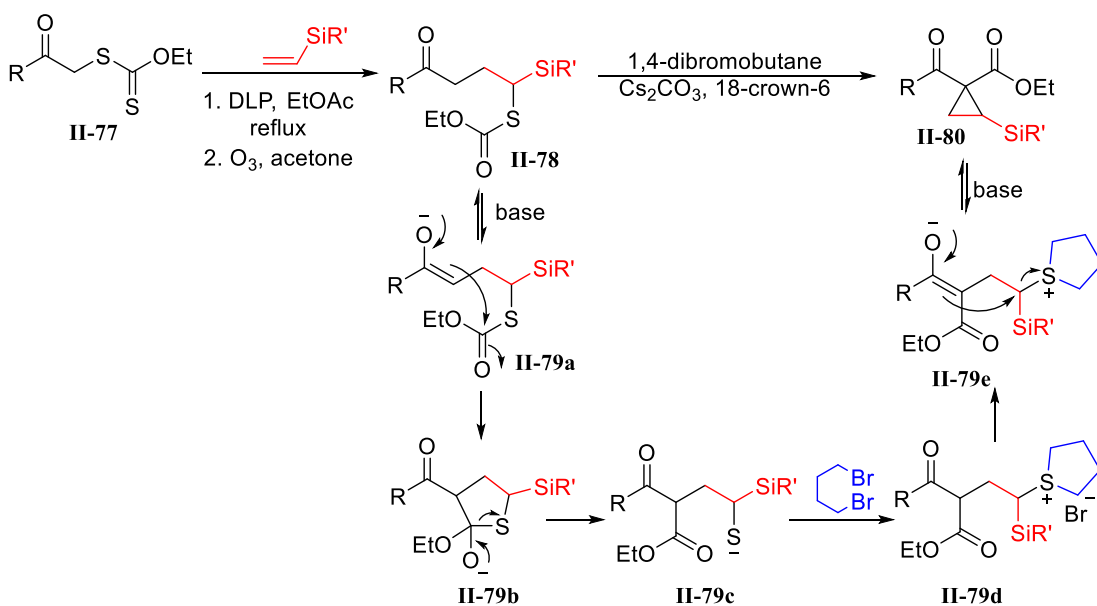
(ii) dialkylation of ketone

The xanthate addition also offers a solution to the synthesis of α, α' -dialkyl unsymmetrical ketones which can be troublesome to construct by the enolate pathway.³³ By exploiting the difference in stability between the secondary radical **II-75a** and primary radical **II-75c**, it is possible to accomplish a sequential regioselective addition to two different alkenes. The dioxanthate also shows high reactivity, the yields being 82% and 86% when the addition carried out with allyl phthalimide and then with allyltrimethylsilane. The final unsymmetrical α, α' -dialkylated ketone product **II-75a** was obtained in 86% yield by a simple reduction with Barton's hypophosphorus reagent.³⁴⁻³⁵ The depicted examples of MIDA boronate **II-75b**, malonate **II-75c** further illustrate the functional group tolerance of this chemistry (**Scheme 2.23**).

Scheme 2.23 Synthesis of α, α' -dialkyl unsymmetrical ketones

2.6.2 Formation of cyclopropanes

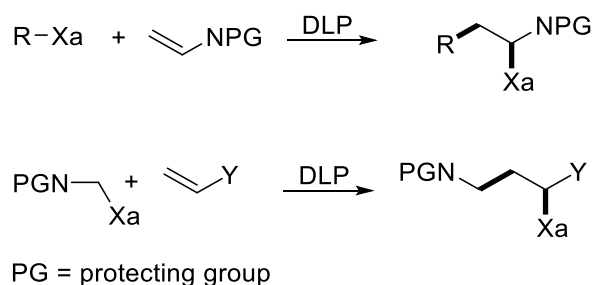
The cyclopropane ring is the smallest cyclic structure and constitutes a very attractive building block in organic synthesis. Many cyclopropane natural products show significant biological activity. Besides the Simmons–Smith cyclopropanation and the Johnson–Corey–Chaykovsky reaction, the xanthate based radical addition can also be applied for the synthesis of substituted cyclopropanes.³⁶ Thus, ozonolyzed product³⁷ **II-78** exists in an equilibrium with its enolate **II-79a** in the presence of a base and undergoes acyl shift to free thiolate anion **II-79c**. This is trapped by 1,4-dibromobutane to form the corresponding sulfonium salt **II-79d**, which is a good leaving group and reacts as shown in **II-79e** to furnish cyclopropane **II-80** (Scheme 2.24).



Scheme 2.24 The synthesis of triethylsilyl-substituted cyclopropanes

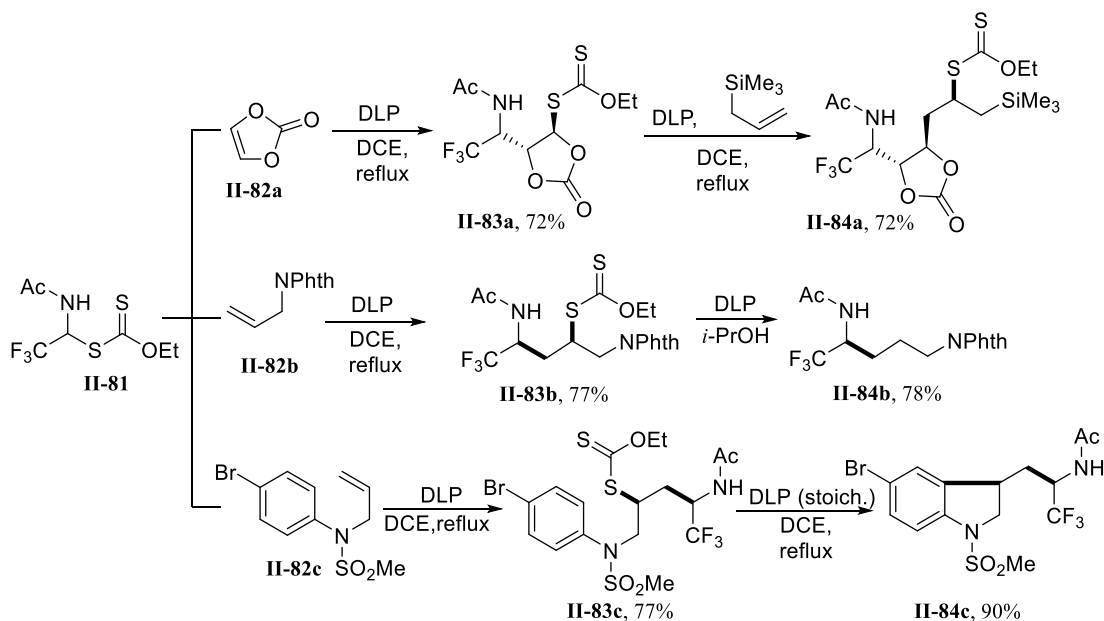
2.6.3 The xanthate route to amines and anilines

The amino group is a fundamental entity in organic chemistry, amines are ubiquitous and can be found in natural products, drug candidates, and polymers.³⁸ The protected amine can be present either on the alkene or on the xanthate partner when taking advantage of the xanthate transfer process for the synthesis of various (protected) amines (Scheme 2.25).



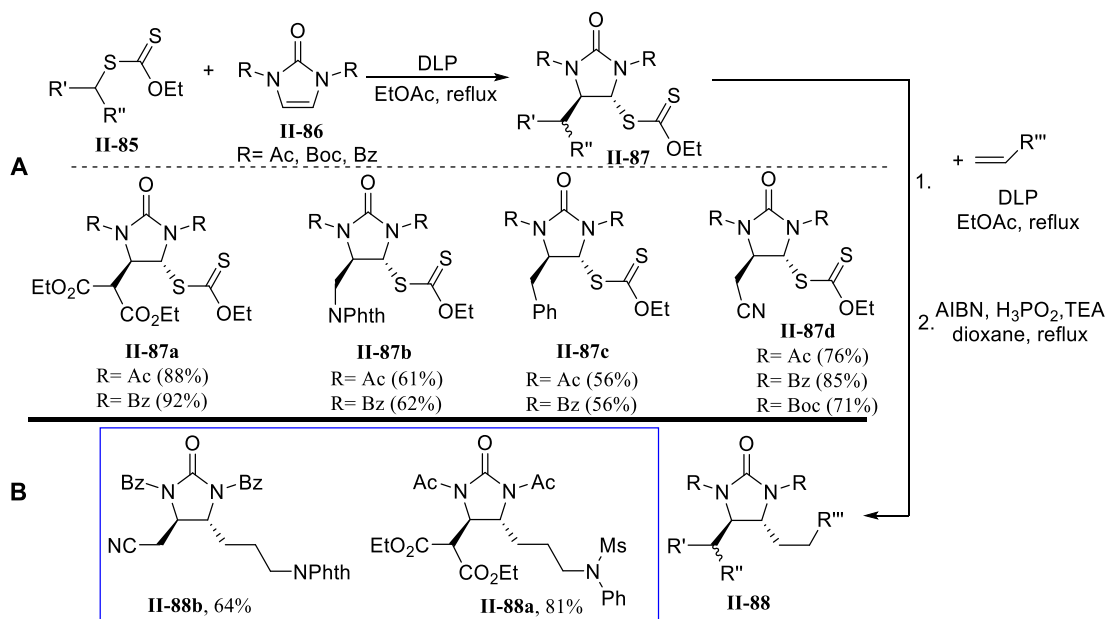
Scheme 2.25 Xanthate route to protected amines

α -Trifluoromethylamine derivatives can be obtained efficiently by adding the corresponding xanthate **II-81** to various functionalized olefins.³⁹ In the case of adduct **II-83a**, a second addition with allyltrimethylsilane furnishes highly functionalized product **II-84a** in 72% yield. Product **II-84b** bearing two differently protected amino groups was obtained in 78% yield by this tin-free procedure.⁴⁰ A useful application of xanthate chemistry is the ring-closure onto aromatic rings, as illustrated by the synthesis of indoline **II-84c**. This transformation requires a stoichiometric amount of peroxide, which acts as both as the initiator and as the oxidant for the intermediate cyclohexadienyl radical (not shown) (Scheme 2.26).



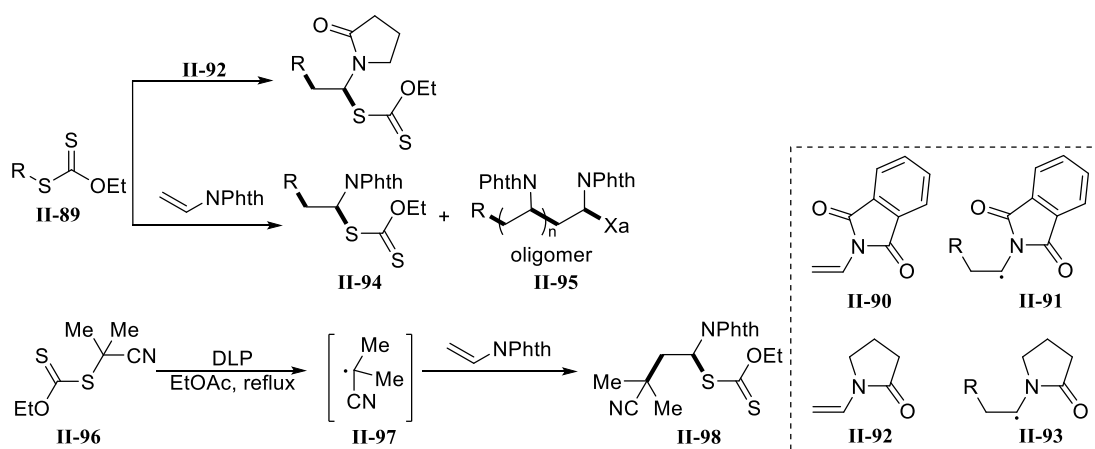
Scheme 2.26 Xanthate route to protected amines

Protected 1,2-diamines were also readily synthesized by adding various xanthates to *N,N'*-diacylimidazol-2-one.⁴¹ A few examples **II-87a-d** are listed in **Scheme 2.27-A** to illustrate the formation of masked diamines by the first radical addition. A second addition to unactivated alkenes is possible due to the sufficient stabilization of the adduct radical by the imide group. Reductive dexanthylation using Barton's method finally affords highly functionalized diamines **II-88**. Examples **II-88a, b** illustrate a convenient access to protected triamines (**Scheme 2.27-B**).

Scheme 2.27 Adding to *N,N'*-diacylimidazol-2-one to give di- and triamines

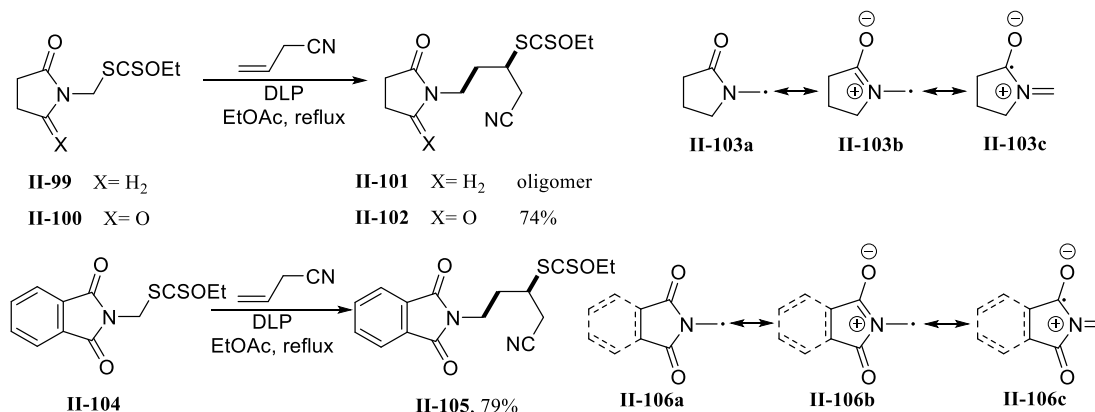
2.6.4 Stabilization of Radicals by Imides.

It is worth noting the imide group imparts a non-obvious stabilization of radicals that has been exploited in the xanthate radical addition. Under standard conditions,³⁹ xanthate **II-89** reacted cleanly with *N*-vinyl pyrrolidone, while similar reactions with vinyl *N*-phthalimide gave mostly oligomers **II-95**. In contrast, highly stabilized radical **II-97** generated from xanthate **II-96** can be trapped by alkene **II-90** to furnish adduct **II-98** cleanly with almost no formation of oligomer (**Scheme 2.28**).⁴² According to the mechanism of radical addition (*see*: **Scheme 2.13**), the formation of oligomer is favored when adduct radical **II-91** is more stable than starting radical **R•** derived from xanthate **II-89**. Besides, the first two reactions also indicate that radical **II-91** is significantly more stable than radical **II-93**.



Scheme 2.28 Different fates of *N*-vinyl pyrrolidone and *N*-vinyl phthalimide

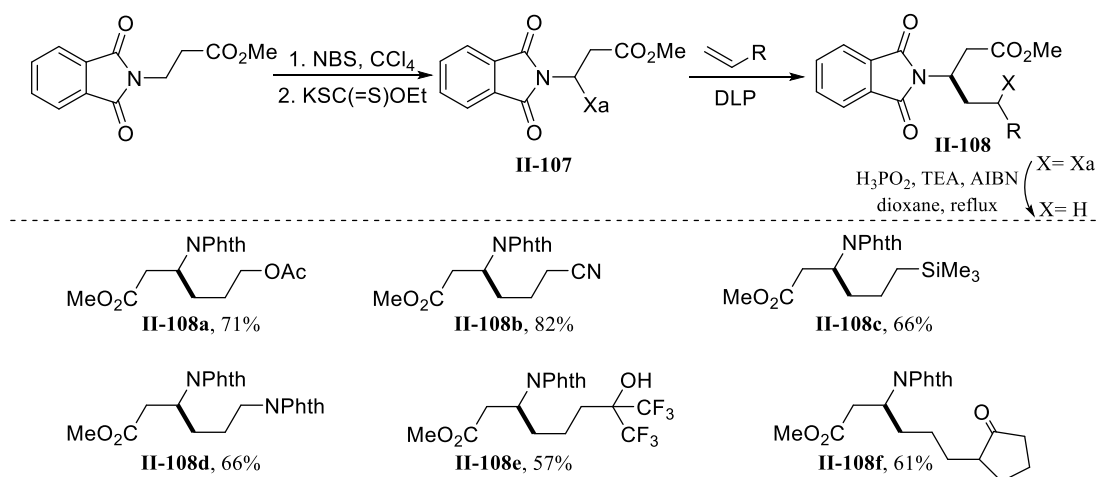
To confirm this unanticipated observation, pyrrolidonyl and succinimidyl groups were set up in the xanthate part (**II-99** and **II-100**). Now the effect is reversed (**Scheme 2.29**). The reaction of allylcyanide and pyrrolidonyl xanthate **II-99** gave mostly oligomers while succinimidyl xanthate **II-100** and phthalimidoyl xanthate **II-104** give the expected products **II-102** and **II-105**. These results proved the fact that the pyrrolidone-substituted radical **II-103a** is less stable than phthalimide- and succinimide-substituted radicals **II-106a**. This speculation would be explained by the resonance structures below. The radical **II-106a** has more allylic character than radical **II-103a**.



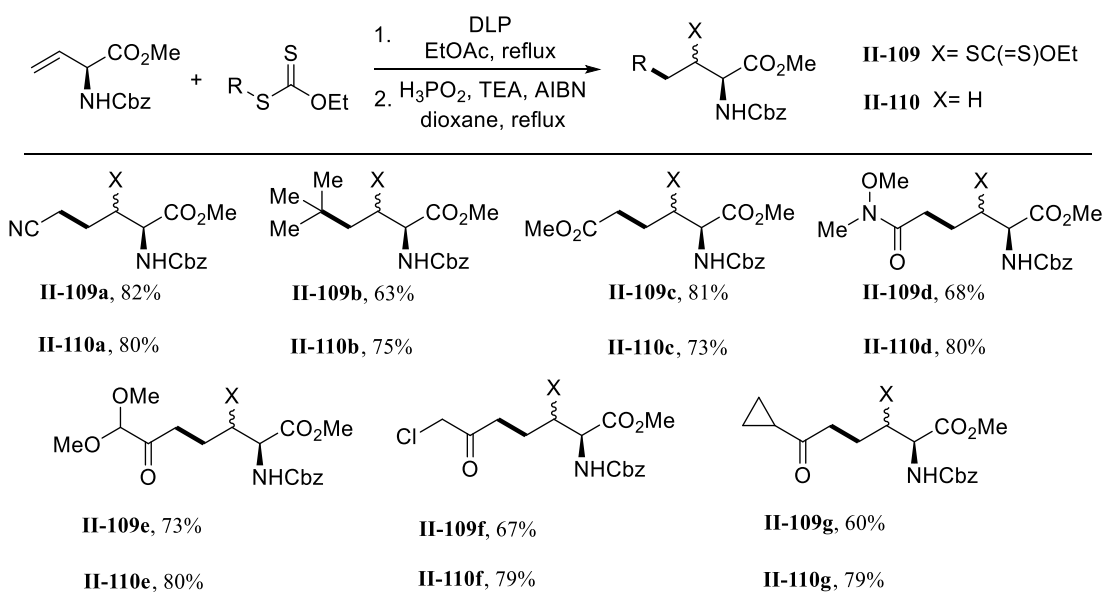
Scheme 2.29 Stabilization effect of adjacent radicals by an imide group

2.6.5 Synthesis of protected amino acid derivatives

Reaction of amino acid bearing xanthates with various alkene coupling partners is a powerful strategy to produce various amino acids. Initiated by peroxide, NBS reacts with phthalimide protected amines to form brominated derivatives, which can be substituted with a xanthate salt to form the corresponding xanthate. Xanthate **II-107** was prepared in this manner and its addition to numerous alkenes, provides a convenient pathway to substituted protected β -amino acids **II-108a-f**.⁴³ It is worth pointing out the adduct **II-108d** (Scheme 2.30) is the methyl ester of β -lysine which is produced by platelets during coagulation. It also has antibacterial activity by causing lysis of many Gram-positive bacteria by acting as a cationic detergent.⁴⁴

Scheme 2.30 Synthesis of protected β -amino acids

Another protocol to synthesize amino acid derivatives is to set up an amino acid motif on the alkenes and introduce substituents through the xanthate partner. Adding various xanthates to enantiopure vinylglycine provides access to a series of non-racemic α -amino acids.⁴⁵ Diverse functional groups such as nitrile **II-110a**, tertiary butyl group **II-110b**, ester **II-110c**, and Weinreb amide **II-110d** are all easily introduced. By using substituted α -ketonyl xanthates, various amino acids **II-110e-g** can be rapidly produced which would otherwise be exceedingly tedious to obtain by conventional methods (Scheme 2.31).



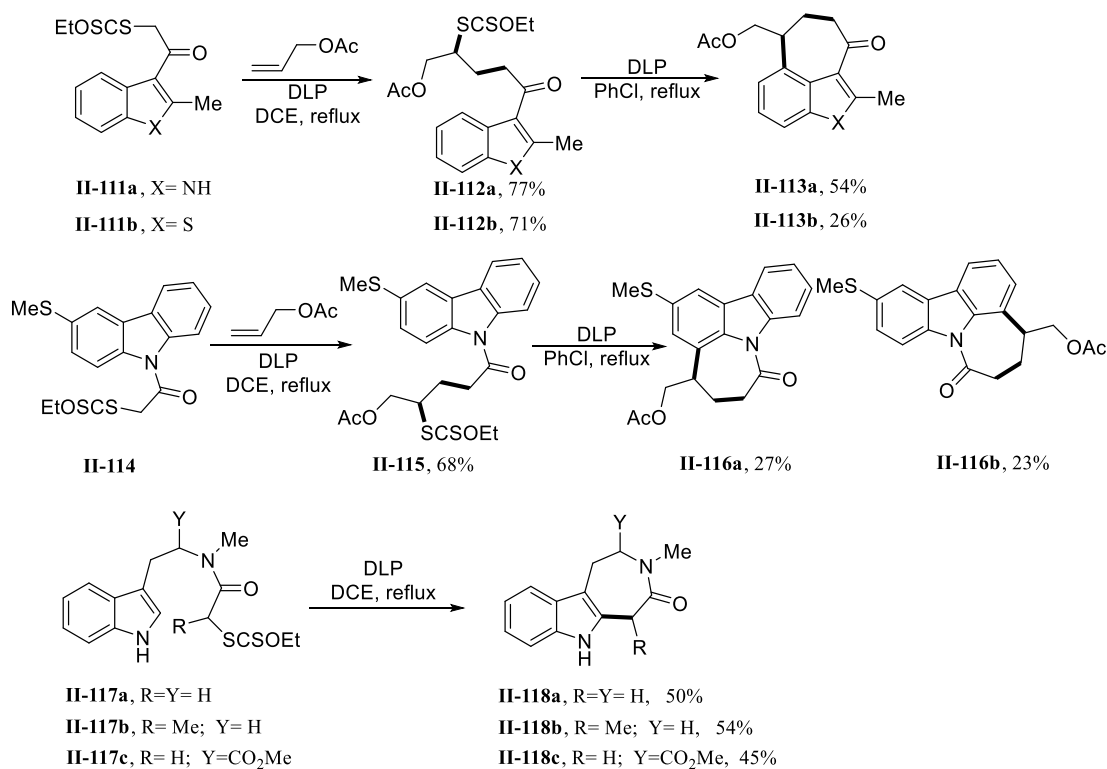
Scheme 2.31 Synthesis of enantiopure α -amino acids

2.6.6 Modification of heterocycles

Heteroaromatic compounds are important constituents of drugs and bioactive molecules and are the focus of intense study by medicinal chemists.⁴⁶ In addition to ionic chemistry, pathways to modify heterocycles based on the unique radical chemistry of xanthes constitute complementary approaches.

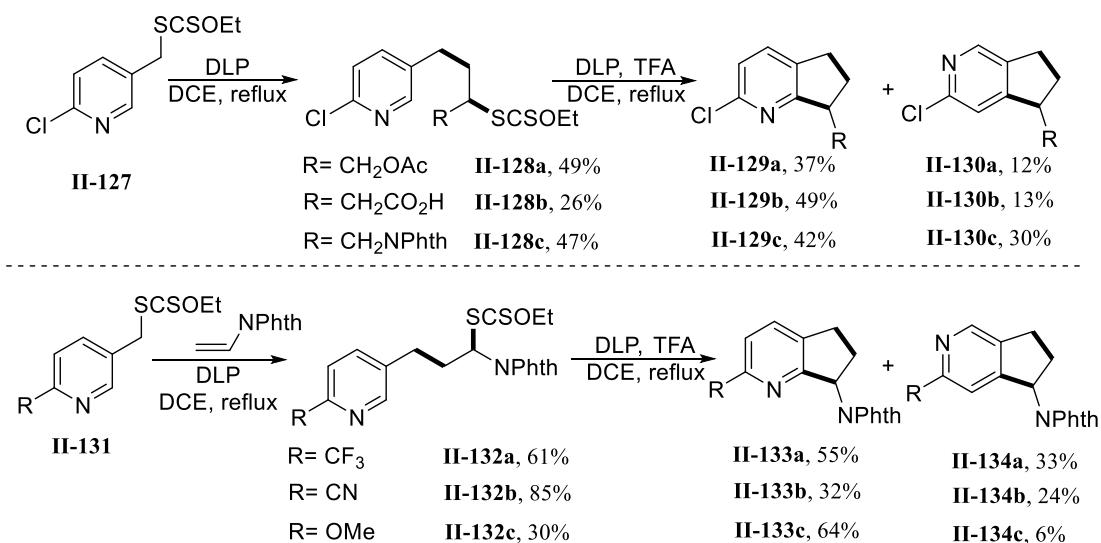
(i) Cyclization onto aromatic ring

Xanthes bearing an indole or benzothiophene ring **II-111a, b** react smoothly with allyl acetate and result in the corresponding radical adduct **II-112a, b** in good yields. This can be followed by reaction using a stoichiometric amount of lauroyl peroxide to furnish cyclized products **II-113a, b**, respectively. The addition of xanthate **II-114** to allyl acetate gives adduct **II-115** which can cyclize in the next step to form isomers **II-116a** and **II-116b** containing a fused seven-membered ring. The combined yield of the two isomeric products is moderate, but the cyclization exhibits no regioselectivity. Tryptophan derivatives **II-118a-c** could be obtained in similar yields from their xanthate precursors **II-117a-c** under the same conditions (**Scheme 2.32**).⁴⁷ The formation of seven-membered rings by direct radical cyclization onto aromatic and heteroaromatic rings is very rare. It is a slow process and difficult to accomplish by most radical methods. The examples in **Scheme 2.32** further highlight the unique features of the xanthate-based technology.



Scheme 2.32 Xanthate-mediated annulations of seven-membered rings.

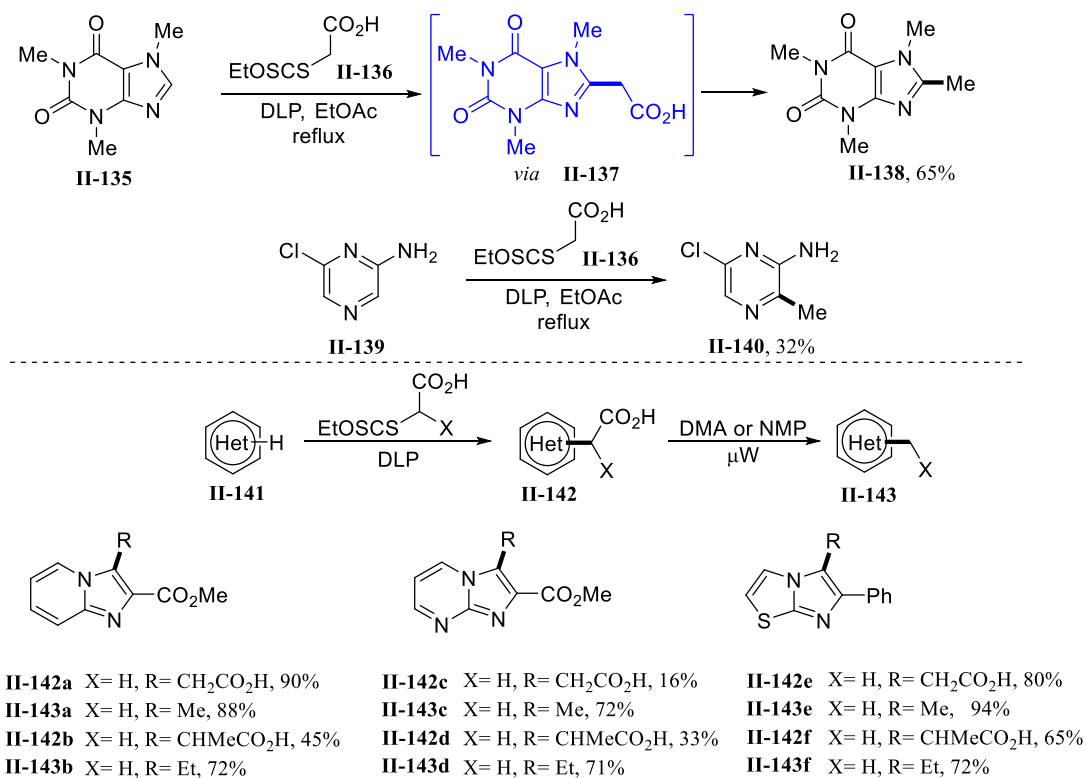
Bicyclic pyridine derivatives have been rapidly constructed by the xanthate route, including five, six, seven membered-rings (**Scheme 2.32**).⁴⁸ For example, direct cyclization of xanthates **II-119** furnish 7-azaioxindoles **II-120a-d** in good yields. In the synthesis of 7-azaindolines, a radical addition-cyclization sequence gives rise efficiently to the desired products **II-123a-c**. Adding xanthate **II-124** onto allyl acetate resulted in the formation of radical adduct **II-125**, which was closed into tetrahydro-5H-pyrido[2,3-b]azepin-8-ones **II-126** by the action of stoichiometric peroxide.



Scheme 2.34 Modular route to azaindanes

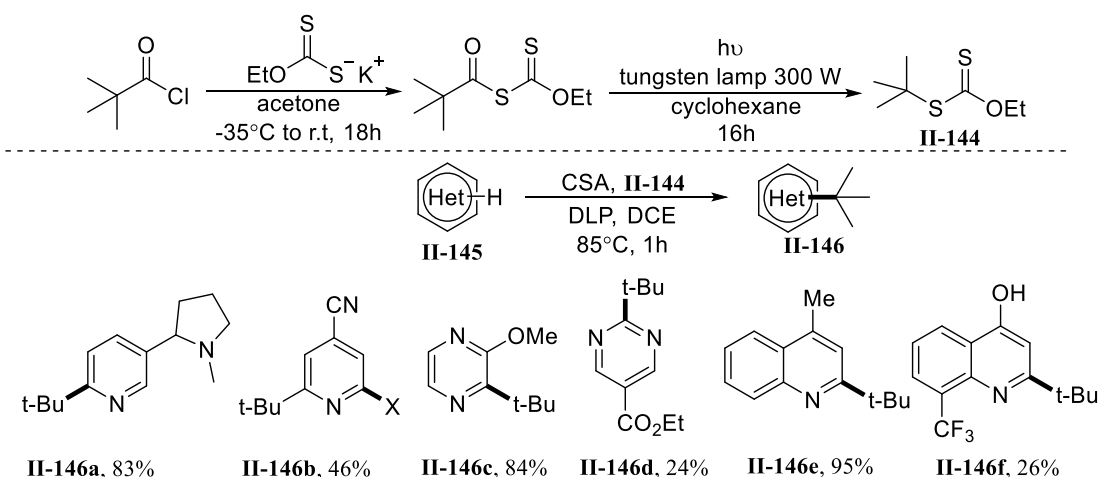
(ii) Direct alkylation of heteroaromatic rings

Methyl and ethyl groups can be introduced indirectly via the carboxylic acid derived xanthates. The radical addition is followed by decarboxylation. Depending on the heteroarene structure, spontaneous or microwave assisted decarboxylation can be accomplished efficiently⁵⁰ For example, exposure of caffeine **II-135** or pyrazine **II-139** to xanthate **II-136** in refluxing ethyl acetate using stoichiometric quantities of DLP added portion-wise provides the methylation products **II-138** and **II-140** directly. For other heteroarenes, incomplete or no decarboxylation was observed and the adducts had to be heated in a microwave oven to induce the elimination of carbon dioxide. Alkylated products **II-143a-f** were obtained in this manner (Scheme 2.35).



Scheme 2.35 Direct alkylations of heteroarenes

The xanthate-mediated radical addition offers an alternative for introducing *tert*-butyl group into heteroaromatic rings. The starting xanthate **II-144** was synthesized under photolysis conditions⁵¹ and then added to various heterocycles to form the desired products **II-146a-f** in moderate to good yields (**Scheme 2.36**).⁵²



Scheme 2.36 Introduction of *t*-butyl groups by xanthate

2.7 Conclusion

The unique degenerative addition transfer mechanism of xanthates has been extensively

studied the past three decades. Numerous applications of this methodology have been implemented including the addition to unactivated alkenes and the cyclization onto heteroarenes to afford complex heterocycles. Highly functionalized compounds can be accessed via inter or intramolecular alkylation that would be very tedious to perform with other methods. In the practical sense, this radical chemistry of xanthates features easily handled reaction conditions, low cost of starting materials, versatility, ease of scale-up and broad functional groups tolerance, especially polar groups that are often not compatible with conditions prevailing in ionic and organometallic reactions. The versatility of this xanthate chemistry opens up vast possibilities for the rapid synthesis of complex structures and the late-stage modification of natural products and drugs.

In this thesis, we have utilized these advantages for the synthesis of ketones and esters, β -amino acid derivatives as well as β -heteroarylethylamines.

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**Chapter 3 A Convergent Route to β -Amino Acids and
 β -Heteroarylethylamines. An Unexpected Vinylation
Reaction**

3.1 Introduction

Although not as common as their α -analogues, β -amino acids are useful as intermediates for the synthesis of variety of pharmaceutical targets,¹ natural products,² and peptidic materials bearing distinct structural properties.³⁻⁵ β -Amino acids are precursors of β -lactams,⁶⁻⁹ a class of potentially bioactive molecules widely present in nature.¹⁰⁻¹¹ Bestatin(A)¹²⁻¹⁴ is a competitive protease inhibitor and being studied for the treatment of acute myelocytic leukemia due to the fact that it is an inhibitor of aminopeptidase B, leukotriene A4 hydrolase and aminopeptidase N. Enantiomerically pure α -hydroxy- β -amino acid is also the crucial component of the anti-tumour drug, Taxol (B).¹⁵⁻¹⁷ Andrimid (C), an intracellular symbiont of the brown planthopper and was isolated from cultures of an *Enterobacter* sp. It shows activity against *Xanthomonas campestris* pv. *oryzae* NIAES 1225 (MIC 0.1 mg/mL), the pathogen responsible for causing bacterial blight in rice plants.¹⁸ Structure-activity relationship investigations with synthetic andrimid (C) suggests that the antibacterial activity against *S. aureus* and *Haemophilus influenzae* arises from the central lipophilic β -amino acid moiety (Figure 3.1).¹⁹ Apart from the pharmaceutical utility, amino acids have broadly emerged as chiral starting materials, auxiliaries and catalysts in organic transformations.²⁰

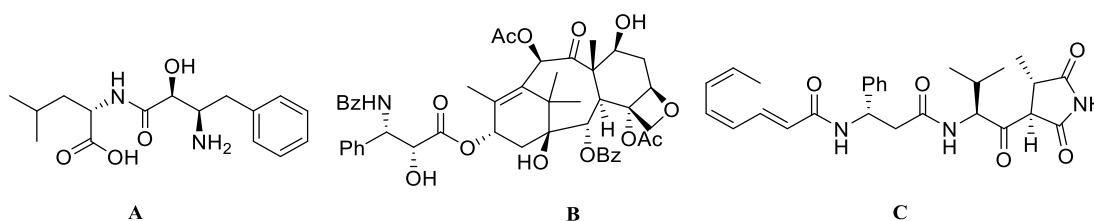


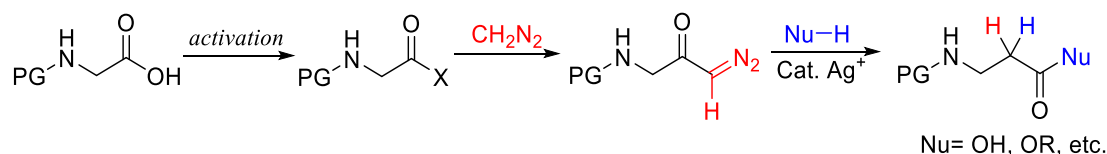
Figure 3.1 Examples of bioactive amino acids

3.2 Synthetic routes to β -amino acids

Generally speaking, the most common methods to prepare β -amino acid and related derivatives are the Arndt–Eistert homologation and the Mannich reaction. Other alternatives include biosynthetic method,²¹ the addition of enolates to *t*-butanesulfinyl imines, conjugated addition to α , β -unsaturated carbonyl compounds and the ring-opening of β -lactams will also be described in this chapter. The synthesis of β -amino acids via a radical process is also discussed.

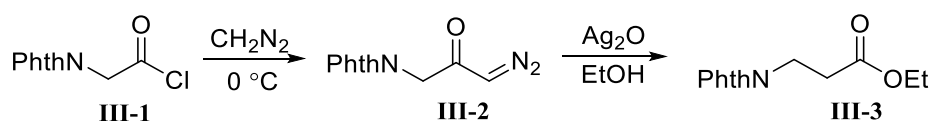
3.2.1 Arndt–Eistert homologation of α -amino acids

α -Amino acids are ideal raw materials for preparing β -amino acids, not only because a number are present in nature but also due to the fact that there are many approaches available to accomplish the conversion between the two. Among the vast majority of methods, the Arndt–Eistert's route (Scheme 3.1) is one of the most successful processes to access β -amino acids.



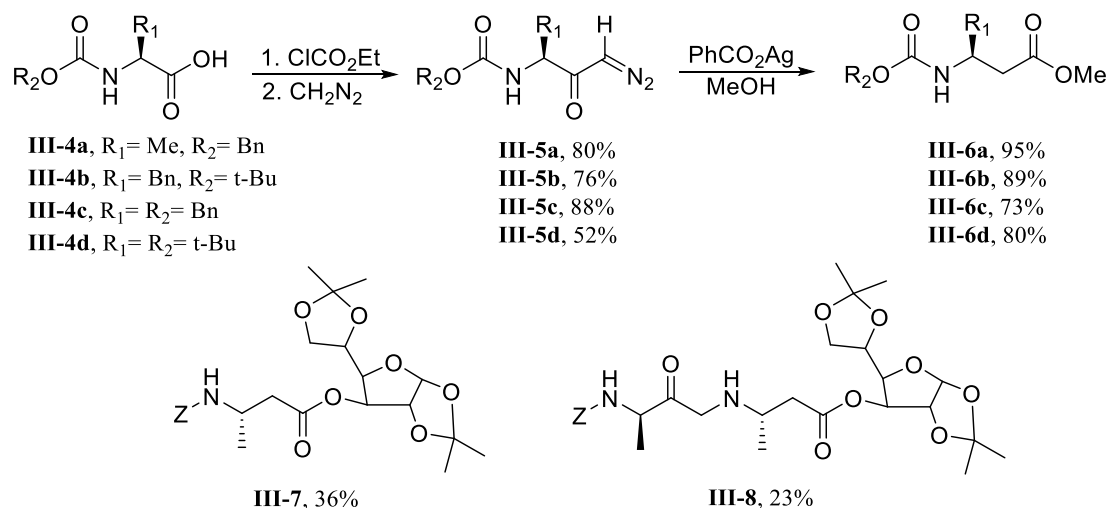
Scheme 3.1 General process of Arndt–Eistert homologation

In the 1950s, Balenović and co-workers made great efforts towards the preparation of β -amino acids using the Arndt–Eistert sequence.^{22–26} They applied this method by reacting diazomethane with N-phthaloylglycyl chloride **III-1** to give the expected diazoketone intermediate **III-2** in 75%. The diazoketone was then simply treated with silver oxide which furnished the desired homologated product **III-3** in 35% yield (**Scheme 3.2**).²⁷



Scheme 3.2 Synthesis of β -alanine derivatives

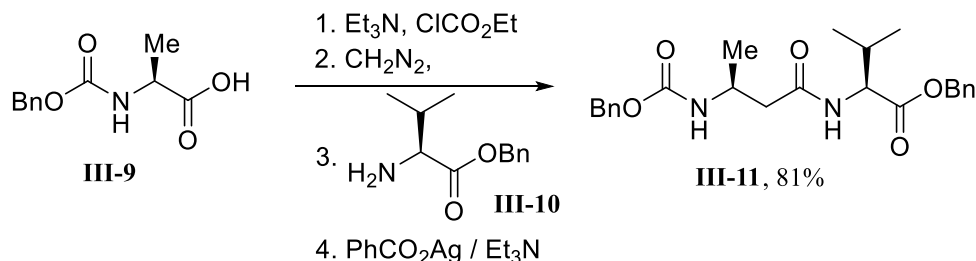
In 1995, the Seebach group investigated the scope, limitations, and stereoselectivity for the preparation of β -amino acids from α -amino acids by using the Arndt–Eistert method.²⁸ They found almost all the homologated products retained the initial configuration and gave good to excellent yields **III-6a–c**. Treatment of the diazo ketones (derived from amino acids or dipeptides) with more hindered nucleophiles such as partially protected sugars, furnished only low yields of products **III-7**, **III-8** (**Scheme 3.3**). This indicates that the yield of homologated products strongly depends on the degree of steric hindrance of the nucleophiles.



Scheme 3.3 Scope, limitations and stereoselectivity of Arndt–Eistert homologation

A more interesting application of the Arndt–Eistert reaction involves this transformation in peptide synthesis. Seebach and co-workers activated the protected α -amino acid **III-9** using

ethyl chlorocarbonate to give the mixed anhydride, which was followed by the formation of the corresponding diazoketone in THF or Et₂O. In the presence of triethylamine and silver benzoate, the diazoketone reacted with the nucleophilic valine benzyl ester **III-10** resulting in the formation of the desired peptide **III-11** in 81% (**Scheme 3.4**).²⁹

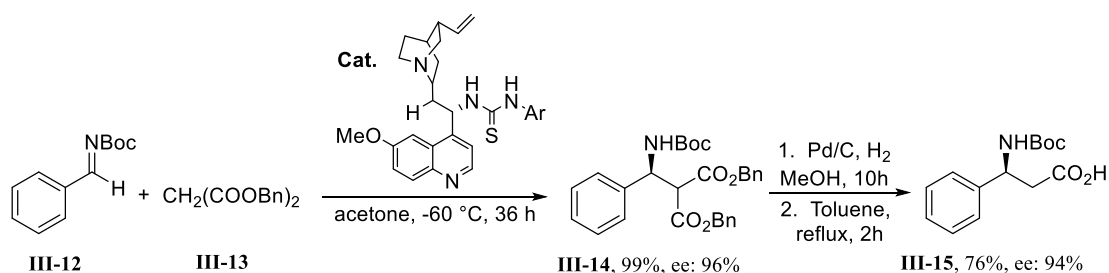


Scheme 3.4 Peptide synthesis by the Arndt-Eistert reaction

3.2.2 Mannich-type reaction

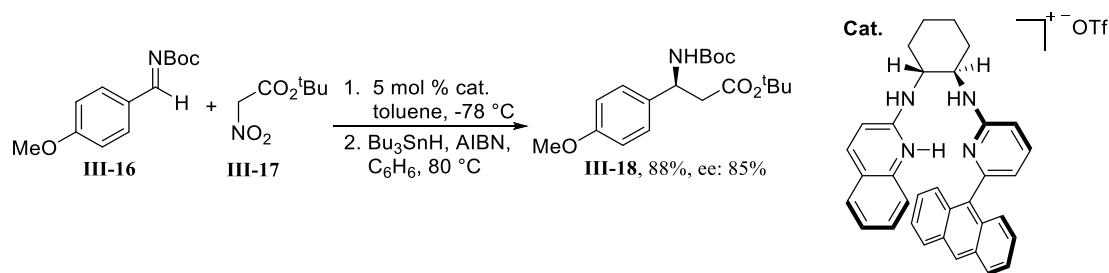
Another mature strategy for the preparation of β -alanine derivatives is to use the Mannich reaction. Apart from carbonyl compounds, any α -CH-acidic compound including nitriles, acetylenes, aliphatic nitro compounds, α -alkyl-pyridines or imines can act as nucleophiles, therefore making the Mannich process highly versatile.

The bifunctional cinchona alkaloid catalyzed enantioselective Mannich reaction was carried out by Deng's group using malonates and imines to synthesize β -amino acids.³⁰ The reaction using imine **III-12** and malonate **III-13** as starting materials almost quantitatively formed adduct **III-14** and exhibited high stereoselectivity. Instead of using strong acidic or basic conditions, β -amino acid **III-15** can be obtained by hydrogenation and decarboxylation (**Scheme 3.5**).



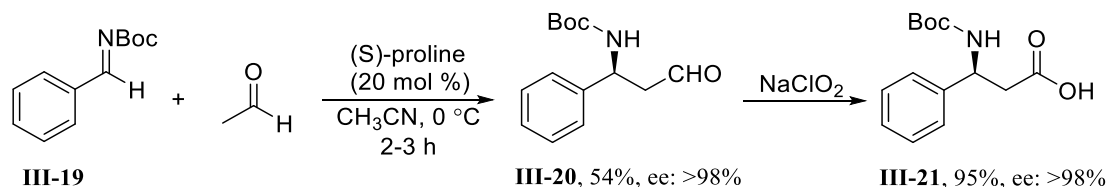
Scheme 3.5 Enantioselective synthesis of β -amino acids

In 2008, Johnston and co-workers developed an enantioselective method to synthesize β -amino acids by nucleophilic addition and radical reduction in a two-step protocol.³¹ In this transformation, imine **III-16** and α -nitro esters **III-17** provided a stereospecific aza-Henry product in the presence of the chiral catalyst. This was followed by a reductive denitration to give the desired product **III-18** in 88% yield and 85% *ee* (**Scheme 3.6**).



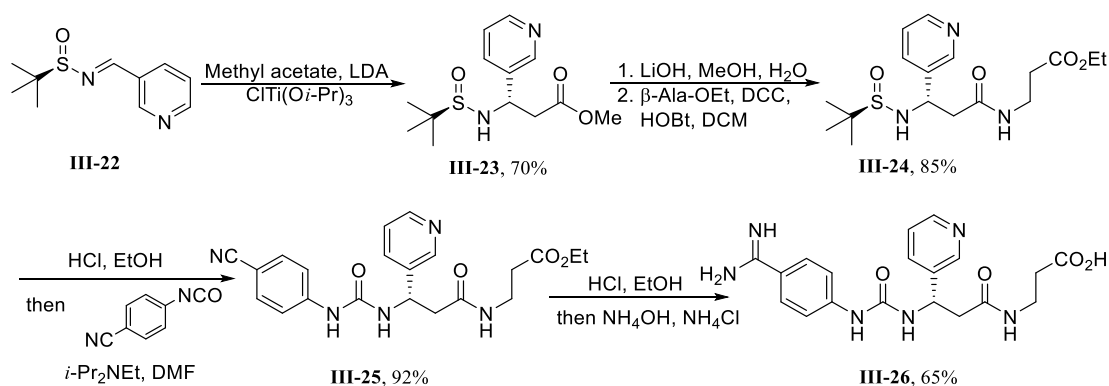
Scheme 3.6 Nitro group as a traceless agent and activator in the Mannich reaction

List described an asymmetric, proline-catalyzed Mannich reaction.³² Under very mild reaction conditions, the nucleophile, acetaldehyde, efficiently attacked the electrophilic *N*-*tert*-butoxycarbonyl (*N*-Boc)-imine **III-19** resulting in the formation of a very versatile intermediate β -amino aldehyde **III-20** with extremely high enantioselectivities (>98% *ee*). The aminoaldehyde was oxidized by sodium chlorite to the corresponding *N*-Boc amino acid **III-21** in high yield without any racemization (**Scheme 3.7**).



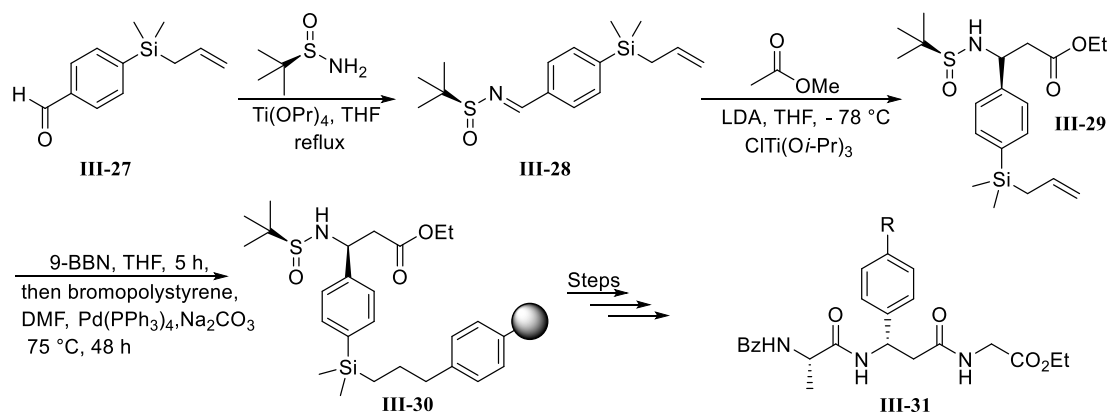
Scheme 3.7 Mannich reaction of acetaldehyde catalyzed by proline

A GPIIbIIIa antagonist was synthesized for the first time by the β -amino acid methodology by Tjoeng and co-workers.³³ In the presence of the Lewis acid $\text{CITi}(\text{O}i\text{-Pr})_3$, *N*-*t*-butanesulfinyl imine **III-22** was attacked by methyl acetate derived enolate to furnish *N*-sulfinyl β -amino ester **III-23** in 70% yield. The newly formed ester was hydrolyzed by LiOH to the free acid and then coupled with β -Ala-OEt to afford **III-24**. Removal of the *N*-sulfinyl group with HCl and further reaction with 4-cyanophenylisocyanate gave the corresponding urea **III-25**. The nitrile group was converted to amidine **III-26** to complete the formal synthesis of the agonist (**Scheme 3.8**).



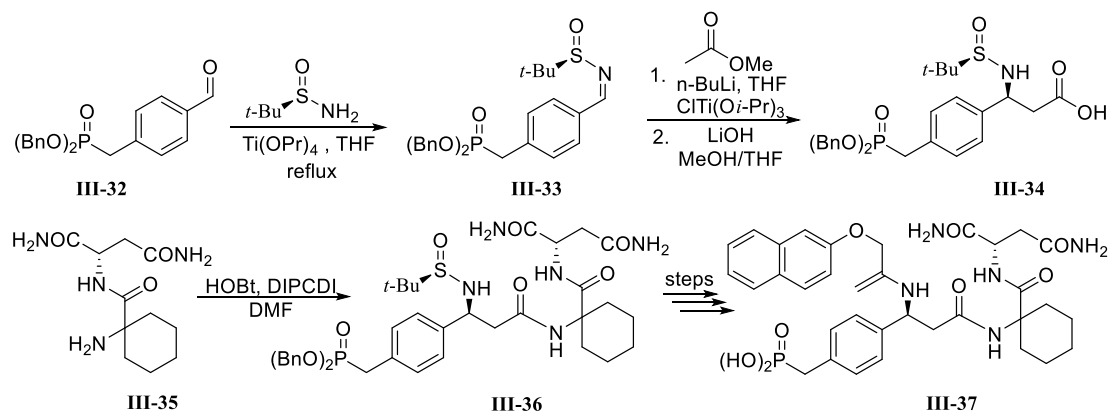
Scheme 3.8 Sulfinamide β -amino acid methodology involved in GPIIbIIIa antagonist synthesis

The Silverman group reported a traceless solid-phase synthetic route to chiral 3-aryl β -amino acid-containing peptides.³⁴ Butanesulfinyl imine **III-28** was obtained by condensing (R)-(-)-*t*-butanesulfinamide and aryl aldehyde **III-27** in the presence of titanium propoxide. The imine product was then treated with the titanium enolate (which was in turn generated by transmetalation of the lithiated methyl acetate with $\text{ClTi}(\text{O}i\text{-Pr})_3$), and provided the β -amino acid ester **III-29**. This was followed by hydroboration and Suzuki coupling reactions to access intermediate **III-30**. Several more steps eventually gave the desired 3-aryl- β -alanine-containing tripeptides **III-31** (Scheme 3.9).



Scheme 3.9 Traceless solid-phase synthesis of chiral 3-aryl β -amino acid containing peptides

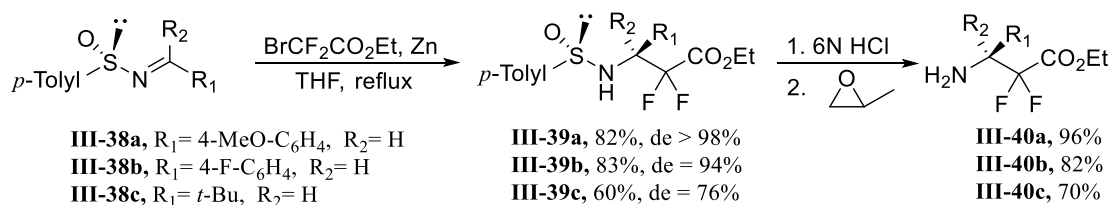
A joint research group at the National Institutes of Health and the University of Michigan developed suitably protected β -amino phosphotyrosyl mimetic for peptide synthesis.³⁵ A Mannich-type reaction took place between *N*-sulfinyl imine **III-33** and the enolate of methyl acetate, followed by hydrolysis to afford *N*-sulfinyl-protected β -amino acid **III-34**. The condensation of amine **III-35** and acid **III-34** resulted in formation of the intermediate amide **III-36**, which eventually delivered the final product **III-37** within a few steps (Scheme 3.10). These transformations further demonstrate the suitability of this methodology in the synthesis of Grb2 SH2 domain-binding ligand.



Scheme 3.10 Synthesis of Grb2 SH2 domain-binding ligand

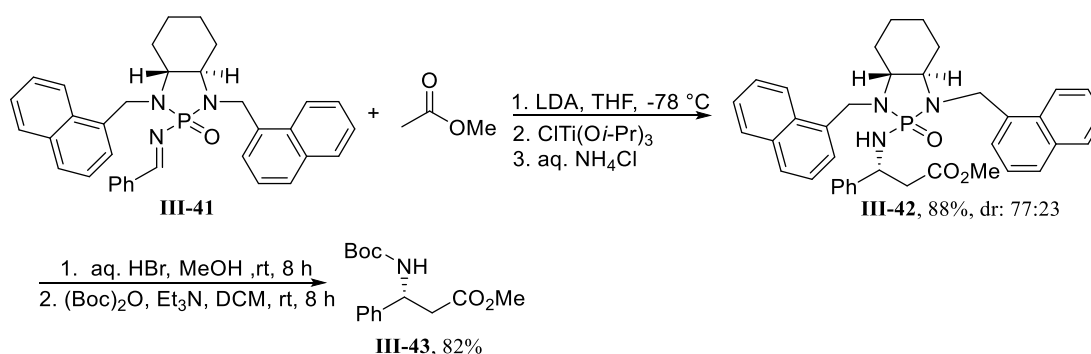
carried out in Seebach's group.³⁶ The development of his synthetic methods allows such compounds to be obtained on a relatively large scale and in an enantiomerically pure form, in order to meet the needs of systematic biological research.

The sulfinyl group's use as a chiral auxiliary in the asymmetric synthesis of α,α -difluoro- β -amino acids using the Reformatsky reaction was described by Sorochinsky and co-workers.³⁷ The reaction was carried out between enantiomerically pure aryl *N*-*p*-toluenesulfinyl imines (**S**)-**III-38** and ethyl bromodifluoroacetate in the presence of Zn dust, which yielded the desired *p*-toluenesulfinamides **III-39** with a high ratio of diastereomers. Both electro and stereo effects were tested. High diastereoselectivity was observed in substituted aromatic substrates **III-39a**, **b**. However, bulky substituent **III-39c** resulted in lower yield and diastereoselectivity. Hydrolysis of the sulfinamides with 6N HCl, followed by treatment with propylene oxide afforded the corresponding α,α -difluoro- β -amino acids **III-39a, b** (Scheme 3.11).



Scheme 3.11 Asymmetric synthesis of α,α -difluoro- β -amino acids

N-phosphonyl imine also can act as a chiral auxiliary group to stereoselectively synthesize β -amino acids.³⁸ Phosphoryl imine **III-41** when reacted with the enolate of methyl acetate in the presence of triisopropoxytitanium(IV) chloride and then quenched by aqueous ammonium chloride to furnish a high yield but medium diastereoselectivity of intermediate **III-42**. Subjecting the intermediate to HBr/MeOH, followed by a protection step provided the optically pure product **III-43** in 82% over all yield (Scheme 3.12).



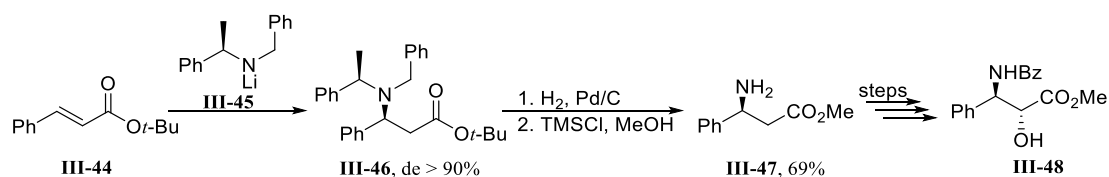
Scheme 3.12 Chiral *N*-phosphonyl group assisted asymmetric synthesis of β -amino acids

3.2.3 Conjugated addition to α , β -unsaturated carbonyl compounds

From a retrosynthetic perspective, β -amino acids can be disconnected into two parts: a nitrogen-based nucleophile and an appropriately functionalized α , β -unsaturated carbonyl compound. Hence, the Michael reaction stands out to be an attractive approach.

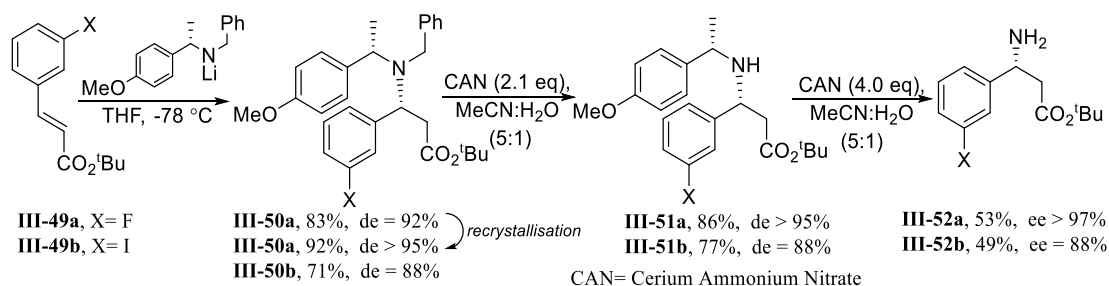
(i) Additions of stereocenter bearing nitrogen nucleophiles to Michael Acceptors

Enantiopure 2(R)-hydroxy-3(R)-*N*-benzoylamino-3-phenylpropionic acid, the stereoisomer of Taxol's side chain was produced in Juaristi's group through a chiral Michael addition manner.³⁹ *tert*-Butyl cinnamate **III-44** was reacted with chiral lithium amide **III-45** derived from (*R*)-benzyl(α -methylbenzyl)amine to afford highly diastereoselectively Michael adduct **III-46**. This was followed by hydrogenation and esterification which yielded an enantiopure β -amino acid intermediate **III-47**. Since the chiral center was contained in the intermediate, it allowed the possibility to stereoselectively introduce another hydroxyl group in the final product **III-48** (Scheme 3.13).



Scheme 3.13 High 1,2-stereoiduction in the preparation of stereoisomer of Taxol's side chain

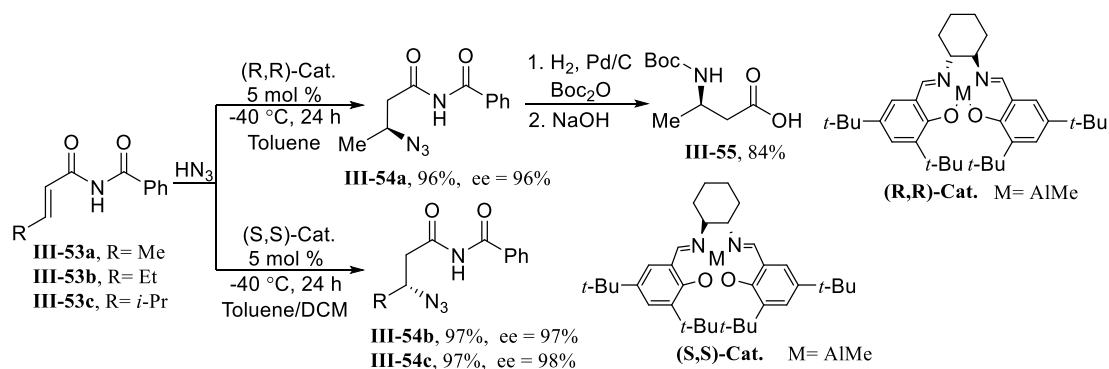
In 2000, Davies *et al.* reported a method for the asymmetric synthesis of β -haloaryl- β -amino acids.⁴⁰ In this process, *t*-butyl cinnamates **III-49** was coupled with lithium amide to furnish adducts **III-50** in high yields and *de*. It is noteworthy that the *de* of adduct **III-50a** can be enhanced to > 95% after a simple recrystallization. The stepwise deprotection was carried out using aqueous cerium ammonium nitrate (CAN) rather than by hydrogenation due to the incompatibility of the sensitive haloaryl functionality within the substrate. The desired β -haloaryl- β -amino esters **III-51a, b** were obtained in good yields and high *ee* (Scheme 3.14).



Scheme 3.14 The asymmetric synthesis of β -haloaryl- β -amino acids

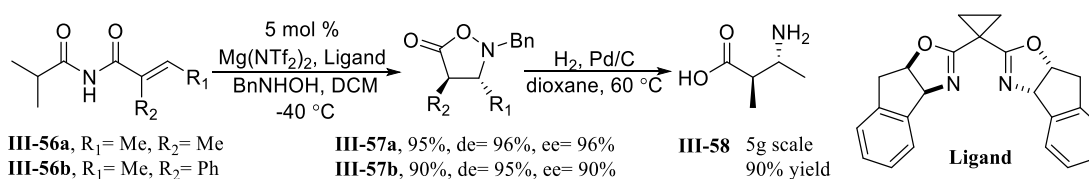
(ii) Enantioselective organocatalytic methods

Jacobsen's group reported a chiral (salen)Al(III) complex catalyzed asymmetric conjugate addition of hydrazoic acid to α , β -unsaturated imides for the synthesis of β -amino acids.⁴¹ Imides **III-53a-c**, prepared by the Horner-Emmons reaction, reacted enantioselectively with hydrazoic acid in the presence of the chiral (salen) aluminum complex. All the Michael adducts gave excellent yields and enantioselectivity, but the configuration depends on the catalyst type **III-54a** vs **III-53b, c**. The β -azido imide adduct **III-54a** is the precursor to a β -amino acid. A hydrogenation and hydrolysis thus furnished the *N*-Boc-protected carboxylic acid **III-55** in 84% yield (Scheme 3.15).



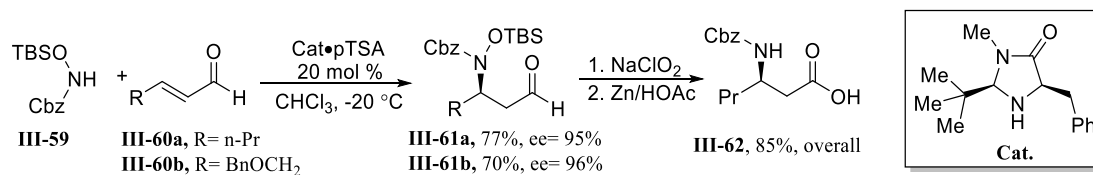
Scheme 3.15 Organocatalyzed conjugate addition of hydrazoic acid to unsaturated imides

Sibi *et al.* synthesized a variety of α , β -disubstituted- β -amino acids with high diastereo- and enantioselectivity by using a chiral Lewis acid-mediated conjugate addition of an amine to various unsaturated imides.⁴² In the presence of the chiral catalyst the reaction proceeded smoothly between imides **III-56a, b** and *N*-benzylhydroxylamine to provide isoxazolidinones **III-57a, b** in good diastereoselectivity and enantioselectivity. Conversion of the isoxazolidinones to the corresponding amino acids was accomplished by a simple hydrogenolysis. Catalytic hydrogenation of **III-57a** by H₂, Pd/C system on a 5 g scale gave (2*R*,3*R*)-3-amino-2-methylbutanoic acid **III-58** in 90% yield (Scheme 3.16).



Scheme 3.16 Enantioselective synthesis of α , β -disubstituted- β -amino acids

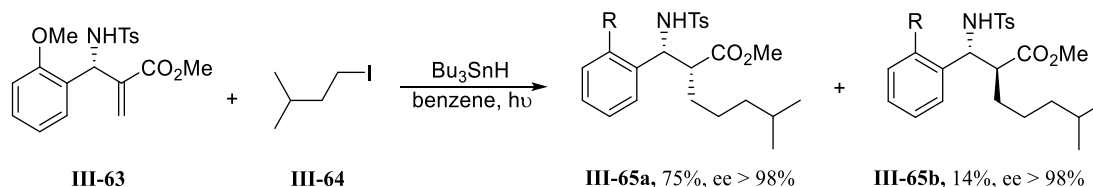
The MacMillan group reported firstly the enantioselective conjugate addition to unsaturated aldehydes by a rationally designed N-centered nucleophile.⁴³ In this process, the catalyst reacted with aldehydes **III-60** to form iminium while carbamate **III-59**, activated by silyloxyl group, acted as the nucleophile to enantioselectively form β -amino aldehydes **III-61a and b** in good yield. In-situ Pinnick oxidation provided the corresponding β -oxyamino acid which was followed by an N-O bond cleavage using Zn/AcOH to give the final protected amino acid **III-62** in 85% yield (Scheme 3.17).



Scheme 3.17 Enantioselective organocatalytic amine conjugate addition

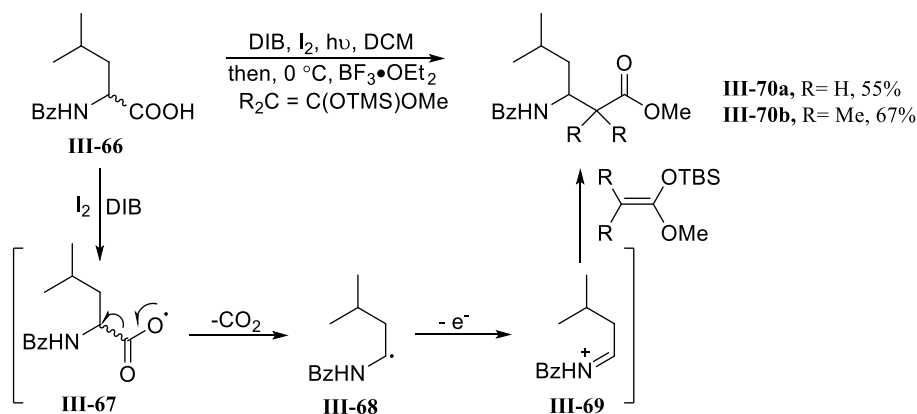
3.2.4 Radical approaches to β -amino acids

Kündig *et al.* developed a stereospecific radical route to β -amino acid derivatives.⁴⁴ It involves the reaction between an enantiomerically pure alkene **III-63** and iodide **III-64**, which afforded the two diastereomeric β -amino acid derivatives **III-65a** and **III-65b** in the ratio of 5.4/1 and in combined 89% yield (**Scheme 3.18**). This transformation demonstrates that a chiral amine is able to induce a hydrogen transfer reaction to an adjacent radical in a stereoselective way.



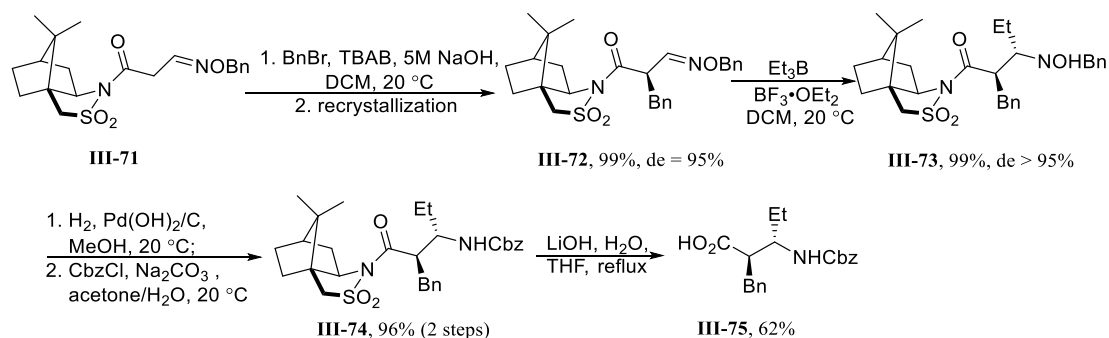
Scheme 3.18 1,2-asymmetric induction in the synthesis of β -amino acid derivatives

In the synthesis of β -amino acids from α -amino acids, Boto and co-workers reported a one-pot procedure that involves a radical fragmentation–nucleophilic addition sequence.⁴⁵ The mixture of starting α -amino acid, DIB ((diacetoxyiodo)benzene), and iodine **III-66** was subjected to visible light to generate carboxyl radical **III-67**, which then fragmented into radical **III-68** with loss of CO_2 . By losing an electron, intermediate **III-68** is oxidized into a carbocation corresponding to acyliminium ion **III-69**. Addition of the nucleophilic enolsilyl ether to the electrophilic **III-69** afforded the β -amino acid **III-70a, b** in 55% and 67% yield, respectively (**Scheme 3.19**).



Scheme 3.19 One-pot synthesis of β -amino acid from α -amino acid

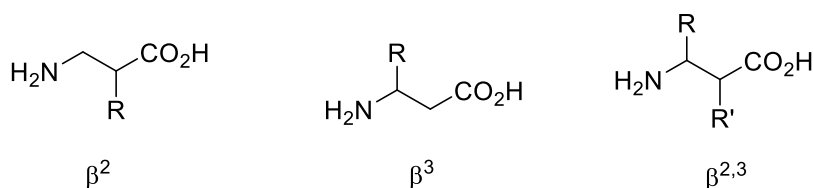
Naito's group has applied a radical addition to oxime ethers for the asymmetric synthesis of α , β -dialkyl- β -amino acids.⁴⁶ The benzylation of sultam derivative **III-71** took place in alkali solution using alkyl bromides in the presence of tetrabutylammonium bromide as the phase-transfer catalyst. This afforded benzylated oxime ether **III-72** in 99% yield and 95% *de*. The second step is a radical addition to the oxime ether catalyzed by $\text{BF}_3 \cdot \text{OEt}_2$, which gave the ethylated α, β -dialkyl- β -amino acid derivative **III-73** with high diastereoselectivity (*de* > 95%) in almost quantitative yield (99%). No reaction was observed in the absence of $\text{BF}_3 \cdot \text{OEt}_2$. The post modification was a hydrogenation and protection sequence to form intermediate **III-74** in 96% yield. Finally, a hydrolysis step to remove the sultam auxiliary afforded the enantiomerically pure α , β -dialkyl- β -amino acid **III-75** in 62% yield without any loss of stereochemical purity (**Scheme 3.20**).



Scheme 3.20 Sultam assisted asymmetric synthesis of β -amino acid derivatives

3.3 The xanthate route to β^2 -amino acids and to β -heteroarylethylamines

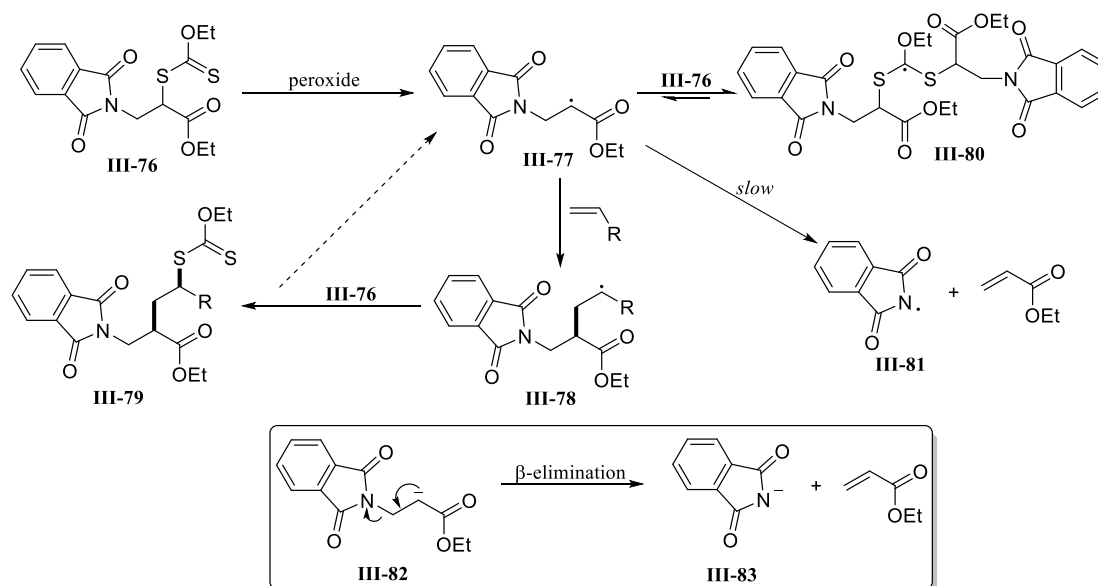
Although various methods have been developed for the synthesis of β -amino acids, drawbacks such as harsh reaction conditions, incompatibility with some functional groups and the utilization of toxic reagents still remain. Moreover, most of the approaches mentioned above are concerned with β^3 -amino acids (*The β -amino acids can be named by β^2 -, β^3 -, and $\beta^{2,3}$ -amino acids which indicated the position of the side chain(s) on the 3-aminoalkanoic acid skeleton, Scheme 3.21*) according to the nomenclature introduced by Seebach.⁴⁷⁻⁴⁸ However, while β^2 -amino acids have drawn comparatively less attention, they have nevertheless shown much potential in organic synthesis and in pharmaceutical application.⁴⁹⁻⁵⁰ A convenient route to access β^2 -amino acids is therefore highly desired.



Scheme 3.21 Definition of substituted β -amino acids

Over the past years, our group has explored the potential of the degenerative xanthate addition-transfer process for the synthesis of various amino acid derivatives. Although α -, β^3 -, and γ -amino acids were successfully synthesized using the xanthate method, access to β^2 -amino acids is still needed due to their various applications. In this section, we describe a convergent and flexible approach to β^2 -amino acids that takes advantage of β -imido radicals as synthons and the unique degenerative addition transfer of xanthate.

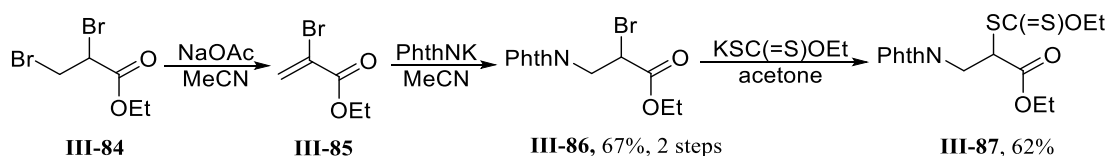
With the mechanism of degenerative radical addition-transfer of xanthates in mind, we designed a process involving β -imido radicals in order to synthesize β^2 -amino acids (**Scheme 3.22**). The radical chain would be initiated by a peroxide in order to generate the β -imido radical **III-77** from xanthate **III-76**. Most of the time, the concentration of the β -imido radical remains very low because it is stored in a dormant state **III-80**. Furthermore, β -elimination to phthalimidyl radical **III-81** is expected to be relatively slow compared to the addition to the alkene. The β -imido anion **III-82** which would readily eliminate phthalimidyl anion **III-83**. Unlike the anionic intermediate, this method used to generate the β -imido radical does not require any alkaline reagents, which means that this radical approach would be compatible with a broad range of polar functional groups.



Scheme 3.22 Radical-based route to β^2 -amino acids

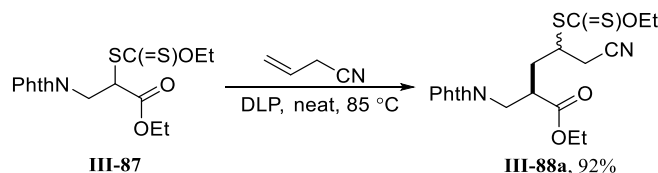
3.3.1 Preliminary experiments

To achieve this goal, it was first necessary to synthesize the requisite starting xanthate. To this end, the starting material ethyl 2,3-dibromopropionate **III-84** was treated with sodium acetate which afforded the β -elimination intermediate **III-85**. This intermediate can be directly used in the Michael addition to give intermediate **III-86** in 67% yield over two steps by simple filtration. The substitution reaction between the bromide and potassium-*O*-ethyl dithiocarbonate provided the final xanthate **III-87** in a useful yield of 62% (**Scheme 3.23**).



Scheme 3.23 Preparation of the starting xanthate

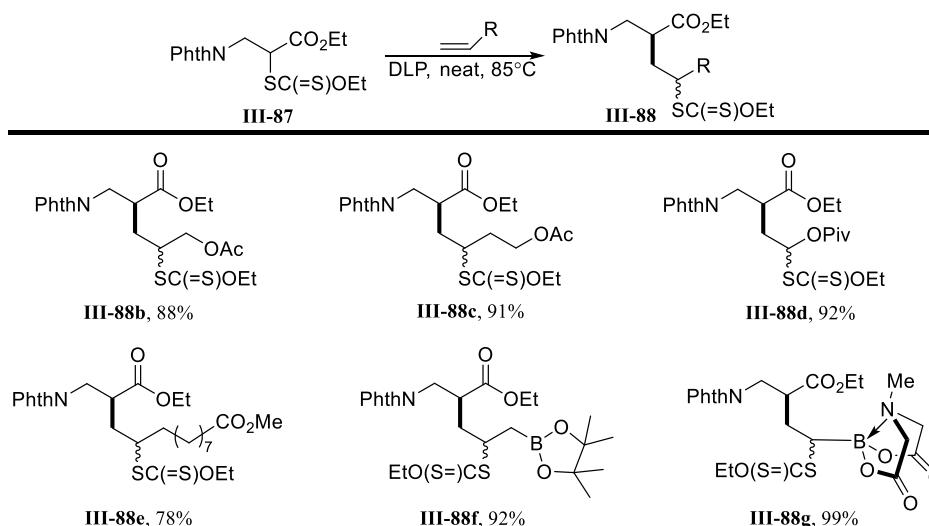
With the xanthate in hand, we carried out the first reaction with allyl cyanide and were pleased to find that no β -scission of the phthalimide was observed and the desired radical adduct was isolated in excellent yield (92%) (Scheme 3.24). From an economical and practical perspective, the reaction conditions are also attractive: the reaction can be performed neat. This observation strongly supports the mechanism of the xanthate degenerative radical addition-transfer process, in contrast an organotin hydride mediated radical reaction which would have to be accomplished in a highly diluted solution. Moreover, the reaction is efficient enough to be complete in only a few hours, and the non-toxic initiator DLP (dilauroyl peroxide) is only needed in small amount.



Scheme 3.24 Addition of xanthate **III-87** to allyl cyanide

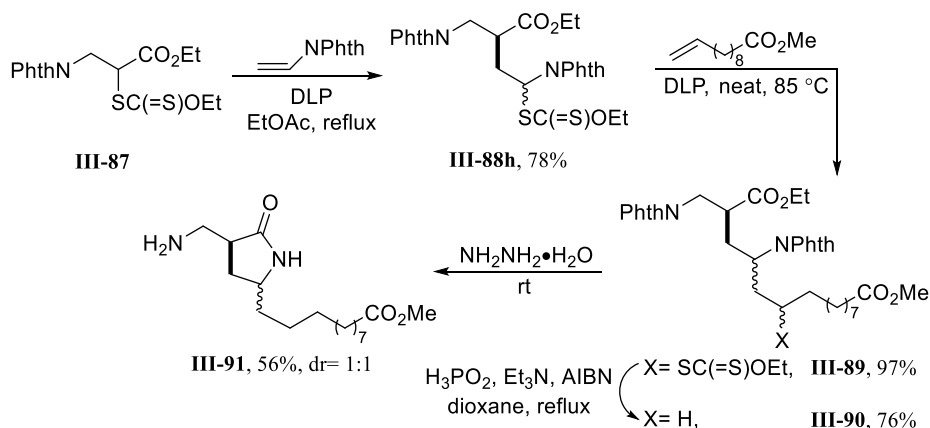
3.3.2 Scope of the xanthate route to β^2 -amino acid derivatives

Encouraged by the first radical addition, we extended the scope to alkenes bearing various functional groups (Scheme 3.25). The yield of radical adducts are slightly higher than typical xanthate additions. It is speculated that the electrophilic properties of the β -imido radical **III-77** are increased because of the presence of adjacent phthalimide group. All the reactions were performed neat, without solvent, except for the addition to vinyl MIDA boronate (example **III-88g**), which was performed at a 1 M concentration in ethyl acetate. Moreover, the yield of the vinyl MIDA boronate adduct was almost quantitative. To explain this efficiency, we postulate that the polarity of electrophilic β -imido radical **III-77** and electron-rich vinyl MIDA boronate are matched with each other. The hybridization of boron has changed from sp^2 to sp^3 , through coordination with the nitrogen of the MIDA group, which leads to the boron being electron rich and releases electrons into the attached vinyl group.⁵¹ In addition to the mild conditions, these reactions are all performed very efficiently with the reaction time being typically 2 hours. Unlike the base-catalyzed alkylation, the radical route shows its advantages in functional group compatibility. Addition of xanthate to vinyl pivalate (Piv = pivalate) provided a particularly interesting adduct (**III-88g**) where the carbon attached to the xanthate and the pivalate has the same oxidation level of an aldehyde. Such compounds have a very rich chemistry.⁵² In all of these additions, a 1:1 mixture of diastereoisomers is produced.



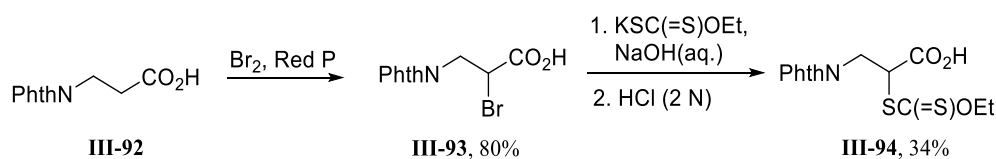
Scheme 3.25 Synthesis of protected β^2 -amino acid derivatives

The xanthate group in the adduct can either act as another starting point for a second radical addition to create another carbon-carbon bond or can be reductively removed to simplify the structures. Both of these possibilities are illustrated in the sequence in **Scheme 3.26**. The radical addition of xanthate **III-87** to *N*-vinyl phthalimide was carried out at a 1 M concentration in ethyl acetate to afford the first adduct **III-88h** in a good yield of 78%. Without any purification, adduct **III-88h** serves as a new starting xanthate and adds to methyl 10-undecenoate to give a second adduct **III-89** in 97% yield. Based on previous findings discussed earlier, xanthates geminal to imide groups are suitable partners for radical additions, and provide a very powerful route to functional amines.⁵³ Indeed, this property has been utilized for the preparation of β^3 -amino acids.⁵⁴ The xanthate group of the second adduct **III-89** was reductively removed using Barton's method⁵⁵ to furnish intermediate **III-90**, and this was followed by the deprotection of phthalimide group which resulted in a spontaneous ester aminolysis to afford aminomethyl substituted lactam **III-91** in 56%. Thus, the xanthate addition-transfer has been successfully used to achieve two successive intermolecular additions, and therefore allows a convenient and efficient construction of complex structures that would be very tedious to obtain by conventional ionic or organometallic methods.



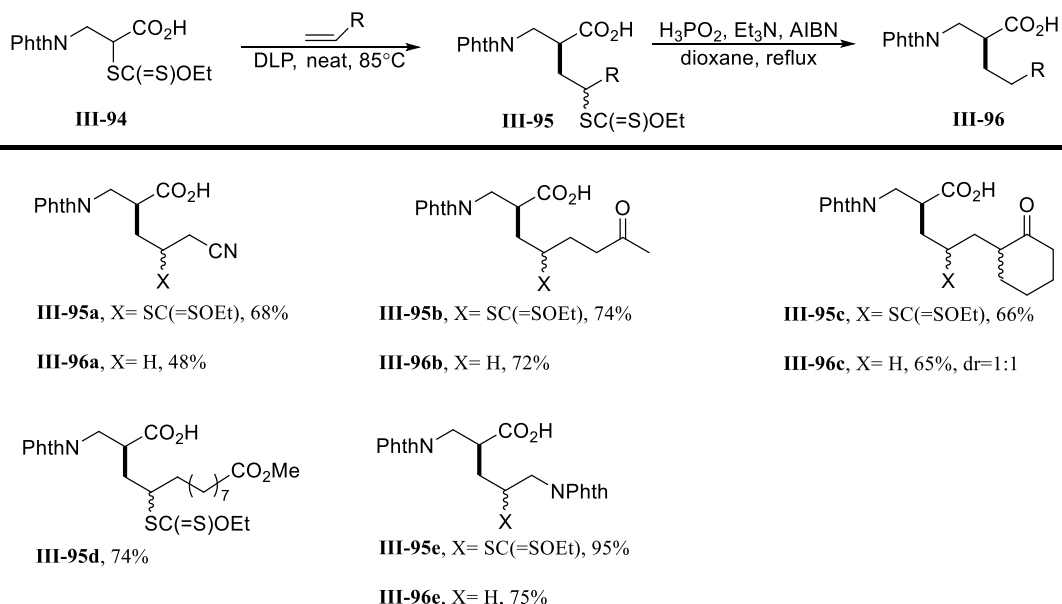
Scheme 3.26 Example of successive radical additions

Other than an ester group, we extended our radical precursor to the free carboxylic acid bearing xanthate **III-94**. To obtain this xanthate, we used 2-phthalimidopropionic acid **III-92** as the starting material. The bromination was conducted by the classical Hell-Volhard-Zelinsky reaction,⁵⁶ where 2-phthalimidopropionic acid **III-92** was reacted with bromine in the presence of a catalytic amount of red phosphorus. The bromide intermediate **III-93** underwent a substitution with the xanthate salt to provide the desired xanthate **III-94** in 34% yield (Scheme 3.27). This substitution reaction leading to the desired xanthate was surprisingly inefficient and more work is still needed to improve the yield.



Scheme 3.27 Synthesis of free carboxylic acid bearing xanthate

As expected, the presence of a free carboxylic acid did not significantly impact the radical process and all of the radical additions proceeded as expected, although the yields of adducts **III-95a-e** were not as high as the corresponding ester **III-87**. By using Barton's reagent, the adducts could be reduced easily and afforded the corresponding dexanthylated products **III-96a-e** (Scheme 3.28).



Scheme 3.28 Synthesis of *N*-Protected β^2 -amino acid derivatives

Direct alkylation of free carboxylic acids by the ionic approach would require two equivalents of lithium amide and would also suffer from issues of functional group compatibility. Although the unique advantages of α -alkylation of a free carboxylic acid through radical intermediates is obvious, it has been seldom used hitherto. The easily broken carbon-

iodine bond has been exploited in the case of iodoacetic and 2-iodopropionic acids to accomplish intermolecular radical additions to unactivated alkenes but the scope of this methodology remains undefined.⁵⁷⁻⁶⁵ By using the Hell-Volhard-Zelinsky reaction and other methods, such as the radical addition of a xanthate to acrylic acid, many α -xanthylic carboxylic acids could be accessed and applied to the synthesis of numerous diverse structures.

3.3.3 Synthesis of N-protected heteroarylethylamines

Another fruitful application is the direct introduction of an ethylamine moiety into heteroaromatics using xanthate **III-94**. This cheaper and easily handled radical process is an ideal alternative to the traditional methods for Csp²-Csp³ bond formation, such as Kumada, Still, Negishi, and Suzuki couplings. β -(Hetero)arylethylamines represent perhaps the most important class of substances interacting with the central nervous system (CNS).⁶⁶ Some of these compounds are listed below (**Figure 3.2**). These include endogenous neurotransmitters, such as dopamine **III-97** and serotonin **III-98**, drugs used for the treatment of attention deficit hyperactivity disorder (ADHD), narcolepsy, and obesity. Amphetamine **III-99** and natural products with psychedelic and hallucinogenic activity or even synthetic drugs such as Venlafaxine **III-102** are used for the treatment of depression, general anxiety disorder, social phobia, panic disorder, and vasomotor symptoms. Another example is the weight-loss drug, Lorcaserine **III-103**. The ethylamine motif highlighted in bolded format can be a simple pendant, substituted on the carbon chain or on the nitrogen, or even part of a ring.

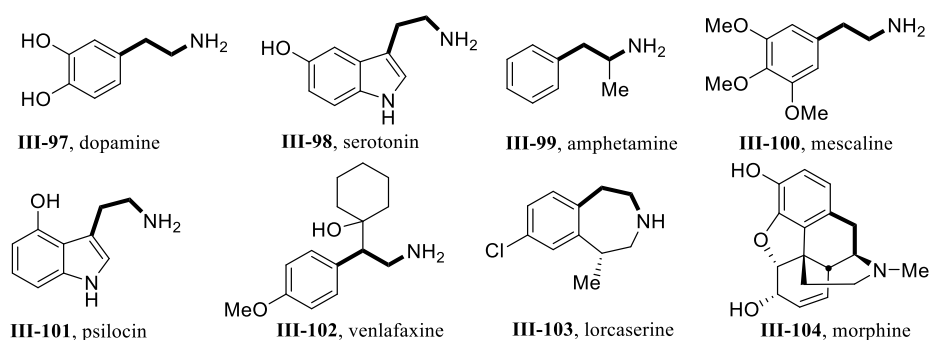
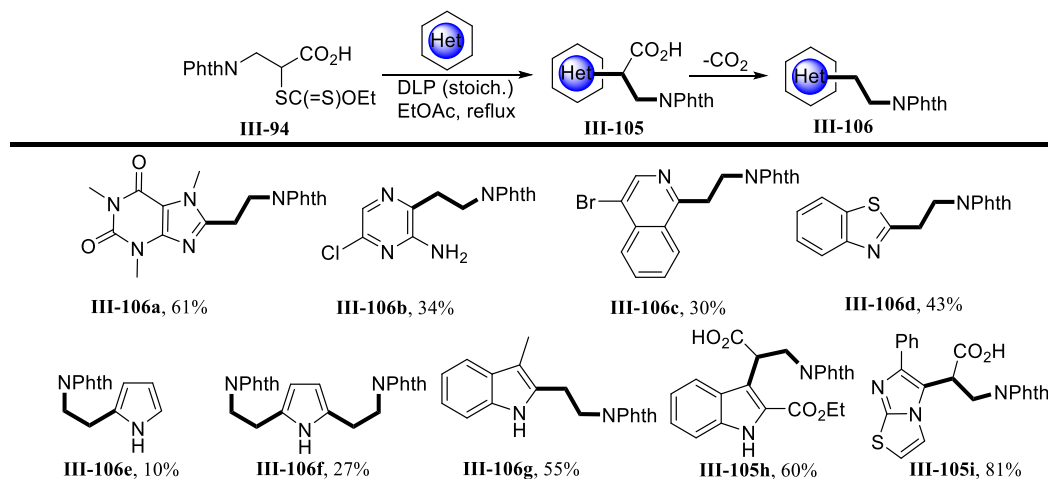


Figure 3.2 Examples of biologically active β -(hetero)arylethylamines.

In the presence of stoichiometric amounts of peroxide,⁶⁷ xanthate **III-94** was successfully added to a series of heteroaromatic structures albeit in low to moderate yield. In the case of compounds **III-106a-g**, the addition to the heteroaromatic ring resulted in the corresponding phthalimide protected β -aminoethyl derivative **III-106** by spontaneous decarboxylation of primary adducts **III-105**. Presumably, the ring nitrogen adjacent to the alkyl substituent, could in some cases form a six-membered ring transition state with the carboxylic acid group to facilitate the spontaneous decarboxylation to give the decarboxylated products **III-106**. It is interesting to note the reaction with pyrrole gave rise to both the monoadduct **III-106e** and bis-adduct **III-106f** with the latter being the major product. The observation of the xanthate adding to different positions on the substituted indole supported our hypothesis. The addition of xanthate to 3-methylindole afforded the decarboxylation product **III-106g** while coupling with

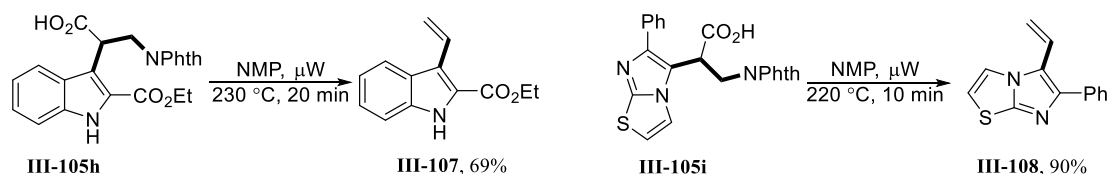
ethyl 2-indolecarboxylate gave the carboxylic acid preserved product **III-105h**, in 60% yield. The reaction of xanthate **III-94** and 6-phenyl imidazo[2,1-b]thiazole did not give the decarboxylated product. However, this transformation proceeded with high efficiency and the product **III-105i** crystallized directly from the reaction mixture and was isolated by simple filtration in 81% yield. This reaction was easily scaled up (1.2 g) albeit with a somewhat lower yield (60%) (**Scheme 3.29**).



Scheme 3.29 Synthesis of N-protected heteroarylethylamines

3.3.4 An unexpected vinylation reaction

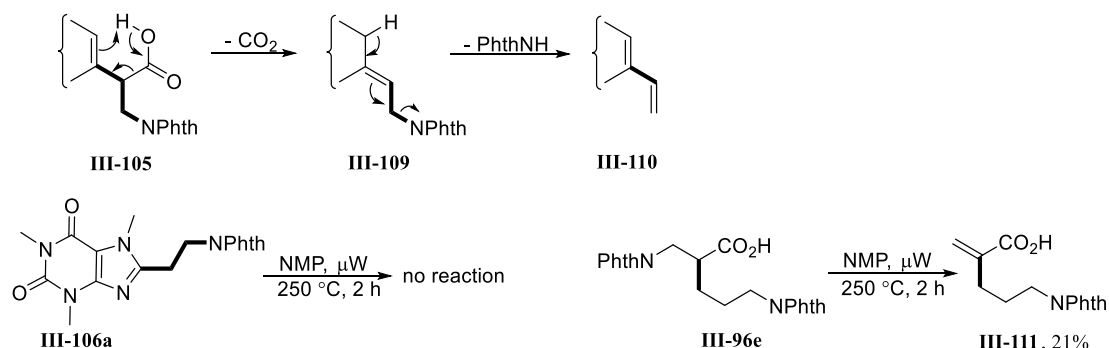
In an attempt to decarboxylate radical adducts **III-105h** and **III-105i**, we briefly heated a solution of the carboxylic acids in *N*-methylpyrrolidone (NMP) in a microwave oven at 220–230°C,⁶⁸ but the reaction afforded instead vinyl derivatives **III-107** and **III-108**, respectively. (**Scheme 3.30**)



Scheme 3.30 Unexpected formation of vinyl derivatives

To explain the formation of these vinyl groups, we assume that the high temperature facilitates the decarboxylation of adducts **III-105** and the retro-ene reaction leads to intermediate **III-109** which then eliminates phthalimide to restore the aromaticity of the heteroaromatic ring (**Scheme 3.31**). To verify this hypothesis, a few control experiments were conducted. In order to obtain the decarboxylated compound without concomitant elimination of the phthalimide, we gradually heated the adduct **III-105i** as a solution in NMP in a microwave oven. Despite this precaution decarboxylative elimination could not be avoided and the formation of the vinyl derivatives **III-108** obtained at 170°C. The decarboxylation process appears to be necessary for the elimination of the phthalimide. Heating caffeine derivative **III-**

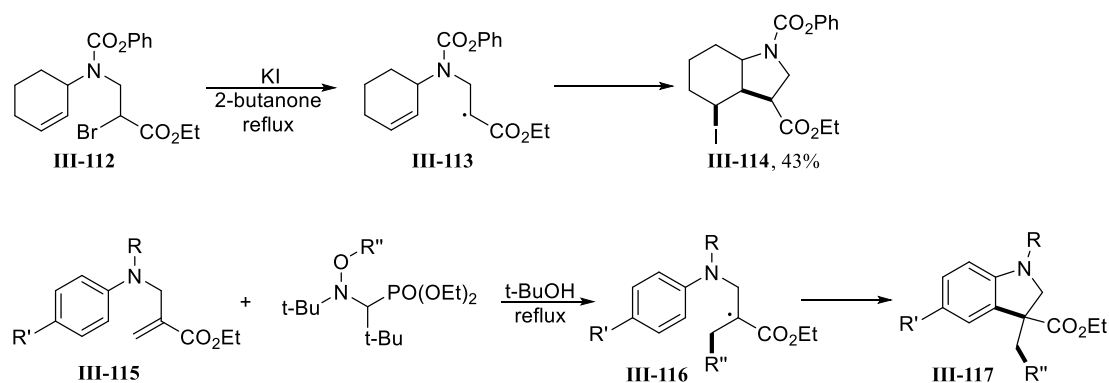
106a at 250°C in a microwave oven for a longer period of time did not result in any reaction. Furthermore, we found that under these harsher conditions, aliphatic acid **III-96e**, which cannot undergo a retro-ene reaction with loss of CO₂, was converted in poor yield into acrylic acid product **III-111**.



Scheme 3.31 Possible pathway for vinylation

3.4 Conclusion and perspective

The pathway for the preparation of (hetero)arylamines complements the method recently described by Jui and co-workers, in which (hetero)arylamines were synthesized by adding (hetero)aryl radicals to enamide.⁶⁹ It is further noteworthy that radical reactions have almost never been used for the synthesis of β^2 -amino acids. In the literature, we only found two research groups engaged in the radical route to β^2 -amino acids derivatives and in both cases an intramolecular reaction was involved (Scheme 3.31).⁷⁰⁻⁷³



Scheme 3.31 Literature examples of β^2 -amino acid esters obtained by radical cyclization

Xanthates give a larger scope for intermolecular additions, especially to unactivated alkenes. This leads to a versatile, modular and flexible approach to diverse β^2 -amino acids thereby greatly expanding the range of available structures. As mentioned in the introduction, β^2 -amino acids are much less accessible than the more common β^3 -amino acids. Furthermore, both β^2 -amino acids and β -heteroarylethylamines can be prepared from the same xanthate **III-94**, which is convenient for synthesis and valuable for medicinal chemists. The cheapness and ready

availability of the reagents, the mildness of the experimental conditions, and the compatibility with many functionalities, especially polar groups are significant practical advantages.

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**Chapter 4 Application of radical reactions for the
synthesis of ketones**

4.1 Introduction

Arguably, the carbonyl group is the most ubiquitous and most important functional group in organic synthesis.¹ Not only is it ubiquitous in natural products, but it is also considered to be key element in most synthetic schemes due to the electrophilicity of the carbon-oxygen double bond.² Piroxicam which is sold under the trade name ‘Feldene’ (**IV-1**) was developed by the Pfizer company and approved for medical use in 1979. It is used as a nonsteroidal anti-inflammatory drug (NSAID) of the oxicam class to relieve the symptoms of painful inflammatory conditions like arthritis.³⁻⁵ It should be noted that Piroxicam exists as a stable enol form of a 1,3-dicarbonyl compound. Prostaglandin E₂ (**IV-2**) is an essential medicine used to induce labor and recommended by the WHO.⁶ Besides, it has a specialized role in controlling the potentially harmful activation of CTL-, Th1-, and NK cell-mediated type 1 (cytotoxic) immunity, especially at later stages of immune responses.⁷ Research also indicates that it acts as a potent regulator of haematopoietic stem cells in vertebrates, and is probably useful in treating patients with bone marrow failure or following transplantation.⁸ Raspberry ketone (**IV-3**) is a natural phenolic compound which can be found in raspberries and also in various fruits.⁹ It is not only frequently used as a spice in cosmetics and as a flavoring agent in food but also helps prevent obesity and activate lipid metabolism in rodents.¹⁰ As well as having useful reactivity, aldehydes are frequently used in perfumes due to their pleasant odour. It is found that α -alkylated aldehydes have a stronger and sweeter smell than their straight-chain isomers. Among this series of aldehydes, a very popular component in perfume is 2-methylundecanal (**IV-4**), which is a key component of the fragrance of Chanel No. 5 because of the pleasant, stable, citrus-ambergris-like fragrance (**Figure 4.1**).¹¹

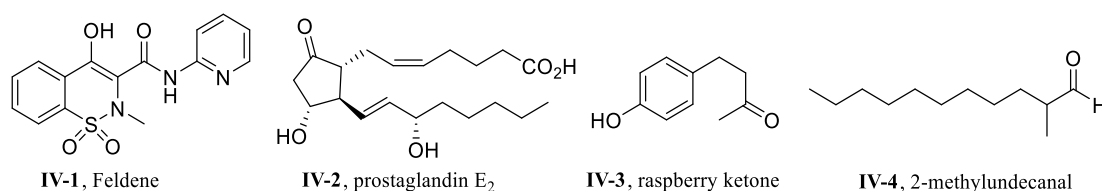
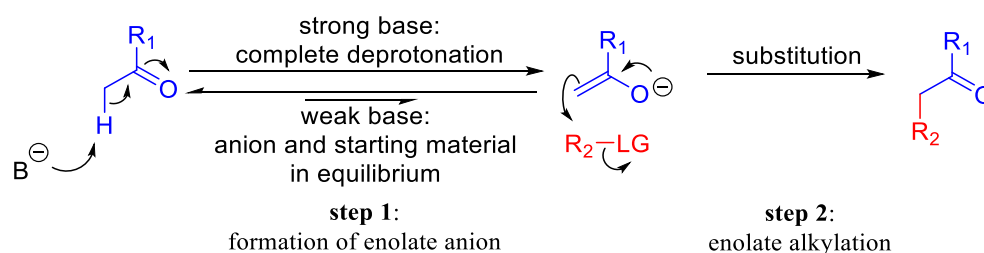


Figure 4.1 Carbonyl derivatives presented in pharmaceutical and fine chemicals

To diversify carbonyl derivatives, the alkylation of enolates plays a central role. As discussed at the beginning of this section, the C-O double bond gives aldehydes and ketones high reactivity but also can be problematic. Generally speaking, the alkylation of ketone faces many limitations such as chemo and regioselectivity problems, poly alkylation, competing aldol reaction and lack of polar functional group compatibility. To overcome these drawbacks, enormous efforts have been devoted to enolate chemistry. In this section, we will briefly review previous work from two aspects, ionic methods and radical based methods in the synthesis of ketones.

4.2 Ionic methods in the synthesis of ketones and other carbonyl derivatives

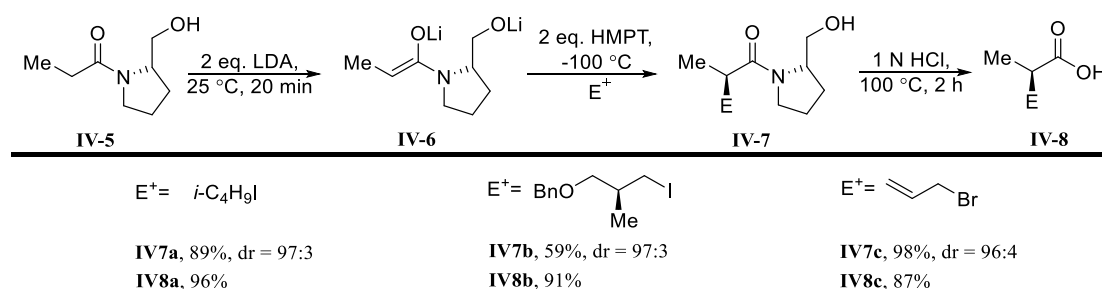
The ionic route to ketones still remains the primary tool for synthetic chemists. This type of alkylation consists of two steps: the first is the formation of a stable enolate by deprotonation with a base or the acid-catalyzed enol formation. The second is the nucleophilic attack on electrophiles either in an S_N2 or S_N1 manner.



Scheme 4.1 The general principle of enolate alkylation

4.2.1 Alkylation of enolates

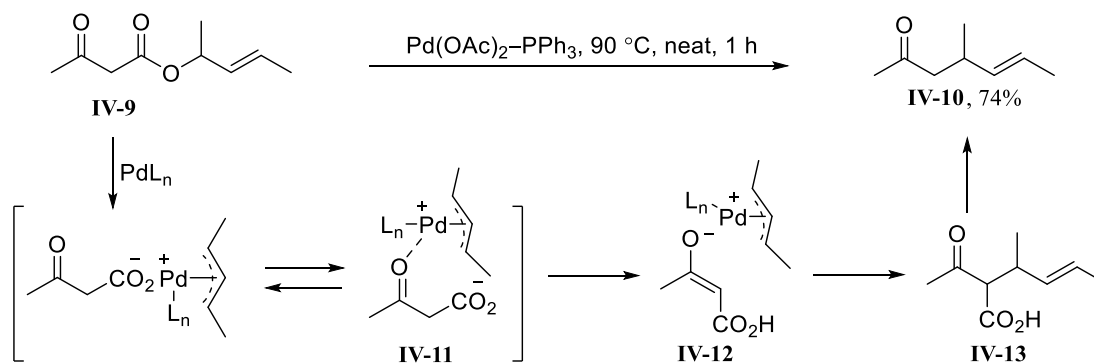
Evans's group reported an asymmetric alkylation of chiral amide enolates derived from (1)-prolinol which are then hydrolyzed to afford optically active carboxylic acids.¹² In this reaction, one equivalent of the hydroxy-amides **IV-5** starting material is added to two equivalents of LDA to produce the dianion enolate **IV-6**, which is subsequently mixed with various alkyl halides to afford the desired carbonyl derivatives **IV-7a-c** in high diastereomeric purity. The optically pure carboxylic acids **IV-7a-c** were readily prepared by hydrolysis of the chiral auxiliary in hot hydrochloric acid via an acid-catalyzed N to O acyl transfer process (Scheme 4.2).¹³ It is noteworthy that through chelation of the enolate, the hydroxyl group plays a crucial role in establishing an enantiotopic bias in the alkylation of enolate.



Scheme 4.2 Enantioselective alkylation of chiral enolates

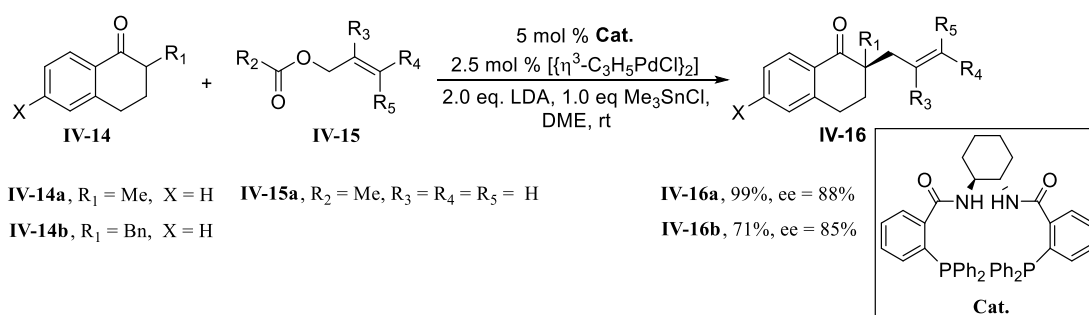
Jiro Tsuji *et al.* developed a palladium catalyzed decarboxylation-allylation of allylic β -keto carboxylates to give α -allylated ketones with high regioselectivity.¹⁴ Unlike the Carroll reaction,¹⁵⁻¹⁶ which requires high temperatures, this decarboxylation-allylation proceeds rapidly under mild condition. In the presence of a catalytic amount of Pd(OAc)₂-PPh₃ complex, the

starting material **IV-9** is smoothly converted into α -allylated ketone **IV-10** in 74% yield. In the mechanistic study, they speculated the allylic esters react with palladium-phosphine complex to generate a (π -allyl)palladium complexes **IV-11**. The chelation of palladium with the carbonyl oxygen in intermediate **IV-11** is crucial for the activation of the α -hydrogen to accomplish the intramolecular proton transfer. Once the intermediate **IV-12** is formed, the enolate attacks intramolecularly the (π -allyl)palladium complex electrophile resulting in the formation of β -keto acid **IV-13**, undergoes decarboxylation to give the α -allylated ketone (**Scheme 4.3**).



Scheme 4.3 The palladium catalyzed α -allylated ketone synthesis and plausible mechanism

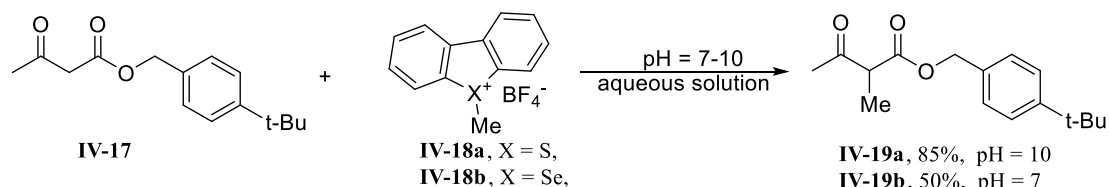
Palladium-catalyzed asymmetric alkylation of ketones to generate quaternary centers has been reported by Trost's group.¹⁷ The initial reaction carried out between the six-membered ring ketone **IV-14a** and allylic ester **IV-15a**, gave allylated product **IV-16a** in 99% yield and 88% *ee*. Switching the R_1 substituent to benzyl group **IV-14b** resulted in a lower yield of product **IV-16b** but had little impact on the stereochemistry (**Scheme 4.4**). It was also found that smaller Lewis acids gave the higher yields and *ee* value. The type of base significantly affects the outcome, and only lithium diisopropylamide resulted in the formation of the desired product whereas sodium and potassium bases only gave recovered starting material. No asymmetric alkylation is observed without the palladium catalyst.



Scheme 4.4 Palladium-catalyzed asymmetric alkylation of enolates

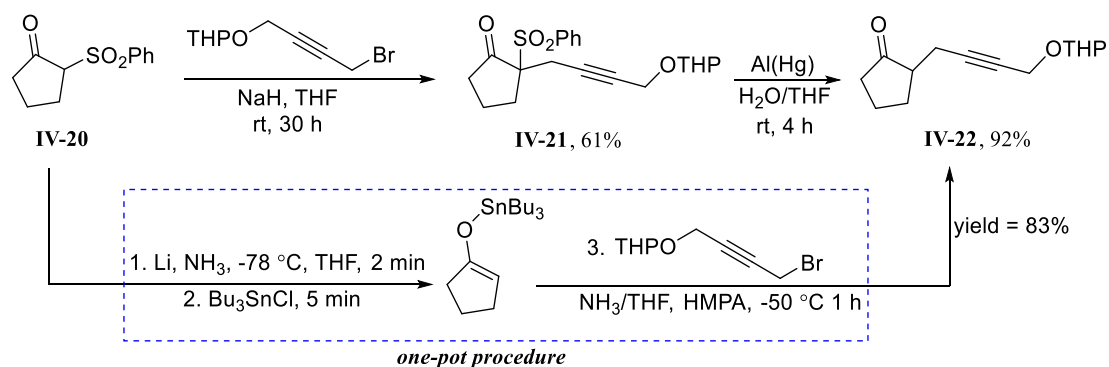
The pK_a (measured in DMSO) of the α -hydrogen of ketones is approximately 26.¹⁸ Therefore, deprotonation of this hydrogen requires a strong base, which can cause some side reactions and many polar functional groups are incompatible. One solution to overcome this drawback is to modify the pK_a of the enolizable hydrogen with an auxiliary group to make the deprotonation easier.

By using the ester group as an auxiliary, the carbon-carbon bond formation can take place even in aqueous solution.¹⁹ The reaction of β -keto ester **IV-17** and methyl dibenzothiophenium salt **IV-18a** in a basic solution (pH = 10) afforded the desired alkylated β -keto ester **IV-19a** in 85% yield. Changing the electrophile to the more electrophilic methyl selenonium salt **IV-18b**, the reaction proceeded smoothly in neutral solution although in diminished yield of **IV-19b** (**Scheme 4.5**).



Scheme 4.5 Methylation of β -keto ester in aqueous solution

With the same concept of the β -keto ester, Kurth and co-workers exploited the use of β -keto sulfones as temporary activating groups to secure the regioselectivity of unsymmetrical ketone α -alkylation.²⁰ The initial desulfurization/ α -alkylation of 2-oxocyclopentyl phenyl sulfone **IV-20** and benzyl bromide showed that the additive trialkylstannyl chloride is the key element to secure the monoalkylation of the ketone, and the HMPA cosolvent is necessary for high reactivity. To compare the efficiency of the desulfurization/ α -alkylation and α -alkylation/desulfurization, 2-oxocyclopentyl phenyl sulfone **IV-20** was selected to test the two pathways. The sodium hydride catalyzed alkylation with propargylic bromide needed 30 hours to complete and afforded the α -alkylated β -keto sulfone **IV-21** in 61% yield. This was followed by desulfurization with aluminum amalgam in aqueous THF, which provided the desired cyclopentanone **IV-22** in 92% yield. The overall yield from 2-oxocyclopentyl phenyl sulfone **IV-20** is 56%. However, the one-pot procedure only needed 1.5 hours for completion and produced cyclopentanone **IV-22** in 83% yield (**Scheme 4.6**).



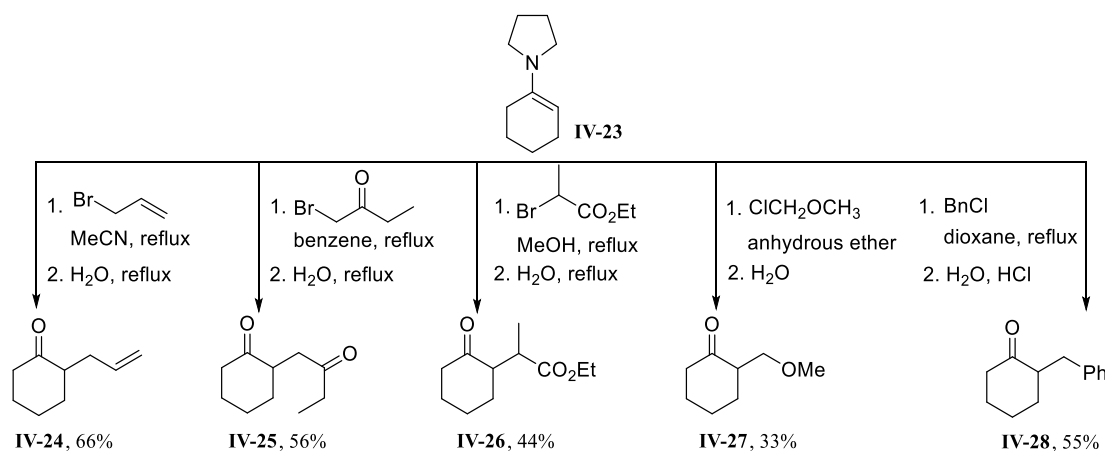
Scheme 4.6 Desulfurization/ α -alkylation of β -keto sulfones

4.2.2 Stork enamine alkylation

As mentioned in the introduction, it is problematic to use a strong base in the enolate alkylation. Since no strong base or enolate is involved in the enamine alkylation, therefore,

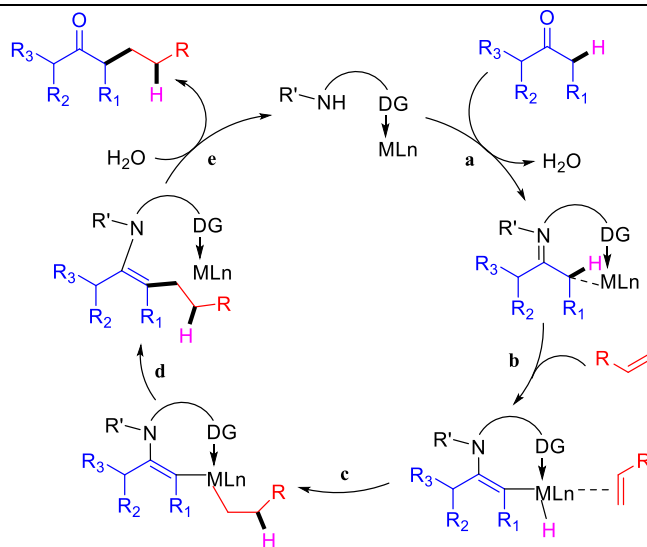
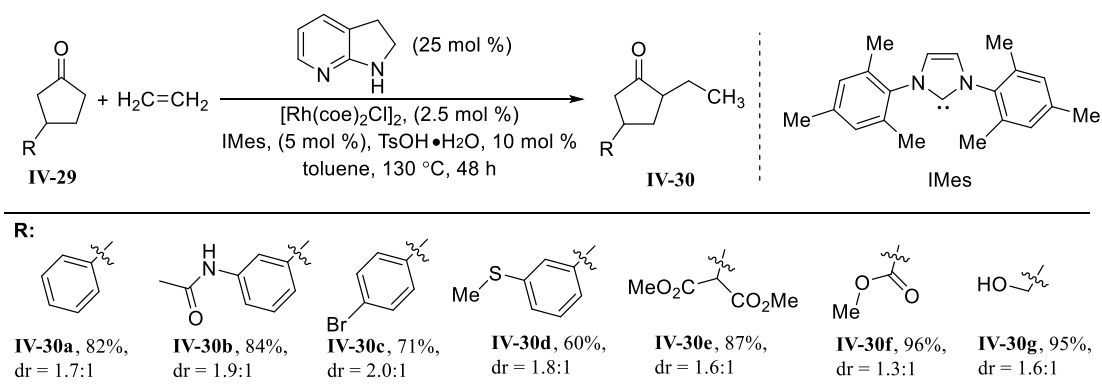
there is less danger of self-condensation and polyalkylation.

Stork and co-workers pioneered the work on enamine alkylation.²¹⁻²⁴ They found that the polyalkylation of the enolates could be overcome by using enamines. For unsymmetrical ketones, the substitution is preferred on the less hindered carbon. Moreover, the more electrophilic the alkyl halide, the better is yield for alkylation of the enamine. Some strongly electrophilic halides such as allyl halides, benzyl halides, α -halo ethers, α -haloketones and esters were used to react with enamine **IV-23** and the corresponding alkylated ketone **IV-24-28** were obtained in moderate yields. Because these functional groups are generally incompatible with conventional sequences involving conversion of ketones to β -keto esters followed by alkylation, acid hydrolysis and then decarboxylation, the enamine-alkyl halide reaction represents a good alternative (**Scheme 4.7**).



Scheme 4.7 Examples of enamine alkylation

Dong's group developed a novel method of regioselective α -alkylation of ketones with simple terminal alkenes in the presence of a bifunctional catalyst.²⁵ This transformation takes advantage of the bifunctional catalyst containing a secondary amine and a low-valent rhodium complex capable of activating both the ketones and the olefins. The alkylation takes place at the less substituted site and is compatible with a broad range of functional groups. It is worth noting that besides the well-designed rhodium and secondary amine complex, the additive $\text{TsOH}\cdot\text{H}_2\text{O}$ is crucial for the enamine formation. Without this additive, no alkylation was observed. The ethylation of various substituted cyclopentanones **IV-29** proceeded smoothly to afford the desired products **IV-30a-g** in moderate to excellent yield. An amide, aryl bromide, thioether, carboxylic ester, free alcohol and other functional groups proved compatible. The proposed mechanism of this process is given below: (a) enamine formation; (b) oxidative addition of enamine C–H bond; (c) migratory insertion into the olefin; (d) reductive elimination to form C–C bond; (e) enamine hydrolysis (**Scheme 4.8**).



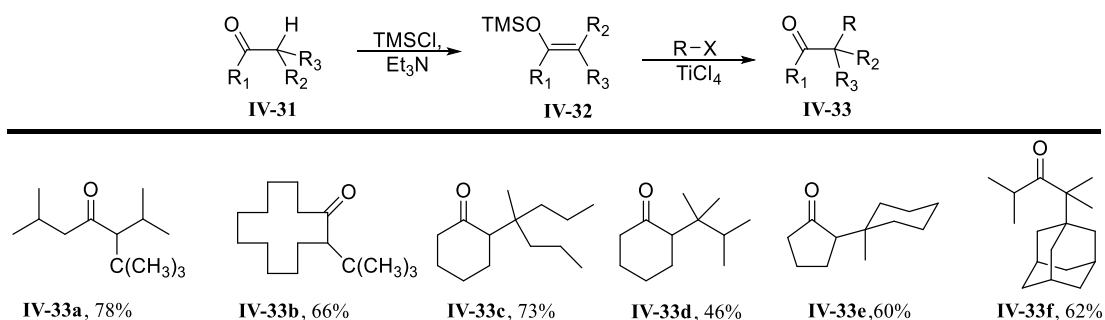
Scheme 4.8 Regioselective ketone α -alkylation with simple olefins via dual activation and possible mechanism

4.2.3 Alkylation of silyl enol ethers

Enolates usually undergo an S_N2 reaction with rather reactive alkylating agents such as methyl, allyl, benzyl, and some primary alkyl halides. Treatment of the enolate with secondary alkyl halides results in competitive β -elimination byproducts due to the basicity of the enolate. The reaction is also sluggish and the regioselectivity cannot always be ensured. The worst situation is the reaction of enolates with tertiary alkyl halides, which generally provides the β -elimination compound. Although enamines are less basic and reactive, they also fail to form new carbon-carbon bonds with tertiary alkyl halides.²⁶

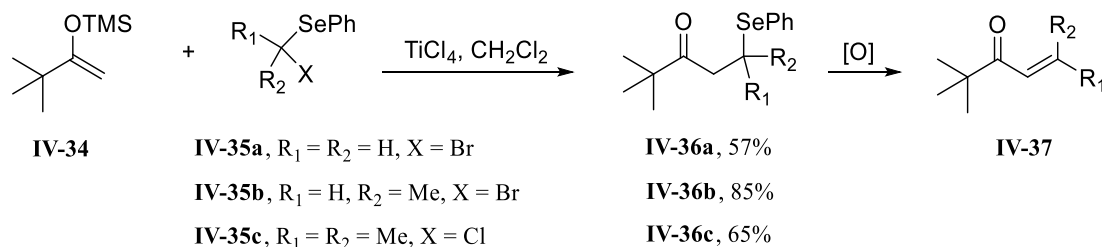
To overcome the limitations discussed above, Reetz and co-workers offered an alternative for the α -*tert*-alkylation of ketones by using silyl enol ethers as the enolate equivalent.²⁷⁻²⁹ Thus, ketone **IV-31** was converted into the trimethylsilyl enol ether **IV-32** with triethylamine and trimethylsilyl chloride, and treated with titanium tetrachloride and a variety of structurally different *tert*-alkyl halides to afford α -*tert*-alkylated ketones **IV-33a-f** in moderate yields (**Scheme 4.9**). Among these reactions, no di- or polyalkylation products were observed. It is noteworthy that the undesired Wagner-Meerwein rearrangements did not take place when using branched alkyl halides. Reactive but slightly-strained bridgehead alkyl halide also underwent

the alkylation as illustrated by product **IV-33f**.



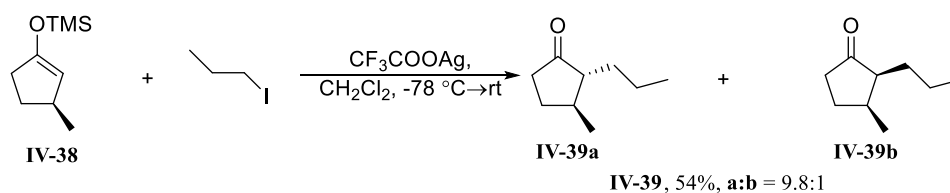
Scheme 4.9 Lewis acid catalyzed α -*tert*-alkylation of ketones

Organoseleniums are important intermediates in organic synthesis. They can be oxidized to the corresponding selenoxides which undergo facile syn β -eliminations to generate an unsaturated bond.³⁰ If an organoselenium group is present on the β -position of the carbonyl compound, then the formation of α,β -unsaturated carbonyl compounds becomes easier. Based on this principle, Comasseto *et al.* reported the reaction of silyl enol ether with α -halo- β -(phenylseleno) alkanes to introduce the organoselenium group onto the β -position of ketones (**Scheme 4.10**).³¹ The titanium tetrachloride catalyzed transformation shows efficiency with different substituted alkylating agents **IV-35a-c** and gives the desired β -(phenylseleno) ketones **IV-36a-c** in moderate to good yields.



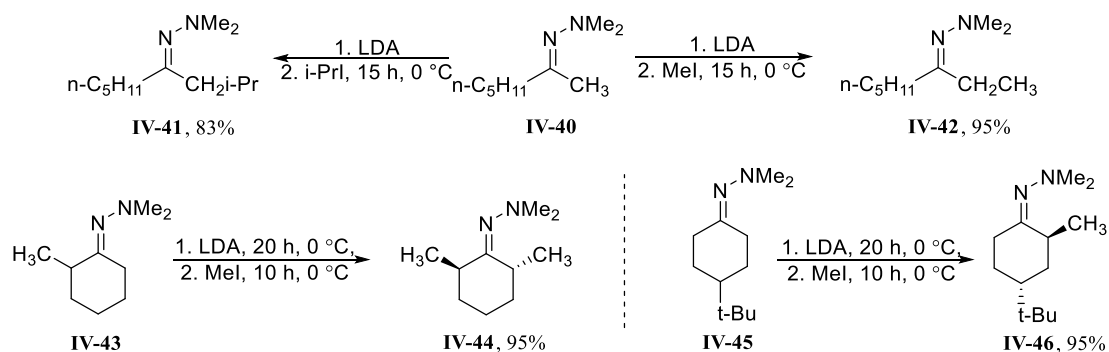
Scheme 4.10 Synthesis of β -(phenylseleno) ketones via silyl enol ether reaction

Lewis acids such as ZnCl_2 , TiCl_4 and SnCl_4 catalyzed silyl enol ether alkylation is limited to the carbocation formation mechanism. To extend the application of silyl enol ether alkylation, Canonne *et al.* exploited the use of silver trifluoroacetate as a catalyst to promote the alkylation of the silyl enol ethers with primary alkyl halides.³² This work was carried out for the synthesis of 2,3-disubstituted cyclopentanones which are important synthetic blocks for the preparation of naturally occurring and biologically active compounds. Treatment of the silyl enol ether **IV-38** with propyl iodide afforded the *trans*-isomer **IV-39** with high stereoselectivity, and no polyalkylated and polymeric compounds were detected (**Scheme 4.11**).

Scheme 4.11 $\text{CF}_3\text{CO}_2\text{Ag}$ catalyzed silyl enol ether alkylation in the synthesis of substituted cyclanones

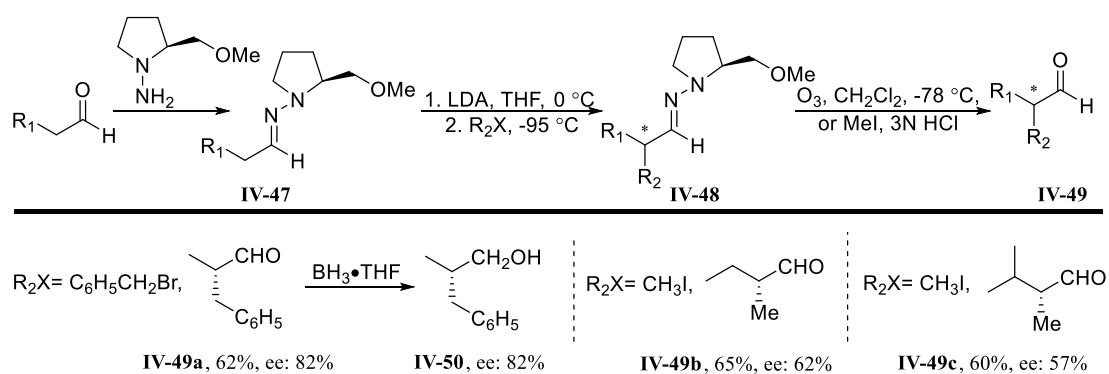
4.2.4 The Enders SAMP/RAMP hydrazone alkylation.

The Enders SAMP / RAMP hydrazone alkylation reaction is a pyrrolidine chiral auxiliary facilitated asymmetric carbon-carbon bond formation process. In 1976, Corey and Enders first reported this methodology for the asymmetric α -alkylation of ketones via the corresponding (S)-1-amino-2-methoxymethylpyrrolidine (SAMP) hydrazone derivatives.³³ Hydrazones **IV-40**, **43**, **45** can be totally deprotonated by lithium diisopropylamide to form the aza-enolates which can be further reacted with alkyl halides to provide the corresponding desired products **IV-41**, **42**, **44**, **46** in good to excellent yield. Generally, the alkylation occurs very selectively at the less hindered site and no formation of regioisomers or poly-alkylated products was observed. In the case of cyclohexanone derivatives **IV-43**, **45**, the methylation was highly preferred at the axial position (Scheme 4.12). The carbonyl group can be regenerated by ozonolysis or direct hydrolysis with aqueous acid.



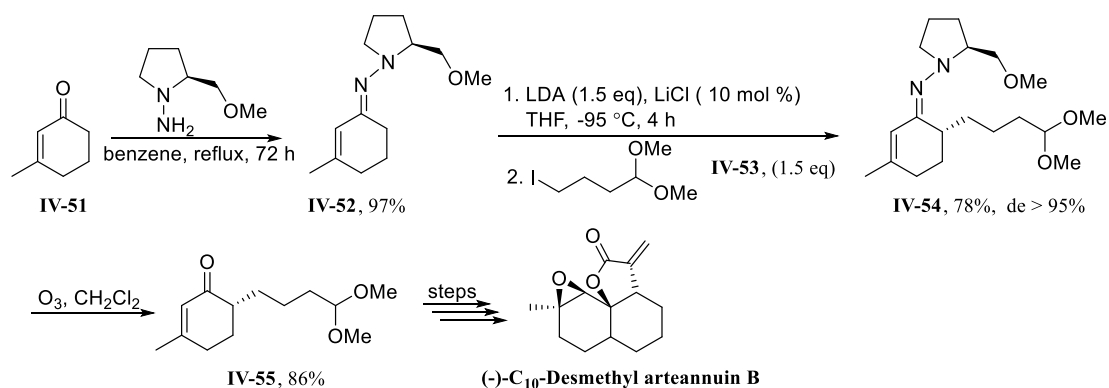
Scheme 4.12 Alkylation of metalated hydrazone

α -Chiral aldehydes are valuable building blocks in organic synthesis due to their high reactivity. But methods to introduce a chiral center at the α -position are rare. Based on the asymmetric α -alkylation of ketones by chiral hydrazones,³⁴ Enders and co-workers extended this methodology to the enantioselective alkylation of aldehydes.³⁵ Treatment of various aldehydes with (S)-1-amino-2-methoxymethylpyrrolidine provided chiral hydrazone derivatives **IV-47**. It was subsequently deprotonated by lithium diisopropylamide (LDA) in THF at 0°C to give the aza-enolate, which could be alkylated by alkyl halides to afford the α -alkylated hydrazone derivatives **IV-48**. Ozonolysis or hydrolysis regenerated the carbonyl group, furnishing α -chiral aldehydes **IV-49a-c** in moderate yields and in some case in high enantiomeric purity **IV-49a**. Moreover, the α -chiral aldehydes can be reduced without racemization to the corresponding β -chiral alcohols **IV-50** (Scheme 4.13).



Scheme 4.13 Chiral hydrazone promoted enantioselective α -alkylation of aldehydes

The synthesis of (–)-C₁₀-desmethyl arteannuin B, a natural product which is the structural analog of the antimalarial artemisinin reported by Little *et al.* is an illustration.³⁶ These authors introduced the stereo center at an early stage using the Enders SAMP/RAMP hydrazone alkylation method. Refluxing the mixture of 3-methylcyclohexenone **IV-51** and (S)-1-amino-2-methoxymethylpyrrolidine in benzene almost quantitatively provided the corresponding (S)-(-)-1-amino-2-(methoxymethyl)pyrrolidine (SAMP) hydrazone **IV-52**. Deprotonation by lithium diisopropylamide in tetrahydrofuran, followed by alkylation with iodide **IV-53** in the presence of lithium chloride at -95°C resulted in the formation of the alkylated hydrazone as a single diastereomer **IV-54**, in 78% yield. Cleavage of the chiral auxiliary was achieved by ozonolysis to provide intermediate **IV-55** in 86% yield (**Scheme 4.14**).

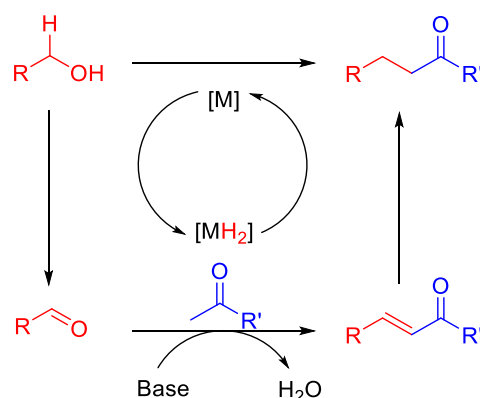


Scheme 4.14 Hydrazone induced absolute stereochemistry in the synthesis of (–)-C₁₀-desmethyl arteannuin B

4.2.5 Borrowing Hydrogen (BH) strategy for ketone alkylation

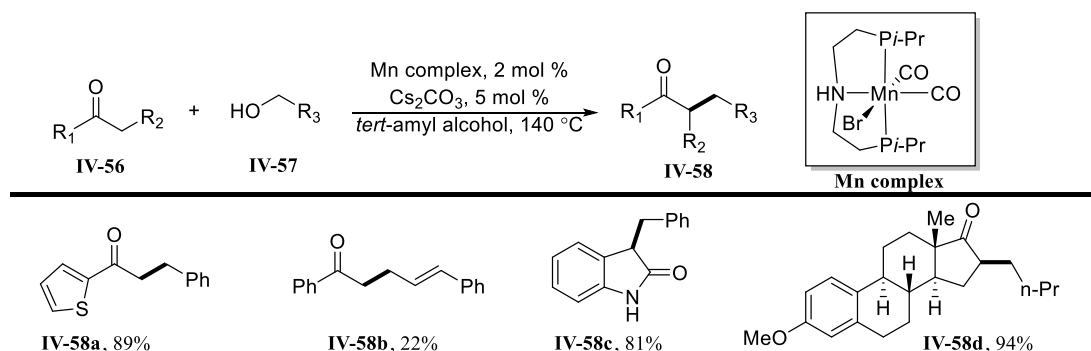
In recent years, a protocol called ‘borrowing hydrogen’ (BH) has risen for the alkylation of ketones. This transition metal catalyzed method uses alcohols as alkylating agents instead of the environmental unfriendly alkyl halides. Water is the only byproduct in this process, making the borrowing hydrogen (BH) method very atom-economical. The mechanism of this transformation is depicted below: the alcohol is firstly oxidized to the aldehyde by the transition metal and this is followed by an aldol reaction with the starting ketone in the presence of base. The newly formed unsaturated ketone will further be reduced by metal hydride to provide the

new carbon-carbon bond (**Scheme 4.15**).



Scheme 4.15 The mechanism of borrowing-hydrogen process

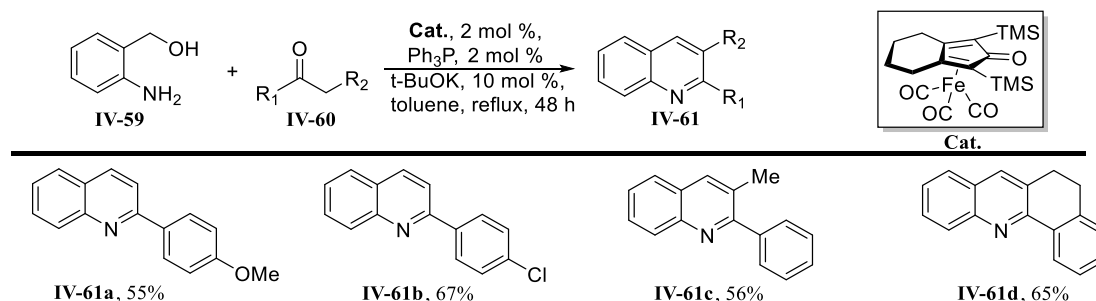
A manganese complex catalyzed BH process for the alkylation of ketones with primary alcohols was first developed by Beller and co-workers.³⁷ Various ketones **IV-56** and primary alcohols **IV-57** were transformed into the corresponding α -alkylated ketones **IV-58**, catalyzed by the air- and water-stable manganese(I) PNP pincer catalyst and Cs_2CO_3 . In the scope section, they found that 2-acetylthiophene reacted efficiently to give the desired product **IV-58a** in 89% yield, while the coupling partner cinnamyl alcohol only provided the alkylated ketone **IV-58b** in 22% yield. To diversify the applications of this method, they tested the α -alkylation of 2-oxindole, a relevant heterocycle presented in many bio-active molecules.³⁸⁻³⁹ Under the optimized conditions, the 2-oxindole was converted into the desired product **IV-58c** in good yield. Estrone derivatives could also be readily modified by using simple alcohols as alkylating agents, affording product **IV-58d** in excellent yield (94%) (**Scheme 4.16**).



Scheme 4.16 Manganese complex catalyzed alkylation of ketones with primary alcohols

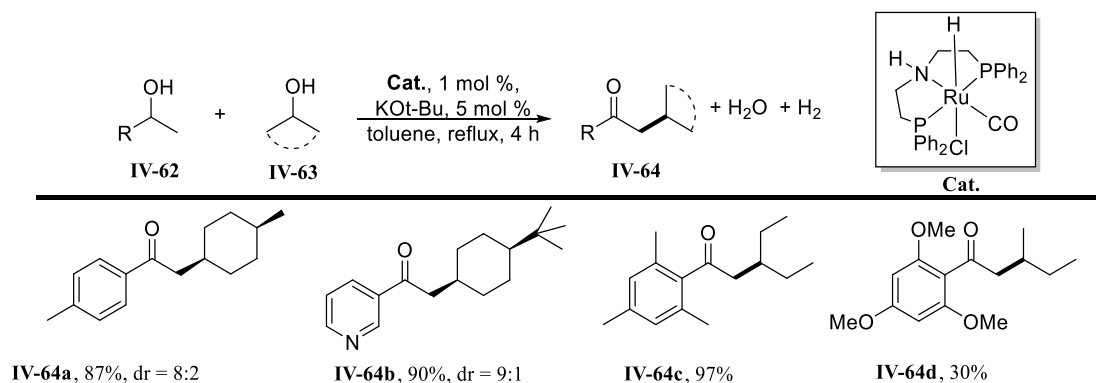
Darcel *et al.* reported another BH-based iron-catalyzed α -alkylation of ketones with alcohols.⁴⁰ The use of a Knölker complex as catalyst in the presence of Cs_2CO_3 as base is key to the success of this transformation. This method is not only suitable for the simple coupling of ketones and alcohols but also allows the ‘green’ synthesis of quinoline derivatives when using 2-aminobenzyl alcohol as the alkylation reagent (**Scheme 4.17**). The classical Friedländer Reaction is still a simple and straightforward method for synthesis of quinolines, but this acid- or base-promoted reaction of 2-aminobenzaldehyde and ketones suffers from self-condensation

and the low stability of the 2-aminobenzaldehyde.⁴¹ By contrast, the iron-catalyzed BH approach using the more stable 2-aminobenzyl alcohol **IV-59** as the coupling counterpart gives the corresponding quinoline derivatives **IV-61a-d** in moderate yields. The only observed byproduct in this sequence is 2-phenylethanol.



Scheme 4.17 Iron-catalyzed α -alkylation of ketones with alcohols

The BH strategy can be applied not only to the coupling of ketones and alcohols but also to the formation of new carbon-carbon bonds by the reaction of two secondary alcohols. In 2019, Gunanathan *et al.* developed the selective coupling reactions of alcohols for the synthesis of ketones.⁴² Aromatic benzylic alcohols react with a broad range of cyclic, acyclic, symmetrical, and unsymmetrical secondary alcohols. The reaction of 4-alkylcyclohexanol and 1-arylethanol derivatives provided products **IV-64a, b** in good yield as a mixture of diastereoisomers. Unactivated acyclic aliphatic secondary alcohols with 1-phenylethanol derivatives efficiently gave the desired products **IV-64c, d**, albeit with a higher catalyst loading (4 mol %) and more base (20 mol %) (**Scheme 4.18**).



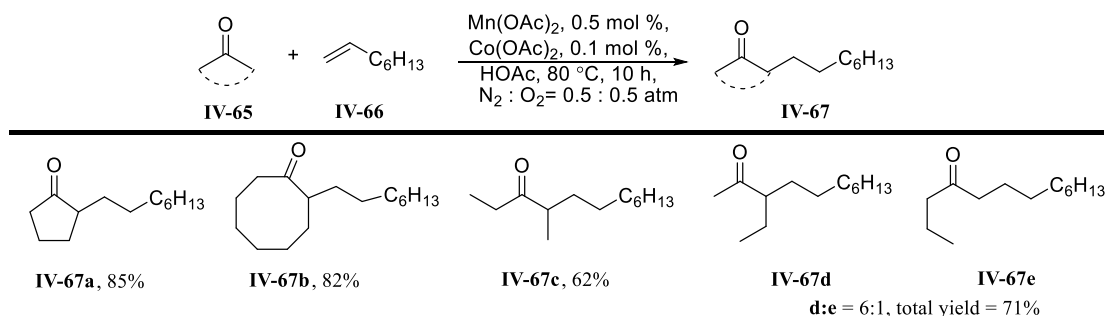
Scheme 4.18 Ruthenium (II) catalyzed direct cross-coupling of two different secondary alcohols

4.3 Radical routes to ketones

Although free radicals are considered to be a powerful tool for carbon-carbon bond formation, a limited number of methods have emerged to generate α -keto carbon radicals. Among the methods developed for this purpose metal ions such as Mn(III), Ce(IV), Ag(II) and Pb(IV) catalyzed α -keto radical addition to alkenes have played a crucial role.⁴³⁻⁴⁷ But the main

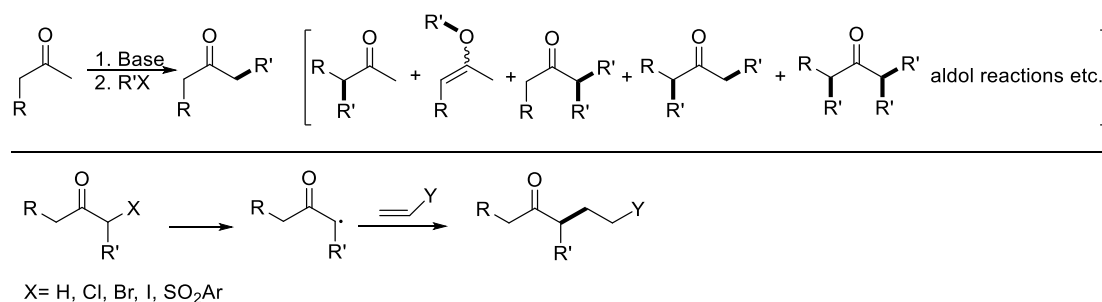
disadvantage of these approaches is the use of stoichiometric quantities of the metal reagent.

To overcome these drawbacks, Ishii *et al.* used a catalytic amount of Mn(II) and Co(II) salts and dioxygen as an oxidant to promote the α -alkylation of ketones via a radical pathway.⁴⁸ Both cyclic and aliphatic ketones reacted smoothly with oct-1-ene **IV-66** to give the desired products **IV-67a-e** in fair to good yield. The reaction of unsymmetrical ketones with oct-1-ene **IV-66** provided two structural isomers, 3-ethylundecan-2-one **IV-67d** and tridecan-4-one **IV-67e**, in a ratio of 6:1. Isomer **IV-67d** is the major product probably because the secondary radical intermediate is more stable than the primary one (**Scheme 4.19**).



Scheme 4.19 Metal-oxygen catalytic system promoted addition of ketones to alkenes

MacMillan's group reported the enantioselective α -cyanoalkylation of aldehydes via the synergistic combination of photoredox and organocatalysis.⁴⁹ The plausible mechanism is illustrated below: exposure of the α -bromoacetonitrile to light in the presence of ruthenium catalyst generates a cyanoalkyl radical which is trapped by the enamine formed by the condensation of aldehyde and organocatalyst. The resulting intermediate undergoes a series of transformations to give the desired product and regenerate the catalyst. A broad range of substrates were tested for this transformation and the application of this methodology was also investigated. Under standard conditions, the coupling of aldehyde **IV-68** and α -bromoacetonitrile proceeded smoothly to provide the alkylated product **IV-69** in high efficiency and excellent enantioselectivity. Treatment **IV-69** with sodium borohydride and subsequent cyclization under basic conditions afforded lactone **IV-70**. To finalize the synthesis, the lactone was alkylated with α -3,4-dimethoxybenzyl bromide with high selectivity to give natural product **IV-71** in 80% overall yield from bromoacetonitrile (**Scheme 4.20**).

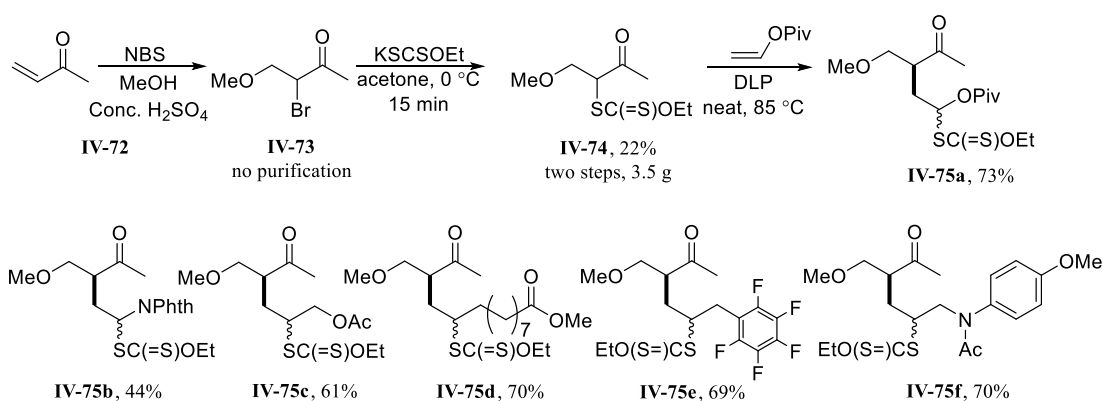


Scheme 4.21 Byproducts in the alkylation of ketones

The main problem is how to generate the α -ketonyl radicals cleanly and how to capture them, especially via intermolecular reactions. During the past few years, the generation of α -ketonyl radicals has relied on the oxidation of enols or enolates using metal salts (especially Mn^{III} salts), on the use of α -iodo ketones, or even by the direct oxidation of ketones. The α -ketonyl radicals were mostly trapped by internal carbon-carbon multiple bonds. Successful intermolecular additions were very limited.⁵³⁻⁵⁴ The rates of typical intramolecular 5-exo cyclizations are 2 to 3 orders of magnitude greater than those of intermolecular additions to unactivated alkenes,⁵⁵ and conditions that favor the intermolecular coupling (e.g., high concentration) also lead to unwanted byproducts. Therefore, the radical based route for intermolecular carbon-carbon bond formation starting from unactivated alkenes still poses a great challenge. Our group has found that the degenerative exchange of xanthates represents an ideal method to generate radicals and store them in a dormant state. This process greatly extends the half-life of reactive radicals and diminishes the unwanted radical-radical interactions. More details of the mechanism have been discussed in Section 2.4 (**Chapter 2**). This chemistry has proved particularly useful for the synthesis of ketones.

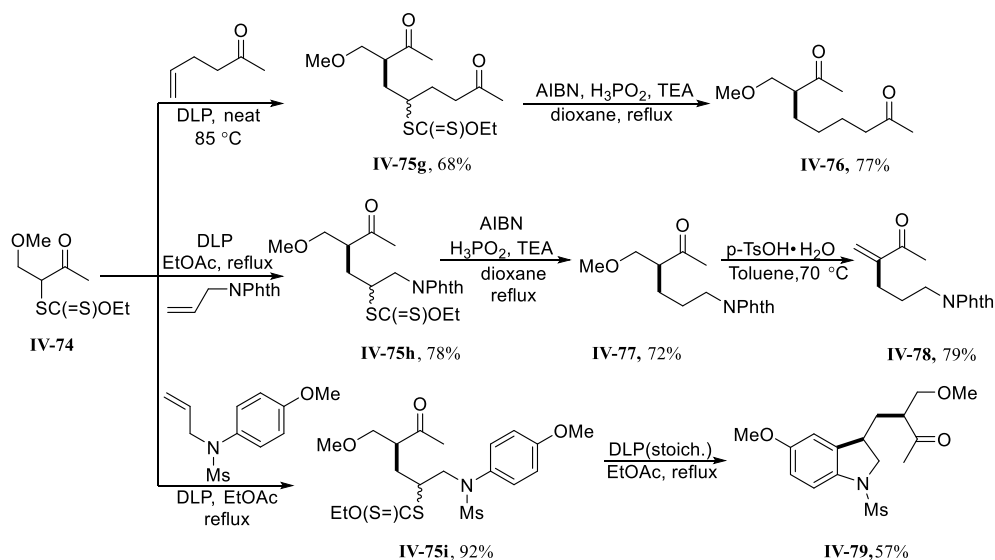
4.3.1 The xanthate transfer process in the synthesis of acyclic ketones

In line with our previous studies,⁵⁶ the direct addition of α -xanthyl ketones to unactivated alkenes to obtain functionalized ketones should be applicable to the synthesis of 2-alkoxy ketones which are not readily available by other routes. Xanthate **IV-74** was easily prepared in a two-step sequence from methyl vinyl ketone (**Scheme 4.22**). To our surprise, the overall yield of the xanthate formation reaction was only moderate, and more optimization work should be conducted to improve the yield. Nevertheless, all reagents are readily available and the xanthate could be easily synthesized in 3.5g scale. The first radical addition to vinyl pivalate took place efficiently without any solvent and afforded the adduct **IV-75a** in 73% yield. This adduct is a masked 1,4-keto aldehydes with vast synthetic potential, including the synthesis of thiophenes and pyrroles.⁵⁷⁻⁵⁸ All of the other additions were carried out neat, providing the desired products in good yields and showing broad functional group compatibility. In all cases, a 1:1 mixture of diastereoisomers was produced (**Scheme 4.22**). For reasons not yet clear, the addition to vinyl phthalimide was found to be inefficient and gave a lower yield (44%).



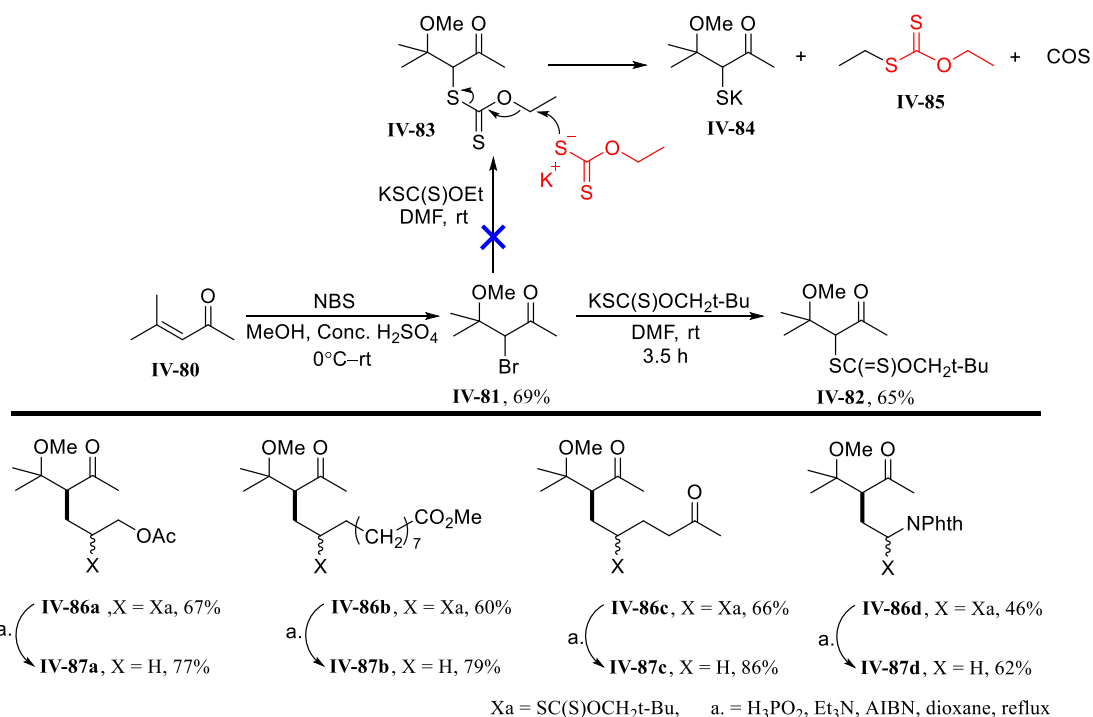
Scheme 4.22 Preparation of xanthate **IV-74** and addition to olefins

The xanthate group can be reductively removed to simplify the structure, or act as a springboard for further transformations. Both possibilities are shown in **Scheme 4.23**. The addition of xanthate **IV-74** to allyl acetone was performed neat and provided adduct **IV-75g** in a useful yield. Treatment of the adduct with Barton's reagent⁵⁹ reductively removed the xanthate group to furnish diketone **IV-76** in 77% yield. The reaction of xanthate **IV-74** and allyl phthalimide was conducted in ethyl acetate at a 1 M concentration and subsequently underwent reductive dexanthylation followed by acid-catalyzed β -elimination resulting in the formation of the useful building block, α -substituted α , β -unsaturated ketone **IV-78** in 79% yield. Several ionic methods have been developed in the synthesis of α -substituted α , β -unsaturated ketones, including the Negishi coupling of alkylzinc and α -iodoenones,⁶⁰ the syn elimination of selenoxides reported by Barton *et al.*⁶¹⁻⁶² and the alkylation of α -ketovinyl anion equivalent.⁶³ By contrast, the radical route to α -substituted unsaturated ketones demonstrates advantages such as no need for metal catalysts and organometallic reagents, high regio-selectivity and mild reaction conditions. The addition of xanthate to protected allyl amine was also performed in refluxed ethyl acetate, affording the adduct **IV-75i** in an excellent yield of 92%. The cyclization to aromatic ring could be accomplished by using stoichiometric amounts of peroxide to give indoline derivative **IV-79** in good yield. Compared to metal catalyzed coupling reactions,⁶⁴⁻⁶⁶ this xanthate transfer procedure rapidly constructs the indoline ring in a cheaper manner.



Scheme 4.23 Further transformation of radical adducts

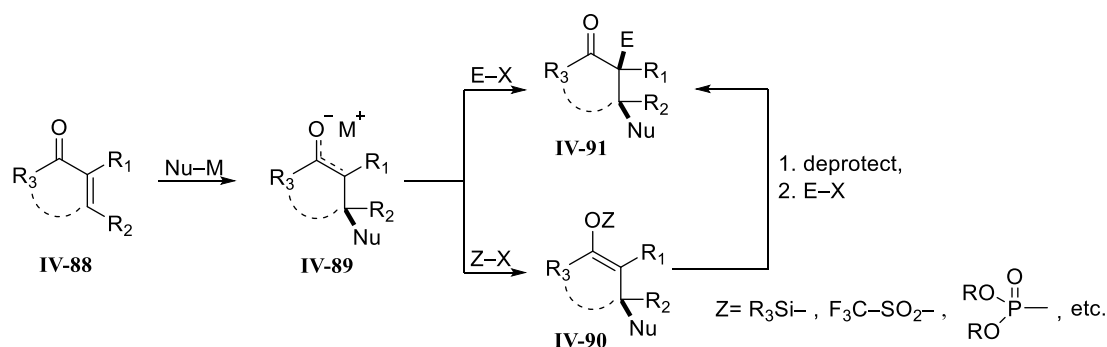
To extend the scope, we decided to prepare the more hindered derivative, **IV-83**. Bromination of ketone **IV-80** with NBS in methanol as solvent provided bromide **IV-81** in a useful yield of 69%. In contrast to the first step, the substitution of the hindered bromide with potassium *O*-ethyl xanthate proved to be difficult. This substitution was carried out under various conditions but all failed to provide the desired product **IV-83** which appeared to be decomposing as fast as it was being formed (Scheme 4.24). We assumed that the carbon attached to the oxygen atom in the *O*-alkyl xanthate could undergo nucleophilic attack by potassium xanthate, resulting in degradation. Indeed, we and other groups have observed such behaviour before.⁶⁷⁻⁶⁸ To suppress the unwanted side-reactions, we replaced the potassium *O*-ethyl xanthate with potassium *O*-neopentyl xanthate, thereby making the xanthate **IV-82** less accessible toward nucleophilic attack due to the bulky *tert*-butyl group. To our delight, mixing the bromide **IV-81** and the neopentyl xanthate salt in DMF at room temperature formed the desired xanthate **IV-82** in 65% yield after purification by column chromatography. With this xanthate in hand, we examined its reaction with unactivated alkenes. All of the examples are pictured in Scheme 4.24. Even with a bulky group adjacent to the xanthate group, the addition to the alkenes proceeded smoothly to afford the radical adducts **IV-86a-d** in good yield, thus highlighting the advantages of radicals compared to enolate chemistry. It is not surprising to observe a lower yield of adduct **IV-86d** because of the radical stability we have discussed. All adducts are essentially 1:1 mixture of diastereoisomers that could be simplified by dexanthylation using Barton method.⁵⁹



Scheme 4.24 Preparation of xanthate **IV-82** and its addition to olefins

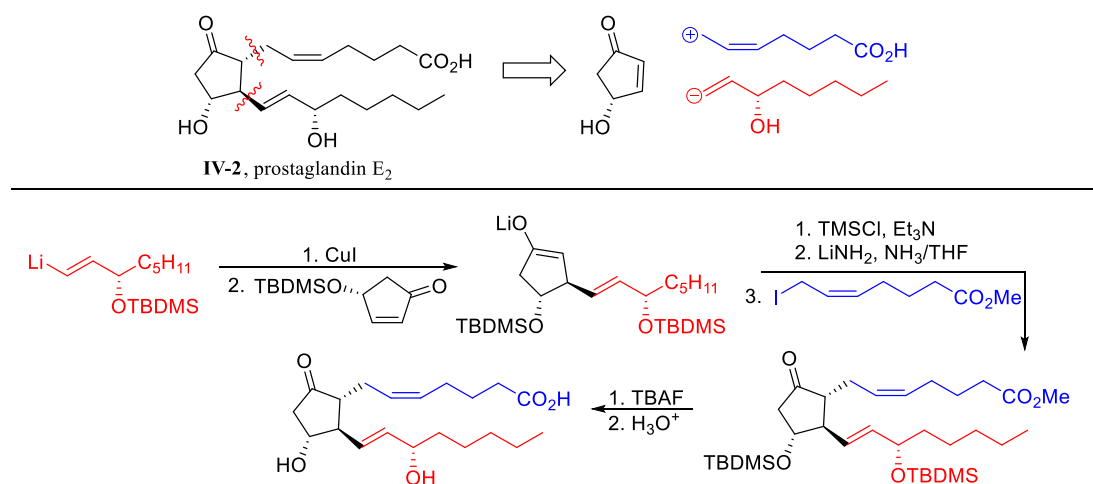
4.3.2 The vicinal dialkylation of enones by ionic and radical reactions

Reactions allowing vicinal difunctionalization open a rapid, convergent routes for constructing complex structures and have been extensively applied in organic synthesis, especially in the dialkylation of unsaturated ketones.⁶⁹⁻⁷³ The concept of this tandem vicinal difunctionalization is depicted in **Scheme 4.25**. The process consists of two reactions, one enabling the other to proceed. The initial Michael-type reaction takes place between the nucleophilic organometallic reagent (Nu-M) and the α, β-unsaturated ketone **IV-88** to afford the β-substituted enolate **IV-89**, which has nucleophilic character on the α-carbon. The enolate **IV-89** can be trapped in-situ by an electrophile (E-X) thus forming the difunctionalized ketone **IV-91**. The intermediate enolate **IV-89** can also undergo *O*-functionalization reactions with various *O*-trapping reagents (Z-X) to form the neutral species **IV-90** as enolate equivalents. The enolate equivalent **IV-90** can be isolated prior to deprotonation and alkylation to access dialkylated ketone **IV-91**, or to other further chemical manipulations.



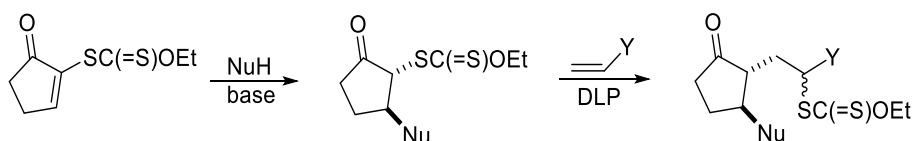
Scheme 4.25 General procedure for the tandem vicinal dialkylation of ketones

Noyori *et al.* reported the formation of prostaglandin E₂ based on a conjugate addition-enolate alkylation procedure.⁷⁴ Since the starting enone already has a stereogenic centre, a vinyl lithium conjugate addition to cyclopentenone in the presence of copper iodide is stereoselective and gives the *trans* intermediate enolate which can stereoselectively attack the allylic iodide to assemble the required *trans* target in protected form. Deprotection with TBAF and hydrolysis eventually furnishes the desired product (**Scheme 4.26**).



Scheme 4.26 Synthesis of prostaglandin E₂ by a tandem vicinal dialkylation protocol

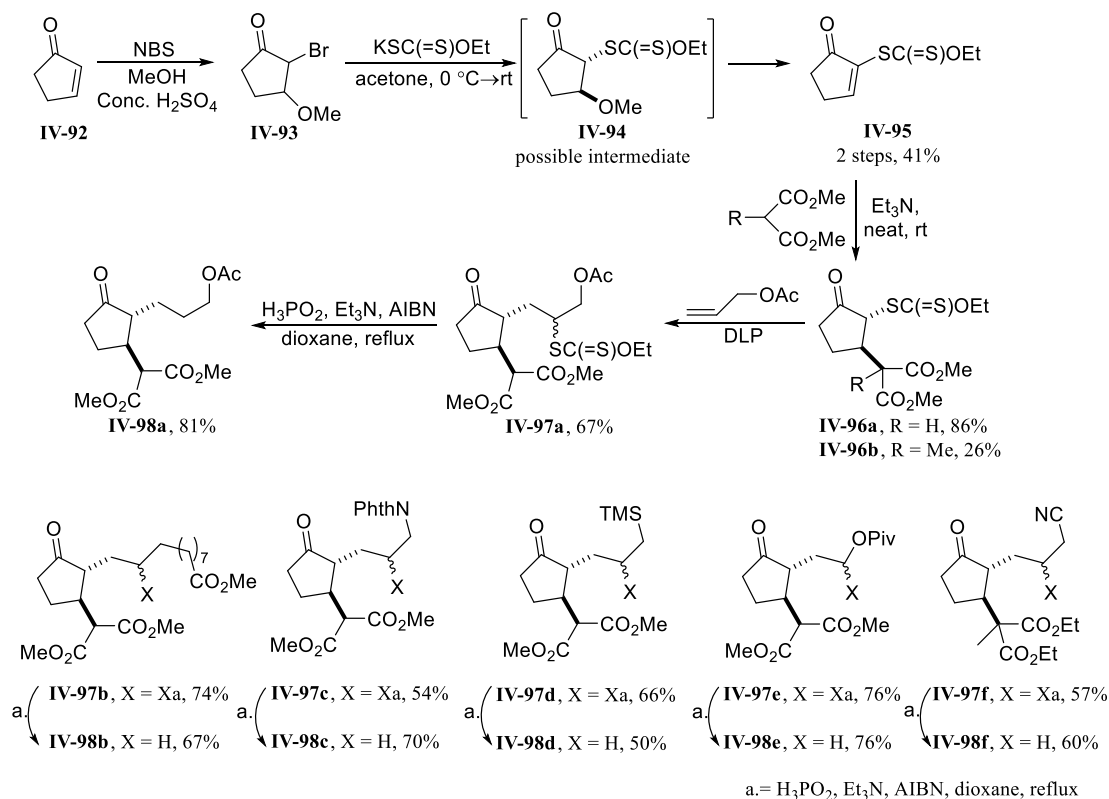
In this section, we describe a vicinal dialkylation of α , β -unsaturated ketones which incorporates a Michael addition and a xanthate addition transfer. The general process is illustrated in **Scheme 4.27**. This method avoids using an organocopper reagent for the β -addition, thus making the reaction easier to handle. For the α -alkylation step, we replace the alkyl halides with much cheaper and environmentally friendly alkenes as alkylating agents.



Scheme 4.27 General process for radical based vicinal dialkylation of ketones

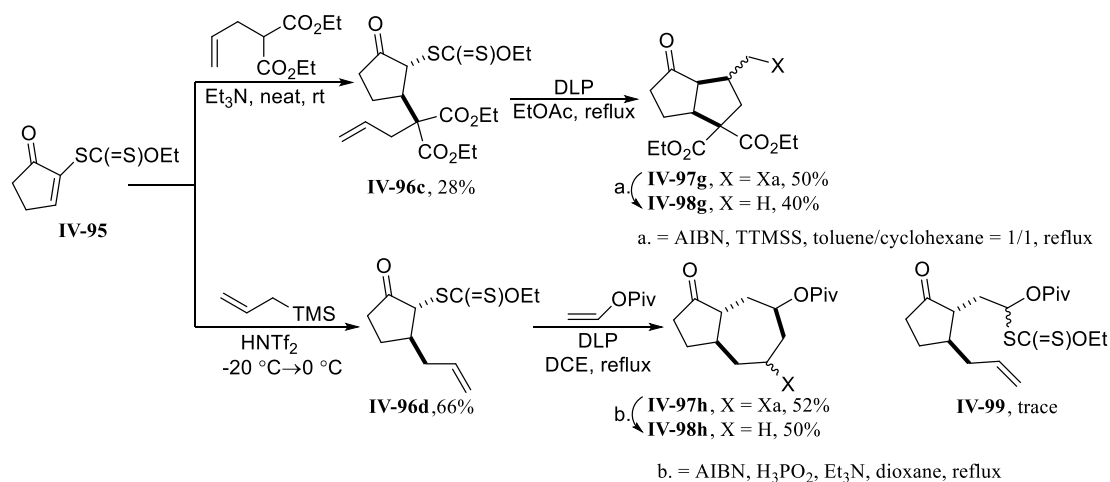
Encouraged by the radical addition of acyclic ketones to various olefins, we tried to extend scope to cyclic ketones widely present in natural products.⁷⁵⁻⁷⁶ Initially, we envisioned using the identical route to synthesize xanthate **IV-94**. However, an unexpected but reasonable product **IV-95** was separated in a useful yield of 41% over two steps. Presumably, the xanthate group of the possible intermediate **IV-94** decreased the pKa of the α -hydrogen, making the elimination of methoxy group even though alkoxy group is a weak leaving group. In this procedure, the excess potassium xanthate acts as both nucleophile and base, and this type of reaction is already known.⁷⁷ With a good supply of the requisite reagent in hand, we proceeded with the Michael addition using dimethyl malonate. The reaction was carried neat in the presence of triethylamine and rapidly afforded β -substituted ketone **IV-96a** in good yield. In contrast to the highly efficient addition of dimethyl malonate, the conjugate addition adduct **IV-96b** was obtained in only 26% yield when using dimethyl methylmalonate as the Michael donor. Not only was the yield dramatically diminished, but also the rate of the reaction was also sluggish. This proved the reactivity of the addition step was significantly affected by steric bulk.

The radical addition of the β -substituted ketones to various unactivated alkenes was next examined. All reactions were conducted with or without solvent and smoothly afforded radical adducts **IV-97a-f** in good yield. This one-step convenient α -alkylation exhibited its great advantages compared to the ionic tandem vicinal dialkylation of unsaturated ketones. The latter intermediate enolate fails to be alkylated in-situ, and has to be *O*-silylated followed by regeneration of the enolate with a lithium reagent and then be alkylated using alkyl halides⁷⁴ All of the products **IV-98a-f** were essentially 1:1 mixtures of diastereoisomers that were simplified by reductively removing the xanthate group using Barton's reagent (**Scheme 4.28**).⁵⁹ It is worth noting that γ -cyano ketone **IV-98f** is the starting material of α -hydroxycyclopentanone.⁷⁸⁻⁸⁰ Depending on the ring size, the α -hydroxycycloketone is a key intermediate in the synthesis of guaiazulene, (-)-valeranone and polyquinanes.⁸¹



Scheme 4.28 Preparation of xanthate IV-95 and examples of dialkylation

The synthetic utility of intramolecular radical cyclization reactions has been proven repeatedly in the synthesis of fused carbocyclic and heterocyclic structures.⁸²⁻⁸⁵ The application of this methodology in the total synthesis of natural products further demonstrates the popularity of this reaction.⁸⁶⁻⁸⁸ Such a strategy could also be adopted in an case. For example, the addition of diethyl allylmalonate to xanthate IV-95 to introduces an alkene in the β -position of cyclopentanone IV-96c, not surprisingly, in only 28% yield. The ring-closing reaction was performed in refluxing ethyl acetate at a 0.025 M concentration, providing bicyclic ketone IV-97g in 50% yield. We also prepared the β -allyl cyclopentanone IV-96d in fair yield using a triflimide (HNTf₂) catalyzed Sakurai-type reaction.⁸⁹ We then carried out the radical addition to vinyl pivalate in dichloroethane at a 1 M concentration. The major product was the ring-closed product IV-97h, and only trace amount of adduct IV-99 was detected. This cyclization appears to be occurred spontaneously. Finally, the xanthate group in IV-97g–h was reductively removed in order to simplify the characterization (Scheme 4.29). Two methods have been used in the reduction step: Barton's reagent⁵⁹ and tris(trimethylsilyl)silane,⁹⁰ providing the desired product IV-98g, IV-98h in 40% and 57%, respectively.



Scheme 4.29 Synthesis of bicyclic ketone derivatives

4.3.3 Alkylation of esters

Esters are important chemicals in daily life. Short-chain esters are the most common and versatile components of natural flavors and fragrances, they are in high demand and are widely used in the food, beverage, cosmetic, and pharmaceutical industries.⁹¹⁻⁹² Long-chain esters are the main ingredient of biodiesels.⁹³⁻⁹⁴ Among the reactions of carboxylic acid derivatives, the α -alkylation of esters represents an essential reaction for modifying the ester structure. Although the enolizable hydrogens of esters are somewhat weaker in acidity than aldehydes and ketones, it is generally possible to quantitatively deprotonate them with strong base to form the corresponding metal enolates, followed by nucleophilic attack to various electrophiles to provide the desired alkylated esters. When more hindered systems are involved, HMPA is added to promote the substitution.⁹⁵⁻⁹⁶ However, the ester enolates have the potential to eliminate the alkoxides when sodium and potassium enolates are formed. Moreover, competing Claisen condensation can occur when weaker bases such as alkoxides are used. Other disadvantages of such methods are the use of toxic alkylating agents, and the reaction having to be performed in strongly alkaline medium, leading to incompatibility with sensitive functional groups.

As part of our work on xanthate,⁹⁷⁻¹⁰² a series of carboxylic acid derivatives bearing xanthate group have been prepared over the years and made to undergo radical additions to unactivated alkenes, and this has provided various modified esters, lactones, amides and lactams,¹⁰³⁻¹⁰⁷ thereby greatly enriching the applications of radical chemistry. There are nevertheless further opportunities for diversifying the ester structures and more work is justified to generalize the α -alkylation of esters and lactones.

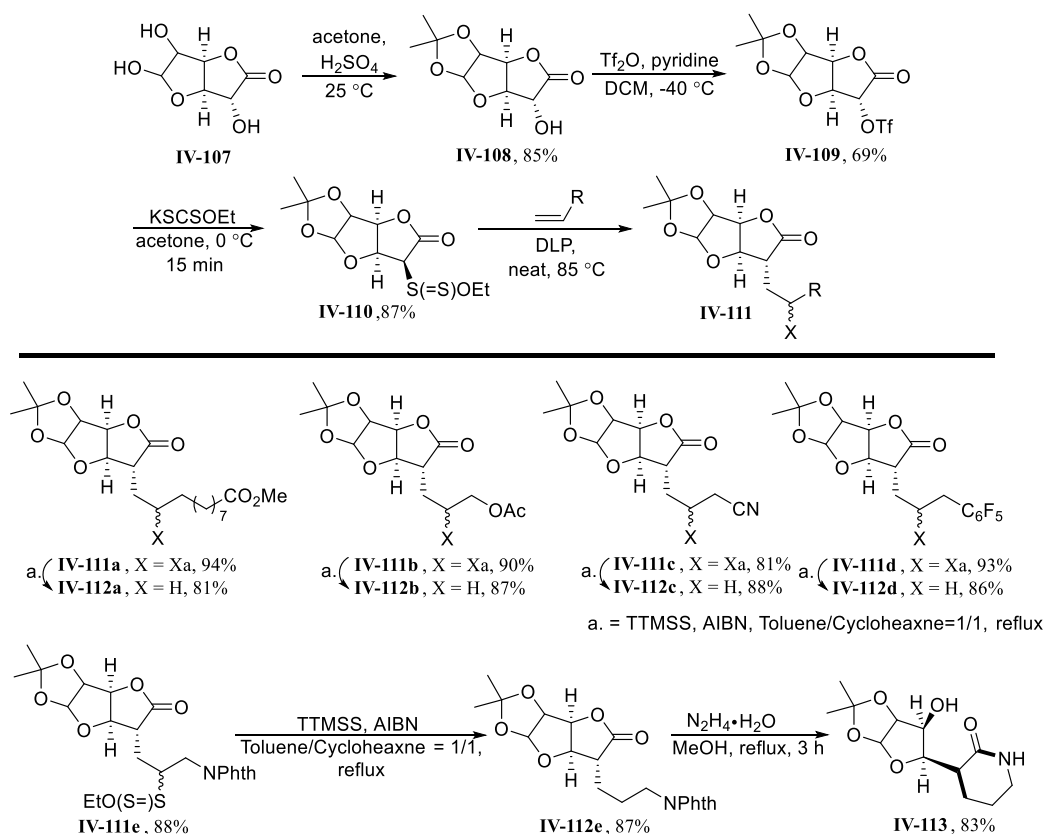
Our work was commenced with the synthesis of xanthate **IV-102** from commercially available ethyl 2,3-dibromopropionate **IV-100**. Treatment with sodium methoxide in methanol triggered the substitution of one bromine atom and transesterification simultaneously, which furnished intermediate **IV-101** in 76% yield.¹⁰⁸ Exposure of **IV-101** to potassium *O*-ethyl xanthate in acetone afforded desired xanthate **IV-102** in fair yield. With a good supply of the requisite starting xanthate in hand, we examined the behavior of radical additions to various

functionalized alkenes and the corresponding results are displayed in **Scheme 4.30**. All reactions were performed in ethyl acetate at 1 M concentration or neat. This xanthate-based alkylation of esters proved to be very general, and afforded the desired products in good to excellent yield. The transformation also showed good compatibility with various polar functional groups, such as cyanide **IV-103a**, esters **IV-103b**, **IV-103n**, sulfone **IV-103j**, phosphonate **IV-103k**, epoxide **IV-103p**, and free alcohols **IV-103r**.

In the scope extension, we prepared various γ - and δ -amino acids **IV-103e**, **IV-103f**, **IV-103g**, **IV-103h**, **IV-103i** and **IV-103q**. These types of unnatural peptidic amino acids have drawn much attention in drug discovery, especially in the peptidomimetic area. The generation of γ -amino butyric acid (GABA) analogues mostly relied on γ -amino acids. δ -Amino acids are building blocks for constructing peptide nucleic acid (PNA) because the chain length of these amino acid homologues corresponds to the optimal distance to mimic the ribose unit found in RNA and DNA polymers.¹⁰⁹ Although many synthetic strategies for the synthesis of γ - and δ -amino acids derivatives have been reported,¹⁰⁹⁻¹¹¹ this direct radical addition of ester bearing xanthate to vinyl or allylamines can be a complement.

The example **IV-103s** illustrates that the xanthate group can be reductively removed by using the triethylammonium salt of hypophosphorus acid, which afforded the corresponding product **IV-104** in high yield. The addition of xanthate **IV-102** to allyl ethyl acetate and hept-1-en-3-yl acetate provided adducts **IV-103b** and **IV-103t**. Reductive removal of the xanthate group using Barton's reagent. The methoxy group can be eliminated by heating in toluene in the presence of *p*-toluenesulfonic acid furnished the corresponding α -methylene lactones **IV-106a** and **IV-106b**, respectively (**Scheme 4.30**).¹¹²

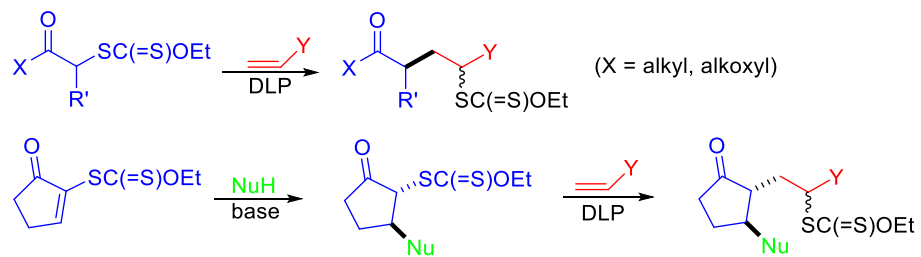
various radical additions were carried out neat and provided radical adducts **IV-111a-d** in good to excellent yield. In order to simplify characterization by eliminating an asymmetric center, the Barton's method was used to reductively remove the xanthate group, affording the desired products in very poor yield. Presumably, the mildly basic conditions caused the elimination of the P-oxygen to the carbonyl and opening of the tetrahydrofuran ring. When the reducing agent was changed to tris(trimethylsilyl)silane,⁹⁰ all the reduced products were obtained in high yield. Deprotection of the phthalimide in adduct **IV-112e** by hydrazine hydrate furnished substituted lactam **IV-113** in 83% yield,¹¹⁴ where the ring closure occurred spontaneously (**Scheme 4.31**).



Scheme 4.31 Synthesis of xanthate **IV-110** and examples of radical additions

4.4 Conclusion and perspective

In summary, we have developed a convenient approach for the alkylation of carbonyl compounds based on the xanthate transfer process. This method features high chemo- and regioselectivity and no *O*-alkylation and polyalkylation was observed. Because of the neutral condition, it exhibits excellent functional group tolerance. In contrast to tin radical chemistry which has to be conducted in very diluted medium, most of the xanthate based radical additions can be performed neat or in concentrated solution. For the dialkylation of ketones, the xanthate method avoids using organocopper and organolithium reagents and uses unactivated alkenes as alkylating agents, making this method easy to handle and more environmental friendly. (**Scheme 4.32**).



Scheme 4.32 Xanthate transfer process for alkylation of carbonyl compounds

Considering the advantages of this method, numerous variations and extensions can be contemplated, such as the synthesis of natural products and the late stage modification of biologically active substances.

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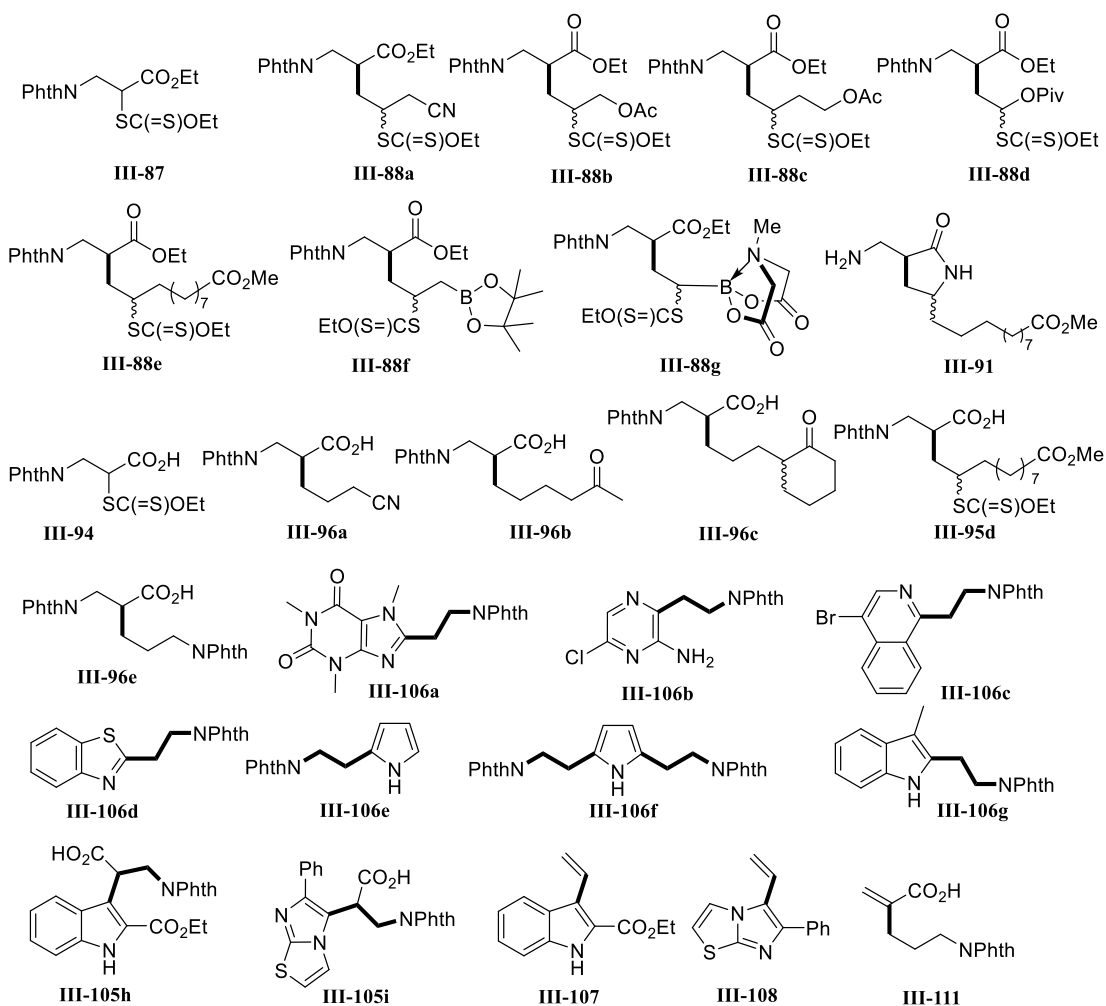
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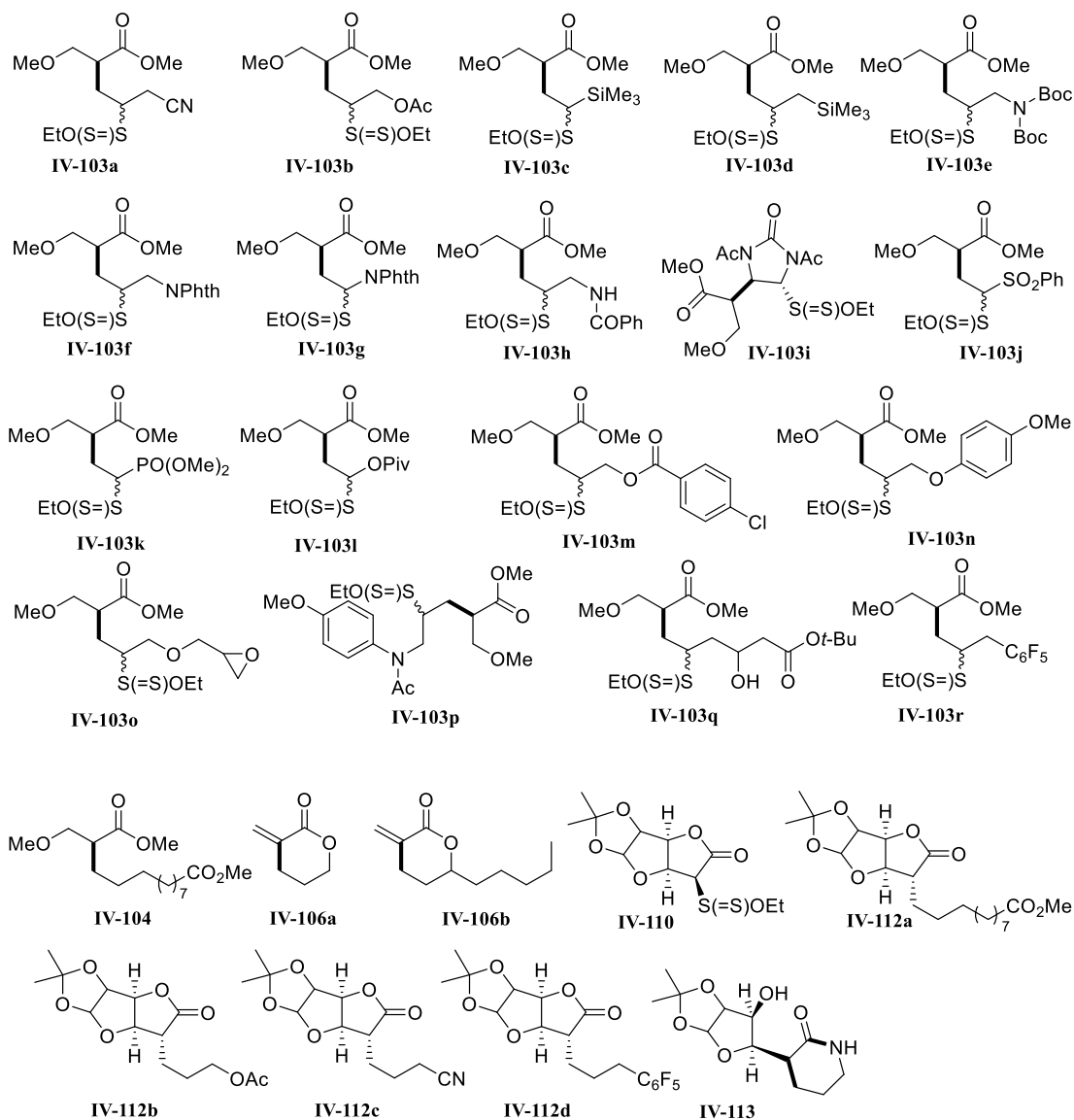
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Experimental part

Molecules of chapter 3





General Experimental Methods

All reactions were carried out under dry, oxygen free nitrogen. All commercially available reagents were used as received without further purification. Thin Layer Chromatography (TLC) was performed on alumina plates precoated with silica gel (Merck silica gel, 60 F254), which were visualized by the quenching of UV fluorescence when applicable (max = 254 nm and/or 366 nm) and/or by staining with vanillin in acidic ethanol solution and/or KMnO_4 in basic water followed by heating. Flash chromatography was carried out on Kieselgel 60 (40-63 μm). Petroleum ether refers to the fraction of petroleum boiling between 40 °C and 60 °C. Infrared spectra were recorded on a Perkin-Elmer Spectrum Two. Absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}). Nuclear Magnetic Resonance spectra were recorded at ambient temperature on a Bruker Avance DPX 400 instrument. Proton magnetic resonance spectra (^1H NMR) were recorded at 400 MHz and coupling constants (J) are reported to ± 0.5 Hz. The following abbreviations were utilized to describe peak patterns when appropriate: br = broad, s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet. Carbon magnetic resonance spectra (^{13}C NMR) were recorded at 100 MHz. Chemical shifts (H, C) are quoted in parts per million (ppm) and are referenced to the residual solvent peak (CDCl_3 : $\delta\text{H}= 7.27$ and $\delta\text{C}= 77.1$; DMSO: $\delta\text{H}= 2.50$ and $\delta\text{C}= 39.5$; CD_3COCD_3 , $\delta\text{H}= 2.05$ and $\delta\text{C}= 29.8$; CD_3OD : $\delta\text{H}= 3.31$ and $\delta\text{C}= 49.0$). High-resolution mass spectra were recorded by electron impact ionization (EI) on a JMS-GCmateII mass spectrometer. The quoted masses are accurate to ± 5 ppm. Microwave-assisted decarboxylation was performed using an Anton Paar® Monowave 300 microwave reactor.

Experimental Procedures and Spectroscopic Data

Chapter 3

General procedure A: Radical addition with unactivated alkene

Xanthate (1.0 equiv), olefin (1.5-3.0 equiv) and dilauroyl peroxide (DLP) (5 mol %) were mixed in a tube with neat condition, then air in the tube was excluded by nitrogen. The tube was sealed and heated in oil bath at 85°C. Additional dilauroyl peroxide (DLP) was added portionwise (5 mol %) every hour until total consumption of the starting xanthate (typically 2-3 portions of DLP). The reaction mixture was then cooled down to room temperature, purified by flash chromatography on silica gel.

General procedure B: The addition of Xanthate to Heteroarenes

A solution of xanthate (2.0-3.0 equiv) and heteroarene (1.0 equiv) in ethyl acetate or 1,2-dichloroethane (1 M) was refluxed in oil bath under nitrogen for 15 min. Then dilauroyl peroxide (DLP) was added portionwise (20 mol %) every hour until total consumption of the starting xanthate. [for substrates that were not completely consumed in 6 h, a second addition of xanthate(2.0-3.0 equiv) was performed at room temperature, followed by heating at reflux for 15 min and portionwise addition of DLP (20 mol % per hour) was performed] The reaction mixture was then cooled down to room temperature, concentrated by vacuum and purified by flash chromatography on silica gel or washed with appropriate solvent to obtain desired product.

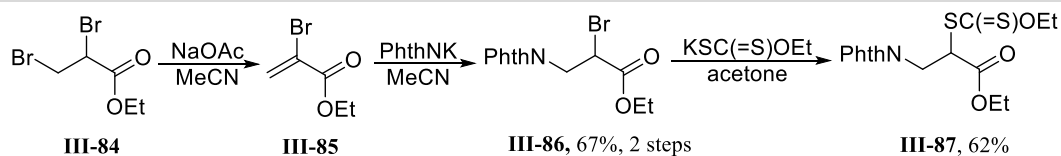
General procedure C: Reduction of xanthate with Barton's hypophosphorus reagent

A solution of radical adduct (1.0 equiv), H₃PO₂ (50% in H₂O, 2.6 equiv), triethylamine (2.8 equiv) in dioxane (0.1 M) was refluxed in oil bath for 15 min. Then, AIBN (10 mol%) was added every hour until total consumption of the adduct (typically, reaction time is 2-3hours). The reaction mixture was cooled down to room temperature, and then partitioned between H₂O and EtOAc. The combined organic layer was washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. Flash chromatography afforded reduced compound.

General procedure D: microwave-assisted decarboxylation

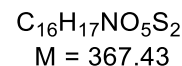
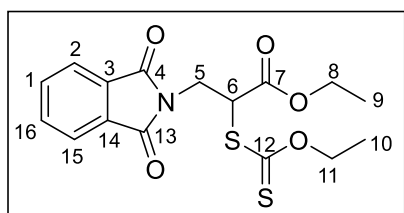
A solution of the carboxylic acid (1 mmol) in N-methyl-2-pyrrolidone (10 mL) in a sealed tube was irradiated in a microwave reactor at 220 °C and the reaction was monitored by TLC plate. In cases that the starting material was not totally consumed, the reaction temperature was increased by 10°C and irradiated for another 10 min. And this procedure was repeated several times until the total consumption of the starting material. Upon cooling to room temperature, the reaction mixture was poured into water (50 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were washed with brine and dried over anhydrous sodium sulfate. After removal of the solvent, the residue was purified by flash chromatography on silica gel.

ethyl 3-(1,3-dioxisoindolin-2-yl)-2-((ethoxycarbonothioyl)thio) propanoate (**III-87**)



Ethyl 2,3-dibromopropanoate (3.9 g, 15 mmol, 1.0 equiv) was dissolved in 60 mL MeCN, then anhydrous sodium acetate (1.41 g, 17.25 mmol, 1.15 equiv) was added in 4 portions every 20min, stirred for 30h. The suspension was filtered. Potassium phthalimide (5.6 g, 30 mmol, 2.0 equiv) was added in 5 portions every 30min. Filtered reaction mixture after 48h, the filtrate was concentrated under reduced pressure, afforded a reported compound **III-86** as brown oil which can be used directly without any purification (3.3 g, 10.1 mmol, 67%, two steps, HRMS (EI⁺) *m/z*: [M-Br]⁺, Calcd for C₁₃H₁₂NO₄⁺: 246.0766; Found 246.0759)

Potassium O-ethylxanthate salt (1.7 g, 10.6 mmol, 1.05 equiv) was added portionwise over 15min to a solution of intermediate **III-86** in 35 mL acetone. After 1h, ice water was added to the suspension and the resulted aqueous solution was extracted twice with dichloromethane. The combined organic layer was washed by brine and dried over anhydrous MgSO₄. Filtered and concentrated under reduced pressure. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 8/1 to 4/1) afforded desired product **III-87** as a white solid (2.3 g, 6.26 mmol, 62%).



¹H NMR (400 MHz, CDCl₃) δ (ppm) = 7.90 – 7.79 (m, 2H, H₂, H₁₅), 7.77 – 7.67 (m, 2H, H₁, H₁₆), 4.71 (t, *J* = 7.2 Hz, 1H, H₆), 4.60 (dd, *J* = 7.1, 6.3 Hz, 2H, H_{5a}, H_{5b}), 4.29 – 4.12 (m, 4H, H₈, H₁₁), 1.40 (t, *J* = 7.1 Hz, 3H H₁₀), 1.22 (t, *J* = 7.1 Hz, 3H, H₉).

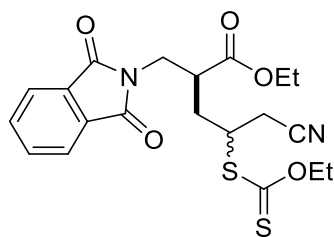
¹³C NMR (101 MHz, CDCl₃) δ (ppm) = 210.1 (C₁₂), 168.4 (C₇), 167.6 (C₄, C₁₃), 134.2 (C₁, C₁₆), 131.7 (C₃, C₁₄), 123.5 (C₂, C₁₅), 70.7 (C₁₁), 62.3 (C₈), 50.3 (C₆), 38.1 (C₅), 14.0 (C₉), 13.6 (C₁₀).

IR (neat) *ν* (cm⁻¹) = 2989, 2907, 1771, 1732, 1699, 1398, 1225, 1044, 944, 714

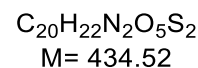
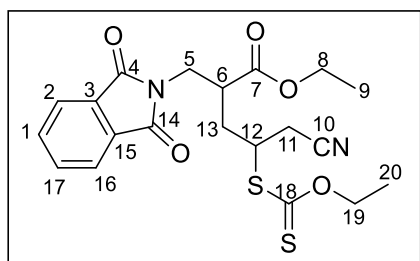
HRMS (EI⁺) *m/z*: [M-C₃H₅OS₂]⁺, Calcd for C₁₃H₁₂NO₄⁺: 246.0766; Found 246.0761

mp: 84-85°C

ethyl 5-cyano-2-((1,3-dioxisoindolin-2-yl)methyl)-4-((ethoxycarbonylthio)pentanoate (**III-88a**)



Following general procedure A, xanthate **III-87** (367.4 mg, 1.0 mmol, 1.0 equiv), allyl cyanide (168.0 mg, 2.5 mmol, 2.5 equiv) and dilauroyl peroxide (5 mol %) were mixed in a tube with neat condition, air in the tube was excluded by nitrogen, then sealed and heated in oil bath at 85°C. The reaction required 10 mol % DLP to consume xanthate completely. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 6/1 to 1/1) afforded radical adduct **III-88a** as a light-yellow liquid (400 mg, 0.92 mmol, 92% yield).



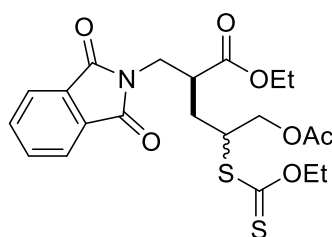
¹H NMR (400 MHz, CDCl₃) δ (ppm) = 7.91 – 7.81 (m, 2H, H₂, H₁₆), 7.79 – 7.69 (m, 2H, H₁, H₁₇), 4.62 (dq, J = 8.6, 7.1 Hz, 2H), 4.19 – 3.79 (m, 5H), 3.16 – 2.82 (m, 3H), 2.33 – 2.15 (m, 1H), 2.08 – 1.87 (m, 1H, H₆), 1.41 (td, J = 7.1, 5.5 Hz, 3H, H₂₀), 1.19 (dt, J = 24.3, 7.2 Hz, 3H, H₉).

¹³C NMR (101 MHz, CDCl₃) δ (ppm) = 211.8 (C₁₈), 172.1 (C₇), 168.2 (C₁₄), 168.0 (C₄), 134.3 (C₁, C₁₇), 131.8 (C₃, C₁₅), 123.5 (C₂, C₁₆), 116.8 (C₁₀), 116.7 (C₁₀), 70.7 (C₁₉), 61.6 (C₈), 44.9 (C₁₂), 44.5 (C₁₂), 42.1 (C₆), 42.0 (C₆), 39.4 (C₅), 38.8 (C₅), 32.2 (C₁₃), 31.6 (C₁₃), 24.7 (C₁₁), 23.9 (C₁₁), 14.0 (C₉), 13.8 (C₂₀), 13.7 (C₂₀).

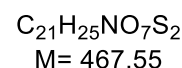
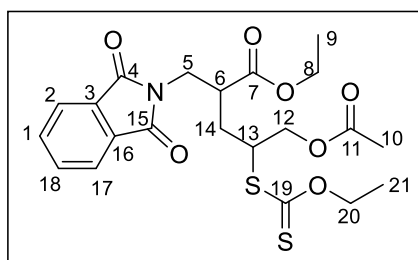
IR (neat) ν (cm⁻¹) = 2982, 2938, 1774, 1712, 1439, 1393, 1220, 1046, 721

HRMS (EI⁺) m/z: Calcd for C₂₀H₂₂N₂O₅S₂⁺: 434.0970; Found 434.0976

ethyl 5-acetoxy-2-((1,3-dioxoisindolin-2-yl)methyl)-4-((ethoxycarbonothioyl)thio)pentanoate (**III-88b**)



Following general procedure A, xanthate **III-87** (367.4 mg, 1.0 mmol, 1.0 equiv), allyl acetate (250.3 mg, 2.5 mmol, 2.5 equiv) and dilauroyl peroxide (5 mol %) were mixed in a tube with neat condition, air in the tube was excluded by nitrogen, then sealed and heated in oil bath at 85°C. Additional dilauroyl peroxide (DLP) is added portionwise (5 mol %) every hour to consume xanthate completely. The reaction required 5 mol % DLP to consume xanthate completely. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 10/1 to 5/1) afforded radical adduct **III-88b** as a light-yellow liquid (410 mg, 0.88 mmol, 88% yield).



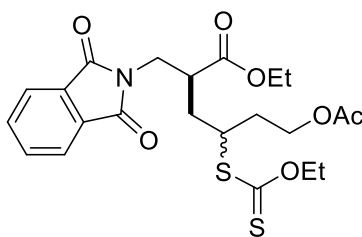
¹H NMR (400 MHz, CDCl₃) δ (ppm) = 7.81 (ddd, $J = 5.5, 3.0, 2.1$ Hz, 2H, H₂, H₁₇), 7.75 – 7.66 (m, 2H, H₁, H₁₈), 4.58 (dq, $J = 9.4, 7.1$ Hz, 2H, H₂₀), 4.28 (ddd, $J = 13.1, 11.4, 4.5$ Hz, 1H, H_{12a}), 4.22 – 4.14 (m, 1H, H_{12b}), 4.13 – 3.89 (m, 4H), 3.81 (ddd, $J = 17.8, 13.9, 5.8$ Hz, 1H), 3.13 – 2.95 (m, 1H), 2.28 – 2.06 (m, 1H), 1.99 (d, $J = 24.0$ Hz, 3H, H₁₀), 1.95 – 1.69 (m, 1H), 1.37 (td, $J = 7.1, 5.6$ Hz, 3H, H₂₁), 1.14 (dt, $J = 20.1, 7.2$ Hz, 3H, H₉).

¹³C NMR (101 MHz, CDCl₃) δ (ppm) = 212.4 (C₁₉), 172.6 (C₇), 172.5 (C₇), 170.6 (C₁₁), 170.5 (C₁₁), 168.0 (C₄), 167.9 (C₁₅), 134.2 (C₁, C₁₈), 131.8 (C₃, C₁₆), 123.4 (C₂, C₁₇), 70.4 (C₂₀), 65.9 (C₁₂), 65.3 (C₁₂), 61.3 (C₈), 47.7 (C₅), 47.3 (C₅), 42.1 (C₁₃), 42.0 (C₁₃), 39.7 (C₆), 39.3 (C₆), 30.5 (C₁₄), 30.4 (C₁₄), 20.8 (C₁₀), 20.6 (C₁₀), 14.0 (C₉), 13.7 (C₂₁).

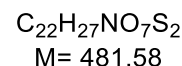
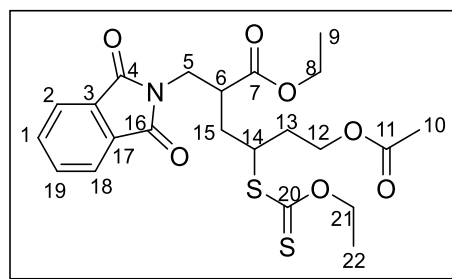
IR (neat) ν (cm⁻¹) = 2981, 1774, 1712, 1437, 1378, 1215, 1110, 1042, 853, 719.

HRMS (EI⁺) m/z : [M + H]⁺, Calcd for [C₂₁H₂₅NO₇S₂+H]⁺: 468.1145; Found 468.1148

ethyl 6-acetoxy-2-((1,3-dioxisoindolin-2-yl) methyl)-4-((ethoxycarbonothioyl)thio) hexanoate (**III-88c**)



Following general procedure A, xanthate **III-87** (367.4 mg, 1.0 mmol, 1.0 equiv), 3-butenyl acetate (285.3 mg, 2.5 mmol, 2.5 equiv) and dilauroyl peroxide (5 mol %) were mixed in a tube with neat condition, air in the tube was excluded by nitrogen, then sealed and heated in oil bath at 85°C. Additional dilauroyl peroxide (DLP) is added portionwise (5 mol %) every hour to consume xanthate completely. The reaction required 5 mol % DLP to consume xanthate completely. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 8/1 to 3/1) afforded desired product **III-88c** as a light-yellow liquid (467 mg, 0.91 mmol, 91% yield).



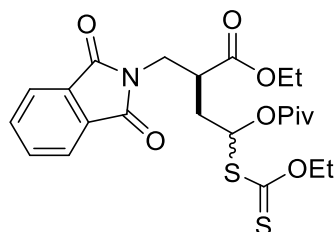
1H NMR δ (ppm) = 7.90 – 7.81 (m, 2H, H₂, H₁₈), 7.79 – 7.70 (m, 2H, H₁, H₁₉), 4.67 – 4.55 (m, 2H, H₁₂), 4.20 – 4.08 (m, 4H, H₈, H₂₁), 4.07 – 3.81 (m, 3H, H₅, H₁₄), 3.14 – 2.99 (m, 1H, H₆), 2.26 – 2.06 (m, 2H), 2.06 – 2.05 (m, 2H), 2.03 – 1.75 (m, 3H), 1.46 – 1.36 (m, 3H, H₂₂), 1.19 (dtt, J = 13.2, 7.1, 0.6 Hz, 3H, H₉).

^{13}C NMR δ (ppm) = 213.3 (C₂₀), 213.2 (C₂₀), 172.8 (C₇), 172.6 (C₇), 170.9 (C₁₁), 168.0 (C₄, C₁₆), 134.1 (C₁, C₁₉), 131.9 (C₃, C₁₇), 123.4 (C₂, C₁₈), 70.2 (C₂₁), 70.1 (C₂₁), 61.6 (C₁₂), 61.3 (C₈), 46.7 (C₁₄), 46.2 (C₁₄), 42.3 (C₆), 39.7 (C₅), 39.5 (C₅), 34.2 (C₁₃), 34.1 (C₁₃), 33.0 (C₁₅), 21.0 (C₁₀), 14.0 (C₉), 13.8 (C₂₂), 13.7 (C₂₂).

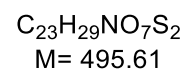
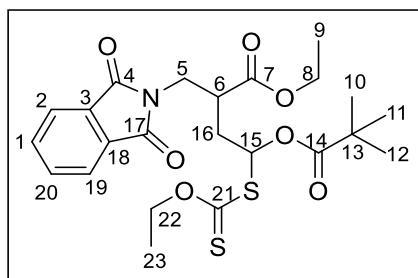
IR (neat) ν (cm⁻¹) = 2981, 1774, 1712, 1435, 1364, 1213, 1110, 1037, 854, 793, 719

HRMS (EI⁺) m/z : [M-C₃H₅OS₂]⁺, Calcd for C₁₉H₂₂NO₆⁺: 360.1447; Found 360.1448

ethyl 2-((1,3-dioxoisindolin-2-yl) methyl)-4-((ethoxycarbonothioyl)thio)-4-(pivaloyloxy) butanoate (**III-88d**)

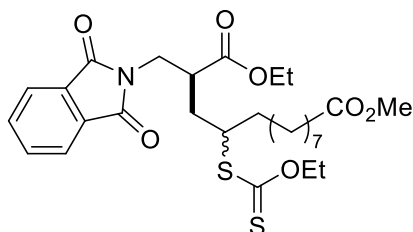


Following general procedure A, xanthate **III-87** (183.7 mg, 0.5 mmol, 1.0 equiv), allyl pivalate (96.1 mg, 0.75 mmol, 1.5 equiv) and dilauroyl peroxide (5 mol %) were mixed in a tube with neat condition, air in the tube was excluded by nitrogen, then sealed and heated in oil bath at 85°C. Additional dilauroyl peroxide (DLP) is added portionwise (5 mol %) every hour to consume xanthate completely. The reaction required 10 mol % DLP to consume xanthate completely. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 12/1 to 7/1) afforded desired product **III-88d** as a light-yellow liquid (230 mg, 0.46 mmol, 92% yield).

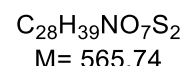
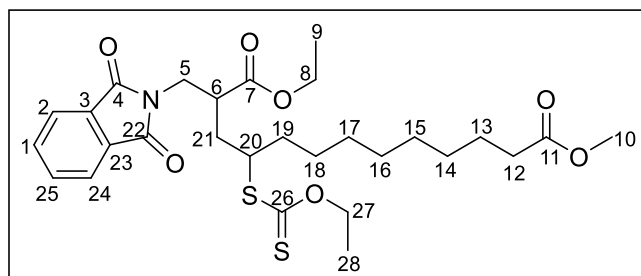


- ¹H NMR** (400 MHz, CDCl₃) δ (ppm) = 7.87 – 7.82 (m, 2H, H₂, H₁₉), 7.76 – 7.70 (m, 2H, H₁, H₂₀), 6.73 – 6.53 (m, 1H, H₁₅), 4.60 (qdd, J = 7.1, 3.6, 1.7 Hz, 2H, H₂₂), 4.17 – 4.06 (m, 2H, H₈), 3.99 (ddd, J = 17.1, 13.8, 7.9 Hz, 1H, H_{5a}), 3.85 (ddd, J = 15.7, 13.8, 6.0 Hz, 1H, H_{5b}), 2.98 (dd, J = 10.4, 8.0 Hz, 1H, H₆), 2.52 – 2.30 (m, 1H, H_{16a}), 2.24 – 2.06 (m, 1H, H_{16b}), 1.39 (td, J = 7.1, 3.4 Hz, 3H, H₂₃), 1.20 – 1.13 (m, 12H, H₉, H₁₀, H₁₁, H₁₂).
- ¹³C NMR** (101 MHz, CDCl₃) δ (ppm) = 209.6 (C₂₁), 176.5 (C₇), 176.4 (C₇), 172.1 (C₁₄), 171.9 (C₁₄), 167.9 (C₄, C₁₇), 134.2 (C₁, C₂₀), 131.9 (C₃, C₁₈), 123.5 (C₂, C₁₉), 79.0 (C₁₅), 78.2 (C₁₅), 70.3 (C₂₂), 70.2 (C₂₂), 61.5 (C₈), 61.4 (C₈), 41.1 (C₅), 41.0 (C₅), 39.6 (C₆), 39.3 (C₆), 38.8 (C₁₃), 34.3 (C₁₆), 33.9 (C₁₆), 26.9 (C₁₀, C₁₁, C₁₂), 14.0 (C₉), 13.9 (C₉), 13.7 (C₂₃), 13.6 (C₂₃).
- IR** (neat) ν (cm⁻¹) = 2978, 1775, 1714, 1438, 1392, 1224, 1127, 1030, 856, 735, 719
- HRMS** (EI⁺) m/z : [M-C₃H₅OS₂]⁺, Calcd for C₂₀H₂₄NO₆⁺: 374.1604; Found 374.1612

1-ethyl 13-methyl 2-((1,3-dioxoisindolin-2-yl) methyl)-4-((ethoxy carbonothioyl)thio) tridecanedioate (**III-88e**)



Following general procedure A, xanthate **III-87** (367.4 mg, 1.0 mmol, 1.0 equiv), methyl undec-10-enoate (496 mg, 2.5 mmol, 2.5 equiv) and dilauroyl peroxide (5 mol %) were mixed in a tube with neat condition, air in the tube was excluded by nitrogen, then sealed and heated in oil bath at 85°C. Additional dilauroyl peroxide (DLP) is added portionwise (5 mol %) every hour to consume xanthate completely. The reaction required 10 mol % DLP to consume xanthate completely. Flash chromatography on silica gel (petroleum ether/ethyl acetate =10/1 to 5/1) afforded the desired product **III-88e** as a yellow liquid (440 mg, 0.78 mmol, 78% yield).



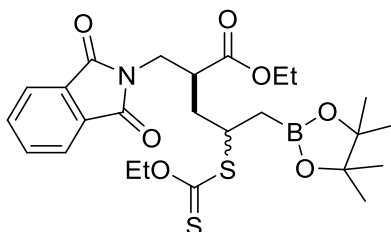
¹H NMR (400 MHz, CDCl₃) δ (ppm) = 7.84 – 7.78 (m, 2H, H₂, H₂₄), 7.69 (ddd, J = 5.7, 2.9, 0.5 Hz, 2H, H₁, H₂₅), 4.62 – 4.49 (m, 2H, H₂₇), 4.16 – 4.02 (m, 2H, H₈), 3.94 (ddd, J = 24.4, 13.8, 7.7 Hz, 1H, H_{5a}), 3.85 – 3.66 (m, 2H, H_{5b}, H₂₀), 3.62 (d, J = 0.6 Hz, 3H, H₁₀), 3.01 (ddt, J = 7.9, 6.0, 2.0 Hz, 1H, H₆), 2.30 – 2.23 (m, 2H, H₁₂), 2.22 – 2.04 (m, 1H, H_{21a}), 1.89 – 1.49 (m, 5H), 1.36 (td, J = 7.1, 5.0 Hz, 4H), 1.28 – 1.19 (m, 8H), 1.14 (dt, J = 16.8, 7.2 Hz, 3H, H₉).

¹³C NMR (101 MHz, CDCl₃) δ (ppm) = 214.1 (C₂₆), 213.9 (C₂₆), 174.3 (C₁₁), 172.9 (C₇), 168.0 (C₄, C₂₂), 134.1 (C₁, C₂₅), 131.9 (C₃, C₂₃), 123.4 (C₂, C₂₄), 69.9 (C₂₇), 69.8 (C₂₇), 61.1 (C₈), 51.4 (C₁₀), 49.7 (C₂₀), 49.2 (C₂₀), 42.4 (C₆), 42.2 (C₆), 39.8 (C₅), 39.6 (C₅), 35.2, 34.2, 34.1, 33.7, 29.3, 29.2, 29.1, 26.6, 26.5, 24.9, 14.0 (C₉), 13.8 (C₂₈).

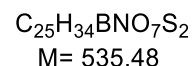
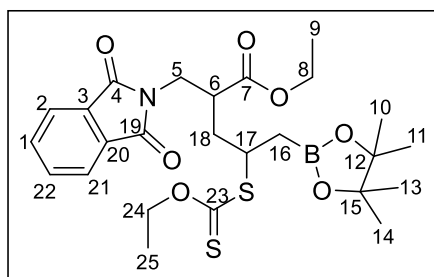
IR (neat) ν (cm⁻¹) = 2928, 2854, 1774, 1714, 1435, 1392, 1359, 1208, 1110, 1044, 914, 719

HRMS (EI⁺) m/z : [M-C₃H₅OS₂]⁺, Calcd for C₂₅H₃₄NO₆⁺: 444.2386; Found 444.2384

ethyl2-((1,3-dioxoisindolin-2-yl)methyl)-4-((ethoxycarbonylthio)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) pentanoate (**III-88f**)

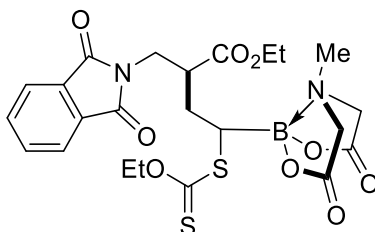


Following general procedure A, xanthate **III-87** (183.7 mg, 0.5 mmol, 1.0 equiv), 2-allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (126.0 mg, 0.75 mmol, 1.5 equiv) and dilauroyl peroxide (5 mol %) were mixed in a tube with neat condition, air in the tube was excluded by nitrogen, then sealed and heated in oil bath at 85°C. Additional dilauroyl peroxide (DLP) is added portionwise (5 mol %) every hour to consume xanthate completely. The reaction required 10 mol % DLP to consume xanthate completely. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 10/1 to 4/1) afforded desired product **III-88f** as a light-yellow liquid (248 mg, 0.46 mmol, 92% yield).

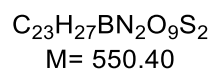
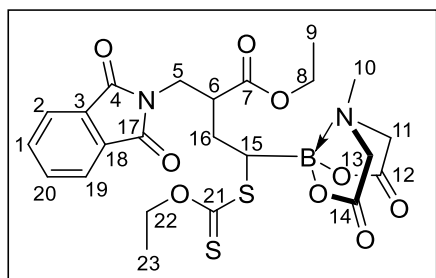


- ¹H NMR** (400 MHz, CDCl₃) δ (ppm) = 7.86 – 7.79 (m, 2H, H₂, H₂₁), 7.75 – 7.66 (m, 2H, H₁, H₂₂), 4.62 – 4.53 (m, 2H, H₈), 4.12 – 4.04 (m, 2H, H₂₄), 4.00 – 3.89 (m, 2H, H₅), 3.85 – 3.76 (m, 1H, H₁₇), 3.10 – 2.95 (m, 1H, H₆), 2.27 – 2.12 (m, 1H, H_{18a}), 1.96 – 1.84 (m, 1H, H_{18b}), 1.41 – 1.25 (m, 7H), 1.17 (dd, *J* = 11.5, 5.8 Hz, 13H).
- ¹³C NMR** (101 MHz, CDCl₃) δ (ppm) = 213.9 (C₂₃), 213.6 (C₂₃), 173.0 (C₇), 172.9 (C₇), 168.0 (C₄, C₁₉), 134.0 (C₁, C₂₂), 132.0 (C₃, C₂₀), 123.3 (C₂, C₂₁), 83.5 (C₁₂, C₁₅), 69.6 (C₂₄), 61.1 (C₈), 46.0 (C₁₇), 45.4 (C₆), 42.4 (C₅), 39.7 (C₁₆), 35.8 (C₁₈), 35.4 (C₁₈), 24.8 (C_{10,11,13,14}), 14.0 (C₉), 13.8 (C₂₅).
- IR** (neat) ν (cm⁻¹) = 2978, 2934, 1775, 1714, 1438, 1361, 1211, 1141, 1110, 1044, 967, 845, 718
- HRMS** (EI⁺) *m/z*: [M-C₃H₅OS₂]⁺, Calcd for C₂₂H₂₉BNO₆⁺: 414.2088; Found 414.2085

Ethyl2-((1,3-dioxoisindolin-2-yl)methyl)-4-((ethoxycarbonothioyl)thio)-4-(4-methyl-2,6-dioxotetrahydro-2H-4H,8H- [1,3,2] oxazaborolo[2,3-b] [1,3,2] oxazaborol-8-yl) butanoate (**III-88g**)

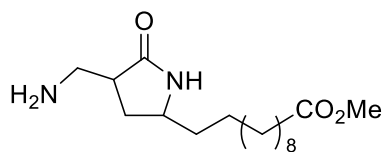


By using a modified procedure A, xanthate **III-87** (367.4 mg, 1.0 mmol, 2.0 equiv) and vinyl boronic acid MIDA ester (91.5 mg, 0.5 mmol, 1.0 equiv) in ethyl acetate (0.5 mL) was refluxed in oil bath under N₂. Then dilauroyl peroxide (DLP) was added portionwise (5 mol %, according to xanthate) every hour to consume xanthate completely. The reaction required 5 mol % DLP to consume xanthate completely. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 3/1 to 1/3) afforded the desired product **III-88g** as an off white solid (273.0 mg, 0.496 mmol, 99% yield).



- ¹H NMR** (400 MHz, CDCl₃) δ (ppm) = 7.86 – 7.79 (m, 2H, H₂, H₁₉), 7.77 – 7.68 (m, 2H, H₁, H₂₀), 4.71 – 4.51 (m, 2H, H₂₂), 4.16 – 3.83 (m, 8H, H₈, H₅, H₁₁, H₁₃), 3.44 (dd, $J = 10.7, 3.6$ Hz, 1H, H₁₅), 3.11 (d, $J = 25.4$ Hz, 4H, H₆, H₁₀), 2.44 (ddd, $J = 14.2, 10.2, 3.6$ Hz, 1H, H_{16a}), 1.81 – 1.71 (m, 1H, H_{16b}), 1.47 – 1.37 (m, 3H, H₂₃), 1.16 (dt, $J = 43.8, 7.2$ Hz, 3H, H₉).
- ¹³C NMR** (101 MHz, CDCl₃) δ (ppm) = 214.9 (C₂₁), 173.3 (C₇), 168.1 (C₄, C₁₇), 167.3 (C₁₂), 167.0 (C₁₄), 134.1 (C₁, C₂₀), 131.9 (C₃, C₁₈), 123.4 (C₂, C₁₉), 71.0 (C₂₂), 63.3 (C₈), 63.1 (C₈), 61.1 (C₁₁, C₁₄), 46.3 (C₁₅), 42.1 (C₁₀), 39.9 (C₅), 31.2 (C₁₆), 13.9 (C₉), 13.8 (C₂₃).
- IR** (neat) ν (cm⁻¹) = 2961, 1771, 1708, 1441, 1393, 1282, 1209, 1182, 1106, 1034, 1001, 897, 863, 720
- HRMS** (EI⁺) m/z : [M-C₃H₅OS₂]⁺, Calcd for C₂₀H₂₂BN₂O₈⁺: 429.1469; Found 429.1452
- mp**: 113-115°C

methyl 11-(4-(aminomethyl)-5-oxopyrrolidin-2-yl)undecanoate (**III-91**)

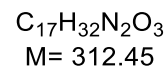
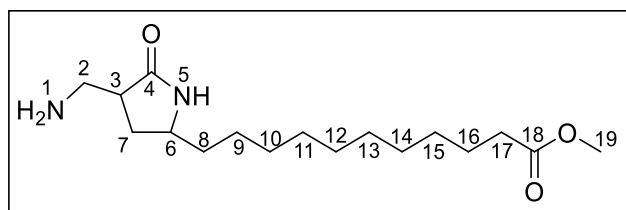


By using a modified procedure A, xanthate **III-87** (367.4 mg, 1.0 mmol, 2.0 equiv) and N-vinylphthalimide (86.6 mg, 0.5 mmol, 1.0 equiv) in ethyl acetate (0.5 mL) was refluxed in oil bath under N₂. Then dilauroyl peroxide (DLP) was added portionwise (5 mol %, according to xanthate) every hour to consume xanthate completely. The reaction required 5 mol % DLP to consume xanthate completely. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 5/1 to 2/1) afforded the desired product **III-88h** as a yellow oil (213.0 mg, 0.39 mmol, 78% yield).

Then following procedure A, the intermediate **III-88h** conducted a second radical addition with methyl undec-10-enoate (154.6 mg, 0.78 mmol, 2.0 eq) to afford a slightly yellow oil **III-89** (281 mg, 0.38 mmol, 97%) which been used directly in next step without any further purification.

Following general procedure C, a solution of xanthate **III-89** (281.0 mg, 0.38 mmol, 1.0 equiv), H₃PO₂ (50% in H₂O, 132.0 mg, 1.0 mmol, 2.6 equiv), triethylamine (106.0 mg, 1.1 mmol, 2.8 equiv) in dioxane (0.1 M) was refluxed in oil bath in the presence of AIBN. The reaction required 30 mol % AIBN to reduce xanthate completely. The reaction mixture cooled down to room temperature and then partitioned between H₂O and EtOAc. The combined organic layer was washed with brine, dried over MgSO₄, filtered, and concentrated under reduced pressure afforded the reductive product **III-90** (178.0 mg, 0.29 mmol, 76% yield) as a colorless oil used in next step without any purification.

According to the literature reported method,⁵ intermediate **III-90** (100 mg, 0.16 mmol, 1.0 eq) was treated with hydrazine hydrate (31.1 mg, 0.48 mmol, 3.0 eq, Assay: 50-60%) in methanol (3.0 mL) for 16h. Then the solution was poured into water (15 mL) and extracted with dichloromethane (3 × 10 mL), combined organic layer dried over anhydrous MgSO₄ and concentrated under reduced pressure. Flash chromatography on silica gel (dichloromethane/methanol = 20/1 to 15/1) afforded the cyclized lactam **III-91** as a colorless oil (28 mg, 0.09 mmol, 56% yield).



¹H NMR (400 MHz, CDCl₃) δ (ppm) = 7.57 – 7.36 (m, 2H, H₅, H_{1a}), 7.20 – 7.01 (m, 1H, H_{1b}), 3.77 – 3.68 (m, 0.5H), 3.65 (d, *J* = 1.6 Hz, 3H, H₁₉), 3.62 – 3.42 (m, 2H, H₂), 2.66 (dd, *J* = 15.0, 7.9 Hz, 0.5H), 2.29 (t, *J* = 7.5 Hz, 2H, H₁₇),

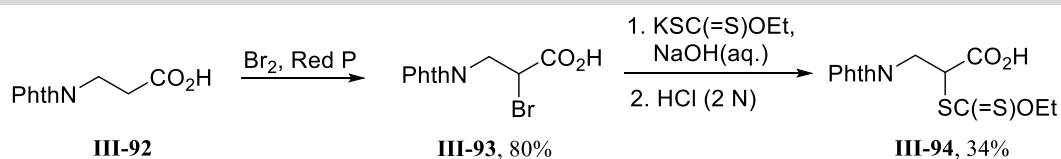
2.17 – 2.06 (m, 0.5H), 1.93 (ddd, $J = 21.4, 12.5, 6.2$ Hz, 0.5H), 1.59 (q, $J = 7.3$ Hz, 2H), 1.51 – 1.35 (m, 2H), 1.34 – 1.17 (m, 16H).

^{13}C NMR δ (ppm) = 178.8 (C₄), 174.3 (C₁₈), 52.7 (C₆), 51.4 (C₁₉), 42.7 (C₃), 42.2 (C₂), 36.7, 34.0 (C₁₈), 30.9, 29.4, 29.3, 29.2, 29.1, 25.8, 25.0, 24.9, 14.8.
(101 MHz, CDCl₃)

IR (neat) ν (cm⁻¹) = 3248, 3068, 2923, 2852, 1735, 1689, 1637, 1540, 1435, 1365, 1306, 1171, 1112, 725.

HRMS (EI⁺) m/z : Calcd for C₁₇H₃₂N₂O₃⁺: 312.2413; Found 312.2404

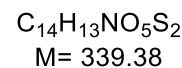
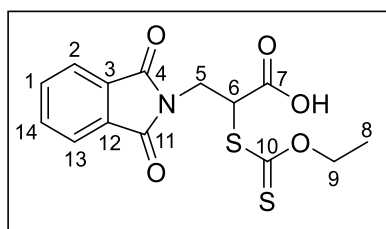
3-(1,3-dioxisoindolin-2-yl)-2-((ethoxycarbonothioyl)thio) propanoic acid (III-94)



According to reported method, phthalic acid anhydride (37 g, 0.25 mol, 1.0 equiv) and β -alanine (22.3 g, 0.25 mol, 1.0 equiv) were refluxed in oil bath in 150 mL toluene in the presence of triethylamine (2.53 g, 0.025 mol, 10%) for 2h in a Dean-Stark apparatus. The organic solvents were removed in vacuo, 350 mL of water and 5 mL of concentrated Hydrochloric Acid were added, then stirred for 30min followed by filtration and drying. Then the crude 2-phthalimidoacetic acid **III-92** is recrystallized from hot ethanol as a white solid (46.7 g, 0.21 mol, 85%).

According to literature reported method, 2-phthalimidoacetic acid **III-92** (24.6 g, 0.11 mol, 1.0 equiv) and red phosphorus (1.55 g, 0.05 mol, 0.5 equiv) mixed homogeneously in a flask equipped with condenser, bromine (17 mL, 0.3 mol, 3.0 equiv) was dropped slowly within 2h, then allow the reaction reflux in oil bath for 16h (until no more hydrogen bromide given off), then the reaction solution mixed with water and boiled until the bromine disappeared. cooled to room temperature followed by filtration, the crude product recrystallized in a mixed solvent (water/ethanol = 6/4) to give a white solid **III-93** (26.4 g, 88.5 mmol, 80%).

By using a modified method, the suspension of **III-93** (25.8 g, 86.6 mmol, 1.0 equiv) and water (100 mL) was heated in oil bath to 40°C followed by the drop of sodium hydroxide solution (1.9mol/L, 50 mL). the solution allowed to stir for 30min, then potassium O-ethylxanthate salt (55.5 g, 346.4 mmol, 4.0 equiv) is added in 5 portions every hour. After 6 hours, the pH value of the reaction mixture is adjusted to 4-5 by 2.0 mol/L hydrochloric acid. Then extracted by ethyl acetate, the organic layer dried over MgSO₄ and concentrated in vacuo to afford crude product which could be recrystallized from ethyl acetate to give desired xanthate **III-94** as an off-white solid (10.0 g, 29.4 mmol, 34%).



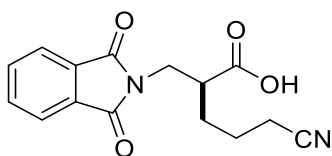
¹H NMR δ (ppm) = 7.93 – 7.86 (m, 4H, H₁, H₂, H₁₃, H₁₄), 4.82 (dd, $J = 8.6, 6.6$ Hz, 1H, H₆), 4.70 – 4.54 (m, 2H, H₅), 4.32 – 4.20 (m, 2H, H₉), 1.42 (t, $J = 7.1$ Hz, 3H, H₈).

¹³C NMR δ (ppm) = 211.7 (C₁₄), 169.9 (C₁₂), 168.3 (C₄, C₁₁), 135.4 (C₁, C₁₄), 132.8 (C₃, C₁₂), 124.1 (C₂, C₁₃), 71.6 (C₉), 51.1 (C₆), 38.9 (C₅), 13.7 (C₈).

IR (neat) ν (cm⁻¹) = 3176, 2983, 1770, 1744, 1694, 1464, 1430, 1406, 1362, 1236, 1151, 1049, 814, 719, 668

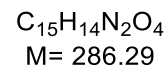
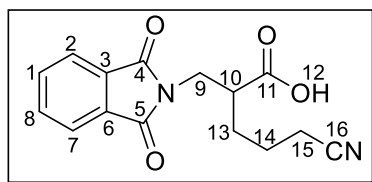
HRMS (EI⁺) m/z: [M-C₃H₅OS₂]⁺, Calcd for C₁₁H₈NO₄⁺: 218.0453; Found 218.0452

mp: 180-182°C

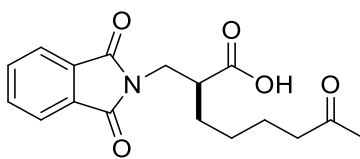
5-cyano-2-((1,3-dioxoisindolin-2-yl)methyl)pentanoic acid (III-96a)

Following general procedure A, xanthate **III-94** (169.7 mg, 0.5 mmol, 1.0 equiv), allyl cyanide (67.1 mg, 1.0 mmol, 2.0 equiv) and dilauroyl peroxide (5 mol %) were mixed in a tube with neat condition, air in the tube was excluded by nitrogen, then sealed and heated in oil bath at 85°C. Additional dilauroyl peroxide (DLP) is added portionwise (5 mol %) every hour to consume xanthate completely. The reaction required 5mol % DLP to consume xanthate completely. Flash chromatography on silica gel (petroleum ether/ethyl acetate/acetic acid = 6/1/0.5 to 3/1/0.5) afforded radical adduct **III-95a** as a light-yellow oil (140.0 mg, 0.34 mmol, 68% yield).

Following general procedure C, a solution of radical adduct **III-95a** (135.0 mg, 0.33 mmol, 1.0 equiv), H₃PO₂ (50% in H₂O, 115.4 mg, 0.87 mmol, 2.6 equiv), triethylamine (91.8 mg, 0.91 mmol, 2.8 equiv) in dioxane (0.1 M) was refluxed in oil bath in the presence of AIBN. The reaction required 20 mol % AIBN to reduce xanthate completely. The reaction mixture partitioned between H₂O and EtOAc. The combined organic layer was washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. Flash chromatography on silica gel (petroleum ether/ethyl acetate/acetic acid = 5/1/0.5 to 1/1/0.5) afforded the reduced product **III-96a** as a white solid (46.0 mg, 0.16 mmol, 48% yield).

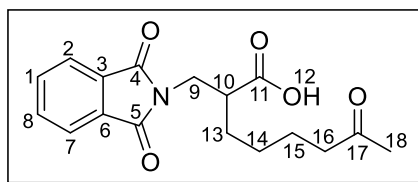


¹H NMR (400 MHz, CDCl ₃)	δ (ppm) = 7.84 – 7.77 (m, 2H, H ₂ , H ₇), 7.70 (dd, <i>J</i> = 5.5, 3.1 Hz, 2H, H ₁ , H ₈), 3.97 (dd, <i>J</i> = 13.9, 7.8 Hz, 1H, H _{9a}), 3.82 – 3.69 (m, 1H, H _{9b}), 2.81 (d, <i>J</i> = 7.6 Hz, 1H, H ₁₀), 2.39 – 2.31 (m, 2H, H ₁₅), 1.85 – 1.62 (m, 4H, H ₁₃ , H ₁₄).
¹³C NMR (101 MHz, CDCl ₃)	δ (ppm) = 178.2 (C ₁₁), 168.4 (C ₄ , C ₅), 134.3 (C ₁ , C ₈), 131.8 (C ₃ , C ₆), 123.5 (C ₂ , C ₇), 119.3 (C ₁₆), 44.4 (C ₁₀), 39.4 (C ₉), 28.5 (C ₁₃), 22.9 (C ₁₄), 17.1 (C ₁₅).
IR (neat)	<i>ν</i> (cm ⁻¹) = 3372, 2942, 2861, 1772, 1707, 1566, 1393, 1359, 1190, 722
HRMS (EI ⁺) <i>m/z</i> :	Calcd for C ₁₅ H ₁₄ N ₂ O ₄ ⁺ : 286.0954; Found 286.0945
mp :	128-130°C

2-((1,3-dioxoisindolin-2-yl) methyl)-7-oxooctanoic acid (III-96b)

Following general procedure A, xanthate **III-94** (169.7 mg, 0.5 mmol, 1.0 equiv), 5-hexen-2-one (98.1 mg, 1.0 mmol, 2.0 equiv) and dilauroyl peroxide (5 mol %) were mixed in a tube with neat condition, air in the tube was excluded by nitrogen, then sealed and heated in oil bath at 85°C. Additional dilauroyl peroxide (DLP) is added portionwise (5 mol %) every hour to consume xanthate completely. The reaction required 5 mol % DLP to consume xanthate completely. Flash chromatography on silica gel (petroleum ether/ethyl acetate/acetic acid = 7/1/0.5 to 3/1/0.5) afforded radical adduct **III-95b** as a light-yellow oil (162.0 mg, 0.37 mmol, 74% yield).

Following general procedure C, a solution of radical adduct obtained above (157.0 mg, 0.36 mmol, 1.0 equiv), H₃PO₂ (50% in H₂O, 125.9 mg, 0.95 mmol, 2.6 equiv), triethylamine (100.2 mg, 0.99 mmol, 2.8 equiv) in dioxane (0.1 M) was refluxed in oil bath in the presence of AIBN. The reaction required 20 mol % AIBN to reduce xanthate completely. The reaction mixture partitioned between H₂O and EtOAc. The combined organic layer was washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. Flash chromatography on silica gel (petroleum ether/ethyl acetate/acetic acid = 6/1/0.5 to 2/1/0.5) afforded the reduced product **III-96b** as a colorless oil (82.0 mg, 0.26 mmol, 72% yield).



C₁₇H₁₉NO₅
M= 317.34

¹H NMR (400 MHz, CDCl₃) δ (ppm) = 7.83 – 7.79 (m, 2H, H₂, H₇), 7.70 (dd, *J* = 5.5, 3.0 Hz, 2H, H₁, H₈), 3.95 (dd, *J* = 13.9, 7.8 Hz, 1H, H_{9a}), 3.77 (dd, *J* = 13.9, 6.4 Hz, 1H, H_{9b}), 2.92 – 2.81 (m, 1H, H₁₀), 2.41 (t, *J* = 7.3 Hz, 2H, H₁₆), 2.10 (d, *J* = 0.5 Hz, 3H, H₁₈), 1.68 – 1.47 (m, 4H, H₁₃, H₁₅), 1.46 – 1.24 (m, 2H, H₁₄).

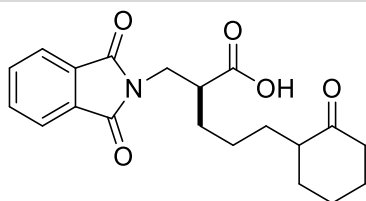
¹³C NMR (101 MHz, CDCl₃) δ (ppm) = 209.2 (C₁₇), 178.7 (C₁₁), 168.2 (C₄, C₅), 134.1 (C₁, C₈), 131.9 (C₃, C₆), 123.4 (C₂, C₇), 44.2 (C₁₀), 43.3 (C₁₆), 39.3 (C₉), 29.9 (C₁₈), 29.3 (C₁₃), 26.3 (C₁₅), 23.5 (C₁₄).

IR (neat) ν (cm⁻¹) = 2938, 2864, 1773, 1705, 1394, 1360, 1190, 721

HRMS (EI⁺) *m/z*: [M-H₂O]⁺, Calcd for C₁₇H₁₇NO₄⁺: 299.1158; Found 299.1150

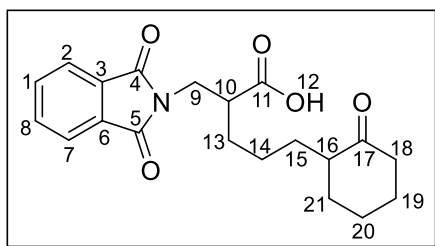
mp: 90-91°C

2-((1,3-dioxisoindolin-2-yl)methyl)-5-(2-oxocyclohexyl)pentanoic acid (**III-96c**)



Following general procedure A, xanthate **III-94** (169.7 mg, 0.5 mmol, 1.0 equiv), 2-allylcyclohexan-1-one (138.2 mg, 1.0 mmol, 2.0 equiv) and dilauroyl peroxide (5 mol %) were mixed in a tube with neat condition, air in the tube was excluded by nitrogen, then sealed and heated in oil bath at 85°C. Additional dilauroyl peroxide (DLP) is added portionwise (5 mol %) every hour to consume xanthate completely. The reaction required 5mol % DLP to consume xanthate completely. Flash chromatography on silica gel (petroleum ether/ethyl acetate/acetic acid = 7/1/0.5 to 3/1/0.5) afforded radical adduct **III-95c** as a light-yellow oil (158.0 mg, 0.33 mmol, 66% yield).

Following general procedure C, a solution of radical adduct obtained above (158.0 mg, 0.33 mmol, 1.0 equiv), H₃PO₂ (50% in H₂O, 115.4 mg, 0.87 mmol, 2.6 equiv), triethylamine (91.8 mg, 0.91 mmol, 2.8 equiv) in dioxane (0.1 M) was refluxed in oil bath in the presence of AIBN. The reaction required 20 mol % AIBN to reduce xanthate completely. The reaction mixture partitioned between H₂O and EtOAc. The combined organic layer was washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. Flash chromatography on silica gel (petroleum ether/ethyl acetate/acetic acid = 6/1/0.5 to 3/1/0.5) afforded the reduced product **III-96c** as a colorless oil (77.0 mg, 0.22 mmol, 65% yield).



C₂₀H₂₃NO₅
M= 357.41

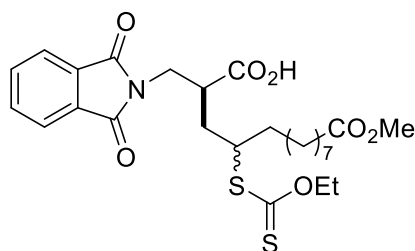
¹H NMR (400 MHz, CDCl₃) δ (ppm) = 7.82 (ddd, *J* = 5.5, 3.2, 0.5 Hz, 2H, H₂, H₇), 7.70 (ddd, *J* = 5.7, 3.0, 0.5 Hz, 2H, H₁, H₈), 3.96 (ddd, *J* = 13.9, 7.8, 2.3 Hz, 1H, H_{9a}), 3.78 (ddd, *J* = 13.9, 6.5, 1.2 Hz, 1H, H_{9b}), 2.90 (d, *J* = 7.6 Hz, 1H, H₁₀), 2.41 – 2.32 (m, 1H, H₁₆), 2.27 (tt, *J* = 11.4, 5.5 Hz, 2H, H₁₈), 2.13 – 1.96 (m, 2H), 1.87 – 1.72 (m, 2H), 1.70 – 1.58 (m, 3H), 1.51 (tq, *J* = 15.7, 5.2 Hz, 1H), 1.45 – 1.25 (m, 3H), 1.24 – 1.09 (m, 1H).

¹³C NMR (101 MHz, CDCl₃) δ (ppm) = 213.5 (C₁₇), 178.6 (C₁₁), 168.2 (C₄, C₅), 134.1 (C₁, C₈), 131.9 (C₃, C₆), 123.4 (C₂, C₇), 50.6 (C₁₆), 50.4 (C₁₆), 44.2 (C₁₀), 44.1 (C₁₀), 42.0 (C₉), 39.3 (C₁₈), 39.2 (C₁₈), 34.1, 33.6, 29.7, 29.6, 29.3, 29.0, 28.1, 28.0, 25.0, 24.9, 24.5, 24.3.

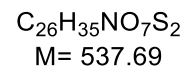
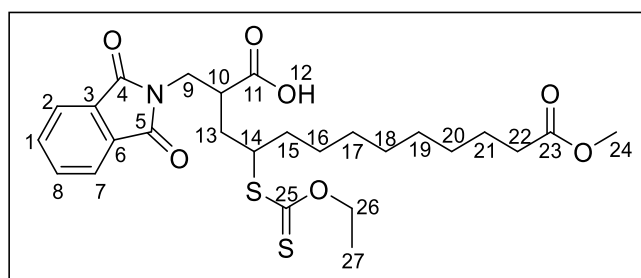
IR (neat) ν (cm⁻¹) = 2935, 2861, 1773, 1709, 1434, 1395, 1364, 1190, 722

HRMS (EI⁺) m/z: [M-C₆H₉O]⁺, Calcd for C₁₄H₁₄NO₄⁺: 260.0923; Found 260.0914

2-((1,3-dioxoisindolin-2-yl)methyl)-4-((ethoxycarbonothioyl)thio)-13-methoxy-13-oxotridecanoic acid
(III-95d)



Following general procedure A, xanthate **III-94** (169.7 mg, 0.5 mmol, 1.0 equiv), methyl 10-undecenoate (198.3 mg, 1.0 mmol, 2.0 equiv) and dilauroyl peroxide (5 mol %) were mixed in a tube with neat condition, air in the tube was excluded by nitrogen, then sealed and heated in oil bath at 85°C. Additional dilauroyl peroxide (DLP) is added portionwise (5 mol %) every hour to consume xanthate completely. The reaction required 5mol % DLP to consume xanthate completely. Flash chromatography on silica gel (petroleum ether/ethyl acetate/acetic acid = 6/1/0.5 to 2/1/0.5) afforded radical adduct **III-95d** as a light-yellow oil (200.0 mg, 0.37 mmol, 74% yield).



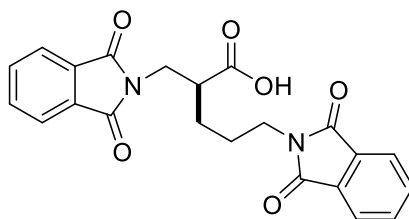
¹H NMR (400 MHz, CDCl₃) δ (ppm) = 7.83 (ddd, J = 5.5, 3.2, 0.6 Hz, 2H, H₂, H₇), 7.71 (dd, J = 5.5, 3.0 Hz, 2H, H₁, H₈), 4.56 (qdd, J = 7.1, 5.4, 3.7 Hz, 2H, H₂₆), 4.02 (ddd, J = 16.9, 13.9, 7.2 Hz, 1H, H₁₄), 3.89 – 3.73 (m, 2H, H₉), 3.65 (d, J = 1.0 Hz, 3H, H₂₄), 3.18 – 3.04 (m, 1H, H₁₀), 2.28 (t, J = 7.5 Hz, 2H, H₂₂), 2.22 – 2.11 (m, 1H), 1.71 (ddt, J = 23.3, 14.7, 4.2 Hz, 2H), 1.56 (dt, J = 13.9, 6.8 Hz, 3H), 1.39 – 1.34 (m, 4H), 1.25 (d, J = 4.3 Hz, 9H).

¹³C NMR (101 MHz, CDCl₃) δ (ppm) = 213.8 (C₂₅), 213.7 (C₂₅), 178.1 (C₁₁), 178.0 (C₁₁), 174.6 (C₂₃), 174.5 (C₂₃), 168.1 (C₄, C₅), 134.2 (C₁, C₈), 131.9 (C₃, C₆), 123.5 (C₂, C₇), 69.9 (C₂₆), 51.5 (C₂₄), 49.6 (C₁₄), 48.9 (C₁₄), 42.2 (C₁₀), 41.8 (C₁₀), 39.6 (C₉), 39.5 (C₉), 34.9, 34.2, 34.1, 33.5, 29.2, 29.2, 29.1, 29.0, 26.6, 26.5, 24.9, 13.7 (C₂₇).

IR (neat) ν (cm⁻¹) = 2926, 2854, 1774, 1712, 1436, 1393, 1361, 1209, 1110, 1044, 719

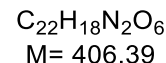
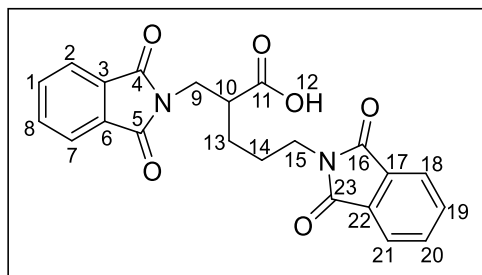
HRMS (EI⁺) m/z : [M-C₃H₅OS₂]⁺, Calcd for C₂₃H₃₀NO₆⁺: 416.2073; Found 416.2074

5-(1,3-dioxoisindolin-2-yl)-2-((1,3-dioxoisindolin-2-yl)methyl)pentanoic acid (**III-96e**)



By using a modified procedure A, xanthate **III-94** (339.4 mg, 1.0 mmol, 1.0 equiv) and N-allylphthalimide (280.7 mg, 1.5 mmol, 1.5 equiv) in ethyl acetate (1.0 mL) was refluxed in oil bath under N₂. Then dilauroyl peroxide (DLP) was added portionwise (5 mol %,) every hour to consume xanthate completely. The reaction required 5 mol % DLP to consume xanthate completely. Evaporating solvent afforded the desired radical adduct **III-95e** (500.0 mg, 0.95 mmol, 95% yield) as a colorless oil which was used directly in next step without purification.

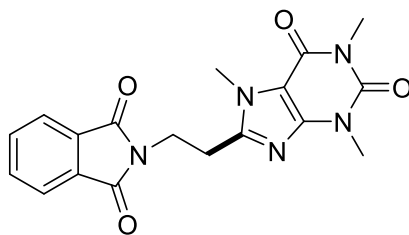
Following general procedure C, a solution of **III-95e** (500.0 mg, 0.95 mmol, 1.0 equiv), H₃PO₂ (50% in H₂O, 332.0 mg, 2.5 mmol, 2.6 equiv), triethylamine (265.0 mg, 2.6 mmol, 2.8 equiv) in dioxane (0.1 M) was refluxed in oil bath in the presence of AIBN. The reaction required 30 mol % AIBN to reduce xanthate completely. The reaction mixture partitioned between H₂O and EtOAc. The combined organic layer was washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. Flash chromatography on silica gel (petroleum ether/ethyl acetate/acetic acid = 5/1/0.5 to 1/1/0.5) afforded the reduced product **III-96e** (292.0 mg, 0.72 mmol, 75% yield) as a known structure⁷ and not fully characterized.



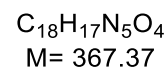
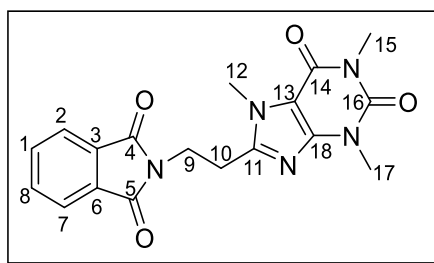
¹H NMR (400 MHz, CDCl₃) δ (ppm) = 10.42 – 9.99 (m, 1H, H₁₂), 7.74 (ddd, J = 5.5, 3.7, 2.9 Hz, 4H, H₂, H₇, H₁₈, H₂₁), 7.70 – 7.63 (m, 4H, H₁, H₈, H₁₉, H₂₀), 3.94 (dd, J = 13.9, 7.4 Hz, 1H, H_{9a}), 3.76 (dd, J = 13.9, 6.8 Hz, 1H, H_{9b}), 3.66 (t, J = 6.4 Hz, 2H, H₁₅), 3.00 – 2.85 (m, 1H, H₁₀), 1.90 – 1.78 (m, 1H, H_{14a}), 1.75 – 1.66 (m, 2H, H_{14b}, H_{13a}), 1.64 – 1.53 (m, 1H, H_{13b}).

¹³C NMR (101 MHz, CDCl₃) δ (ppm) = 178.3 (C₁₁), 168.4 (C₄, C₅), 168.1 (C₁₆, C₂₃), 134.0 (C₁, C₈), 133.7 (C₁₉, C₂₀), 132.0 (C₃, C₆), 131.9 (C₁₇, C₂₂), 123.4 (C₂, C₇), 123.2 (C₁₈, C₂₁), 43.6 (C₁₀), 38.9 (C₉), 37.4 (C₁₅), 26.6 (C₁₃), 25.8 (C₁₄).

8-(2-(1,3-dioxoisindolin-2-yl)ethyl)-1,3,7-trimethyl-3,7-dihydro-1H-purine-2,6-dione (III-106a)

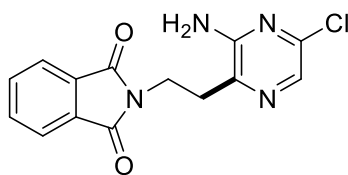


Following general procedure B, xanthate **III-94** (305.5 mg, 0.9 mmol, 3.0 equiv), caffeine (58.2 mg, 0.3 mmol, 1.0 equiv) in ethyl acetate (0.9 mL) was refluxed in oil bath under N₂ then dilauroyl peroxide (DLP) was added portionwise (20 mol %) every hour, the reaction required 140 mol % DLP to consume xanthate completely. Flash chromatography on silica gel (ethyl acetate/methanol = 25/1 to 20/1) afforded the radical adduct **III-106a** as a white solid (68.0 mg, 0.18 mmol, 61% yield).

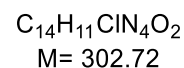
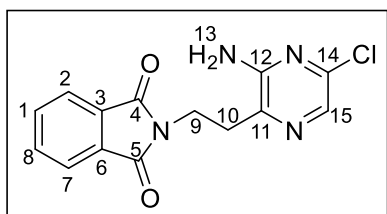


- ¹H NMR** (400 MHz, CDCl₃) δ (ppm) = 7.88 – 7.82 (m, 2H, H₂, H₇), 7.77 – 7.71 (m, 2H, H₁, H₈), 4.11 (dd, *J* = 7.5, 6.8 Hz, 2H, H₉), 3.94 (s, 3H, H₁₂), 3.38 (d, *J* = 1.9 Hz, 6H, H₁₅, H₁₇), 3.14 (t, *J* = 7.1 Hz, 2H, H₁₀).
- ¹³C NMR** (101 MHz, CDCl₃) δ (ppm) = 168.0 (C₁₆, C₂₃), 155.3 (C₁₄), 151.6 (C₁₆), 150.2 (C₁₁), 147.8 (C₁₈), 134.2 (C₁, C₈), 132.0 (C₃, C₆), 123.4 (C₂, C₇), 35.35 (C₉), 31.8 (C₁₂), 29.5 (C₁₇), 27.9 (C₁₅), 25.4 (C₁₀).
- IR** (neat) ν (cm⁻¹) = 2920, 2851, 1769, 1697, 1650, 1542, 1429, 1392, 1291, 1216, 975, 720
- HRMS** (EI⁺) *m/z*: Calcd for C₁₈H₁₇N₅O₄⁺: 367.1281; Found 367.1274
- mp**: >230°C

2-(2-(3-amino-5-chloropyrazin-2-yl)ethyl)isoindoline-1,3-dione (**III-106b**)

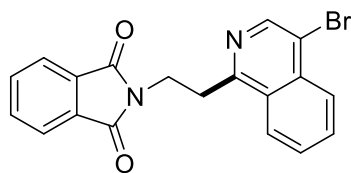


Following general procedure B, xanthate **III-94** (339.4 mg, 1.0 mmol, 2.0 equiv), 6-chloropyrazin-2-amine (64.8 mg, 0.5 mmol, 1.0 equiv) in ethyl acetate (1.0 mL) was refluxed in oil bath under N₂ then dilauroyl peroxide (DLP) was added portionwise (20 mol %) every hour, the reaction required 80 mol % DLP to consume xanthate completely. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 6/1 to 1/1) afforded the radical adduct **III-106b** as a white solid (52 mg, 0.17 mmol, 34% yield).

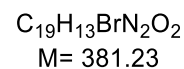
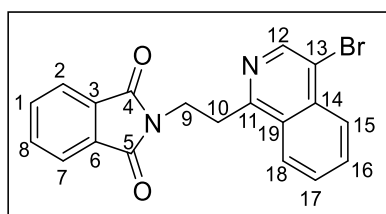


¹H NMR (400MHz, CDCl ₃)	δ (ppm) = 7.91 – 7.81 (m, 3H, H ₂ , H ₇ , H ₁₅), 7.79 – 7.70 (m, 2H, H ₁ , H ₈), 5.17 (s, 2H, H ₁₃), 4.09 – 3.97 (m, 2H, H ₉), 3.07 – 2.95 (m, 2H, H ₁₀).
¹³C NMR (101MHz, CDCl ₃)	δ (ppm) = 168.4 (C ₄ , C ₅), 152.3 (C ₁₂), 145.3 (C ₁₄), 136.3 (C ₁₁ , C ₁₅), 134.3 (C ₁ , C ₈), 132.0 (C ₃ , C ₆), 123.5 (C ₂ , C ₇), 34.8 (C ₉), 31.8 (C ₁₀).
IR (neat)	ν (cm ⁻¹) = 3457, 3284, 1766, 1706, 1628, 1447, 1402, 1367, 1215, 990, 868, 726
HRMS (EI ⁺) m/z:	Calcd for C ₁₄ H ₁₁ ClN ₄ O ₂ ⁺ : 302.0571; Found 302.0577
mp:	215-217°C

2-(2-(4-bromoisoquinolin-1-yl)ethyl)isoindoline-1,3-dione (**III-106c**)

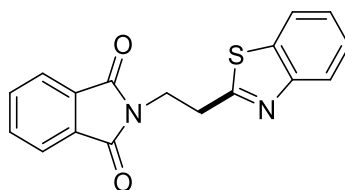


Following general procedure B, xanthate **III-94** (305.5 mg, 0.9 mmol, 3.0 equiv), 4-bromoisoquinoline (62.4 mg, 0.3 mmol, 1.0 equiv) and trifluoroacetic acid (41.0 mg, 0.36 mmol, 1.2 equiv) in 1,2-dichloroethane (1.0 mL) was refluxed in oil bath under N₂ then dilauroyl peroxide (DLP) was added portionwise (20 mol %) every hour, the reaction required 120 mol % DLP to consume xanthate completely. Flash chromatography on silica gel (petroleum ether/ethyl acetate =10/1 to 2/1) afforded the radical adduct **III-106c** as a slight yellow solid (35 mg, 0.09 mmol, 30% yield).

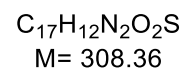
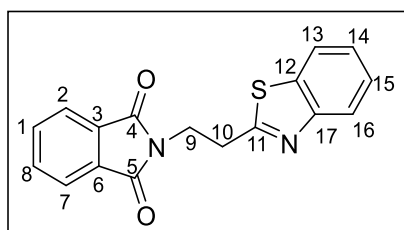


¹H NMR (400MHz, CDCl ₃)	δ (ppm) = 8.62 (s, 1H, H ₁₂), 8.24 (ddd, J = 8.5, 1.2, 0.7 Hz, 1H, H ₁₈), 8.19 (ddd, J = 8.4, 1.2, 0.7 Hz, 1H, H ₁₅), 7.86 – 7.81 (m, 2H, H ₂ , H ₇), 7.78 (ddd, J = 8.5, 6.9, 1.2 Hz, 1H, H ₁₇), 7.74 – 7.70 (m, 2H, H ₁ , H ₈), 7.67 (ddd, J = 8.3, 6.9, 1.3 Hz, 1H, H ₁₆), 4.27 – 4.21 (m, 2H, H ₉), 3.68 – 3.62 (m, 2H, H ₁₀).
¹³C NMR (101MHz, CDCl ₃)	δ (ppm) = 168.2 (C ₄ , C ₅), 157.6 (C ₁₁), 143.6 (C ₁₂), 134.8 (C ₁₄), 134.0 (C ₁ , C ₈), 132.1 (C ₃ , C ₆), 131.2 (C ₁₇), 128.4 (C ₁₆), 126.8 (C ₁₅), 125.3 (C ₁₉), 123.28 (C ₂ , C ₇), 37.0 (C ₉), 33.4 (C ₁₀).
IR (neat)	ν (cm ⁻¹) = 1769, 1710, 1438, 1385, 1237, 1108, 996, 765, 719
HRMS (EI ⁺) m/z:	Calcd for C ₁₉ H ₁₃ BrN ₂ O ₂ ⁺ : 380.0160; Found 380.0166
mp:	210-213°C

2-(2-(benzo[d]thiazol-2-yl)ethyl)isoindoline-1,3-dione (**III-106d**)



Following general procedure B, xanthate **III-94** (305.5 mg, 0.9 mmol, 3.0 equiv), benzo[d]thiazole (40.6 mg, 0.3 mmol, 1.0 equiv) in ethyl acetate (1.0 mL) was refluxed in oil bath under N₂ then dilauroyl peroxide (DLP) was added portionwise (20 mol %) every hour. After 6 h, another 3.0 equiv of xanthate was added and needed 6 h for the reaction to go to completion. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 7/1 to 4/1) afforded the radical adduct **III-106d** as a slight yellow solid (40.0 mg, 0.13 mmol, 43% yield).



¹H NMR (400MHz, CDCl₃) δ (ppm) = 7.93 (ddd, J = 8.2, 1.2, 0.6 Hz, 1H, H₁₆), 7.87 – 7.80 (m, 3H, H₁₃, H₂, H₇), 7.74 – 7.69 (m, 2H, H₁, H₈), 7.44 (ddd, J = 8.2, 7.2, 1.3 Hz, 1H, H₁₄), 7.35 (ddd, J = 8.0, 7.2, 1.2 Hz, 1H, H₁₅), 4.26 – 4.20 (m, 2H, H₉), 3.52 (dd, J = 7.6, 6.9 Hz, 2H, H₁₀).

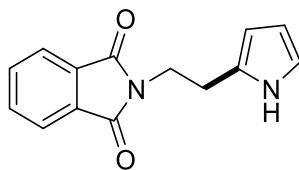
¹³C NMR (101MHz, CDCl₃) δ (ppm) = 168.0 (C₄, C₅), 167.0 (C₁₁), 153.3 (C₁₇), 135.2 (C₁₂), 134.0 (C₁, C₈), 132.0 (C₃, C₆), 126.0 (C₁₅), 125.0 (C₁₄), 123.4 (C₂, C₇), 122.8 (C₁₃), 121.6 (C₁₆), 37.1 (C₉), 32.7 (C₁₀).

IR (neat) ν (cm⁻¹) = 2924, 2853, 1772, 1704, 1520, 1433, 1391, 1353, 1170, 993, 879, 766, 711

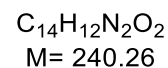
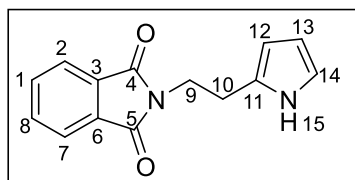
HRMS (EI⁺) m/z: Calcd for C₁₇H₁₂N₂O₂S⁺: 308.0619; Found 308.0619

mp: 142-143°C

2-(2-(1H-pyrrol-2-yl)ethyl)isoindoline-1,3-dione (**III-106e**)

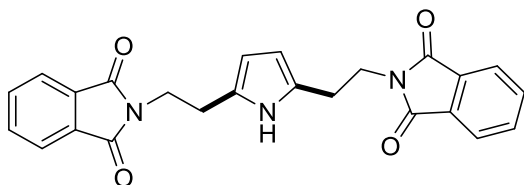


Following general procedure B, xanthate **III-94** (305.5 mg, 0.9 mmol, 3.0 equiv), pyrrole (20.1 mg, 0.3 mmol, 1.0 equiv) in ethyl acetate (0.5 mL) was refluxed in oil bath under N₂ then dilauroyl peroxide (DLP) was added portionwise (20 mol %) every hour, the reaction required 100 mol % DLP to consume xanthate completely. Flash chromatography on silica gel (petroleum ether/ethyl acetate/acetic acid = 7/1/0.2 to 2/1/0.2) afforded the monosubstituted product **III-106e** as a brown oil (7.0 mg, 0.03 mmol, 10% yield)

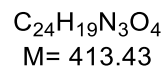
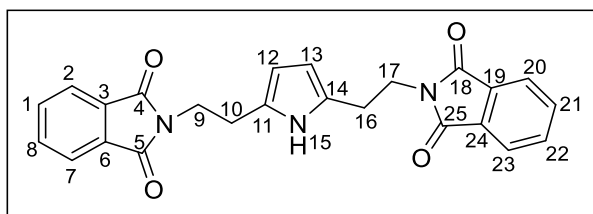


¹H NMR (400MHz, CDCl ₃)	δ (ppm) = 8.26 (s, 1H, H ₁₅), 7.85 – 7.82 (m, 2H, H ₂ , H ₇), 7.73 – 7.70 (m, 2H, H ₁ , H ₈), 6.70 (td, J = 2.7, 1.5 Hz, 1H, H ₁₄), 6.13 – 6.08 (m, 1H, H ₁₃), 5.99 (dtd, J = 3.3, 1.6, 0.7 Hz, 1H, H ₁₂), 3.97 – 3.91 (m, 2H, H ₉), 3.03 (t, J = 7.5 Hz, 2H, H ₁₀).
¹³C NMR (101MHz, CDCl ₃)	δ (ppm) = 168.3 (C ₄ , C ₅), 134.0(C ₁ , C ₈), 123.3(C ₂ , C ₇), 117.1 (C ₁₄), 108.6, 106.7 (C ₁₃), 49.1 (C ₁₂), 37.7 (C ₉), 26.9 (C ₁₀).
IR (neat)	ν (cm ⁻¹) = 3380, 2925, 1770, 1708, 1437, 1395, 1361, 1098, 990, 794, 716
HRMS (EI ⁺) m/z:	[M+H] ⁺ , Calcd for [C ₁₄ H ₁₂ N ₂ O ₂ +H] ⁺ : 241.0972; Found 241.0974

2,2'-((1H-pyrrole-2,5-diyl)bis(ethane-2,1-diyl))bis(isoindoline-1,3-dione) (III-106f)

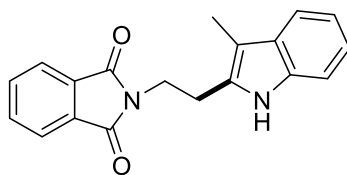


Following general procedure B, xanthate **III-94** (305.5 mg, 0.9 mmol, 3.0 equiv), pyrrole (20.1 mg, 0.3 mmol, 1.0 equiv) in ethyl acetate (0.5 mL) was refluxed in oil bath under N₂ then dilauroyl peroxide (DLP) was added portionwise (20 mol %) every hour, the reaction required 100 mol % DLP to consume xanthate completely. Flash chromatography on silica gel (petroleum ether/ethyl acetate/acetic acid = 7/1/0.2 to 2/1/0.2) afforded the disubstituted product **III-106f** as a purple solid (34.0 mg, 0.08 mmol, 27% yield).

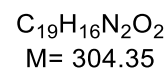
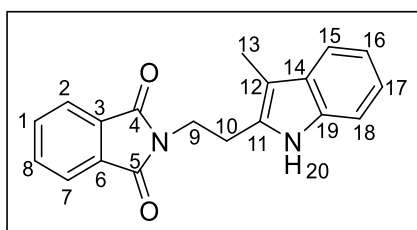


¹H NMR (400MHz, CDCl ₃)	δ (ppm) = 8.36 (s, 1H, H ₁₅), 7.85 – 7.79 (m, 4H, H ₂ , H ₇ , H ₂₀ , H ₂₃), 7.72 – 7.67 (m, 4H, H ₁ , H ₈ , H ₂₁ , H ₂₂), 5.82 (d, J = 2.7 Hz, 2H, H ₁₂ , H ₁₃), 3.94 – 3.86 (m, 4H, H ₉ , H ₁₇), 3.00 – 2.93 (m, 4H, H ₁₀ , H ₁₆).
¹³C NMR (101MHz, CDCl ₃)	δ (ppm) = 168.3 (C ₄ , C ₅ , C ₁₈ , C ₂₅), 134.0 (C ₁₁ , C ₁₄), 132.1 (C ₁ , C ₈ , C ₂₁ , C ₂₂), 127.3 (C ₃ , C ₆ , C ₁₉ , C ₂₄), 123.3 (C ₂ , C ₇ , C ₂₀ , C ₂₃), 106.8 (C ₁₂ , C ₁₃), 37.8 (C ₉ , C ₁₇), 26.9 (C ₁₀ , C ₁₆).
IR (neat)	ν (cm ⁻¹) = 3378, 2941, 1770, 1702, 1614, 1436, 1395, 1361, 1187, 1088, 999, 777, 715
HRMS (EI ⁺) m/z:	[M+H] ⁺ , Calcd for [C ₂₄ H ₁₉ N ₃ O ₄ +H] ⁺ : 414.1448; Found 414.1457
mp:	203-205°C

2-(2-(3-methyl-1H-indol-2-yl)ethyl)isoindoline-1,3-dione (**III-106g**)

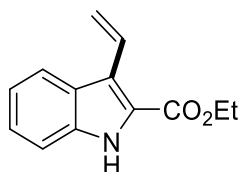


Following general procedure B, xanthate **III-94** (204 mg, 0.6 mmol, 2.0 equiv), 3-methyl-1H-indole (39.4 mg, 0.3 mmol, 1.0 equiv) in ethyl acetate (0.6 mL) was refluxed in oil bath under N₂ then dilauroyl peroxide (DLP) was added portionwise (20 mol %) every hour, the reaction required 100 mol % DLP to consume xanthate completely. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 7/1 to 3/1) afforded the radical adduct **III-106g** as a yellow solid (50.0 mg, 0.16 mmol, 55% yield).



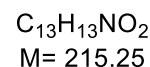
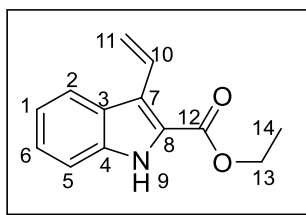
¹H NMR (400MHz, CDCl ₃)	δ (ppm) = 8.13 (s, 1H, H ₂₀), 7.86 – 7.81 (m, 2H, H ₂ , H ₇), 7.74 – 7.69 (m, 2H, H ₁ , H ₈), 7.46 (ddt, J = 7.7, 1.4, 0.7 Hz, 1H, H ₁₅), 7.31 (ddd, J = 8.0, 0.8 Hz, 1H, H ₁₈), 7.13 (ddd, J = 8.0, 7.1, 1.3 Hz, 1H, H ₁₇), 7.07 (ddd, J = 7.7, 7.1, 1.1 Hz, 1H, H ₁₆), 4.02 – 3.96 (m, 2H, H ₉), 3.19 – 3.12 (m, 2H, H ₁₀), 2.23 (d, J = 0.4 Hz, 3H, H ₁₃).
¹³C NMR (101MHz, CDCl ₃)	δ (ppm) = 168.3 (C ₄ , C ₅), 135.5 (C ₁₉), 134.1 (C ₁ , C ₈), 132.0 (C ₃ , C ₆), 130.4 (C ₁₁), 129.1 (C ₁₄), 123.4 (C ₂ , C ₇), 121.5 (C ₁₇), 119.1 (C ₁₆), 118.3 (C ₁₅), 110.5 (C ₁₂), 108.8 (C ₁₈), 37.1 (C ₉), 25.5 (C ₁₀), 8.4 (C ₁₃).
IR (neat)	ν (cm ⁻¹) = 3356, 2941, 1764, 1698, 1613, 1398, 1080, 986, 869, 744, 716
HRMS (EI ⁺) m/z:	[M+H] ⁺ , Calcd for [C ₂₂ H ₁₅ N ₃ O ₄ S+H] ⁺ : 305.1285; Found 305.1289
mp:	>230°C

ethyl 3-vinyl-1H-indole-2-carboxylate (**III-107**)

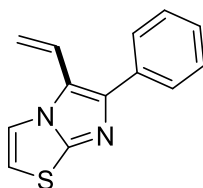


Following general procedure B, xanthate **III-94** (339.4 mg, 1.0 mmol, 2.0 equiv), ethyl indole-2-carboxylate (95.0 mg, 0.5 mmol, 1.0 equiv) in ethyl acetate (1.0 mL) was refluxed in oil bath under N₂ then dilauroyl peroxide (DLP) was added portionwise (20 mol %) every hour, the reaction required 140 mol % DLP to consume xanthate completely. Flash chromatography on silica gel (petroleum ether/ethyl acetate/acetic acid = 6/1/0.5 to 2/1/0.5) afforded the radical adduct **III-105h** as a yellow solid (123.0 mg, 0.30 mmol, 60% yield, Mp: 195-197°C).

According to the general procedure D, the reaction was carried out with **III-105h** (24 mg, 0.06 mmol) in N-methyl-2-pyrrolidone (0.6 mL) and was heated at 220 °C for 10 min and 230°C for 20min. Flash chromatography on silica gel (petroleum ether/ ethyl acetate = 15/1 to 10/1) afforded product **III-107** (9 mg, 0.04 mmol, 69% yield) as a white solid. The spectra data are in agreement with the literature report.⁶

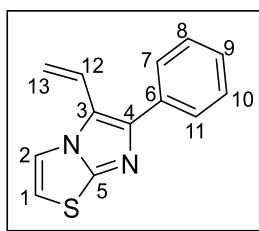


¹H NMR (400MHz, CDCl ₃)	δ (ppm) = 8.82 (s, 1H, H ₉), 8.02 (dd, J = 8.3, 1.0 Hz, 1H, H ₂), 7.54 (dd, J = 18.1, 11.6 Hz, 1H, H ₅), 7.43 – 7.32 (m, 2H, H ₁ , H ₆), 7.20 (ddd, J = 8.1, 6.8, 1.2 Hz, 1H, H ₁₀), 5.96 (dd, J = 18.1, 1.6 Hz, 1H, H _{11a}), 5.50 (dd, J = 11.6, 1.6 Hz, 1H, H _{11b}), 4.44 (q, J = 7.1 Hz, 2H, H ₁₃), 1.44 (t, J = 7.1 Hz, 3H, H ₁₄).
¹³C NMR (101MHz, CDCl ₃)	δ (ppm) = 162.0 (C ₁₂), 136.1 (C ₄), 129.4 (C ₁₀), 125.7 (C ₈), 123.7 (C ₆), 122.4 (C ₃), 121.2 (C ₂), 120.9 (C ₁₁), 116.7 (C ₁), 111.9 (C ₇), 61.1 (C ₁₃), 14.4 (C ₁₄).
IR (neat)	ν (cm ⁻¹) = 3331, 2980, 1676, 1519, 1443, 1326, 1249, 1194, 1100, 1016, 742
HRMS (EI ⁺) m/z:	Calcd for C ₁₃ H ₁₃ NO ₂ ⁺ : 215.0946; Not Found
mp:	99-101°C (lit.:104-106°C)

6-phenyl-5-vinylimidazo[2,1-b]thiazole (III-108)

Following general procedure B, xanthate **III-94** (339.4 mg, 1.0 mmol, 2.0 equiv), 6-phenylimidazo[2,1-b]thiazole (100.0 mg, 0.5 mmol, 1.0 equiv) in 1,2-dichloroethane (1.0 mL) was refluxed in oil bath under N₂ then dilauroyl peroxide (DLP) was added portionwise (20 mol %) every hour, the reaction required 60 mol % DLP to consume xanthate completely. The reaction suspension was filtered followed by washing with methanol three times to give desired product **III-105i** as a white solid (170.0 mg, 0.41 mmol, 81% yield, Mp: >230°C).

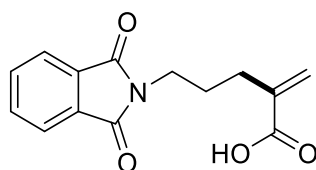
According to the general procedure D, the reaction was carried out with **III-105i** (69 mg, 0.165 mmol) in N-methyl-2-pyrrolidone (1.7 mL) and was heated at 220 °C for 10 min. Flash chromatography on silica gel (petroleum ether/ ethyl acetate = 6/1 to 2/1) afforded product **III-108** (33.9 mg, 0.15 mmol, 90% yield) as a white solid.



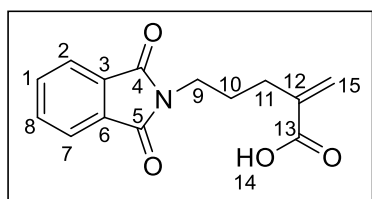
C₁₃H₁₀N₂S
M= 226.30

¹H NMR (400MHz, CDCl ₃)	δ (ppm) = 7.88– 7.75 (m, 1H, H ₁), 7.72 – 7.70 (m, 2H, H ₁₀ , H ₈), 7.47 – 7.42 (m, 2H, H ₇ , H ₉), 7.37 – 7.32 (m, 1H, H ₁₁), 7.00 – 6.90 (m, 2H, H ₂ , H ₁₂), 5.52 (dd, J = 18.0, 0.6 Hz, 1H, H _{13a}), 5.34 (dd, J = 11.8, 0.5 Hz, 1H, H _{13b}).
¹³C NMR (101MHz, CDCl ₃)	δ (ppm) = 134.3 (C ₅), 128.5 (C ₄), 128.4 (C ₆), 127.6 (C ₉), 124.9 (C ₈ , C ₁₀), 123.6 (C ₇ , C ₁₁), 118.8 (C ₁₂), 112.7 (C ₁₃), 111.5 (C ₁)
IR (neat)	ν (cm ⁻¹) = 3116, 3059, 2726, 1769, 1724, 1625, 1451, 1352, 1252, 1138, 774, 700, 663.
HRMS (EI ⁺) m/z:	[M+H] ⁺ , Calcd for [C ₁₃ H ₁₀ N ₂ S+H] ⁺ : 227.0637; Found 227.0643
mp:	165°C, decomposed

5-(1,3-dioxisoindolin-2-yl)-2-methylenepentanoic acid (III-111)



According to the general procedure D, the reaction was carried out with **III-96e** (260 mg, 0.64 mmol) in N-methyl-2-pyrrolidone (6.4 mL) and was heated at 220°C for 10 min and 250°C for 2 h. Flash chromatography on silica gel (petroleum ether/ ethyl acetate = 6/1 to 2/1) afforded product **III-111** (35.0 mg, 0.13 mmol, 21% yield) as a white solid.



$C_{14}H_{13}NO_4$
M= 259.26

1H NMR (400MHz, $CDCl_3$)	δ (ppm) = 7.88 – 7.82 (m, 2H, H_2, H_7), 7.75 – 7.68 (m, 2H, H_1, H_8), 6.33 (dd, $J = 1.2, 0.6$ Hz, 1H, H_{15a}), 5.74 (d, $J = 1.3$ Hz, 1H, H_{15b}), 3.77 – 3.69 (m, 2H, H_9), 2.37 (t, $J = 7.7$ Hz, 2H, H_{11}), 1.96 – 1.85 (m, 2H, H_{10}).
^{13}C NMR (101MHz, $CDCl_3$)	δ (ppm) = 171.8 (C_{13}), 168.4 (C_4, C_5), 138.7 (C_{12}), 133.9 (C_1, C_8), 132.1 (C_3, C_6), 127.7 (C_{15}), 123.3 (C_2, C_7), 37.4 (C_9), 28.7 (C_{11}), 27.1 (C_{10}).
IR (neat)	ν (cm^{-1}) = 2932, 2876, 2613, 1766, 1708, 1676, 1622, 1436, 1391, 1226, 1109, 1008, 968, 946, 874, 796, 721, 675.
HRMS (EI ⁺) m/z:	$[M+H]^+$, Calcd for $[C_{14}H_{13}NO_4+H]^+$: 260.0917; Found 260.0923
mp:	132-134°C

Chapter 4

General procedure A: Radical addition with neat conditions

Xanthate (1.0 equiv), olefin (1.5-3.0 equiv) and dilauroyl peroxide (DLP) (5 mol % according to xanthate) were mixed in a tube with neat condition, then air in the tube was excluded by nitrogen. The tube was sealed and heated in oil bath at 85°C. Additional dilauroyl peroxide (DLP) was added portionwise (5 mol %) every hour until total consumption of the starting xanthate (typically 2-3 portions of DLP). The reaction mixture was then cooled down to room temperature, purified by flash chromatography on silica gel.

General procedure B: Radical addition in solvent

A solution of xanthate (1.0 equiv) and olefin (1.5-3.0 equiv) in ethyl acetate (1 M according to xanthate) was refluxed under nitrogen for 15 min. Then dilauroyl peroxide (DLP) was added portionwise (5 mol %) every hour until total consumption of the starting xanthate. The reaction mixture was then cooled down to room temperature, concentrated by vacuum and purified by flash chromatography on silica gel.

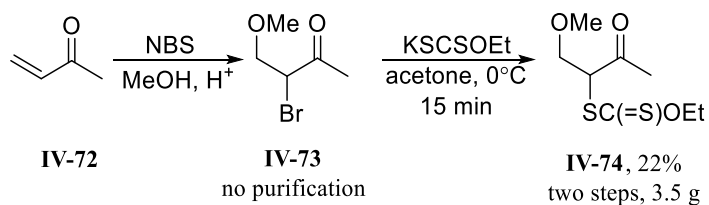
General procedure C: Reduction of xanthate with Barton's hypophosphorus reagent

A solution of radical adduct (1.0 equiv), H₃PO₂ (50% in H₂O, 2.6 equiv), triethylamine (2.8 equiv) in dioxane (0.1 M) was refluxed in oil bath for 15 min. Then, AIBN (10 mol%) was added every hour until total consumption of the adduct (typically, reaction time is 2-3hours). The reaction mixture was cooled down to room temperature, and then partitioned between H₂O and EtOAc. The combined organic layer was washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. Flash chromatography afforded reduced compound.

General procedure D: Reduction of xanthate with tris(trimethyl)silane

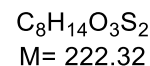
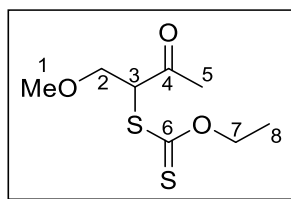
A solution of xanthate (1.0 equiv) and tris(trimethylsilyl)silane (TTMSS, 1.1 equiv) in toluene/cyclohexane (1:1, 0.25 M) was refluxed under nitrogen for 15 min. Then AIBN was added portionwise (10 mol %) every hour until total consumption of the starting xanthate (typically, after 1-2hours). The reaction mixture was then cooled down to room temperature and volatiles were removed under a nitrogen stream. Flash chromatography on silica gel of the residue gave the desired product.

O-ethyl S-(1-methoxy-3-oxobutan-2-yl) carbonodithioate (IV-74)



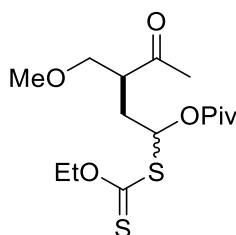
A solution of methyl vinyl ketone **IV-72** (5.0 g, 71 mmol, 1.0 equiv) in 100 mL MeOH was cooled to 0°C, then the suspension was allowed warm up to room temperature naturally after NBS (12.7 g, 71 mmol, 1.0 equiv) was added. 2~3 drops Conc. H₂SO₄ were added to reaction mixture and stirred for 30min. Saturated NaHCO₃ was added and extracted with dichloromethane twice, the combined organic layer was washed with brine and dried over anhydrous Na₂SO₄, filtered and the solvent was removed under reduced pressure, the crude intermediate **IV-73** was directly used in next step without further purification.

Potassium O-ethylxanthate salt (11.9 g, 74.5 mmol, 1.05 equiv) was added portionwise over 15min to a solution of intermediate **IV-73** in 35 mL acetone. After 10min, ice water was added to the suspension and the resulted aqueous solution was extracted twice with dichloromethane. The combined organic layer was washed by brine and dried with anhydrous MgSO₄. Filtered and concentrated under reduced pressure. Flash chromatography afforded desired product **IV-74** as a yellow oil (3.5 g, 15.7 mmol, 22 % in total yields).

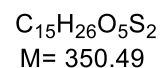
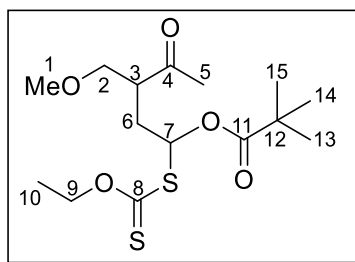


¹H NMR (400 MHz, CDCl ₃)	δ (ppm) = 4.56 – 4.46 (m, 3H, H ₃ , H ₇), 3.70 – 3.60 (m, 2H, H ₂), 3.21 (s, 3H, H ₁), 2.19 (s, 3H, H ₅), 1.28 (t, <i>J</i> = 7.1 Hz, 3H, H ₈).
¹³C NMR (101 MHz, CDCl ₃)	δ (ppm) = 212.2 (C ₆), 203.0 (C ₄), 71.1 (C ₂), 70.7 (C ₇), 59.1 (C ₁), 58.7 (C ₃), 29.0 (C ₅), 13.6 (C ₈).
IR (neat)	<i>ν</i> (cm ⁻¹) = 2985, 2930, 2894, 1716, 1450, 1355, 1212, 1108, 1040
HRMS (EI ⁺)	[M-C ₃ H ₅ OS ₂] ⁺ , Calcd for C ₅ H ₉ O ₂ ⁺ : 101.0603; Found 101.0957

methyl 10-((ethoxycarbonothioyl)thio)-12-(methoxymethyl)-13-oxotetradecanoate (IV-75a)

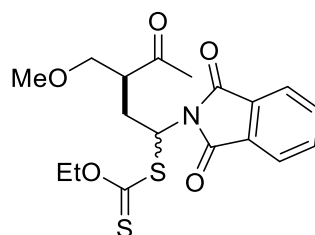


Following general procedure A, xanthate **IV-74** (222.3 mg, 1.0 mmol, 1.0 equiv), vinyl pivalate (236.2 mg, 2.0 mmol, 2.0 equiv) and dilauroyl peroxide (5 mol %) were mixed in a tube with neat condition, air in the tube was excluded by nitrogen, then sealed and heated at 85°C. Then additional dilauroyl peroxide (DLP) was added portionwise (5 mol %) every hour, the reaction required 10 mol % DLP to consume xanthate completely. Flash chromatography on silica gel (petroleum ether/ethyl acetate =8/1 to 4/1) afforded desired product **IV-75a** as a colorless liquid (296.1 mg, 0.73 mmol, 73% yield).

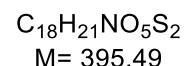
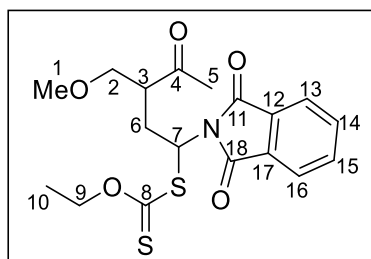


1H NMR (400 MHz, $CDCl_3$)	δ (ppm) = 6.41 (ddd, J = 11.6, 7.8, 5.7 Hz, 1H, H ₇), 4.46 (ddt, J = 7.2, 4.3, 2.5 Hz, 2H, H ₉), 3.45 – 3.30 (m, 2H, H ₂), 3.16 (d, J = 2.1 Hz, 3H, H ₁), 2.79 – 2.66 (m, 1H, H ₃), 2.32 – 2.17 (m, 1H, H _{6a}), 2.06 (d, J = 4.8 Hz, 3H, H ₅), 1.93 – 1.77 (m, 1H H _{6b}), 1.26 (td, J = 7.1, 1.5 Hz, 3H, H ₁₀), 1.03 (t, J = 1.4 Hz, 9H, H ₁₃ , H ₁₄ , H ₁₅).
^{13}C NMR (101 MHz, $CDCl_3$)	δ (ppm) = 209.8 (C ₈), 208.3 (C ₄), 176.5 (C ₁₁), 79.3 (C ₇), 79.0 (C ₇), 73.2 (C ₂), 72.7 (C ₂), 70.1 (C ₉), 58.9 (C ₁), 49.3 (C ₃), 48.8 (C ₃), 38.7 (C ₁₂), 32.4 (C ₆), 32.2 (C ₆), 30.2 (C ₅), 29.6 (C ₅), 26.8 (C ₁₃ , C ₁₄ , C ₁₅), 13.5 (C ₁₀).
IR (neat)	ν (cm^{-1}) = 2977, 2930, 2874, 1736, 1716, 1479, 1364, 1222, 1109, 1041
HRMS (EI ⁺)	$[M-C_3H_5OS_2]^+$, Calcd for $C_{12}H_{21}O_4^+$: 229.1440; Found 229.1446

S-(1-(1,3-dioxoisindolin-2-yl)-3-(methoxymethyl)-4-oxopentyl) O-ethyl carbonodithioate (IV-75b)

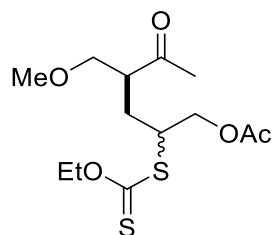


According to a modified procedure A, xanthate **IV-74** (222.3 mg, 1.0 mmol, 2.0 equiv), N-vinylphthalimide (86.6 mg, 0.5 mmol, 1.0 equiv) and dilauroyl peroxide (5 mol %) were mixed in a tube with neat condition, air in the tube was excluded by nitrogen, then sealed and heated at 85°C. Then additional dilauroyl peroxide (DLP) was added portionwise (5 mol %) every hour, the reaction required 15mol % DLP to consume xanthate completely. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 7/1 to 3/1) afforded desired product **IV-75b** as a colorless liquid (88.0 mg, 0.22 mmol, 44% yield).

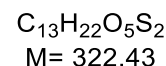
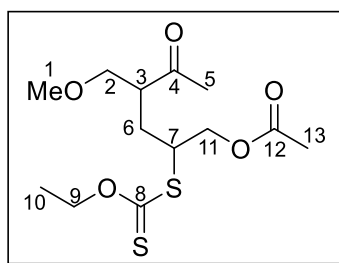


1H NMR (400 MHz, $CDCl_3$)	δ (ppm) = 7.91 – 7.81 (m, 2H, H_{13}, H_{16}), 7.80 – 7.69 (m, 2H, H_{14}, H_{15}), 6.39 – 6.14 (m, 1H, H_7), 4.61 (qd, $J = 7.1, 4.1$ Hz, 2H, H_9), 3.64 – 3.44 (m, 2H, H_2), 3.27 (d, $J = 25.2$ Hz, 3H, H_1), 2.86 – 2.24 (m, 3H, H_3, H_6), 2.17 (dd, $J = 31.2, 0.3$ Hz, 3H, H_5), 1.39 (td, $J = 7.1, 2.2$ Hz, 3H, H_{10}).
^{13}C NMR (101 MHz, $CDCl_3$)	δ (ppm) = 211.0 (C_8), 210.5 (C_8), 208.7 (C_4), 208.5 (C_4), 166.8 (C_{11}, C_{18}), 134.5 (C_{14}, C_{15}), 131.5 (C_{12}, C_{17}), 123.7 (C_{13}, C_{16}), 73.1 (C_2), 72.6 (C_2), 70.6 (C_9), 59.1 (C_1), 56.4 (C_7), 55.8 (C_7), 50.3 (C_3), 49.8 (C_3), 31.6 (C_6), 30.3 (C_5), 29.7 (C_5), 13.7 (C_{10}).
IR (neat)	ν (cm^{-1}) = 2983, 2925, 2894, 1777, 1712, 1467, 1376, 1222, 1107, 1039, 874, 716
HRMS (EI ⁺)	$[M-C_3H_5OS_2]^+$, Calcd for $C_{15}H_{16}NO_4^+$: 274.1079; Found 274.1069

(4S)-2-((ethoxycarbonothioyl)thio)-4-(methoxymethyl)-5-oxohexyl acetate (IV-75c)

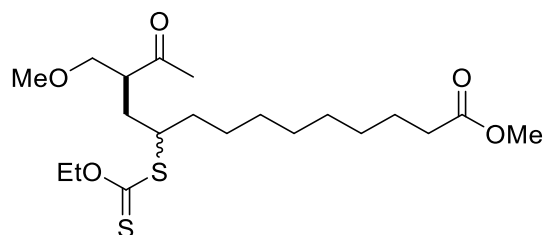


Following general procedure A, xanthate **IV-74** (222.3 mg, 1.0 mmol, 1.0 equiv), allyl acetate (250.3 mg, 2.5 mmol, 2.5 equiv) and dilauroyl peroxide (5 mol %) were mixed in a tube with neat condition, air in the tube was excluded by nitrogen, then sealed and heated at 85°C. Then additional dilauroyl peroxide (DLP) was added portionwise (5 mol %) every hour, the reaction required 10 mol % DLP to consume xanthate completely. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 7/1 to 4/1) afforded radical adduct **IV-75c** as a colorless liquid (196.2 mg, 0.61 mmol, 61% yield).

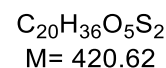
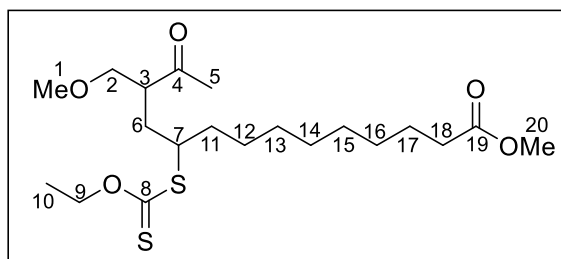


1H NMR (400 MHz, $CDCl_3$)	δ (ppm) = 4.66 – 4.60 (m, 2H, H_9), 4.28 (dd, J = 11.4, 4.7 Hz, 1H, H_{11a}), 4.20 (dd, J = 11.4, 5.9 Hz, 1H, H_{11b}), 3.91 (ddt, J = 10.5, 5.9, 4.6 Hz, 1H, H_7), 3.52 – 3.45 (m, 2H, H_2), 3.30 (d, J = 0.3 Hz, 3H, H_1), 3.05 (dtd, J = 9.8, 6.0, 3.9 Hz, 1H, H_3), 2.28 – 2.20 (m, 4H, H_5 , H_{6a}), 2.11 – 2.06 (m, 3H, H_{13}), 1.63 – 1.55 (m, 1H, H_{6b}), 1.44 – 1.39 (m, 3H, H_{10}).
^{13}C NMR (101 MHz, $CDCl_3$)	δ (ppm) = 212.9 (C_8), 209.5 (C_4), 170.7 (C_{12}), 73.9 (C_2), 70.4 (C_9), 66.1 (C_{11}), 59.1 (C_1), 50.0 (C_3), 48.1 (C_7), 30.6 (C_6), 29.3 (C_5), 20.8 (C_{13}), 13.7 (C_{10}).
IR (neat)	ν (cm^{-1}) = 2929, 2893, 1741, 1713, 1447, 1361, 1215, 1108
HRMS (EI $^+$)	$[M+H]^+$, Calcd for $[C_{13}H_{22}O_5S_2+H]^+$: 323.0981; Found 323.0976

methyl 10-((ethoxycarbonothioyl)thio)-12-(methoxymethyl)-13-oxotetradecanoate (IV-75d)



Following general procedure A, xanthate **IV-74** (222.3 mg, 1.0 mmol, 1.0 equiv), methyl undec-10-enoate (495.8 mg, 2.5 mmol, 2.5 equiv) and dilauroyl peroxide (5 mol %) were mixed in a tube with neat condition, air in the tube was excluded by nitrogen, then sealed and heated at 85°C. Then additional dilauroyl peroxide (DLP) was added portionwise (5 mol %) every hour, the reaction required 10 mol % DLP to consume xanthate completely. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 8/1 to 5/1) afforded desired product **IV-75d** as a colorless liquid (296.2 mg, 0.70 mmol, 70% yield).



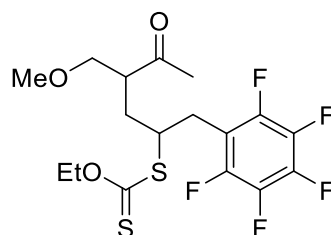
1H NMR δ (ppm) = 4.69 – 4.53 (m, 2H, H₉), 3.64 (s, 4H, H₇, H₂₀), 3.53 – 3.41 (m, 2H, H₂), 3.28 (d, J = 2.8 Hz, 3H, H₁), 3.07 – 2.84 (m, 1H, H₃), 2.27 (t, J = 7.5 Hz, 2H, H₁₈), 2.18 (d, J = 2.4 Hz, 3H, H₅), 2.16 – 1.86 (m, 1H, H_{6a}), 1.82 – 1.72 (m, 1H, H_{6b}), 1.68 – 1.53 (m, 4H), 1.39 (td, J = 7.1, 5.0 Hz, 5H), 1.25 (d, J = 4.2 Hz, 8H).

^{13}C NMR δ (ppm) = 214.5 (C₈), 210.1 (C₄), 174.3 (C₁₉), 74.1 (C₂) 70.0 (C₉), 59.1 (C₁), 51.4 (C₂₀), 50.5 (C₃), 50.3 (C₃), 50.2 (C₇), 49.9 (C₇), 35.4, 35.1, 34.1, 32.9, 32.0, 30.7, 29.7, 29.3, 29.2, 29.1, 26.6, 26.5, 24.9, 13.8.

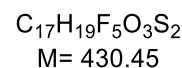
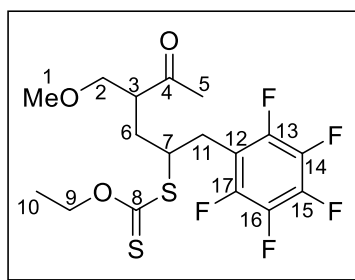
IR (neat) ν (cm⁻¹) = 2925, 2854, 1736, 1714, 1436, 1359, 1208, 1109, 1044

HRMS (EI⁺) [M-C₃H₅OS₂]⁺, Calcd for C₁₇H₃₁O₄⁺: 299.2222; Found 299.2222

O-ethyl S-(4-(methoxymethyl)-5-oxo-1-(perfluorophenyl) hexan-2-yl) carbonodithioate (IV-75e)

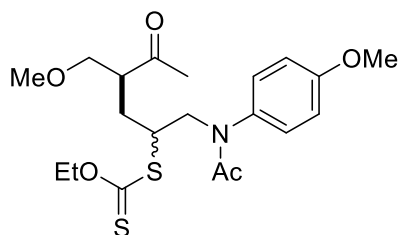


Following general procedure A, xanthate **IV-74** (222.3 mg, 1.0 mmol, 1.0 equiv), allylpentafluorobenzene (520.3 mg, 2.5 mmol, 2.5 equiv) and dilauroyl peroxide were mixed in a tube with neat condition, air in the tube was excluded by nitrogen, then sealed and heated at 85°C. Then additional dilauroyl peroxide (DLP) was added portionwise (5 mol %) every hour, the reaction required 15 mol % DLP to consume xanthate completely. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 8/1 to 5/1) afforded desired product **IV-75e** as a colorless liquid (295.8 mg, 0.69 mmol, 69% yield).

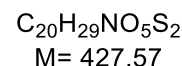
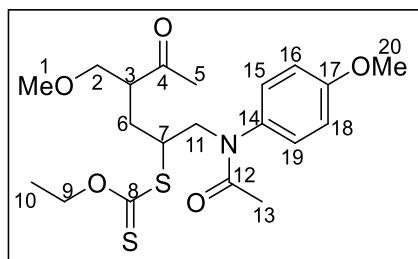


1H NMR (400 MHz, $CDCl_3$)	δ (ppm) = 4.65 – 4.52 (m, 2H, H ₉), 4.10 – 3.87 (m, 1H, H ₇), 3.58 – 3.42 (m, 2H, H ₂), 3.29 (d, J = 3.9 Hz, 3H, H ₁), 3.12 – 2.87 (m, 3H, H ₃ , H ₁₁), 2.20 (dd, J = 10.6, 0.3 Hz, 3H, H ₅), 2.17 – 1.53 (m, 2H, H ₆), 1.40 (td, J = 7.1, 2.5 Hz, 3H, H ₁₀).
^{13}C NMR (101 MHz, $CDCl_3$)	δ (ppm) = 212.7 (C ₈), 212.6 (C ₈), 209.4 (C ₄), 209.2 (C ₄), 146.6 (C ₁₇), 111.5 (C ₁₂), 72.3 (C ₂), 70.4 (C ₉), 59.1 (C ₁), 50.3 (C ₃), 50.2 (C ₃), 48.6 (C ₇), 48.5 (C ₇), 32.0 (C ₆), 31.3 (C ₆), 30.7 (C ₁₁), 29.7 (C ₁₁), 28.5 (C ₅), 28.4 (C ₅), 13.6 (C ₁₀).
IR (neat)	ν (cm ⁻¹) = 2929, 1714, 1656, 1501, 1446, 1358, 1215, 1112, 1044, 964
HRMS (EI ⁺)	$[M-C_3H_5OS_2]^+$, Calcd for $C_{14}H_{14}F_5O_2^+$: 309.0914; Found 309.0914

O-ethyl S-(4-(methoxymethyl)-1-(N-(4-methoxyphenyl) acetamido)-5-oxohexan-2-yl) carbonodithioate (IV-75f)



Following general procedure A, xanthate **IV-75** (222.3 mg, 1.0 mmol, 1.0 equiv), N-allyl-N-(4-methoxyphenyl)acetamide (513.3 mg, 2.5 mmol, 2.5 equiv) and dilauroyl peroxide (5 mol %) were mixed in a tube with neat condition, air in the tube was excluded by nitrogen, then sealed and heated at 85°C. Then additional dilauroyl peroxide (DLP) was added portionwise (5 mol %) every hour, the reaction required 15 mol % DLP to consume xanthate completely. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 5/1 to 2/1) afforded desired product **IV-75f** as a colorless liquid (300.0 mg, 0.70 mmol, 70% yield).

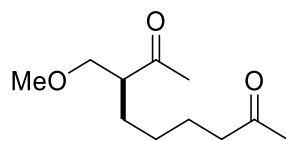


¹H NMR (400 MHz, CDCl₃) δ (ppm) = 7.18 (d, J = 8.6 Hz, 2H, H₁₅, H₁₉), 7.00 – 6.90 (m, 2H, H₁₆, H₁₈), 4.50 (qd, J = 7.1, 1.6 Hz, 2H, H₉), 4.32 (dd, J = 13.5, 9.4 Hz, 1H, H_{11a}), 3.84 (s, 3H, H₂₀), 3.68 – 3.60 (m, 1H, H_{11b}), 3.54 – 3.43 (m, 3H, H₂, H₇), 3.28 (s, 3H, H₁), 3.12 (ddt, J = 9.6, 6.3, 3.1 Hz, 1H, H₃), 2.33 (ddd, J = 14.5, 10.3, 4.0 Hz, 1H, H_{6a}), 2.18 (d, J = 0.3 Hz, 3H, H₅), 1.85 (s, 3H, H₁₃), 1.54 (ddd, J = 14.7, 11.3, 3.3 Hz, 1H, H_{6b}), 1.27 (t, J = 7.1 Hz, 3H, H₁₀).

¹³C NMR (101 MHz, CDCl₃) δ (ppm) = 213.0 (C₈), 210.5 (C₄), 171.5 (C₁₂), 159.1 (C₁₇), 135.0 (C₁₄), 129.5 (C₁₅, C₁₉), 114.8 (C₁₆, C₁₈), 74.3 (C₂), 70.1 (C₉), 59.0 (C₁), 55.5 (C₂₀), 51.8 (C₃), 50.0 (C₁₁), 47.6 (C₇), 31.3 (C₆), 29.5 (C₅), 22.7 (C₁₃), 13.5 (C₁₀).

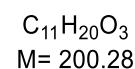
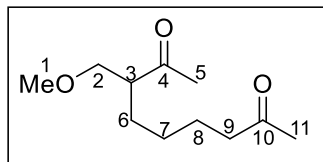
IR (neat) ν (cm⁻¹) = 2982, 2930, 2836, 1713, 1659, 1510, 1440, 1389, 1288, 1211, 1108, 1042, 839, 802

HRMS (EI⁺) Calcd for C₂₀H₂₉NO₅S₂⁺: 427.1487; Found 427.1494

3-(methoxymethyl) nonane-2,8-dione (IV-76)

Following general procedure A, xanthate **IV-74** (222.3 mg, 1.0 mmol, 1.0 equiv), hex-5-en-2-one (147.3 mg, 1.5 mmol, 1.5 equiv) and dilauroyl peroxide (5 mol %) were mixed in a tube with neat condition, air in the tube was excluded by nitrogen, then sealed and heated at 85°C. Then additional dilauroyl peroxide (DLP) was added portionwise (5 mol %) every hour, the reaction required 10 mol % DLP to consume xanthate completely. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 7/1 to 4/1) afforded radical adduct **IV-75g** as a colorless liquid (217.0 mg, 0.68 mmol, 68% yield).

Following general procedure C, a solution of xanthate **IV-75g** (217.0 mg, 0.68 mmol, 1.0 equiv), H₃PO₂ (50 % in H₂O, 236.8 mg, 1.79 mmol, 2.6 equiv), triethylamine (188.4 mg, 1.86 mmol, 2.8 equiv) in dioxane (0.1 M) was refluxed in the presence of AIBN. The reaction required 10 mol % AIBN to reduce xanthate completely. The reaction mixture was cooled down to room temperature, and then partitioned between H₂O and EtOAc. The combined organic layer was washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 6/1 to 3/1) afforded the desired product **IV-76** as a colorless oil (106.0 mg, 0.53 mmol, 77% yield).



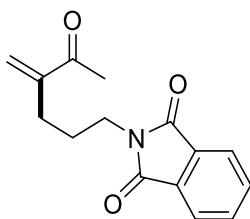
¹H NMR (400 MHz, CDCl₃) δ (ppm) = 3.49 (dd, $J = 9.2, 8.3$ Hz, 1H, H_{2a}), 3.40 (dd, $J = 9.2, 5.1$ Hz, 1H, H_{2b}), 3.28 (s, 3H, H₁), 2.75 (tt, $J = 8.2, 5.4$ Hz, 1H, H₃), 2.41 (t, $J = 7.2$ Hz, 2H, H₉), 2.16 (d, $J = 0.4$ Hz, 3H, H₅), 2.11 (t, $J = 0.5$ Hz, 3H, H₁₁), 1.62 – 1.51 (m, 3H), 1.39 – 1.20 (m, 3H).

¹³C NMR (101 MHz, CDCl₃) δ (ppm) = 211.2 (C₄), 208.8 (C₁₀), 73.5 (C₂), 59.0 (C₁), 52.7 (C₃), 43.3 (C₉), 30.1 (C₁₁), 30.0 (C₅), 28.1 (C₆), 26.8 (C₈), 23.7 (C₇).

IR (neat) ν (cm⁻¹) = 2932, 2862, 1712, 1423, 1358, 1168, 1121, 950

HRMS (EI⁺) Calcd for C₁₁H₂₀O₃⁺: 200.1412; Found 200.1411

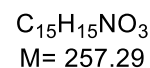
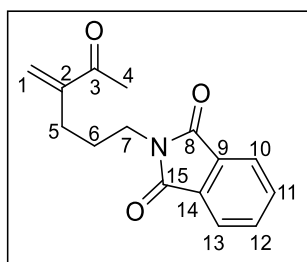
2-(4-methylene-5-oxohexyl) isoindoline-1,3-dione (IV-78)



Following general procedure B, xanthate **IV-74** (222.3 mg, 1.0 mmol, 1.0 equiv) and N-allylphthalimide (280.7 mg, 1.5 mmol, 1.5 equiv) in EtOAc (1.0 mL) was refluxed under N₂ then dilauroyl peroxide (DLP) was added portionwise (5 mol %) every hour, the reaction required 20 mol % DLP to consume xanthate completely. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 4/1 to 2/1) afforded the radical adduct **IV-75h** as a yellow oil (320.0 mg, 0.78 mmol, 78% yield).

Following general procedure C, a solution of xanthate **IV-75h** (146.0 mg, 0.35 mmol, 1.0 equiv), H₃PO₂ (50 % in H₂O, 125.4 mg, 0.95 mmol, 2.6 equiv), triethylamine (97.4 mg, 0.96 mmol, 2.8 equiv) in dioxane (0.1 M) was refluxed in the presence of AIBN. The reaction required 10 mol % AIBN to reduce xanthate completely. The reaction mixture was cooled down to room temperature, and then partitioned between H₂O and EtOAc. The combined organic layer was washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 5/1 to 2/1) afforded the reduced product **IV-77** as a colorless oil (73.0 mg, 0.25 mmol, 72% yield).

To a solution of compound **IV-77** (73.0 mg, 0.25 mmol, 1.0 equiv) in 1.0 mL toluene, p-toluenesulfonic acid monohydrate (228.2 mg, 0.3 mmol, 1.2 equiv) was added. The reaction mixture was heated to 75°C for 10 min, then filtered and washed with saturated NaHCO₃ solution. The aqueous extracted with EtOAc and dried over MgSO₄, filtered and concentrated under reduced pressure. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 6/1 to 2/1) afforded the reduced product **IV-78** as a colorless oil (51.0 mg, 0.20 mmol, 79% yield).



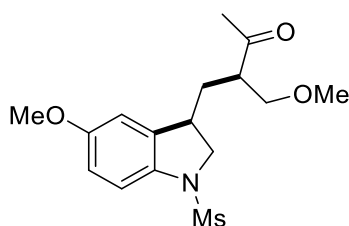
¹H NMR δ (ppm) = 7.88 – 7.79 (m, 2H, H₁₀, H₁₃), 7.74 – 7.67 (m, 2H, H₁₁, H₁₂), 6.04 (s, 1H, H_{1a}), 5.85 (t, *J* = 1.3 Hz, 1H, H_{1b}), 3.71 – 3.66 (m, 2H, H₇), 2.35 – 2.28 (m, 5H, H₄, H₅), 1.86 – 1.76 (m, 2H, H₆).

¹³C NMR δ (ppm) = 199.4 (C₃), 168.4 (C₈, C₁₅), 147.8 (C₂), 133.9 (C₁₁, C₁₂), 132.1 (C₉, C₁₄), 125.5 (C₁), 123.2 (C₁₀, C₁₃), 37.5 (C₇), 27.7 (C₅), 27.1 (C₄), 25.9 (C₆).

IR (neat) ν (cm⁻¹) = 2930, 2874, 1771, 1614, 1436, 1395, 1187, 1110, 1046, 956, 884, 795, 717

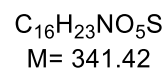
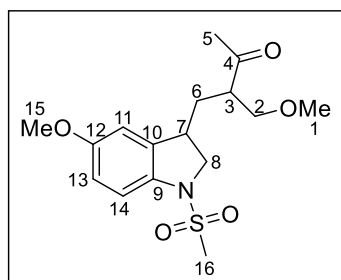
HRMS (EI⁺) [M+H]⁺, Calcd for [C₁₅H₁₅NO₃+H]⁺: 178.0486; Found 258.1125

4-methoxy-3-((5-methoxy-1-(methylsulfonyl) indolin-3-yl) methyl) butan-2-one (IV-79)



By using a modified procedure B, xanthate **IV-74** (333.4 mg, 1.5 mmol, 1.5 equiv) and *N*-allyl-*N*-(4-methoxyphenyl)methanesulfonamide (241.3 mg, 1.0 mmol, 1.0 equiv) in EtOAc (1.0 mL) was refluxed under N₂, the reaction required 15 mol % DLP to consume xanthate completely. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 3/1 to 1/1) afforded the radical adduct **IV-75i** as a colorless oil (426.0 mg, 0.92 mmol, 92% yield).

According to procedure B, xanthate **IV-75i** (426.0 mg, 0.92 mmol, 1.0 equiv) dissolved in EtOAc (9.0 mL) was refluxed under N₂, the reaction required 1.25 equiv DLP to consume xanthate completely. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 3/1 to 1/2) afforded the desired product **IV-79** as a yellow liquid (177.0 mg, 0.52 mmol, 57% yield).



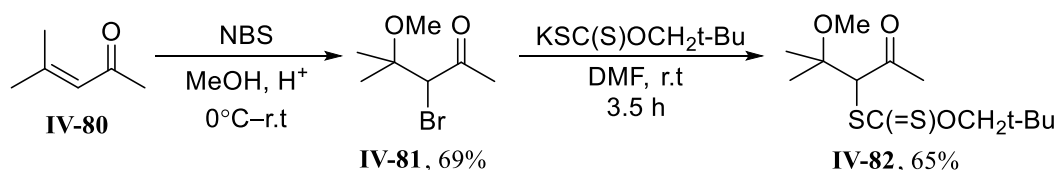
¹H NMR (400 MHz, CDCl₃) δ (ppm) = 7.31 – 7.26 (m, 1H, H₁₄), 6.78 – 6.71 (m, 2H, H₁₁, H₁₃), 3.99 (ddd, *J* = 10.4, 8.8, 1.4 Hz, 1H, H_{8a}), 3.77 (d, *J* = 1.0 Hz, 3H, H₁₅), 3.63 – 3.56 (m, 1H, H_{8b}), 3.50 (ddt, *J* = 8.8, 5.6, 2.8 Hz, 2H, H₂), 3.31 (d, *J* = 2.8 Hz, 4H, H₁₆, H₇), 2.82 (d, *J* = 4.5 Hz, 4H, H₁, H₃), 2.24 – 2.15 (m, 3H, H₅), 2.00 – 1.81 (m, 1H, H_{6a}), 1.54 (ddd, *J* = 14.2, 10.4, 4.2 Hz, 1H, H_{6b}).

¹³C NMR (101 MHz, CDCl₃) δ (ppm) = 209.9 (C₄), 209.8 (C₄), 156.9 (C₁₂), 156.7 (C₁₂), 136.3 (C₉), 135.8 (C₉), 135.1 (C₁₀), 134.8 (C₁₀), 114.7 (C₁₄), 114.6 (C₁₄), 113.5 (C₁₃), 113.3 (C₁₃), 111.2 (C₁₁), 110.8 (C₁₁), 73.9 (C₂), 73.2 (C₂), 59.1 (C₈), 56.8 (C₁), 56.3 (C₁), 55.8 (C₁₅), 50.6 (C₃), 50.3 (C₃), 38.3 (C₇), 33.3 (C₁₆), 32.9 (C₆), 30.4 (C₅), 29.8 (C₅).

IR (neat) ν (cm⁻¹) = 2929, 2835, 1710, 1597, 1485, 1341, 1154, 1114, 1031, 959

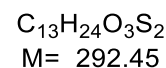
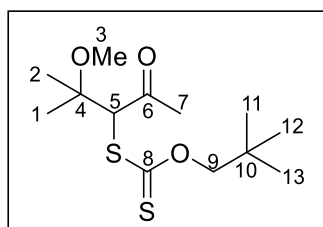
HRMS (EI⁺) [M+Na]⁺, Calcd for [C₁₅H₁₅NO₃+Na]⁺: 364.1189; Found 364.1189

S-(2-methoxy-2-methyl-4-oxopentan-3-yl) O-neopentyl carbonodithioate (**IV-82**)



According to the described procedure¹, a solution of 4-methylpent-3-en-2-one (5.0 g, 50.95 mmol, 1.0 equiv) in 100 mL MeOH was cooled to 0°C, then the suspension was allowed warm up to room temperature naturally after NBS (9.1 g, 50.95 mmol, 1.0 equiv) was added. 2~3 drops Conc. H₂SO₄ were added to reaction mixture and stirred for 1h. Saturated NaHCO₃ was added and extracted with dichloromethane twice, the combined organic layer was washed with brine and dried over anhydrous Na₂SO₄, filtered and the solvent was removed under reduced pressure, the crude intermediate was purified by flash chromatography afford **IV-81** as a yellow oil (7.3 g, 34.9 mmol, 69%).

Potassium O-neopentyl carbonodithioate salt (6.7 g, 33.0 mmol, 1.15 equiv) was added to a solution of intermediate **IV-81** (6.0 g, 28.7 mmol, 1.0 equiv) in 30 mL DMF. After 3.5 h, ice water was added to the reaction mixture and the resulted aqueous solution was extracted three times with EtOAc. The combined organic layer was washed by brine and dried with anhydrous MgSO₄. Filtered and concentrated under reduced pressure. Flash chromatography afforded desired product **IV-82** as a red oil (5.5 g, 18.8 mmol, 65%).

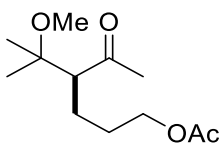


¹H NMR (400 MHz, CDCl₃) δ (ppm) = 4.59 (s, 1H, H₅), 4.21 (s, 2H, H₉), 3.23 (s, 3H, H₃), 2.34 (s, 3H, H₇), 1.30 (s, 6H, H₁, H₂), 0.99 (s, 9H, H₁₁, H₁₂, H₁₃).

¹³C NMR (101 MHz, CDCl₃) δ (ppm) = 213.5 (C₈), 205.4 (C₆), 84.1 (C₄, C₉), 67.3 (C₅), 49.9 (C₃), 31.9 (C₁₀), 31.0 (C₇), 26.6 (C₁₁, C₁₂, C₁₃), 23.8 (C₁), 23.0 (C₂).

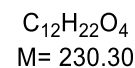
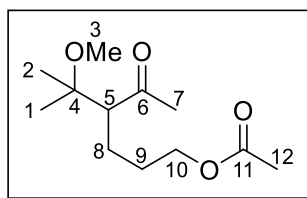
IR (neat) ν (cm⁻¹) = 2958, 2872, 2832, 1705, 1466, 1366, 1222, 1057, 1028, 950

HRMS (EI⁺) Calcd for C₁₃H₂₄O₃S₂⁺: 292.1167; Found 292.1151

4-acetyl-5-methoxy-5-methylhexyl acetate (IV-87a)

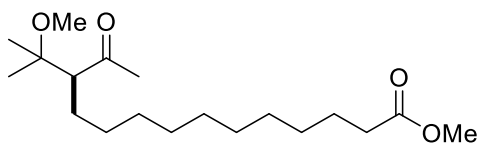
Following general procedure A, xanthate **IV-82** (292.5 mg, 1.0 mmol, 1.0 equiv), allyl acetate (150.2 mg, 1.5 mmol, 1.5 equiv) and dilauroyl peroxide (5 mol %) were mixed in a tube with neat condition, air in the tube was excluded by nitrogen, then sealed and heated at 85°C. Then additional dilauroyl peroxide (DLP) was added portionwise (5 mol %) every hour, the reaction required 10mol % DLP to consume xanthate completely. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 10/1 to 6/1) afforded radical adduct **IV-86a** as a colorless liquid (266.0 mg, 0.67 mmol, 67% yield).

Following general procedure C, a solution of xanthate **IV-86a** (266.0 mg, 0.67 mmol, 1.0 equiv), H₃PO₂ (50% in H₂O, 237.0 mg, 1.8 mmol, 2.6 equiv), triethylamine (186.5mg, 1.86mmol, 2.8 equiv) in dioxane (0.1 M) was refluxed in the presence of AIBN. The reaction required 20 mol % AIBN to reduce xanthate completely. The reaction mixture was cooled down to room temperature, and then partitioned between H₂O and EtOAc. The combined organic layer was washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 10/1 to 5/1) afforded the reduced product **IV-87a** as a colorless oil (120.0 mg, 0.52 mmol, 77% yield).



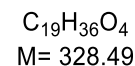
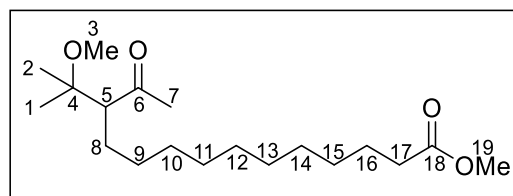
¹H NMR (400 MHz, CDCl ₃)	δ (ppm) = 4.01 (td, <i>J</i> = 6.4, 1.7 Hz, 2H, H ₁₀), 3.17 (s, 3H, H ₃), 2.78 – 2.72 (m, 1H, H ₅), 2.20 (d, <i>J</i> = 0.4 Hz, 3H, H ₇), 2.03 (s, 3H, H ₁₂), 1.79 – 1.70 (m, 1H, H _{8a}), 1.53 – 1.38 (m, 3H, H _{8b} , H ₉), 1.16 (d, <i>J</i> = 0.5 Hz, 3H, H ₁), 1.11 (d, <i>J</i> = 0.5 Hz, 3H, H ₂).
¹³C NMR (101 MHz, CDCl ₃)	δ (ppm) = 212.2 (C ₆), 171.1 (C ₁₁), 64.2 (C ₁₀), 60.8 (C ₂), 49.0 (C ₃), 33.8 (C ₇), 27.3 (C ₉), 24.4 (C ₁ , C ₂), 23.2 (C ₈), 21.1 (C ₁₂).
IR (neat)	<i>ν</i> (cm ⁻¹) = 2943, 2830, 1737, 1709, 1467, 1366, 1234, 1181, 1068
HRMS (EI ⁺)	[M-CH ₃] ⁺ , Calcd for C ₁₁ H ₁₉ O ₄ ⁺ : 215.1283; Found 215.1276

methyl 12-acetyl-13-methoxy-13-methyltetradecanoate (**IV-87b**)

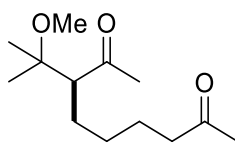


Following general procedure A, xanthate **IV-82** (292.5 mg, 1.0 mmol, 1.0 equiv), methyl undec-10-enoate (297.5 mg, 1.5 mmol, 1.5 equiv) and dilauroyl peroxide (5 mol %) were mixed in a tube with neat condition, air in the tube was excluded by nitrogen, then sealed and heated at 85°C. Then additional dilauroyl peroxide (DLP) was added portionwise (5 mol %) every hour, the reaction required 20 mol % DLP to consume xanthate completely. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 18/1 to 13/1) afforded radical adduct **IV-86b** as a colorless liquid (293.0 mg, 0.60 mmol, 60% yield).

Following general procedure C, a solution of xanthate **IV-86b** (293.0 mg, 0.60 mmol, 1.0 equiv), H₃PO₂ (50% in H₂O, 208.8 mg, 1.58 mmol, 2.6 equiv), triethylamine (164.4 mg, 1.64 mmol, 2.8 equiv) in dioxane (0.1 M) was refluxed in the presence of AIBN. The reaction required 10 mol % AIBN to reduce xanthate completely. The reaction mixture was cooled down to room temperature, and then partitioned between H₂O and EtOAc. The combined organic layer was washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 20/1 to 13/1) afforded the reduced product **IV-87b** as a colorless oil (155.0 mg, 0.47 mmol, 79% yield).

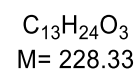
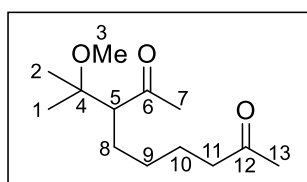


¹H NMR (400 MHz, CDCl ₃)	δ (ppm) = 3.62 (s, 3H, H ₁₉), 3.14 (s, 3H, H ₃), 2.70 (dd, <i>J</i> = 11.7, 2.6 Hz, 1H, H ₅), 2.26 (t, <i>J</i> = 7.5 Hz, 2H, H ₁₇), 2.15 (d, <i>J</i> = 0.4 Hz, 3H, H ₇), 1.70 – 1.53 (m, 3H), 1.34 – 1.18 (m, 13H), 1.15 – 1.05 (m, 8H).
¹³C NMR (101 MHz, CDCl ₃)	δ (ppm) = 212.8 (C ₆), 174.3 (C ₁₈), 61.2 (C ₅), 51.4 (C ₁₉), 48.9 (C ₃), 34.1, 33.7, 29.8, 29.4, 29.4, 29.3, 29.2, 29.1, 28.4, 28.0, 24.9, 23.3, 21.1.
IR (neat)	<i>ν</i> (cm ⁻¹) = 2924, 2853, 1738, 1711, 1436, 1355, 1169, 1075
HRMS (EI ⁺)	[M-CH ₃] ⁺ , Calcd for C ₁₈ H ₃₃ O ₄ ⁺ : 313.2379; Found 313.2380

3-(2-methoxypropan-2-yl)nonane-2,8-dione (IV-87c)

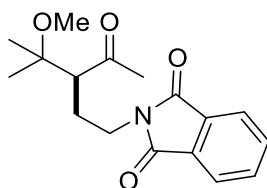
Following general procedure A, xanthate **IV-82** (292.5 mg, 1.0 mmol, 1.0 equiv), hex-5-en-2-one (245.5 mg, 2.5 mmol, 2.5 equiv) and dilauroyl peroxide (5 mol %) were mixed in a tube with neat condition, air in the tube was excluded by nitrogen, then sealed and heated at 85°C. Then additional dilauroyl peroxide (DLP) was added portionwise (5 mol %) every hour, the reaction required 20mol % DLP to consume xanthate completely. Flash chromatography on silica gel (petroleum ether/ethyl acetate =12/1 to 8/1) afforded radical adduct **IV-86c** as a colorless liquid (257.0 mg, 0.66 mmol, 66% yield).

Following general procedure C, a solution of xanthate **IV-86c** (257.0 mg, 0.65 mmol, 1.0 equiv), H₃PO₂ (50% in H₂O, 231.0 mg, 1.75 mmol, 2.6 equiv), triethylamine (183.2 mg, 1.81 mmol, 2.8 equiv) in dioxane (0.1 M) was refluxed in the presence of AIBN. The reaction required 20 mol % AIBN to reduce xanthate completely. The reaction mixture was cooled down to room temperature, and then partitioned between H₂O and EtOAc. The combined organic layer was washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 10/1 to 6/1) afforded the reduced product **IV-87c** as a colorless oil (130.0 mg, 0.57 mmol, 86% yield).



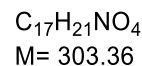
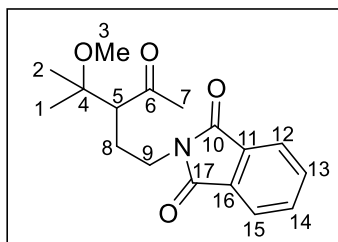
¹H NMR (400 MHz, CDCl ₃)	δ (ppm) = 3.17 (s, 3H, H ₃), 2.73 (dd, J = 11.7, 2.6 Hz, 1H, H ₅), 2.45 – 2.33 (m, 2H, H ₁₁), 2.18 (d, J = 0.4 Hz, 3H, H ₁₃), 2.11 (d, J = 0.5 Hz, 3H, H ₇), 1.70 (dddd, J = 11.5, 7.3, 3.5, 2.5 Hz, 1H, H _{8a}), 1.63 – 1.44 (m, 2H, H ₁₀), 1.35 (dddd, J = 13.1, 10.6, 6.2, 2.6 Hz, 1H, H _{8b}), 1.18 – 1.08 (m, 8H, H ₉ , H ₁ , H ₂).
¹³C NMR (101 MHz, CDCl ₃)	δ (ppm) = 212.7 (C ₆), 208.9 (C ₁₂), 61.0 (C ₅), 49.0 (C ₃), 43.4 (C ₁₁), 33.9 (C ₇), 29.9 (C ₁₃), 27.9 (C ₉), 27.8 (C ₉), 23.8 (C ₈), 23.3 (C ₁₀), 21.1 (C ₁ , C ₂).
IR (neat)	ν (cm ⁻¹) = 2941, 1711, 1357, 1183, 1070
HRMS (EI ⁺)	[M-CH ₃] ⁺ , Calcd for C ₁₂ H ₂₁ O ₃ ⁺ : 213.1491; Found 213.1477

2-(3-acetyl-4-methoxy-4-methylpentyl)isoindoline-1,3-dione (IV-87d)



Following general procedure B, xanthate **IV-82** (438.8 mg, 1.5 mmol, 2.0 equiv) and N-vinylphthalimide (129.9 mg, 0.75 mmol, 1.0 equiv) in EtOAc (0.75 mL) was refluxed under N₂ then dilauroyl peroxide (DLP) was added portionwise (5 mol %) every hour, the reaction required 15 mol % DLP to consume xanthate completely. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 3/1 to 1/1) afforded the radical adduct **IV-86d** as a colorless oil (161.0 mg, 0.34 mmol, 46% yield).

Following general procedure C, a solution of xanthate **IV-86d** (161.0 mg, 0.34 mmol, 1.0 equiv), H₃PO₂ (50% in H₂O, 121.0 mg, 0.92 mmol, 2.6 equiv), triethylamine (96.3 mg, 0.95 mmol, 2.8 equiv) in dioxane (0.1 M) was refluxed in the presence of AIBN. The reaction required 20 mol % AIBN to reduce xanthate completely. The reaction mixture was cooled down to room temperature, and then partitioned between H₂O and EtOAc. The combined organic layer was washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 10/1 to 5/1) afforded the reduced product **IV-87d** as a colorless oil (65.0 mg, 0.21 mmol, 62% yield).

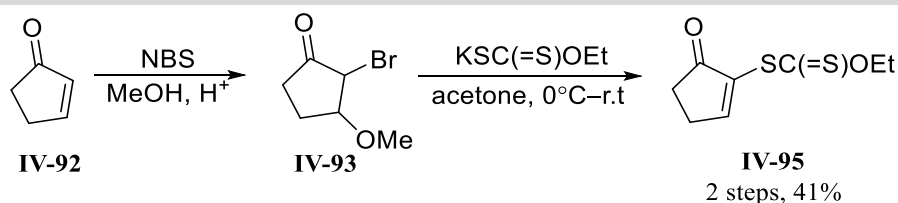


¹H NMR (400 MHz, CDCl₃) δ (ppm) = 7.87 – 7.82 (m, 2H, H₁₂, H₁₅), 7.75 – 7.69 (m, 2H, H₁₃, H₁₄), 3.65 – 3.52 (m, 2H, H₉), 3.13 (s, 3H, H₃), 2.79 (dd, *J* = 11.5, 2.4 Hz, 1H, H₅), 2.29 (d, *J* = 0.4 Hz, 3H, H₇), 2.19 – 2.10 (m, 1H, H_{8a}), 1.81 (dddd, *J* = 13.8, 8.5, 7.1, 2.5 Hz, 1H, H_{8b}), 1.12 (d, *J* = 0.5 Hz, 3H, H₁), 1.09 (d, *J* = 0.5 Hz, 3H, H₂).

¹³C NMR (101 MHz, CDCl₃) δ (ppm) = 211.6 (C₆), 168.4 (C₁₀, C₁₇), 134.0 (C₁₃, C₁₄), 132.0 (C₁₁, C₁₆), 123.3 (C₁₂, C₁₅), 58.2 (C₅), 49.0 (C₃), 36.7 (C₉), 33.4 (C₇), 26.8 (C₈), 23.1 (C₁), 21.3 (C₂).

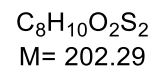
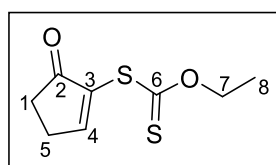
IR (neat) ν (cm⁻¹) = 2977, 2830, 1772, 1709, 1438, 1396, 1369, 1187, 1121, 1073, 1024, 719

HRMS (EI⁺) [M-CH₃]⁺, Calcd for C₁₆H₁₈NO₄⁺: 288.1236; Found 288.1223

O-ethyl S-(5-oxocyclopent-1-en-1-yl) carbonodithioate (IV-95)

According to the described procedure¹, a solution of 2-cyclopenten-1-one (5.0 g, 60.9 mmol, 1.0 equiv) in 100 mL MeOH was cooled to 0°C, then the solution was allowed warm up to room temperature naturally after NBS (11.0 g, 60.9 mmol, 1.0 equiv) was added. 2~3 drops Conc. H₂SO₄ were added to reaction mixture and stirred for 1h. Saturated NaHCO₃ was added and extracted with EtOAc twice, the combined organic layer was washed with brine and dried over anhydrous Na₂SO₄, filtered and the solvent was removed under reduced pressure, the crude intermediate was directly used in next step without further purification.

Potassium O-ethylxanthate salt (10.2 g, 63.9 mmol, 1.05 equiv) was added to a 0°C solution of intermediate **IV-93** in 60 mL acetone. After 30 min, ice water was added to the reaction mixture and the resulted aqueous solution was extracted three times with EtOAc. The combined organic layer was washed by brine and dried with anhydrous MgSO₄. Filtered and concentrated under reduced pressure. Flash chromatography afforded desired product **IV-95** as a yellow oil (5.1 g, 25.2 mmol, 41%, two steps).



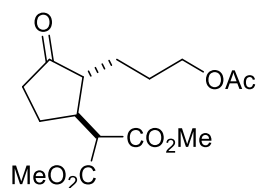
¹H NMR (400 MHz, CDCl₃) δ (ppm) = 7.94 (t, *J* = 2.8 Hz, 1H, H₄), 4.56 (q, *J* = 7.1 Hz, 2H, H₇), 2.85 – 2.79 (m, 2H, H₁), 2.57 – 2.52 (m, 2H, H₅), 1.34 (t, *J* = 7.1 Hz, 3H, H₈).

¹³C NMR (101 MHz, CDCl₃) δ (ppm) = 209.3 (C₂), 203.4 (C₆), 169.3 (C₄), 136.4 (C₃), 70.7 (C₇), 34.0 (C₁), 28.1 (C₅), 13.6 (C₈).

IR (neat) ν (cm⁻¹) = 2981, 2921, 1715, 1584, 1430, 1363, 1220, 1164, 1109, 1034, 952, 781, 750

HRMS (EI⁺) Calcd for C₈H₁₀O₂S₂⁺: 202.0122; Found 202.0118

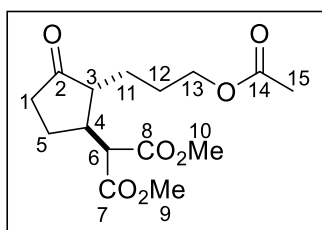
dimethyl 2-((1S,2R)-2-(3-acetoxypropyl)-3-oxocyclopentyl) malonate (**IV-98a**)



Xanthate **IV-95** (101.2 mg, 0.5 mmol, 1.0 equiv), dimethyl malonate (859.0 mg, 6.5 mmol, 13.0 equiv) and triethyl amine (101.2 mg, 1.0 mmol, 2.0 equiv) were mixed in a tube, stirred at 25 °C for 50 min, then flash chromatography on silica gel (petroleum ether/ethyl acetate = 6/1 to 3/1) afforded the michael adduct **IV-96a** as a yellow oil (144.0 mg, 0.43 mmol, 86% yield).

Following general procedure B, xanthate **IV-96a** (175.0 mg, 0.52 mmol, 1.0 equiv) and allyl acetate (156.2 mg, 1.56 mmol, 3.0 equiv) in DCE (0.52 mL) was refluxed under N₂ then dilauroyl peroxide (DLP) was added portionwise (10 mol %) every hour, the reaction required 40 mol % DLP to consume xanthate completely. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 6/1 to 3/1) afforded the radical adduct **IV-97a** as a yellow oil (153.0 mg, 0.35 mmol, 67% yield).

Following general procedure C, a solution of compound **IV-97a** (150.0 mg, 0.35 mmol, 1.0 equiv), H₃PO₂ (50% in H₂O, 121.0 mg, 0.91 mmol, 2.6 equiv), triethylamine (96.1 mg, 0.95 mmol, 2.8 equiv) in dioxane (0.1 M) was refluxed in the presence of AIBN. The reaction required 20 mol % AIBN to reduce xanthate completely. The reaction mixture partitioned between H₂O and EtOAc. The combined organic layer was washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 7/1 to 3/1) afforded the reduced product **IV-98a** as a colorless oil (88.0 mg, 0.28 mmol, 81% yield).



C₁₅H₂₂O₇
M= 314.33

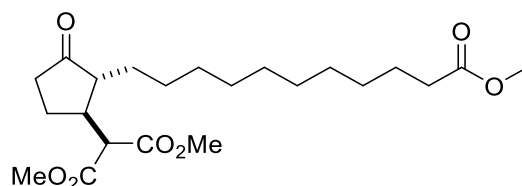
¹H NMR (400 MHz, CDCl₃) δ (ppm) = 4.04 (t, *J* = 6.2 Hz, 2H, H₁₃), 3.77 (d, *J* = 0.3 Hz, 6H, H₉, H₁₀), 3.52 (d, *J* = 7.3 Hz, 1H, H₆), 2.64 (tt, *J* = 9.7, 6.7 Hz, 1H, H₄), 2.41 – 2.33 (m, 1H, H_{1a}), 2.28 – 2.22 (m, 1H, H_{1b}), 2.21 – 2.11 (m, 1H, H₃), 2.11 – 2.06 (m, 1H, H_{5a}), 2.05 (s, 3H, H₁₅), 1.84 – 1.77 (m, 1H, H_{5b}), 1.75 – 1.63 (m, 2H, H₁₂), 1.62 – 1.49 (m, 2H, H₁₁).

¹³C NMR (101 MHz, CDCl₃) δ (ppm) = 218.4 (C₂), 171.1 (C₁₄), 168.7 (C₇), 168.3 (C₈), 64.2 (C₁₃), 54.4 (C₃), 52.6 (C₉, C₁₀), 51.5 (C₆), 40.4 (C₄), 37.2 (C₁), 25.5 (C₁₂), 24.8 (C₅), 24.5 (C₁₁), 21.0 (C₁₅).

IR (neat) ν (cm⁻¹) = 2955, 1728, 1435, 1366, 1235, 1153, 1038

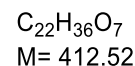
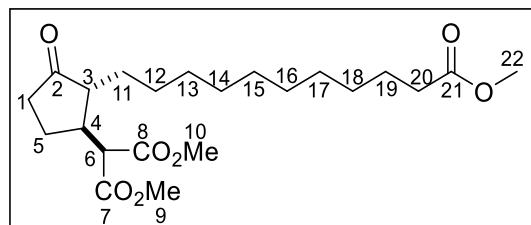
HRMS (EI ⁺) Calcd for C₁₅H₂₂O₇⁺: 314.1366; Found 314.1366

dimethyl 2-((1S,2R)-2-(11-methoxy-11-oxoundecyl)-3-oxocyclopentyl) malonate (IV-98b)



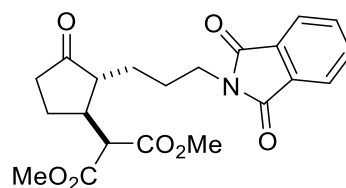
Following general procedure A, xanthate **IV-96a** (130.0 mg, 0.39 mmol, 1.0 equiv), methyl undec-10-enoate (154.2 mg, 0.78 mmol, 2.0 equiv) and dilauroyl peroxide (5 mol %) were mixed in a tube with neat condition, air in the tube was excluded by nitrogen, then sealed and heated at 85°C. Then additional dilauroyl peroxide (DLP) was added portionwise (5 mol %) every hour, the reaction required 15 mol % DLP to consume xanthate completely. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 6/1 to 3/1) afforded radical adduct as a light-yellow oil (154.0 mg, 0.29 mmol, 74% yield).

Following general procedure C, a solution of radical adduct obtained above (132.0 mg, 0.25 mmol, 1.0 equiv), H₃PO₂ (50% in H₂O, 87 mg, 0.67 mmol, 2.6 equiv), triethylamine (69 mg, 0.69 mmol, 2.8 equiv) in dioxane (0.1 M) was refluxed in the presence of AIBN. The reaction required 20 mol % AIBN to reduce xanthate completely. The reaction mixture partitioned between H₂O and EtOAc. The combined organic layer was washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 4/1 to 1/1) afforded the reduced product **IV-98b** as a colorless oil (70.0 mg, 0.17 mmol, 67% yield).



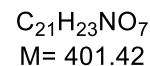
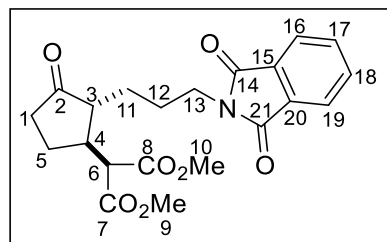
¹H NMR (400 MHz, CDCl ₃)	δ (ppm) = 3.74 (d, <i>J</i> = 1.3 Hz, 6H, H ₉ , H ₁₀), 3.64 (s, 3H, H ₂₂), 3.50 (d, <i>J</i> = 7.3 Hz, 1H, H ₆), 2.63 (tt, <i>J</i> = 9.4, 6.6 Hz, 1H, H ₄), 2.37 – 2.16 (m, 5H, H ₁ , H ₃ , H ₂₀), 2.11 (dd, <i>J</i> = 18.4, 8.8 Hz, 1H, H _{5a}), 2.04 – 1.98 (m, 1H, H _{5b}), 1.73 – 1.51 (m, 5H), 1.43 (d, <i>J</i> = 5.8 Hz, 1H), 1.26 – 1.20 (m, 12H).
¹³C NMR (101 MHz, CDCl ₃)	δ (ppm) = 219.0 (C ₂), 174.3 (C ₂₁), 168.8 (C ₇), 168.4 (C ₈), 54.5 (C ₃), 52.6 (C ₉), 52.5 (C ₁₀), 52.1 (C ₆), 51.4 (C ₂₂), 40.3 (C ₄), 37.3 (C ₁), 34.1 (C ₂₀), 29.8, 29.5, 29.4, 29.2, 29.1, 28.4, 26.3, 24.9, 24.5.
IR (neat)	ν (cm ⁻¹) = 2926, 2854, 1731, 1435, 1195, 1150, 1019, 915, 730
HRMS (EI ⁺)	Calcd for C ₂₂ H ₃₆ O ₇ ⁺ : 412.2461; Found 412.2449

dimethyl 2-((1S,2R)-2-(3-(1,3-dioxisoindolin-2-yl) propyl)-3-oxocyclopentyl) malonate (IV-98c)



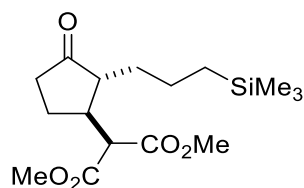
Following general procedure B, xanthate **IV-96a** (130.0 mg, 0.39 mmol, 1.0 equiv), N-Allylphthalimide (145.4 mg, 0.78 mmol, 2.0 equiv) in EtOAc (0.4 mL) was refluxed under N₂ then dilauroyl peroxide (DLP) was added portionwise (5 mol %) every hour, the reaction required 30 mol % DLP to consume xanthate completely. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 3/1 to 1/1) afforded the radical adduct as a yellow oil (111.0 mg, 0.21 mmol, 54% yield).

Following general procedure C, a solution of radical adduct obtained above (104.0 mg, 0.20 mmol, 1.0 equiv), H₃PO₂ (50% in H₂O, 70 mg, 0.53 mmol, 2.6 equiv), triethylamine (55.7 mg, 0.55 mmol, 2.8 equiv) in dioxane (0.1 M) was refluxed in the presence of AIBN. The reaction required 20 mol % AIBN to reduce xanthate completely. The reaction mixture partitioned between H₂O and EtOAc. The combined organic layer was washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 4/1 to 1/1) afforded the reduced product **IV-98c** as a colorless oil (56.0 mg, 0.14 mmol, 70% yield).



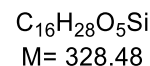
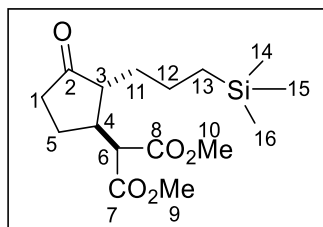
¹H NMR (400 MHz, CDCl ₃)	δ (ppm) = 7.85 – 7.80 (m, 2H, H ₁₆ , H ₁₉), 7.72 – 7.67 (m, 2H, H ₁₇ , H ₁₈), 3.72 (s, 3H, H ₉), 3.69 (s, 3H, H ₁₀), 3.66 (t, <i>J</i> = 6.7 Hz, 2H, H ₁₃), 3.48 (d, <i>J</i> = 7.3 Hz, 1H, H ₆), 2.61 (tt, <i>J</i> = 9.5, 6.7 Hz, 1H, H ₄), 2.37 – 2.28 (m, 1H, H _{1a}), 2.23 – 2.02 (m, 3H, H _{1b} , H ₃ , H _{5a}), 1.88 – 1.77 (m, 1H, H _{5b}), 1.69 – 1.57 (m, 3H, H ₁₂ , H _{11a}), 1.55 – 1.45 (m, 1H, H _{11b}).
¹³C NMR (101 MHz, CDCl ₃)	δ (ppm) = 218.2 (C ₂), 168.6 (C ₇), 168.4 (C ₈), 168.3 (C ₁₄ , C ₂₁), 133.9 (C ₁₇ , C ₁₈), 132.1 (C ₁₅ , C ₂₀), 123.2 (C ₁₆ , C ₁₉), 54.5 (C ₃), 52.6 (C ₉ , C ₁₀), 51.7 (C ₆), 40.2 (C ₄), 37.9 (C ₁₃), 37.2 (C ₁), 25.7 (C ₅), 25.5 (C ₁₁), 24.5 (C ₁₂).
IR (neat)	<i>ν</i> (cm ⁻¹) = 2953, 1732, 1705, 1435, 1396, 1148, 1018, 915, 718
HRMS (EI ⁺)	Calcd for C ₂₁ H ₂₃ NO ₇ : 401.1475; Found 401.1456

dimethyl 2-((1S,2R)-3-oxo-2-(3-(trimethylsilyl) propyl) cyclopentyl) malonate (**IV-98d**)



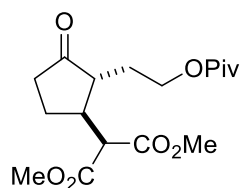
Following general procedure A, xanthate **IV-96a** (125.0 mg, 0.37 mmol, 1.0 equiv), allyltrimethylsilane (84.6 mg, 0.74 mmol, 2.0 equiv) and dilauroyl peroxide (5 mol %) were mixed in a tube with neat condition, air in the tube was excluded by nitrogen, then sealed and heated at 85°C. Then additional dilauroyl peroxide (DLP) was added portionwise (5 mol %) every hour, the reaction required 20 mol % DLP to consume xanthate completely. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 5/1 to 2/1) afforded radical adduct as a light-yellow oil (110.0 mg, 0.24 mmol, 66% yield).

Following general procedure C, a solution of radical adduct obtained above (110.0 mg, 0.24 mmol, 1.0 equiv), H₃PO₂ (50% in H₂O, 86 mg, 0.65 mmol, 2.6 equiv), triethylamine (68 mg, 0.67 mmol, 2.8 equiv) in dioxane (0.1 M) was refluxed in the presence of AIBN. The reaction required 20 mol % AIBN to reduce xanthate completely. The reaction mixture partitioned between H₂O and EtOAc. The combined organic layer was washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 14/1 to 9/1) afforded the reduced product **IV-98d** as a colorless oil (40.0 mg, 0.12 mmol, 50% yield).



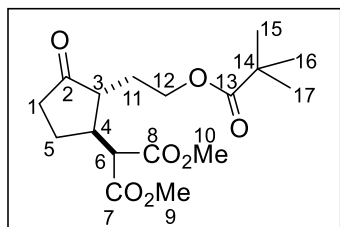
¹H NMR (400 MHz, CDCl ₃)	δ (ppm) = 3.75 (d, <i>J</i> = 1.3 Hz, 6H, H ₉ , H ₁₀), 3.51 (d, <i>J</i> = 7.3 Hz, 1H, H ₆), 2.68 – 2.59 (m, 1H, H ₄), 2.37 – 2.29 (m, 1H, H ₃), 2.25 – 2.10 (m, 2H, H ₁), 2.06 – 2.00 (m, 1H, H _{5a}), 1.78 – 1.69 (m, 1H, H _{5b}), 1.59 – 1.35 (m, 3H, H ₁₁ , H _{12a}), 1.25 – 1.15 (m, 1H, H _{12b}), 0.51 – 0.38 (m, 2H, H ₁₃), -0.04 (s, 9H, H ₁₄ , H ₁₅ , H ₁₆).
¹³C NMR (101 MHz, CDCl ₃)	δ (ppm) = 220.6 (C ₂), 170.4 (C ₇), 170.1 (C ₈), 56.1 (C ₃), 54.3 (C ₉), 54.2 (C ₁₀), 53.7 (C ₆), 42.2 (C ₄), 38.8 (C ₁), 34.2 (C ₁₁), 26.1 (C ₅), 22.6 (C ₁₂), 18.7 (C ₁₃), -0.00 (C ₁₄ , C ₁₅ , C ₁₆),
IR (neat)	ν (cm ⁻¹) = 2952, 1733, 1435, 1246, 1147, 1026, 858, 833
HRMS (EI ⁺)	[M-CH ₃] ⁺ , Calcd for C ₁₅ H ₂₅ O ₅ Si ⁺ : 313.1471; Found 313.1480

dimethyl 2-((1S,2R)-3-oxo-2-(2-(pivaloyloxy) ethyl) cyclopentyl) malonate (**IV-98e**)



Following general procedure A, xanthate **IV-96a** (150.5 mg, 0.45 mmol, 1.0 equiv), vinyl pivalate (153.3 mg, 0.9 mmol, 2.0 equiv) and dilauroyl peroxide (5 mol %) were mixed in a tube with neat condition, air in the tube was excluded by nitrogen, then sealed and heated at 85°C. Then additional dilauroyl peroxide (DLP) was added portionwise (5 mol %) every hour, the reaction required 5mol % DLP to consume xanthate completely. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 6/1 to 3/1) afforded radical adduct as a light-yellow oil (160.0 mg, 0.34 mmol, 76% yield).

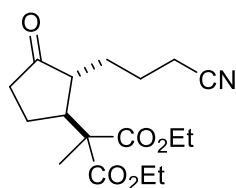
Following general procedure C, a solution of radical adduct obtained above (150.0 mg, 0.32 mmol, 1.0 equiv), H_3PO_2 (50% in H_2O , 113.5 mg, 0.86 mmol, 2.6 equiv), triethylamine (90.3 mg, 0.89 mmol, 2.8 equiv) in dioxane (0.1 M) was refluxed in the presence of AIBN. The reaction required 20 mol % AIBN to reduce xanthate completely. The reaction mixture partitioned between H_2O and EtOAc. The combined organic layer was washed with brine, dried over MgSO_4 , filtered and concentrated under reduced pressure. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 7/1 to 3/1) afforded the reduced product **IV-98e** as a colorless oil (84.0 mg, 0.24 mmol, 76% yield).



$\text{C}_{17}\text{H}_{26}\text{O}_7$
M= 342.39

^1H NMR (400 MHz, CDCl_3)	δ (ppm) = 4.21 – 4.09 (m, 2H, H_{12}), 3.75 (d, $J = 0.8$ Hz, 6H, H_9 , H_{10}), 3.56 (d, $J = 6.7$ Hz, 1H, H_6), 2.64 (tt, $J = 10.0, 6.5$ Hz, 1H, H_4), 2.41 – 2.33 (m, 1H, H_3), 2.28 – 2.13 (m, 3H, H_1 , H_{5a}), 1.96 – 1.87 (m, 1H, H_{5b}), 1.86 – 1.72 (m, 2H, H_{11}), 1.16 (s, 9H, H_{14} , H_{15} , H_{16}).
^{13}C NMR (101 MHz, CDCl_3)	δ (ppm) = 217.8 (C_2), 178.4 (C_{13}), 168.7 (C_7), 168.2 (C_8), 61.7 (C_{12}), 53.9 (C_6), 52.7 (C_9), 52.6 (C_{10}), 49.0 (C_3), 40.5 (C_4), 38.7 (C_{14}), 37.0 (C_1), 27.4 (C_{11}), 27.1 (C_{15} , C_{16} , C_{17}), 24.4 (C_5).
IR (neat)	ν (cm^{-1}) = 2958, 2874, 1724, 1435, 1282, 1146, 1033, 977, 771
HRMS (EI^+)	$[\text{M}-\text{C}_3\text{H}_9\text{O}]^+$, Calcd for $\text{C}_{12}\text{H}_{17}\text{O}_6^+$: 257.1025; Found 257.1029

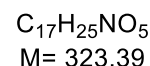
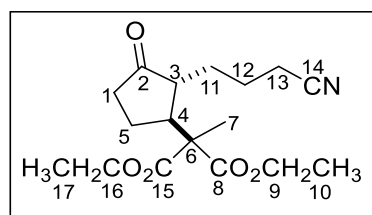
diethyl 2-((1S,2R)-2-(3-cyanopropyl)-3-oxocyclopentyl)-2-methylmalonate (**IV-98f**)



Xanthate **IV-95** (101.2 mg, 0.5 mmol, 1.0 equiv), diethyl 2-methylmalonate (1.13 g, 6.5 mmol, 13.0 equiv) and triethyl amine (101.2 mg, 1.0 mmol, 2.0 equiv) were mixed in a tube, stirred at 25°C for 30 hours, then flash chromatography on silica gel (petroleum ether/ethyl acetate = 10/1 to 6/1) afforded the Michael adduct **IV-96b** as a yellow oil (50.0 mg, 0.13 mmol, 26% yield).

Following general procedure B, xanthate **IV-96b** (50.0 mg, 0.13 mmol, 1.0 equiv) and allyl cyanide (26.8 mg, 0.40 mmol, 3.0 equiv) in DCE (0.13 mL) was refluxed under N₂ then dilauroyl peroxide (DLP) was added portionwise (10 mol %) every hour, the reaction required 50 mol % DLP to consume xanthate completely. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 6/1 to 3/1) afforded the radical adduct **IV-97f** as a yellow oil (34.0 mg, 0.077 mmol, 57% yield).

Following general procedure C, a solution of compound **IV-97f** (34.0 mg, 0.077 mmol, 1.0 equiv), H₃PO₂ (50% in H₂O, 27.0 mg, 0.20 mmol, 2.6 equiv), triethylamine (21.4 mg, 0.21 mmol, 2.8 equiv) in dioxane (0.1 M) was refluxed in the presence of AIBN. The reaction required 20 mol % AIBN to reduce xanthate completely. The reaction mixture partitioned between H₂O and EtOAc. The combined organic layer was washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 9/1 to 5/1) afforded the reduced product **IV-98f** as a colorless oil (15.0 mg, 0.046 mmol, 60% yield).



¹H NMR (400 MHz, CDCl₃) δ (ppm) = 4.28 – 4.09 (m, 4H, H₉, H₁₆), 2.70 (q, *J* = 7.5 Hz, 1H, H₄), 2.37 – 2.32 (m, 2H, H₃, H_{1a}), 2.31 – 2.09 (m, 4H, H_{1b}, H₁₃, H_{5a}), 1.95 – 1.85 (m, 1H, H_{5b}), 1.81 – 1.68 (m, 2H, H₁₂), 1.65 – 1.50 (m, 2H, H₁₁), 1.43 (s, 3H, H₇), 1.26 (td, *J* = 7.1, 3.8 Hz, 6H, H₁₀, H₁₇).

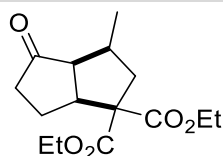
¹³C NMR (101 MHz, CDCl₃) δ (ppm) = 171.4 (C₈), 171.1 (C₁₅), 119.3 (C₁₃), 61.7 (C₉), 61.6 (C₁₆), 56.4 (C₆), 49.9 (C₃), 45.0 (C₄), 36.8 (C₁), 29.7 (C₁₁), 22.5 (C₅), 22.2 (C₁₂), 18.2 (C₇), 17.2 (C₁₃), 14.0 (C₁₀, C₁₇).

IR (neat) ν (cm⁻¹) = 2982, 1723, 1462, 1382, 1244, 1120, 1098, 1019, 860

HRMS (EI ⁺)

Calcd for C₁₇H₂₅NO₅⁺: 323.1733; Found 323.1519

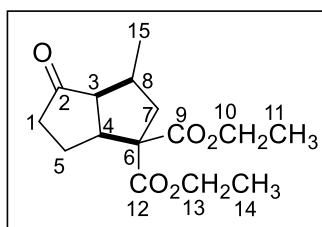
diethyl (3*S*,3*aR*,6*aS*)-3-methyl-4-oxohexahydropentalene-1,1(2*H*)-dicarboxylate (**IV-98g**)



Xanthate **IV-95** (202.3 mg, 1.0 mmol, 1.0 equiv), diethyl 2-allylmalonate (1.60 g, 8.0 mmol, 8.0 equiv) and triethyl amine (202.4 mg, 2.0 mmol, 2.0 equiv) were mixed in a tube, stirred at 25°C for 30 hours, then flash chromatography on silica gel (petroleum ether/ethyl acetate = 7/1 to 3/1) afforded the Michael adduct **IV-96c** as a yellow oil (114.0 mg, 0.28 mmol, 28% yield).

Following general procedure B, xanthate **IV-96c** (114.0 mg, 0.28 mmol, 1.0 equiv) in EtOAc (11.3 mL) was refluxed under N₂ then dilauroyl peroxide (DLP) was added portionwise (10 mol %) every hour, the reaction required 40 mol % DLP to consume xanthate completely. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 11/1 to 6/1) afforded the radical adduct **IV-97g** as a yellow oil (57.0 mg, 0.14 mmol, 50% yield).

Following general procedure D, a solution of xanthate **IV-97g** (57.0 mg, 0.14 mmol, 1.0 equiv) and tris(trimethylsilyl)silane (38.8 mg, 0.16 mmol, 1.1 equiv) in toluene/cyclohexane (1:1, 0.25 M) was refluxed under nitrogen, then AIBN was added portionwise (10 mol %) every hour, the reaction required 20 mol % AIBN to consume xanthate completely. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 5/1 to 2/1) afforded desired product **IV-98g** as a colorless liquid (15.8 mg, 0.06 mmol, 40% yield).



C₁₅H₂₂O₅
M = 282.34

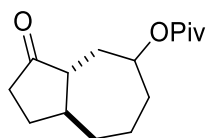
¹H NMR (400 MHz, CDCl₃) δ (ppm) = 4.28 – 4.12 (m, 4H, H₁₀, H₁₃), 3.46 (q, *J* = 8.5 Hz, 1H, H₄), 2.78 (dd, *J* = 11.3, 8.4 Hz, 1H, H₃), 2.36 – 2.25 (m, 2H, H₁), 2.25 – 2.18 (m, 2H, H₇), 2.08 – 1.97 (m, 2H, H_{5a}, H₈), 1.54 – 1.43 (m, 1H, H_{5b}), 1.26 (dt, *J* = 8.5, 7.1 Hz, 6H, H₁₁, H₁₄), 1.06 (dd, *J* = 30.5, 6.7 Hz, 3H, H₅).

¹³C NMR (101 MHz, CDCl₃) δ (ppm) = 171.7 (C₉), 169.8 (C₁₂), 64.3 (C₆), 61.7 (C₁₀), 61.4 (C₁₃), 53.8 (C₃), 46.9 (C₄), 40.6 (C₇), 39.5 (C₁), 34.5 (C₈), 24.1 (C₅), 16.8 (C₁₅), 14.2 (C₁₁), 14.0 (C₁₄).

IR (neat) ν (cm⁻¹) = 2976, 1727, 1467, 1366, 1260, 1181, 1131, 1021, 840

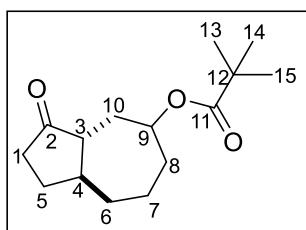
HRMS (EI⁺) Calcd for C₁₅H₂₂O₅⁺: 282.1467; Found 282.1472

(3aR,8aS)-3-oxodecahydroazulen-5-yl pivalate (**IV-98h**)



Following general procedure B, xanthate **IV-96d** (244.4 mg, 1.0 mmol, 1.0 equiv), vinyl pivalate (384.3 mg, 3.0 mmol, 3.0 equiv) in 1,2-dichloroethane (1.0 mL) was refluxed under N₂ then dilauroyl peroxide (DLP) was added portionwise (5 mol %) every hour, the reaction required 15 mol % DLP to consume xanthate completely. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 11/1 to 7/1) afforded the radical adduct **IV-97h** as a yellow oil (197.0 mg, 0.52 mmol, 52% yield).

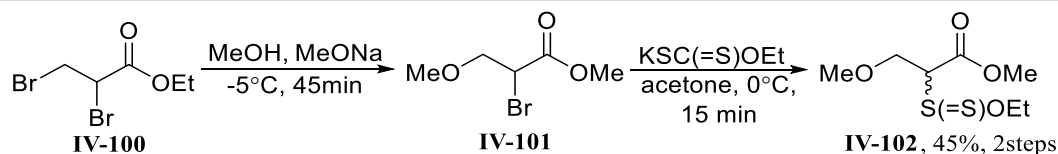
Following general procedure D, a solution of adduct **IV-97h** (197.0 mg, 0.52 mmol, 1.0 equiv) and tris(trimethylsilyl)silane (145 mg, 0.58 mmol, 1.1 equiv) in toluene/cyclohexane (1:1, 0.25 M) was refluxed under nitrogen, then AIBN was added portionwise (10 mol %) every hour, the reaction required 10mol % AIBN to consume xanthate completely. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 8/1 to 5/1) afforded desired product **IV-98h** as a colorless liquid (67.0 mg, 0.26 mmol, 50% yield).



C₁₅H₂₄O₃
M= 252.35

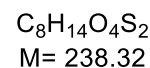
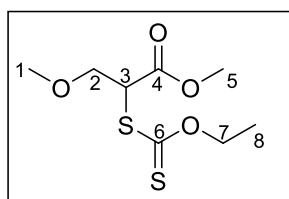
¹H NMR (400 MHz, CDCl ₃)	δ (ppm) = 5.05 – 4.90 (m, 1H, H ₉), 2.42 – 2.32 (m, 1H, H ₃), 2.23 – 1.96 (m, 5H, H ₁ , H ₄ , H ₁₀), 1.92 – 1.78 (m, 3H, H _{5a} , H ₈), 1.74 – 1.66 (m, 2H, H _{5b} , H _{6a}), 1.52 – 1.39 (m, 2H, H _{6b} , H _{7a}), 1.34 – 1.25 (m, 1H, H _{7b}), 1.16 (d, J = 2.0 Hz, 9H, H ₁₃ , H ₁₄ , H ₁₅).
¹³C NMR (101 MHz, CDCl ₃)	δ (ppm) = 177.2 (C ₁₁), 72.3 (C ₉), 71.7 (C ₉), 51.3 (C ₃), 50.7 (C ₃), 43.7 (C ₄), 43.5 (C ₄), 38.1, 37.3, 37.2, 35.1, 33.6, 33.2, 32.4, 32.3, 32.3, 28.2, 26.6 (C ₁₃ , C ₁₄ , C ₁₅), 22.9, 20.9.
IR (neat)	ν (cm ⁻¹) = 2956, 2932, 2870, 1739, 1722, 1480, 1396, 1283, 1159, 1032, 970, 840
HRMS (EI ⁺)	[M-C ₃ H ₆ O] ⁺ , Calcd for C ₁₀ H ₁₅ O ₂ ⁺ : 167.1072; Found 167.1070

methyl 2-((ethoxycarbonothioyl)thio)-3-methoxypropanoate (IV-102)



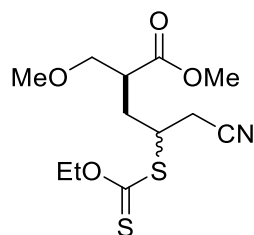
Ethyl 2,3-dibromopropanoate (13.0 g, 50 mmol, 1.0 equiv) was dissolved in MeOH (dried, 25 mL) and cooled to -5°C. Then 25 mL freshly prepared NaOMe/MeOH solution (2.1 M) was added in 45min, which was maintained below 0° C. Followed by adjusting reaction solution pH to 5-6 with 3M HCl. Filtered and washed with cooled MeOH to remove insoluble salts, the filtrate was concentrated under reduced pressure and the residue was re-dissolved in diethyl ether, then filtered and concentrated for the second time to give 7.3g crude intermediate **IV-101** was directly used in next step without further purification.

Potassium O-ethylxanthate salt (6.23 g, 38.85 mmol, 1.05 equiv) was added portionwise over 5min to a cooled solution of intermediate **IV-101** in 77 mL acetone. After 10min ice water was added to the suspension, the resulted aqueous solution was extracted twice by dichloromethane. The organic layer was washed by brine and dried with MgSO₄. Filtered and concentrated under reduced pressure. Flash chromatography afforded desired product **IV-102** as a yellow oil (5.3 g, 22.4 mmol, 45% in total yields).

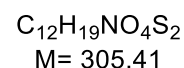
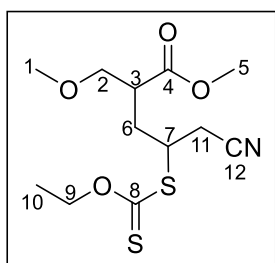


¹H NMR (400 MHz, CDCl ₃)	δ (ppm) = 4.70 – 4.60 (m, 3H, H ₃ , H ₇), 3.86 – 3.78 (m, 2H, H ₂), 3.77 (s, 3H, H ₅), 3.38 (s, 3H, H ₁), 1.46 – 1.37 (t, <i>J</i> = 7.0 Hz, 3H, H ₈).
¹³C NMR (101 MHz, CDCl ₃)	δ (ppm) = 211.9 (C ₆), 169.6 (C ₄), 71.7 (C ₂), 70.7 (C ₇), 59.2 (C ₁), 52.9 (C ₅), 52.3 (C ₃), 13.7 (C ₈).
IR (neat)	ν (cm ⁻¹) = 2986, 2952, 1738, 1435, 1377, 1214, 1109, 1039, 855
HRMS (EI ⁺)	[M-C ₃ H ₅ OS ₂] ⁺ , Calcd for C ₅ H ₉ O ₃ ⁺ : 117.0552; Found 117.0557

methyl 5-cyano-4-((ethoxycarbonothioyl)thio)-2-(methoxymethyl) pentanoate (IV-103a)

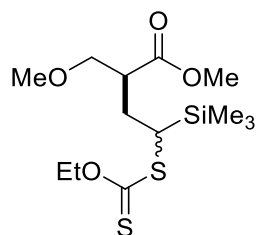


Following general procedure A, xanthate **IV-102** (500.0 mg, 2.1 mmol, 1.0 equiv), allyl cyanide (211.0 mg, 3.2 mmol, 1.5 equiv) and dilauroyl peroxide (5 mol %) were mixed in a tube with neat condition, air in the tube was excluded by nitrogen, then sealed and heated at 85°C. Then additional dilauroyl peroxide (DLP) was added portionwise (5 mol %) every hour, the reaction required 10 mol % DLP to consume xanthate completely. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 10/1 to 7/1) afforded the desired product **IV-103a** as a light-yellow liquid (527 mg, 1.72 mmol, 82% yield).

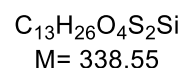
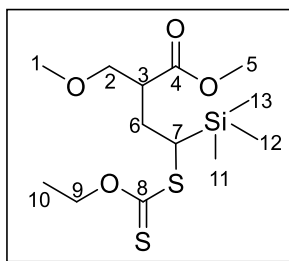


¹H NMR (400 MHz, CDCl ₃)	δ (ppm) = 4.62 (qd, $J = 7.1, 3.4$ Hz, 2H, H ₉), 3.94 (dddd, $J = 15.1, 11.0, 7.5, 5.2$ Hz, 1H, H ₇), 3.69 (d, $J = 3.7$ Hz, 3H, H ₅), 3.59 – 3.48 (m, 2H, H ₂), 3.30 (d, $J = 3.6$ Hz, 3H, H ₁), 3.00 – 2.74 (m, 3H, H ₃ , H ₁₁), 2.28 – 1.88 (m, 2H, H ₆), 1.40 (td, $J = 7.1, 2.0$ Hz, 3H, H ₁₀).
¹³C NMR (101 MHz, CDCl ₃)	δ (ppm) = 212.0 (C ₈), 211.9 (C ₈), 173.2 (C ₄), 116.9 (C ₁₂), 116.8 (C ₁₂), 73.1 (C ₂), 72.1 (C ₂), 70.7 (C ₉), 70.6 (C ₉), 59.1 (C ₁), 59.0 (C ₁), 52.2 (C ₅), 45.1 (C ₇), 44.7 (C ₇), 43.2 (C ₃), 31.7 (C ₆), 30.9 (C ₆), 24.6 (C ₁₁), 24.0 (C ₁₁), 13.7 (C ₁₀).
IR (neat)	ν (cm ⁻¹) = 2923, 2853, 1732, 1438, 1214, 1109, 1042
HRMS (EI ⁺)	[M-C ₃ H ₅ OS ₂] ⁺ , Calcd for C ₉ H ₁₄ NO ₃ ⁺ : 184.0974; Found 184.0976

methyl 4-((ethoxycarbothioly)thio)-2-(methoxymethyl)-4-(trimethylsilyl)butanoate (IV-103c)

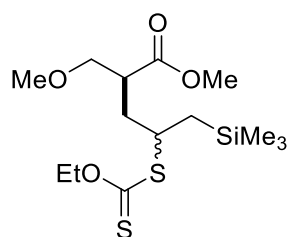


Following general procedure A, xanthate **IV-102** (357.5 mg, 1.5 mmol, 1.0 equiv) and vinyl trimethylsilane (225.5 mg, 2.25 mmol, 1.5 equiv) and dilauroyl peroxide (5 mol %) were mixed in a tube with neat condition, air in the tube was excluded by nitrogen, then sealed and heated at 85°C. Then additional dilauroyl peroxide (DLP) was added portionwise (5 mol %) every hour, the reaction required 5 mol % DLP to consume xanthate completely. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 12/1 to 8/1) afforded the desired product **IV-103c** as a colorless liquid (312 mg, 0.92 mmol, 62% yield).

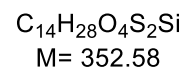
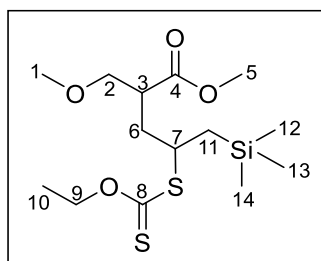


1H NMR (400 MHz, $CDCl_3$)	δ (ppm) = 4.65 – 4.51 (m, 2H, H_9), 3.65 (d, J = 5.9 Hz, 3H, H_5), 3.58 – 3.42 (m, 2H, H_2), 3.27 (d, J = 8.0 Hz, 3H, H_1), 3.15 (ddd, J = 12.0, 3.2, 1.5 Hz, 1H, H_3), 2.93 – 2.73 (m, 1H, H_7), 2.28 – 1.42 (m, 2H, H_6), 1.37 (dt, J = 8.2, 7.1 Hz, 3H, H_{10}), 0.07 (d, J = 2.8 Hz, 9H, H_{11} , H_{12} , H_{13}).
^{13}C NMR (101 MHz, $CDCl_3$)	δ (ppm) = 216.1 (C_8), 174.7 (C_4), 174.0 (C_4), 74.1 (C_2), 72.1 (C_2), 70.4 (C_9), 70.3 (C_9), 59.0 (C_{18}), 58.9 (C_1), 51.8 (C_5), 44.1 (C_7), 43.8 (C_7), 35.2 (C_3), 34.6 (C_3), 29.7 (C_6), 28.8 (C_6), 13.8 (C_{10}), -2.85 (C_{11} , C_{12} , C_{13}).
IR (neat)	ν (cm^{-1}) = 2952, 2895, 1736, 1435, 1209, 1109, 1041, 837
HRMS (EI $^+$)	$[M+H]^+$, Calcd for $[C_{13}H_{26}O_4S_2Si+H]^+$: 339.1115; Found 339.1115

methyl 4-((ethoxycarbothioyl)thio)-2-(methoxymethyl)-5 (trimethylsilyl)pentanoate (IV-103d)

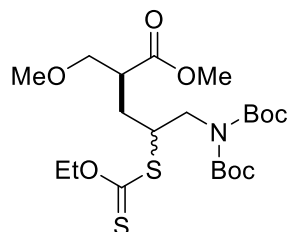


Following general procedure B, xanthate **IV-102** (100.0 mg, 0.42 mmol, 1.0 equiv) and allyl trimethylsilane (72.1 mg, 0.63 mmol, 1.5 equiv) in EtOAc (0.42 mL) then dilauroyl peroxide (DLP) was added portionwise (5 mol %) every hour, the reaction required 15 mol % DLP to consume xanthate completely. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 20/1 to 15/1) afforded the desired product **IV-103d** as a light-yellow liquid (98.2 mg, 0.28 mmol, 66% yield).

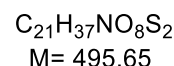
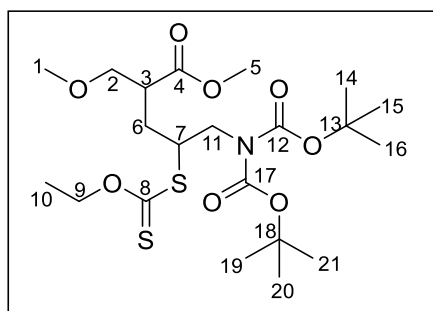


1H NMR (400 MHz, $CDCl_3$)	δ (ppm) = 4.67 – 4.54 (m, 2H, H_9), 3.91 – 3.77 (m, 1H, H_7), 3.69 (d, J = 4.3 Hz, 3H, H_5), 3.59 – 3.43 (m, 2H, H_2), 3.30 (d, J = 3.0 Hz, 3H, H_1), 2.92 – 2.76 (m, 1H, H_3), 2.14 – 1.67 (m, 2H, H_6), 1.39 (td, J = 7.1, 3.7 Hz, 3H, H_{10}), 1.18 – 0.97 (m, 2H, H_{11}), 0.06 (d, J = 3.5 Hz, 9H, H_{12} , H_{13} , H_{14}).
^{13}C NMR (101 MHz, $CDCl_3$)	δ (ppm) = 214.9 (C_8), 174.9 (C_4), 74.4 (C_2), 73.3 (C_2), 70.5 (C_9), 70.4 (C_9), 59.7 (C_1), 52.7 (C_5), 52.6 (C_5), 48.1 (C_3), 47.5 (C_3), 44.5 (C_7), 44.4 (C_7), 36.9 (C_6), 36.5 (C_6), 25.3 (C_{11}), 24.1 (C_{11}), 14.6 (C_{10}), 0.00 (C_{12} , C_{13} , C_{14}).
IR (neat)	ν (cm^{-1}) = 2951, 2895, 1736, 1435, 1206, 1109, 1044, 836
HRMS (EI ⁺)	$[M-C_3H_5OS_2]^+$, Calcd for $C_{11}H_{23}O_3Si^+$: 231.1416; Found 231.1416

methyl 5-(N, N-bis(tert-butoxycarbonyl) amino)-4-((ethoxycarbonothioyl)thio)-2-(methoxymethyl) pentanoate (IV-103e)



Following general procedure B, xanthate **IV-102** (357.5 mg, 1.5 mmol, 1.0 equiv) and N, N-bis(tert-butoxycarbonyl) allylcarbamate (579.0 mg, 2.25 mmol, 1.5 equiv) in EtOAc (1.5 mL) was refluxed under N₂ then dilauroyl peroxide (DLP) was added portionwise (5 mol %) every hour, the reaction required 5 mol % DLP to consume xanthate completely. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 10/1 to 6/1) afforded the desired product **IV-103e** as a light-yellow liquid (635.0 mg, 1.28 mmol, 85% yield).



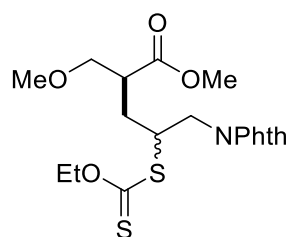
¹H NMR (400 MHz, CDCl₃) δ (ppm) = 4.67 – 4.53 (m, 2H, H₉), 4.20 – 4.04 (m, 1H, H₇), 3.88 (ddd, *J* = 14.4, 8.9, 2.6 Hz, 1H, H_{11a}), 3.77 (ddd, *J* = 14.4, 5.9, 1.3 Hz, 1H, H_{11a}), 3.66 (d, *J* = 2.2 Hz, 3H, H₅), 3.57 – 3.46 (m, 2H, H₂), 3.27 (d, *J* = 2.3 Hz, 3H, H₁), 2.98 – 2.76 (m, 1H, H₃), 2.16 – 1.60 (m, 2H, H₆), 1.47 (d, *J* = 1.5 Hz, 18H, H₁₄, H₁₅, H₁₆, H₁₉, H₂₀, H₂₁), 1.37 (td, *J* = 7.1, 4.5 Hz, 3H, H₁₀).

¹³C NMR (101 MHz, CDCl₃) δ (ppm) = 213.2 (C₈), 174.1 (C₄), 173.7 (C₄), 152.3 (C₁₂), 152.2 (C₁₇), 82.6 (C₁₃, C₁₈), 73.5 (C₂), 72.3 (C₂), 70.1 (C₉), 70.0 (C₉), 59.0 (C₁), 58.9 (C₁), 52.0 (C₅), 51.9 (C₅), 49.2 (C₁₁), 49.0 (C₁₁), 43.2 (C₇, C₃), 31.2 (C₆), 30.4 (C₆), 28.0 (C₁₄, C₁₅, C₁₆, C₁₉, C₂₀, C₂₁), 13.7 (C₁₀).

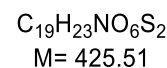
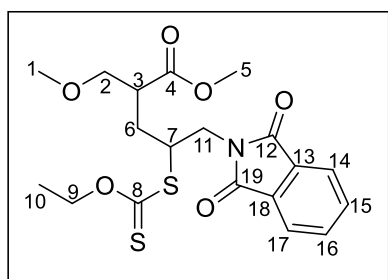
IR (neat) ν (cm⁻¹) = 2980, 1736, 1695, 1436, 1366, 1216, 1138, 1109, 1044, 853, 735

HRMS (EI⁺) [M+Na]⁺, Calcd for C₂₁H₃₇NO₈S₂Na⁺: 518.1853; Found 518.1853

methyl5-(1,3-dioxoisindolin-2-yl)-4-((ethoxycarbonothioyl)thio)-2(methoxymethyl)pentanoate (IV-103f)



Following general procedure B, xanthate **IV-102** (100.1 mg, 0.42 mmol, 1.0 equiv) and N-allylphthalimide (117.8 mg, 0.63 mmol, 1.5 equiv) in EtOAc (0.42 mL) then dilauroyl peroxide (DLP) was added portionwise (5 mol %) every hour, the reaction required 5 mol % DLP to consume xanthate completely. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 8/1 to 5/1) afforded the desired product **IV-103f** as a light-yellow liquid (155.2 mg, 0.36 mmol, 86% yield).



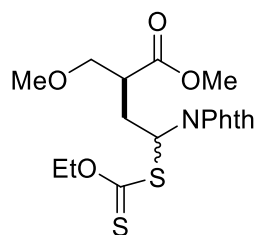
1H NMR δ (ppm) = 7.88 – 7.76 (m, 2H, H₁₄, H₁₇), 7.76 – 7.61 (m, 2H, H₁₅, H₁₆), 4.63 – 4.47 (m, 2H, H₉), 4.27 – 4.05 (m, 1H, H₇), 3.99 – 3.86 (m, 2H, H₁₁), 3.66 (d, J = 17.1 Hz, 3H, H₅), 3.56 – 3.46 (m, 2H, H₂), 3.26 (d, J = 6.9 Hz, 3H, H₁), 3.00 – 2.80 (m, 1H, H₃), 2.21 – 1.69 (m, 2H, H₆), 1.38 (td, J = 7.1, 4.7 Hz, 3H, H₁₀).

^{13}C NMR δ (ppm) = 212.2 (C₈), 212.1 (C₈), 173.8 (C₄), 173.6 (C₄), 168.0 (C₁₂, C₁₉), 134.1 (C₁₅, C₁₆), 131.8 (C₁₃, C₁₈), 123.4 (C₁₄, C₁₇), 73.2 (C₂), 72.1 (C₂), 70.3 (C₁₇), 59.0 (C₁), 58.9 (C₁), 52.1 (C₅), 52.0 (C₅), 47.6 (C₁₁), 47.4 (C₁₁), 43.4 (C₃), 43.3 (C₃), 41.4 (C₇), 41.2 (C₇), 30.6 (C₆), 30.1 (C₆), 13.6 (C₁₀).

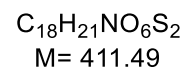
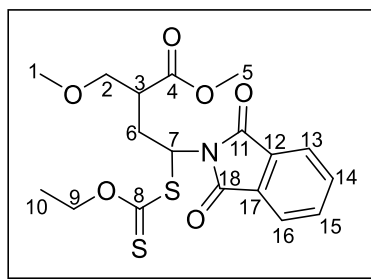
IR (neat) ν (cm⁻¹) = 2985, 2928, 1773, 1713, 1391, 1213, 1110, 1042, 713

HRMS (EI⁺) [M-C₃H₅OS₂]⁺, Calcd for C₁₆H₁₈NO₅⁺: 304.1185; Found 304.1195

methyl 4-(1,3-dioxoisindolin-2-yl)-4-((ethoxycarbonothioyl)thio)-2-(methoxymethyl)butanoate (IV-103g)

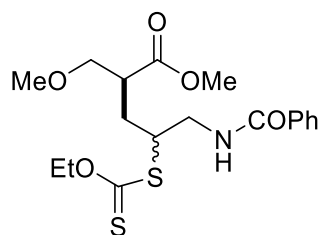


A modified condition from procedure B, xanthate **IV-102** (476.6 mg, 2.0 mmol, 2.0 equiv) and N-vinylphthalimide (173.2 mg, 1.0 mmol, 1.0 equiv) in EtOAc (4.0 mL) was refluxed under N₂ then dilauroyl peroxide (DLP) was added portionwise (5 mol %) every hour, the reaction required 5 mol % DLP to consume olefin completely. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 10/1 to 6/1) afforded the desired product **IV-103g** as a light-yellow liquid (331.0 mg, 0.80 mmol, 80% yield).

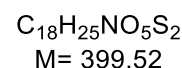
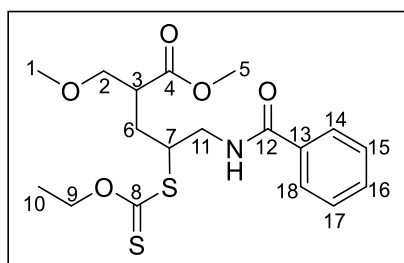


¹H NMR (400 MHz, CDCl ₃)	δ (ppm) = 7.87 – 7.79 (m, 2H, H ₁₃ , H ₁₆), 7.76 – 7.70 (m, 2H, H ₁₄ , H ₁₅), 6.38 – 6.27 (m, 1H, H ₇), 4.60 (qd, <i>J</i> = 7.1, 1.4 Hz, 2H, H ₉), 3.69 – 3.47 (m, 5H, H ₂ , H ₅), 3.28 (d, <i>J</i> = 18.1 Hz, 3H, H ₁), 2.75 – 2.32 (m, 3H, H ₃ , H ₆), 1.38 (td, <i>J</i> = 7.1, 1.3 Hz, 3H, H ₁₀).
¹³C NMR (101 MHz, CDCl ₃)	δ (ppm) = 210.8 (C ₈), 210.3 (C ₈), 173.1 (C ₄), 173.0 (C ₄), 166.7 (C ₁₁), 166.6 (C ₁₈), 134.4 (C ₁₄ , C ₁₅), 131.5 (C ₁₂ , C ₁₇), 123.6 (C ₁₃ , C ₁₆), 72.6 (C ₂), 72.5 (C ₂), 70.5 (C ₉), 59.0 (C ₁), 56.2 (C ₇), 55.4 (C ₇), 52.1 (C ₅), 52.0 (C ₅), 43.5 (C ₃), 43.1 (C ₃), 32.3 (C ₆), 32.0 (C ₆), 13.7 (C ₁₀).
IR (neat)	<i>ν</i> (cm ⁻¹) = 2984, 2926, 1778, 1715, 1437, 1376, 1221, 1108, 1040, 877, 716
HRMS (EI ⁺)	[M-C ₃ H ₅ OS ₂] ⁺ , Calcd for C ₁₅ H ₁₆ NO ₅ ⁺ : 290.1028; Found 290.1030

methyl 5-benzamido-4-((ethoxycarbonothioyl)thio)-2-(methoxymethyl) pentanoate (**IV-103h**)



Following general procedure A, xanthate **IV-102** (100.0 mg, 0.42 mmol, 1.0 equiv), *N*-allylbenzamide (101.6 mg, 0.63 mmol, 1.5 equiv) and dilauroyl peroxide (5 mol %) were mixed in a tube with neat condition, air in the tube was excluded by nitrogen, then sealed and heated at 85°C. Then additional dilauroyl peroxide (DLP) was added portionwise (5 mol %) every hour, the reaction required 10 mol % DLP to consume xanthate completely. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 7/1 to 4/1) afforded the desired product **IV-103h** as a light-yellow liquid (137.4 mg, 0.34 mmol, 82% yield).



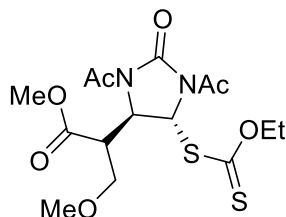
1H NMR δ (ppm) = 7.75 (ddd, J = 7.2, 3.9, 2.1 Hz, 2H, H_{14} , H_{18}), 7.51 – 7.44 (m, 1H, H_{16}), 7.43 – 7.36 (m, 2H, H_{15} , H_{17}), 6.73 (q, J = 6.1 Hz, 1H, NH), 4.65 – 4.53 (m, 2H, H_9), 4.14 – 3.95 (m, 1H, H_7), 3.82 – 3.65 (m, 5H, H_5 , H_{11}), 3.57 – 3.49 (m, 2H, H_2), 3.29 (s, 3H, H_1), 3.01 – 2.85 (m, 1H, H_3), 2.27 – 1.73 (m, 2H, H_6), 1.37 (td, J = 7.1, 2.4 Hz, 3H, H_{10}).

^{13}C NMR δ (ppm) = 213.8 (C_8), 213.4 (C_8), 174.1 (C_4), 173.9 (C_4), 167.6 (C_{12}), 134.2 (C_{13}), 131.6 (C_{16}), 128.6 (C_{15} , C_{17}), 127.0 (C_{14} , C_{18}), 73.3 (C_2), 72.5 (C_2), 70.5 (C_9), 59.1 (C_1), 59.0 (C_1), 52.2 (C_5), 52.1 (C_5), 49.7 (C_7), 49.3 (C_7), 43.9 (C_{11}), 43.4 (C_{11}), 43.3 (C_3), 30.6 (C_6), 30.0 (C_6), 13.7 (C_{10}).

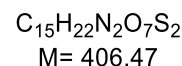
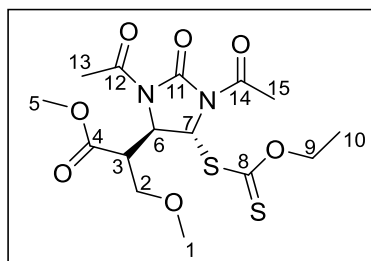
IR (neat) ν (cm^{-1}) = 3324, 2984, 2926, 1732, 1644, 1530, 1211, 1109, 1042, 734

HRMS (EI⁺) $[M-C_3H_5OS_2]^+$, Calcd for $C_{15}H_{20}NO_4^+$: 278.1392; Found 278.1291

methyl(S)-2-((4S,5R)-1,3-diacetyl-5-((ethoxycarbonothioyl)thio)-2-oxoimidazolidin-4-yl)-3-methoxypropanoate (IV-103i)

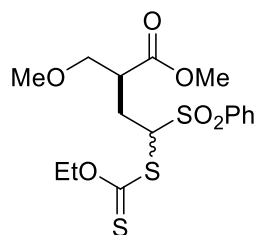


A modified conditions from procedure B, xanthate **IV-102** (283.2 mg, 1.19 mmol, 2.0 equiv) and 1,1'-(2-oxo-1H-imidazole-1,3(2H)-diyl)bis(ethan-1-one) (100.0 mg, 0.59 mmol, 1.0 equiv) in EtOAc (1.2 mL) then dilauroyl peroxide (DLP) was added portionwise (5 mol %) every hour, the reaction required 15 mol % DLP to consume olefin completely. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 6/1 to 3/1) afforded the desired product **IV-103i** as a light-yellow liquid (100.1 mg, 0.25 mmol, 42% yield, d.r = 3/1).

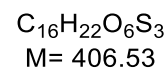
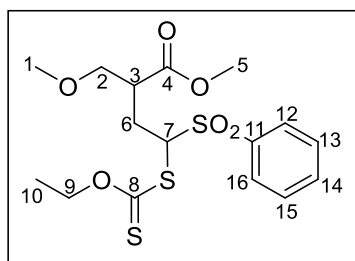


1H NMR (400 MHz, $CDCl_3$)	δ (ppm) = 6.04 – 5.89 (m, 1H, H ₇), 4.95 (ddd, J = 27.3, 3.2, 1.5 Hz, 1H, H ₆), 4.71 – 4.62 (m, 2H, H ₉), 3.78 – 3.70 (m, 2H, H ₂), 3.69 (s, 3H, H ₅), 3.42 (ddd, J = 7.8, 5.0, 2.7 Hz, 1H, H ₃), 3.27 (d, J = 18.8 Hz, 3H, H ₁), 2.55 (d, J = 0.6 Hz, 3H, H ₁₃), 2.51 (d, J = 4.4 Hz, 3H, H ₁₅), 1.41 (td, J = 7.1, 0.6 Hz, 3H, H ₁₀).
^{13}C NMR (101 MHz, $CDCl_3$)	δ (ppm) = 209.4 (C ₈), 170.5 (C ₄), 170.4 (C ₄), 168.8 (C ₁₅ , C ₁₂), 151.4 (C ₁₁), 70.2 (C ₂), 69.6 (C ₉), 69.3 (C ₉), 62.0 (C ₇), 61.9 (C ₇), 59.8 (C ₁), 59.2 (C ₁), 59.1 (C ₁), 58.7 (C ₆), 52.4 (C ₅), 52.3 (C ₅), 47.7 (C ₃), 46.8 (C ₃), 24.4 (C ₁₃), 24.2 (C ₁₅), 13.7 (C ₁₀).
IR (neat)	ν (cm ⁻¹) = 2926, 1762, 1735, 1706, 1435, 1361, 1223, 1110, 1040, 908, 729
HRMS (EI ⁺)	$[M-C_3H_5OS_2]^+$, Calcd for $C_{12}H_{17}N_2O_6^+$: 285.1087; Found 285.1073

methyl 4-((ethoxycarbonothioyl)thio)-2-(methoxymethyl)-4-(phenylsulfonyl) butanoate (IV-103j)

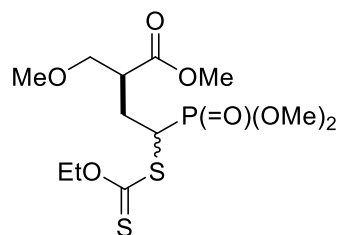


Following general procedure B, xanthate **IV-102** (357.5 mg, 1.5 mmol, 1.0 equiv) and (vinylsulfonyl)benzene (378.5 mg, 2.25 mmol, 1.5 equiv) in EtOAc (1.5 mL) was refluxed under N₂ then dilauroyl peroxide (DLP) was added portionwise (5 mol %) every hour, the reaction required 10 mol % DLP to consume xanthate completely. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 8/1 to 4/1) afforded the desired product **IV-103j** as a light-yellow liquid (473.0 mg, 1.16 mmol, 78% yield).

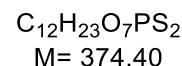
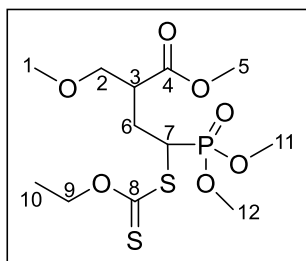


¹H NMR (400 MHz, CDCl ₃)	δ (ppm) = 7.92 (ddd, <i>J</i> = 8.8, 2.5, 1.3 Hz, 2H, H ₁₂ , H ₁₆), 7.66 – 7.57 (m, 1H, H ₁₄), 7.56 – 7.47 (m, 2H, H ₁₃ , H ₁₅), 5.33 (ddd, <i>J</i> = 11.2, 8.6, 3.7 Hz, 1H, H ₇), 4.54 – 4.34 (m, 2H, H ₉), 3.61 (d, <i>J</i> = 17.1 Hz, 3H, H ₅), 3.55 – 3.43 (m, 2H, H ₂), 3.22 (d, <i>J</i> = 17.9 Hz, 3H, H ₁), 2.95 – 2.80 (m, 1H, H ₃), 2.74 – 1.93 (m, 2H, H ₆), 1.29 (td, <i>J</i> = 7.1, 6.4 Hz, 3H, H ₁₀).
¹³C NMR (101 MHz, CDCl ₃)	δ (ppm) = 209.1 (C ₈), 172.9 (C ₄), 172.6 (C ₄), 136.5 (C ₁₁), 136.4 (C ₁₁), 134.2 (C ₁₄), 129.8 (C ₁₃), 129.7 (C ₁₅), 129.0 (C ₁₂ , C ₁₆), 72.8 (C ₂), 71.8 (C ₉), 71.5 (C ₉), 70.4 (C ₇), 70.0 (C ₇), 59.1 (C ₁), 58.0 (C ₁), 52.2 (C ₅), 42.8 (C ₃), 42.5 (C ₃), 26.4 (C ₆), 26.3 (C ₆), 13.6 (C ₁₀).
IR (neat)	<i>ν</i> (cm ⁻¹) = 2984, 2927, 1733, 1446, 1308, 1228, 1147, 1109, 1036, 840, 734, 687
HRMS (EI ⁺)	[M-C ₃ H ₅ OS ₂] ⁺ , Calcd for C ₁₃ H ₁₇ O ₅ S ⁺ : 285.0797; Found 285.0806

methyl 4-(dimethoxyphosphoryl)-4-((ethoxycarbonothioyl)thio)-2-(methoxymethyl) butanoate (IV-103k)

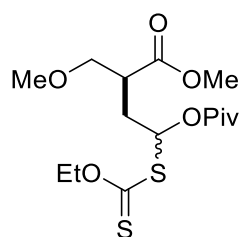


Following general procedure A, xanthate **IV-102** (357.5 mg, 1.5 mmol, 1.0 equiv), dimethyl vinylphosphonate (306.2 mg, 2.25 mmol, 1.5 equiv) and dilauroyl peroxide (5 mol %) were mixed in a tube with neat condition, air in the tube was excluded by nitrogen, then sealed and heated at 85°C. Then additional dilauroyl peroxide (DLP) was added portionwise (5 mol %) every hour, the reaction required 10 mol % DLP to consume xanthate completely. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 1/1 to 1/3) afforded the desired product **IV-103k** as a light-yellow liquid (346.1 mg, 0.92 mmol, 62% yield).

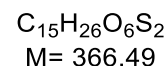
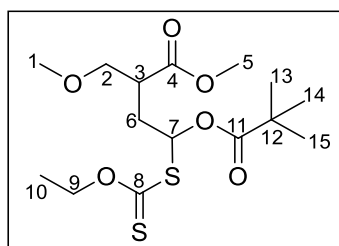


1H NMR (400 MHz, $CDCl_3$)	δ (ppm) = 4.69 – 4.54 (m, 2H, H ₉), 4.27 (dddd, J = 15.7, 13.5, 10.0, 4.3 Hz, 1H, H ₇), 3.80 – 3.68 (m, 6H, H ₁₁ , H ₁₂), 3.64 (t, J = 0.9 Hz, 3H, H ₅), 3.54 – 3.41 (m, 2H, H ₂), 3.25 (dd, J = 5.7, 0.7 Hz, 3H, H ₁), 2.88 (dtd, J = 16.9, 7.7, 6.6, 4.4 Hz, 1H, H ₃), 2.58 – 1.71 (m, 2H, H ₆), 1.42 – 1.32 (m, 3H, H ₁₀).
^{13}C NMR (101 MHz, $CDCl_3$)	δ (ppm) = 212.2 (C ₈), 212.1 (C ₈), 173.6 (C ₄), 173.3 (C ₄), 73.3 (C ₂), 72.2 (C ₂), 71.3 (C ₉), 71.2 (C ₉), 59.0 (C ₁), 58.9 (C ₁), 53.8 (C ₁₁), 53.7 (C ₁₁), 53.6 (C ₁₂), 53.5 (C ₁₂), 52.0 (C ₅), 44.0 (C ₇), 43.7 (C ₇), 42.7 (C ₃), 42.5 (C ₃), 42.2 (C ₃), 28.6 (C ₆), 28.1 (C ₆), 13.7 (C ₁₀).
IR (neat)	ν (cm ⁻¹) = 3479, 2953, 1733, 1441, 1223, 1110, 1019, 821
HRMS (EI ⁺)	Calcd for $C_{12}H_{23}O_7PS_2^+$: 374.0623; Found 374.0612

methyl 4-((ethoxycarbonothioyl)thio)-2-(methoxymethyl)-4-(pivaloyloxy) butanoate (IV-1031)

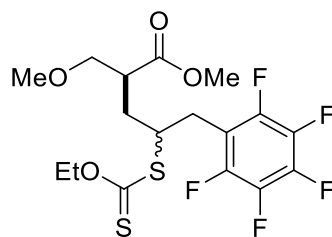


Following general procedure A, xanthate **IV-102** (300.0 mg, 1.26 mmol, 1.0 equiv), vinyl pivalate (242.1 mg, 1.89 mmol, 1.5 equiv) and dilauroyl peroxide (5 mol %) were mixed in a tube with neat condition, air in the tube was excluded by nitrogen, then sealed and heated at 85°C. Then additional dilauroyl peroxide (DLP) was added portionwise (5 mol %) every hour, the reaction required 5 mol % DLP to consume xanthate completely. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 10/1 to 7/1) afforded the desired product **IV-1031** as a light-yellow liquid (333.0 mg, 0.91 mmol, 72% yield).

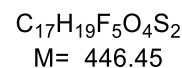
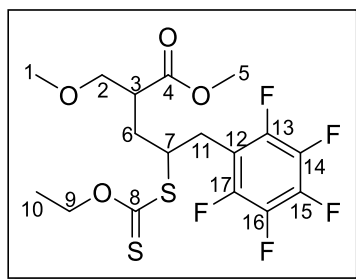


¹H NMR (400 MHz, CDCl ₃)	δ (ppm) = 6.63 – 6.51 (m, 1H, H ₇), 4.58 (qd, <i>J</i> = 7.1, 3.0 Hz, 2H, H ₉), 3.68 (s, 3H, H ₅), 3.57 – 3.43 (m, 2H, H ₂), 3.33 – 3.23 (m, 3H, H ₁), 2.73 (dtd, <i>J</i> = 9.2, 5.6, 1.5 Hz, 1H, H ₃), 2.43 – 2.25 (m, 1H, H _{6a}), 2.23 – 2.07 (m, 1H, H _{6b}), 1.37 (td, <i>J</i> = 7.1, 1.0 Hz, 3H, H ₁₀), 1.14 (d, <i>J</i> = 0.8 Hz, 9H, H ₁₃ , H ₁₄ , H ₁₅).
¹³C NMR (101 MHz, CDCl ₃)	δ (ppm) = 209.8 (C ₈), 176.5 (C ₁₁), 173.2 (C ₄), 79.2 (C ₇), 78.7 (C ₇), 72.9 (C ₂), 72.4 (C ₂), 70.2 (C ₉), 59.0 (C ₁), 58.9 (C ₁), 52.1 (C ₅), 42.4 (C ₁₂), 38.8 (C ₃), 33.4 (C ₆), 33.2 (C ₆), 27.1 (C ₁₃), 26.9 (C ₁₄), 26.8 (C ₁₅), 13.6 (C ₁₀).
IR (neat)	ν (cm ⁻¹) = 2976, 1736, 1219, 1108, 1480, 1366, 1042, 963
HRMS (EI ⁺)	[M-C ₃ H ₅ OS ₂] ⁺ , Calcd for C ₁₂ H ₂₁ O ₅ ⁺ : 245.1389; Found 245.1375

methyl 4-((ethoxycarbonothioyl)thio)-2-(methoxymethyl)-5-(perfluorophenyl) pentanoate (IV-103m)

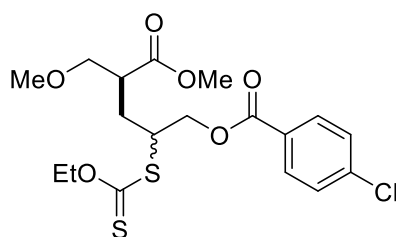


Following general procedure B, xanthate **IV-102** (100.0 mg, 0.42 mmol, 1.0 equiv) and allylpentafluorobenzene (131.1 mg, 0.63 mmol, 1.5 equiv) in EtOAc (0.42 mL) was refluxed under N₂ then dilauroyl peroxide (DLP) was added portionwise (5 mol %) every hour, the reaction required 5 mol % DLP to consume xanthate completely. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 9/1 to 6/1) afforded the desired product **IV-103m** as a light-yellow liquid (160.0 mg, 0.36 mmol, 85% yield).

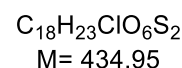
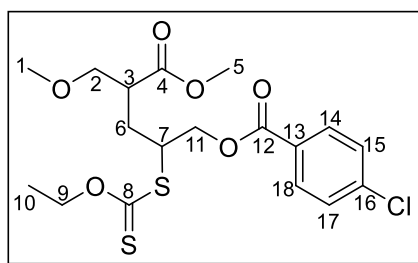


¹H NMR (400 MHz, CDCl ₃)	δ (ppm) = 4.55 (qt, <i>J</i> = 7.1, 1.2 Hz, 2H, H ₉), 4.09 – 3.98 (m, 1H, H ₇), 3.67 (d, <i>J</i> = 14.4 Hz, 3H, H ₅), 3.55 – 3.46 (m, 2H, H ₂), 3.28 (d, <i>J</i> = 1.6 Hz, 3H, H ₁), 3.15 – 2.99 (m, 2H, H ₁₁), 2.95 – 2.79 (m, 1H, H ₃), 2.12 – 1.70 (m, 2H, H ₆), 1.37 (td, <i>J</i> = 7.2, 0.8 Hz, 3H, H ₁₀).
¹³C NMR (101 MHz, CDCl ₃)	δ (ppm) = 212.4 (C ₈), 173.7 (C ₄), 173.5 (C ₄), 146.6 (C ₁₃), 144.2 (C ₁₇), 138.6 (C ₁₄), 136.1 (C ₁₆), 111.7 (C ₁₂), 111.5 (C ₁₂), 111.3 (C ₁₂), 73.3 (C ₂), 72.1 (C ₂), 70.3 (C ₉), 70.2 (C ₉), 59.0 (C ₁), 58.9 (C ₁), 52.0 (C ₅), 48.3 (C ₇), 47.9 (C ₇), 43.4 (C ₃), 43.3 (C ₃), 32.6 (C ₁₁), 32.3 (C ₁₁), 28.4 (C ₆), 27.8 (C ₆), 13.5 (C ₁₀).
IR (neat)	<i>ν</i> (cm ⁻¹) = 2930, 1736, 1502, 1437, 1213, 1111, 1044, 969, 737
HRMS (EI ⁺)	Calcd for C ₁₄ H ₁₄ F ₅ O ₃ , (M-C ₃ H ₅ OS ₂): 325.0863; Found 325.0870

2-((ethoxycarbonothioyl)thio)-5-methoxy-4-(methoxymethyl)-5-oxopentyl 4-chlorobenzoate (IV-103n)

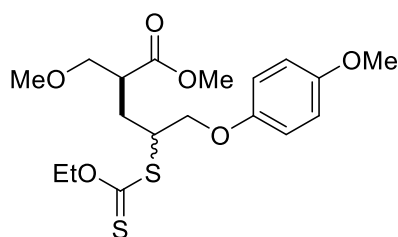


Following general procedure A, xanthate **IV-102** (357.5 mg, 1.5 mmol, 1.0 equiv), allyl 4-chlorobenzoate (442.0 mg, 2.25 mmol, 1.5 equiv) and dilauroyl peroxide (5 mol %) were mixed in a tube with neat condition, air in the tube was excluded by nitrogen, then sealed and heated at 85°C. Then additional dilauroyl peroxide (DLP) was added portionwise (5 mol %) every hour, the reaction required 5 mol % DLP to consume xanthate completely. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 10/1 to 6/1) afforded the desired product **IV-102n** as a light-yellow liquid (508.0 mg, 1.17 mmol, 72% yield).

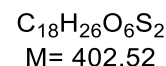
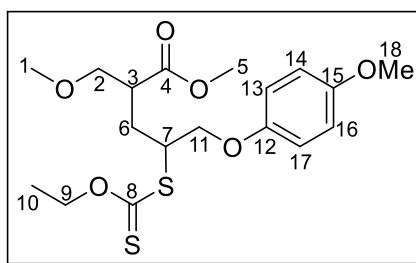


- 1H NMR** δ (ppm) = 8.00 – 7.92 (m, 2H, H₁₄, H₁₈), 7.45 – 7.37 (m, 2H, H₁₅, H₁₇), 4.69 – 4.40 (m, 4H, H₉, H₁₁), 4.16 (ddd, J = 11.4, 5.9, 4.2 Hz, 1H, H₇), 3.70 (d, J = 4.1 Hz, 3H, H₅), 3.62 – 3.51 (m, 2H, H₂), 3.31 (d, J = 2.8 Hz, 3H, H₁), 3.02 – 2.81 (m, 1H, H₃), 2.37 – 1.76 (m, 2H, H₆), 1.40 (td, J = 7.1, 2.5 Hz, 3H, H₁₀).
- ^{13}C NMR** δ (ppm) = 212.6 (C₈), 173.8 (C₄), 173.7 (C₄), 165.3 (C₁₂), 139.7 (C₁₆), 131.1 (C₁₄, C₁₈), 128.8 (C₁₅, C₁₇), 128.2 (C₁₃), 128.1 (C₁₃), 73.4 (C₂), 72.3 (C₂), 70.5 (C₁₁), 70.4 (C₁₁), 66.7 (C₉), 66.2 (C₉), 59.1 (C₁), 59.0 (C₁), 52.1 (C₅), 48.1 (C₃), 47.6 (C₃), 43.3 (C₇), 43.2 (C₇), 30.1 (C₆), 29.3 (C₆), 13.7 (C₁₀).
- IR** (neat) ν (cm⁻¹) = 2985, 2951, 1722, 1594, 1265, 1213, 1090, 1042, 1014, 849, 758, 735
- HRMS** (EI⁺) [M-C₃H₅OS₂]⁺, Calcd for C₁₅H₁₈ClO₅⁺: 313.0843; Found 313.0853

methyl 4-((ethoxycarbonylthio)thio)-2-(methoxymethyl)-5-(4-methoxyphenoxy) pentanoate (IV-103o)



Following general procedure A, xanthate **IV-102** (357.5 mg, 1.5 mmol, 1.0 equiv), 1-(allyloxy)-4-methoxybenzene (369.5 mg, 2.25 mmol, 1.5 equiv) and dilauroyl peroxide (5 mol %) were mixed in a tube with neat condition, air in the tube was excluded by nitrogen, then sealed and heated at 85°C. Then additional dilauroyl peroxide (DLP) was added portionwise (5 mol %) every hour, the reaction required 15 mol % DLP to consume xanthate completely. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 8/1 to 5/1) afforded the desired product **IV-103o** as a light-yellow liquid (376 mg, 0.93 mmol, 62% yield).



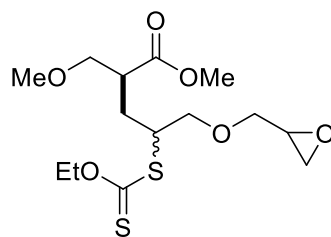
1H NMR δ (ppm) = 6.88 – 6.77 (m, 4H, H₁₃, H₁₄, H₁₆, H₁₇), 4.63 (qd, J = 7.1, 4.0 Hz, 2H, H₉), 4.26 – 4.08 (m, 2H, H₁₁), 4.07 – 3.98 (m, 1H, H₇), 3.75 (d, J = 0.8 Hz, 3H, H₁₈), 3.67 (d, J = 13.1 Hz, 3H, H₅), 3.60 – 3.51 (m, 2H, H₂), 3.31 (d, J = 5.5 Hz, 3H, H₁), 3.03 – 2.79 (m, 1H, H₃), 2.45 – 1.85 (m, 2H, H₆), 1.40 (td, J = 7.1, 4.1 Hz, 3H, H₁₀).

^{13}C NMR δ (ppm) = 213.5 (C₈), 213.4 (C₈), 174.1 (C₄), 174.0 (C₄), 154.2 (C₁₅), 152.6 (C₁₅), 152.5 (C₂), 115.8 (C₁₃, C₁₇), 114.6 (C₁₄, C₁₆), 73.6 (C₁₁), 72.8 (C₁₁), 70.8 (C₂), 70.3 (C₉), 70.2 (C₉), 70.1 (C₉), 59.0 (C₁), 55.7 (C₁₈), 52.0 (C₅), 48.7 (C₃), 48.2 (C₃), 43.5 (C₇), 30.2 (C₆), 29.6 (C₆), 13.8 (C₁₀).

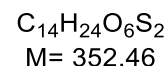
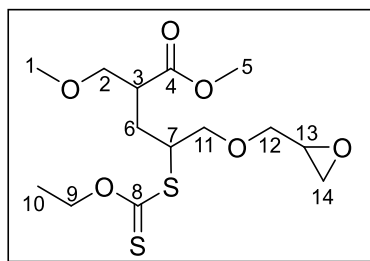
IR (neat) ν (cm⁻¹) = 2928, 2833, 1733, 1506, 1441, 1384, 1210, 1108, 1038, 824, 735

HRMS (EI⁺) Calcd for C₁₈H₂₆O₆S₂⁺: 402.1171; Found 402.1165

methyl 4-((ethoxycarbothioyl)thio)-2-(methoxymethyl)-5-(oxiran-2-ylmethoxy) pentanoate (IV-103p)



Following general procedure A, xanthate **IV-102** (357.5 mg, 1.5 mmol, 1.0 equiv), 2-((allyloxy)methyl) oxirane (324.2 mg, 2.25 mmol, 1.5 equiv) and dilauroyl peroxide (5 mol %) were mixed in a tube with neat condition, air in the tube was excluded by nitrogen, then sealed and heated at 85°C. Then additional dilauroyl peroxide (DLP) was added portionwise (5 mol %) every hour, the reaction required 10 mol % DLP to consume xanthate completely. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 7/1 to 4/1) afforded the desired product **IV-103p** as a light-yellow liquid (428.0 mg, 1.21 mmol, 81% yield).



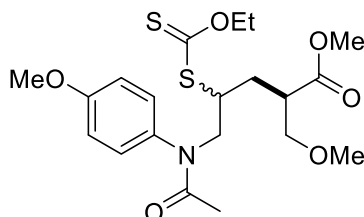
1H NMR (400 MHz, $CDCl_3$) δ (ppm) = 4.70 – 4.59 (m, 2H, H₉), 3.97 (dt, J = 10.3, 4.2, 2.3 Hz, 1H, H₇), 3.86 – 3.73 (m, 2H, H₁₁), 3.71 (d, J = 3.9 Hz, 3H, H₅), 3.69 – 3.49 (m, 3H, H₁₂, H₁₃), 3.48 – 3.38 (m, 1H, H_{2a}), 3.36 – 3.30 (m, 3H, H₁), 3.18 – 3.08 (m, 1H, H_{2b}), 2.98 – 2.82 (m, 1H, H_{14a}), 2.79 (tt, J = 4.4, 0.5 Hz, 1H, H_{14b}), 2.67 – 2.58 (m, 1H, H₃), 2.36 – 1.72 (m, 2H, H₆), 1.42 (td, J = 7.1, 2.4 Hz, 3H, H₁₀).

^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) = 213.8 (C₈), 213.7 (C₈), 174.1 (C₄), 174.0 (C₄), 73.5 (C₁₁), 73.3 (C₁₁), 72.8 (C₂), 72.7 (C₂), 71.8 (C₁₂), 71.6 (C₁₂), 70.1 (C₉), 59.0 (C₁), 58.9 (C₁), 52.0 (C₅), 51.9 (C₅), 50.7 (C₁₃), 49.0 (C₇), 48.9 (C₇), 48.6 (C₇), 48.5 (C₇), 44.1 (C₃), 43.5 (C₁₄), 43.4 (C₁₄), 30.2 (C₆), 30.1 (C₆), 29.6 (C₆), 13.7 (C₁₀).

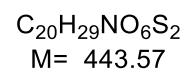
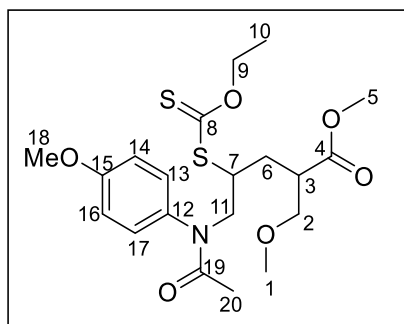
IR (neat) ν (cm⁻¹) = 2986, 2924, 1733, 1437, 1385, 1208, 1107, 1042, 836

HRMS (EI⁺) [M+H]⁺, Calcd for [C₁₄H₂₄O₅S₂+H]⁺: 353.1087; Found 353.1087

methyl 4-((ethoxycarbonothioyl)thio)-2-(methoxymethyl)-5-(N-(4-methoxyphenyl) acetamido) pentanoate (IV-103q)



Following general procedure B, xanthate **IV-102** (100.0 mg, 0.42 mmol, 1.0 equiv) and N-allyl-N-(4-methoxyphenyl) acetamide (129.3 mg, 0.63 mmol, 1.5 equiv) in EtOAc (0.42 mL) was refluxed under N₂ then dilauroyl peroxide (DLP) was added portionwise (5 mol %) every hour, the reaction required 15 mol % DLP to consume xanthate completely. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 6/1 to 3/1) afforded the desired product **IV-103q** as a light-yellow liquid (119.0 mg, 0.27 mmol, 64% yield).



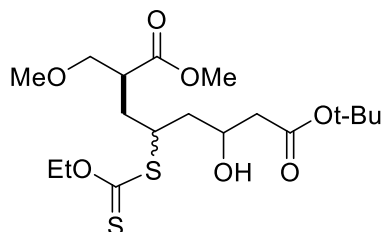
¹H NMR (400 MHz, CDCl₃) δ (ppm) = 7.17 (d, *J* = 8.7 Hz, 2H, H₁₃, H₁₇), 6.99 – 6.88 (m, 2H, H₁₄, H₁₆), 4.49 (qd, *J* = 7.1, 1.5 Hz, 2H, H₉), 4.31 (dd, *J* = 13.5, 9.3 Hz, 1H, H₇), 3.83 (s, 3H, H₁₈), 3.68 – 3.60 (m, 1H, H_{11a}), 3.54 – 3.40 (m, 3H, H_{11b}, H₂), 3.27 (s, 3H, H₅), 3.11 (dtd, *J* = 9.6, 6.2, 3.3 Hz, 1H, H₃), 2.32 (ddd, *J* = 14.6, 10.3, 4.0 Hz, 1H, H_{6a}), 2.17 (d, *J* = 0.3 Hz, 3H, H₁), 1.83 (s, 3H, H₂₀), 1.53 (ddd, *J* = 14.7, 11.3, 3.3 Hz, 1H, H_{6b}), 1.26 (t, *J* = 7.1 Hz, 3H, H₁₀).

¹³C NMR (101 MHz, CDCl₃) δ (ppm) = 213.0 (C₈), 210.4 (C₁₅), 171.5 (C₄), 159.2 (C₁₉), 135.0 (C₁₂), 129.5 (C₁₃, C₁₇), 114.8 (C₁₄, C₁₆), 74.3 (C₂), 70.0 (C₉), 59.0 (C₁), 55.5 (C₁₈), 51.8 (C₅), 50.0 (C₁₁), 47.6 (C₃), 31.2 (C₇), 29.5 (C₆), 22.7 (C₂₀), 13.5 (C₁₀).

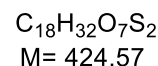
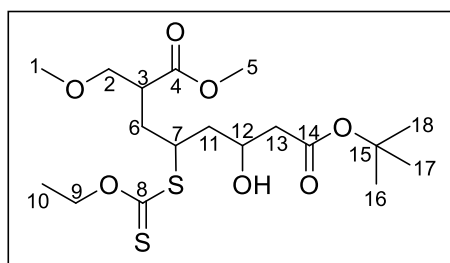
IR (neat) ν (cm⁻¹) = 2930, 1736, 1713, 1659, 1509, 1244, 1210, 1108, 1039, 838, 734

HRMS (EI⁺) Calcd for C₂₀H₂₉NO₆S₂⁺: 178.0486; Not Found

8-(tert-butyl) 1-methyl 4-((ethoxycarbonothioyl)thio)-6-hydroxy-2-(methoxymethyl)octanedioate (IV-103r)



Following general procedure B, xanthate **IV-102** (100.0 mg, 0.42 mmol, 1.0 equiv) and tert-butyl 3-hydroxyhex-5-enoate (117.2 mg, 0.63 mmol, 1.5 equiv) in EtOAc (0.42 mL) was refluxed under N₂ then dilauroyl peroxide (DLP) was added portionwise (5 mol %) every hour, the reaction required 10 mol % DLP to consume xanthate completely. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 8/1 to 4/1) afforded the desired product **IV-103r** as a light-yellow liquid (138.1 mg, 0.32 mmol, 78% yield).



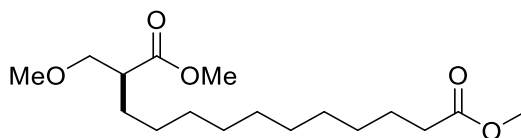
¹H NMR (400 MHz, CDCl₃) δ (ppm) = 4.71 – 4.57 (m, 2H, H₉), 4.23 – 4.10 (m, 1H, OH), 4.06 – 3.87 (m, 1H, H₁₂), 3.75 – 3.68 (m, 3H, H₅), 3.63 – 3.50 (m, 2H, H₇, H_{2a}), 3.35 – 3.30 (m, 3H, H₁), 3.22 (ddd, *J* = 23.0, 12.8, 4.1 Hz, 1H, H_{2b}), 2.99 – 2.80 (m, 1H, H₃), 2.49 – 2.33 (m, 2H, H₁₃), 2.24 – 1.62 (m, 4H, H₆, H₁₁), 1.48 – 1.39 (m, 12H, H₁₀, H₁₆, H₁₇, H₁₈).

¹³C NMR (101 MHz, CDCl₃) δ (ppm) = 214.6 (C₈), 174.3 (C₄), 174.1 (C₄), 171.8 (C₁₄), 81.3 (C₁₅), 73.5 (C₂), 72.7 (C₂), 70.3 (C₉), 70.2 (C₉), 65.7 (C₁₂), 65.5 (C₁₂), 59.1 (C₁), 59.0 (C₁), 52.0 (C₅), 46.5 (C₃), 43.6 (C₇), 43.5 (C₇), 42.3 (C₁₃), 41.5 (C₁₁), 33.9 (C₆), 28.1 (C₁₆, C₁₇, C₁₈), 13.8 (C₁₀).

IR (neat) ν (cm⁻¹) = 3507, 2979, 2929, 1726, 1436, 1367, 1210, 1147, 1109, 1042, 842, 736

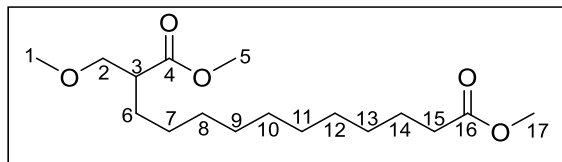
HRMS (EI⁺) [M+H]⁺, Calcd for [C₁₈H₃₂O₇S₂+H]⁺: 425.1662; Found 425.1662

dimethyl 2-(methoxymethyl) tridecanedioate (IV-104)



Following general procedure A, xanthate **IV-102** (357.5 mg, 1.5 mmol, 1.0 equiv), methyl undec-10-enoate (446.2 mg, 2.25 mmol, 1.5 equiv) and dilauroyl peroxide (5 mol %) were mixed in a tube with neat condition, air in the tube was excluded by nitrogen, then sealed and heated at 85°C. Then additional dilauroyl peroxide (DLP) was added portionwise (5 mol %) every hour, the reaction required 5 mol % DLP to consume xanthate completely. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 12/1 to 8/1) afforded the radical adduct **IV-103s** as a light-yellow liquid (438.1 mg, 1.0 mmol, 66% yield).

Following general procedure C, a solution of xanthate **IV-103s** (170.0 mg, 0.39 mmol, 1.0 equiv), H₃PO₂ (50% in H₂O, 138.8 mg, 1.01 mmol, 2.6 equiv), triethylamine (110.5 mg, 1.09 mmol, 2.8 equiv) in dioxane (0.1 M) was refluxed in the presence of AIBN. The reaction required 10 mol % AIBN to reduce xanthate completely. The reaction mixture was cooled down to room temperature, and then partitioned between H₂O and EtOAc. The combined organic layer was washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 8/1 to 5/1) afforded the desired product **IV-104** as a colorless oil (114.0 mg, 0.36 mmol, 92% yield).



C₁₇H₃₂O₅
M= 316.44

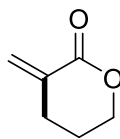
¹H NMR (400 MHz, CDCl₃) δ (ppm) = 3.60 (s, 3H, H₅), 3.56 (s, 3H, H₁₇), 3.46 (dd, *J* = 9.1, 8.4 Hz, 1H, H_{2a}), 3.33 (dd, *J* = 9.1, 5.3 Hz, 1H, H_{2b}), 3.22 (s, 3H, H₁), 2.57 (tt, *J* = 8.6, 5.4 Hz, 1H, H₃), 2.20 (t, *J* = 7.6 Hz, 2H, H₁₅), 1.50 (q, *J* = 7.4 Hz, 3H), 1.41 – 1.33 (m, 1H), 1.22 – 1.13 (m, 14H).

¹³C NMR (101 MHz, CDCl₃) δ (ppm) = 175.0 (C₁₆), 174.1 (C₄), 73.5 (C₂), 58.8 (C₁), 51.5 (C₅), 51.3 (C₁₇), 45.9 (C₃), 34.0 (C₁₅), 29.4, 29.3, 29.1, 29.0, 28.8, 27.1, 24.8.

IR (neat) ν (cm⁻¹) = 2924, 2854, 1736, 1435, 1363, 1194, 1168, 1108

HRMS (EI⁺) Calcd for C₁₇H₃₂O₅⁺: 285.2066; Not Found

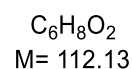
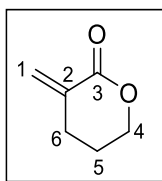
3-methylenetetrahydro-2H-pyran-2-one (IV-106a)



Following general procedure A, xanthate **IV-102** (238.3 mg, 1.0 mmol, 1.0 equiv), allyl acetate (200.2 mg, 2.0 mmol, 2.0 equiv) and dilauroyl peroxide (5 mol %) were mixed in a tube with neat condition, air in the tube was excluded by nitrogen, then sealed and heated at 85°C. Then additional dilauroyl peroxide (DLP) was added portionwise (5 mol %) every hour, the reaction required 5 mol % DLP to consume xanthate completely. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 12/1 to 8/1) afforded the radical adduct **IV-103b** as a light-yellow liquid (246.1 mg, 0.72 mmol, 72% yield).

Following general procedure C, a solution of xanthate **IV-103b** (245.1 mg, 0.72 mmol, 1.0 equiv), H₃PO₂ (50% in H₂O, 252 mg, 1.9 mmol, 2.6 equiv), triethylamine (200.4 mg, 1.98 mmol, 2.8 equiv) in dioxane (0.1 M) was refluxed in the presence of AIBN. The reaction required 10 mol % AIBN to reduce xanthate completely. The reaction mixture was cooled down to room temperature, and then partitioned between H₂O and EtOAc. The combined organic layer was washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 8/1 to 5/1) afforded the intermediate **IV-105a** as a colorless oil (136.0 mg, 0.62 mmol, 86% yield).

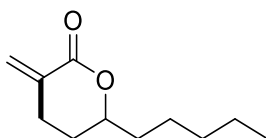
To a solution of reduced intermediate **IV-105a** (136.0 mg, 0.62 mmol, 1.0 equiv) in toluene (6.2 ml), p-toluenesulfonic acid (PTSA; 0.62 mmol) was added and the reaction mixture was heated to 80°C and reacted for 6 hours. Then the reaction solution cooled to room temperature and washed with saturated sodium carbonate, followed by extracted with ethyl acetate. Combined the organic layers and concentrated in vacuum. The residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 8/1 to 5/1) to afford the desired product **IV-106a** as a colorless oil (21.0 mg, 0.19 mmol, 30% yield).



¹H NMR (400 MHz, CDCl ₃)	δ (ppm) = 6.45 – 6.41 (m, 1H, H _{1a}), 5.56 (td, <i>J</i> = 2.0, 1.5 Hz, 1H, H _{1b}), 4.41 – 4.34 (m, 2H, H ₄), 2.70 – 2.62 (m, 2H, H ₆), 2.00 – 1.91 (m, 2H, H ₅).
¹³C NMR (101 MHz, CDCl ₃)	δ (ppm) = 165.5 (C ₃), 134.1 (C ₂), 128.4 (C ₁), 69.7 (C ₄), 28.2 (C ₆), 23.3 (C ₅).
IR (neat)	ν (cm ⁻¹) = 2944, 2160, 1719, 1628, 1443, 1400, 1359, 1296, 1176, 1151, 1072, 1020, 949

HRMS (EI ⁺)

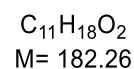
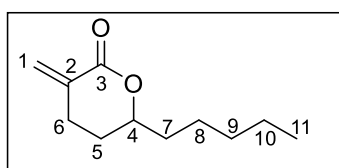
[M+H] ⁺, Calcd for [C₆H₈O₂+H] ⁺: 113.0597; Found 113.0592

3-methylene-6-pentyltetrahydro-2H-pyran-2-one (IV-106b)

Following general procedure A, xanthate **IV-102** (238.3 mg, 1.0 mmol, 1.0 equiv), allyl acetate (255.5 mg, 1.5 mmol, 1.5 equiv) and dilauroyl peroxide (5 mol %) were mixed in a tube with neat condition, air in the tube was excluded by nitrogen, then sealed and heated at 85°C. Then additional dilauroyl peroxide (DLP) was added portionwise (5 mol %) every hour, the reaction required 5 mol % DLP to consume xanthate completely. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 11/1 to 8/1) afforded the radical adduct **IV-103t** as a light-yellow liquid (357.0 mg, 0.87 mmol, 87% yield).

Following general procedure C, a solution of xanthate **IV-103t** (355.1 mg, 0.87 mmol, 1.0 equiv), H₃PO₂ (50% in H₂O, 303.9 mg, 2.3 mmol, 2.6 equiv), triethylamine (241.8 mg, 2.39 mmol, 2.8 equiv) in dioxane (0.1 M) was refluxed in the presence of AIBN. The reaction required 10 mol % AIBN to reduce xanthate completely. The reaction mixture was cooled down to room temperature, and then partitioned between H₂O and EtOAc. The combined organic layer was washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 9/1 to 5/1) afforded the intermediate **IV-105b** as a colorless oil (212.0 mg, 0.73 mmol, 84% yield).

To a solution of intermediate **IV-105b** (210.0 mg, 0.73 mmol, 1.0 equiv) in toluene (7.3 ml), p-toluenesulfonic acid (PTSA; 0.73 mmol) was added and the reaction mixture was heated to 80°C and reacted for 10 hours. Then the reaction solution cooled to room temperature and washed with saturated sodium carbonate, followed by extracted with ethyl acetate. Combined the organic layers and concentrated in vacuum. The residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 9/1 to 5/1) to afford the desired product **IV-106b** as a colorless oil (50.0 mg, 0.27 mmol, 37% yield).



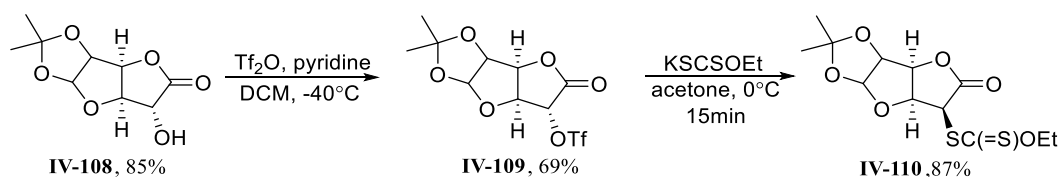
¹H NMR δ (ppm) = 6.42 (ddt, $J = 2.8, 1.4, 0.7$ Hz, 1H), 5.55 (dt, $J = 2.4, 1.5$ Hz, 1H), 4.32 (dtt, $J = 12.7, 5.2, 2.6$ Hz, 1H), 2.76 – 2.49 (m, 2H), 2.00 – 1.90 (m, 1H), 1.78 – 1.57 (m, 3H), 1.44 – 1.23 (m, 6H), 0.91 – 0.86 (m, 3H).

¹³C NMR δ (ppm) = 166.0 (C₃), 133.9 (C₂), 127.8 (C₁), 80.8 (C₄), 35.6 (C₆), 31.6 (C₅), 28.2, 27.2, 24.6, 22.5, 14.0 (C₁₁).

IR (neat) ν (cm⁻¹) = 2936, 2861, 1720, 1627, 1449, 1296, 1185, 1132, 943, 806

HRMS (EI⁺) [M+H]⁺, Calcd for [C₁₁H₁₈O₂+H]⁺: 183.1380; Found 183.1376

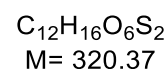
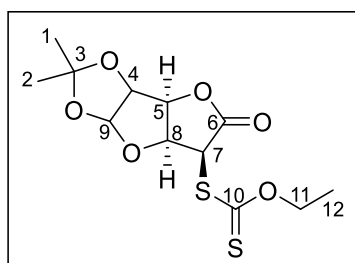
1,2-O-isopropylidene-5-O-ethyl carbonodithionyl- α -D-glucuronolactone (IV-110)



Conc. H_2SO_4 (16 mL) was dropped to a stirred suspension of α -D-glucuronolactone (20.0 g, 110 mmol, 1.0 equiv) in 500 mL acetone at room temperature in 45 min. Stirred for 4 h, the reaction solution was neutralized with solid sodium bicarbonate, filtered and concentrated under reduced pressure. The solid residue was dissolved in EtOAc and washed with brine, then dried over anhydrous Na_2SO_4 . The solution was filtered and concentrated in vacuo, intermediate **IV-108** crystallized from EtOAc, then recrystallized from hot EtOAc as a white solid (20.2 g, 93.4 mmol, 85%).

Under Ar, at -40°C , to a solution of **IV-108** (15.3 g, 71.2 mmol, 1.0 equiv), pyridine (15.5 mL, 199.4 mmol, 2.8 equiv) in 150 mL dichloromethane, trifluoromethane sulphonic anhydride (13.2 mL, 78.4 mmol, 1.1 equiv) was dropped in 45 min, then stirred at this temperature for a further 3 h. Then additional dichloromethane (300 mL) was added and the reaction mixture was washed with 5% aqueous HCl (100 mL \times 3), water (100 mL \times 3) and dried over anhydrous MgSO_4 . Filtered and then crude intermediate **IV-109** crystallized from dichloromethane after concentration in vacuo. Then **IV-109** recrystallized from hot EtOH as a white solid (17.0 g, 48.8 mmol, 69%).

Potassium O-ethylxanthate salt (6.7 g, 41.6 mmol, 1.05 equiv) was added portionwise over 15 min to a 0°C solution of intermediate **IV-109** (13.8 g, 39.6 mmol, 1.0 equiv) in 140 mL acetone. After 10 min, ice water was added to the suspension and the resulted aqueous solution was extracted twice with dichloromethane. The combined organic layer was washed by brine and dried with anhydrous MgSO_4 . Filtered and then crude product crystallized from dichloromethane after concentration in vacuo. Then recrystallized from hot EtOAc afford desired product **IV-110** as an off white solid (10.9 g, 34 mmol, 87%).



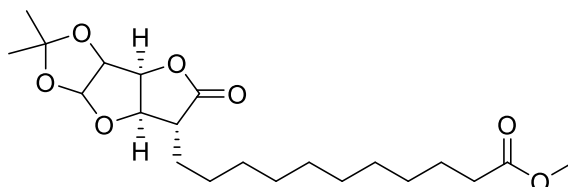
^1H NMR

(400 MHz, CDCl_3)

δ (ppm) = δ 5.95 (dd, $J = 21.0, 3.7$ Hz, 1H, H_9), 5.15 – 5.07 (m, 2H, H_7, H_8), 4.96 – 4.88 (m, 1H, H_5), 4.85 (dt, $J = 3.7, 0.5$ Hz, 1H, H_4),

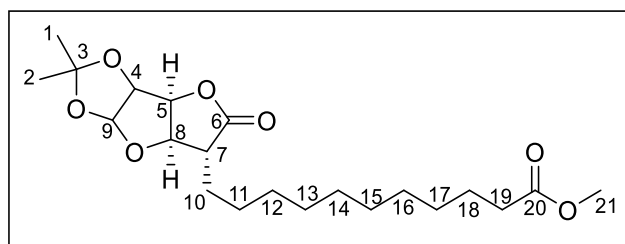
	4.67 (q, J = 7.1 Hz, 2H, H ₁₁), 1.51 – 1.46 (m, 3H H ₁), 1.42 (q, J = 7.2 Hz, 3H, H ₁₂), 1.32 (t, J = 1.7 Hz, 3H, H ₂).
¹³C NMR (101 MHz, CDCl ₃)	δ (ppm) = 212.1 (C ₁₀), 171.1 (C ₆), 113.4 (C ₃), 106.4 (C ₉), 84.8 (C ₄), 83.8 (C ₅), 83.6 (C ₅), 82.7 (C ₈), 82.1 (C ₈), 71.8 (C ₁₁), 71.6 (C ₁₁), 53.6 (C ₇), 27.1 (C ₁), 26.6 (C ₂), 13.8 (C ₁₂), 13.6 (C ₁₂).
IR (neat)	ν (cm ⁻¹) = 2985, 2942, 2916, 1781, 1376, 1228, 1146, 1042, 999, 918
HRMS (EI ⁺)	Calcd for C ₁₂ H ₁₆ O ₆ S ₂ ⁺ : 320.0388; Found 320.0388
M. p.:	84-85°C

methyl 11-((3aR,3bS,6aR)-2,2-dimethyl-5-oxohexahydrofuro[2',3':4,5]furo[2,3-d][1,3]dioxol-6-yl)undecanoate (**IV-112a**)



Following general procedure A, xanthate **IV-110** (160.2 mg, 0.5 mmol, 1.0 equiv), methyl undec-10-enoate (149.0 mg, 0.75 mmol, 1.5 equiv) and dilauroyl peroxide (5 mol %) were mixed in a tube with neat condition, air in the tube was excluded by nitrogen, then sealed and heated at 85°C. Then additional dilauroyl peroxide (DLP) was added portionwise (5 mol %) every hour, the reaction required 10mol % DLP to consume xanthate completely. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 8/1 to 4/1) afforded radical adduct **IV-111a** as a colorless liquid (245.0 mg, 0.47 mmol, 94% yield).

Following general procedure D, a solution of xanthate **IV-111a** (245.0 mg, 0.47 mmol, 1.0 equiv) and tris(trimethylsilyl)silane (TTMSS, 129.2 mg, 0.52 mmol, 1.1 equiv) in toluene/cyclohexane (1:1, 0.25 M) was refluxed under nitrogen, then AIBN was added portionwise (10 mol %) every hour, the reaction required 20mol % AIBN to consume xanthate completely. The reaction mixture was then cooled down to room temperature and volatiles were removed under a nitrogen stream. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 5/1 to 2/1) afforded desired product **IV-112a** as a white solid (152.0 mg, 0.38 mmol, 81% yield).



C₂₁H₃₄O₇
M= 398.50

¹H NMR (400 MHz, CDCl₃) δ (ppm) = 5.93 (d, *J* = 3.8 Hz, 1H, H₉), 4.80 (ddq, *J* = 5.4, 3.4, 0.5 Hz, 2H, H₅, H₈), 4.68 (d, *J* = 3.3 Hz, 1H, H₄), 3.65 (s, 3H, H₂₁), 2.73 – 2.67 (m, 1H, H₇), 2.29 (t, *J* = 7.5 Hz, 2H, H₁₉), 1.67 – 1.42 (m, 9H), 1.34 – 1.23 (m, 15H).

¹³C NMR (101 MHz, CDCl₃) δ (ppm) = 177.1 (C₆), 174.3 (C₂₀), 112.6 (C₃), 106.0 (C₉), 84.3 (C₄), 82.9 (C₈), 82.4 (C₅), 51.4 (C₂₁), 47.4 (C₇), 34.1 (C₁₉), 29.4, 29.3, 29.2, 29.1, 28.2, 27.1, 27.0, 26.4, 24.9.

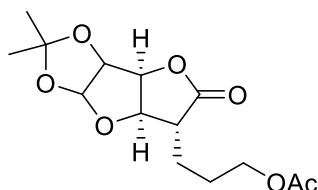
IR (neat) ν (cm⁻¹) = 2922, 2852, 1788, 1723, 1472, 1376, 1202, 1164, 1075,

1055, 1030, 970, 830, 719

HRMS (EI ⁺) [M-CH₃]⁺, Calcd for C₂₀H₃₁O₇⁺: 383.2070; Found 383.2066

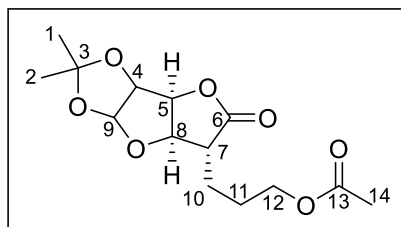
M.p.: 84°C

**3-((3aR,3bS,6aR)-2,2-dimethyl-5-oxohexahydrofuro [2',3':4,5] furo[2,3-d] [1,3] dioxol-6-yl) propyl acetate
(IV-112b)**



Following general procedure A, xanthate **IV-110** (160.2 mg, 0.5 mmol, 1.0 equiv), allyl acetate (75.0 mg, 0.75 mmol, 1.5 equiv) and dilauroyl peroxide (5 mol %) were mixed in a tube with neat condition, air in the tube was excluded by nitrogen, then sealed and heated at 85°C. Then additional dilauroyl peroxide (DLP) was added portionwise (5 mol %) every hour, the reaction required 10mol % DLP to consume xanthate completely. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 7/1 to 4/1) afforded radical adduct **IV-111b** as a colorless liquid (189.0 mg, 0.45 mmol, 90% yield).

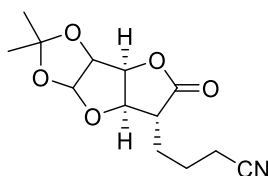
Following general procedure D, a solution of xanthate **IV-111b** (153.0 mg, 0.36 mmol, 1.0 equiv) and tris(trimethylsilyl)silane (TTMSS, 99.5 mg, 0.4 mmol, 1.1 equiv) in toluene/cyclohexane (1:1, 0.25 M) was refluxed under nitrogen, then AIBN was added portionwise (10 mol %) every hour, the reaction required 30mol % AIBN to consume xanthate completely. The reaction mixture was then cooled down to room temperature and volatiles were removed under a nitrogen stream. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 7/1 to 4/1) afforded desired product **IV-112b** as a colorless liquid (95.0 mg, 0.31 mmol, 87% yield).



C₁₄H₂₀O₇
M= 300.31

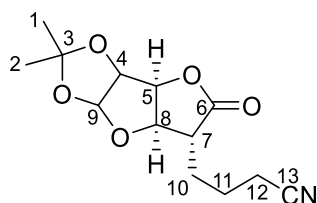
¹H NMR (400 MHz, CDCl ₃)	δ (ppm) = 5.97 – 5.93 (m, 1H, H ₇), 4.82 (dt, <i>J</i> = 3.4, 0.7 Hz, 2H, H ₅ , H ₈), 4.69 (dd, <i>J</i> = 3.3, 0.6 Hz, 1H, H ₄), 4.13 – 4.05 (m, 2H, H ₁₂), 2.73 (t, <i>J</i> = 7.8 Hz, 1H, H ₇), 2.05 (s, 3H, H ₁₄), 1.85 – 1.62 (m, 4H, H ₁₀ , H ₁₁), 1.50 (d, <i>J</i> = 0.7 Hz, 3H, H ₁), 1.34 (q, <i>J</i> = 0.7 Hz, 3H, H ₂).
¹³C NMR (101 MHz, CDCl ₃)	δ (ppm) = 176.5 (C ₆), 171.0 (C ₁₃), 112.7 (C ₃), 106.0 (C ₉), 84.3 (C ₈), 82.8 (C ₄), 82.3 (C ₅), 63.4 (C ₁₂), 46.9 (C ₇), 27.0 (C ₁₁), 26.4 (C ₁), 26.3 (C ₂), 24.9 (C ₁₀), 20.9 (C ₁₄).
IR (neat)	<i>ν</i> (cm ⁻¹) = 2961, 2871, 1781, 1732, 1456, 1374, 1235, 1158, 1019, 909, 822, 730
HRMS (EI ⁺)	[M-CH ₃] ⁺ , Calcd for C ₁₃ H ₁₇ O ₇ ⁺ : 285.0974; Found 285.0965

4-((3aR,3bS,6aR)-2,2-dimethyl-5-oxohexahydrofuro[2',3':4,5]furo[2,3-d][1,3]dioxol-6-yl) butanenitrile
(IV-112c)



Following general procedure A, xanthate **IV-110** (160.2 mg, 0.5 mmol, 1.0 equiv), allyl cyanide (50.3 mg, 0.75 mmol, 1.5 equiv) and dilauroyl peroxide (5 mol %) were mixed in a tube with neat condition, air in the tube was excluded by nitrogen, then sealed and heated at 85°C. Then additional dilauroyl peroxide (DLP) was added portionwise (5 mol %) every hour, the reaction required 15 mol % DLP to consume xanthate completely. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 8/1 to 4/1) afforded radical adduct **IV-111c** as a colorless liquid (158.0 mg, 0.41 mmol, 81% yield).

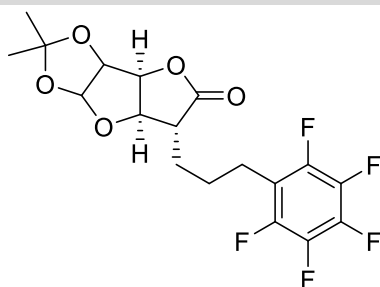
Following general procedure D, a solution of xanthate **IV-111c** (148 mg, 0.38 mmol, 1.0 equiv) and tris(trimethylsilyl)silane (TTMSS, 104.5 mg, 0.42 mmol, 1.1 equiv) in toluene/cyclohexane (1:1, 0.25 M) was refluxed under nitrogen, then AIBN was added portionwise (10 mol %) every hour, the reaction required 20 mol % AIBN to consume xanthate completely. The reaction mixture was then cooled down to room temperature and volatiles were removed under a nitrogen stream. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 5/1 to 2/1) afforded desired product **IV-112c** as a white solid (90.0 mg, 0.33 mmol, 88% yield).



C₁₃H₁₇NO₅
M= 267.28

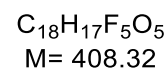
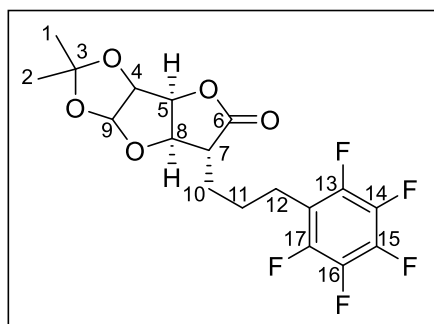
¹H NMR (400 MHz, CDCl ₃)	δ (ppm) = 5.94 (d, <i>J</i> = 3.8 Hz, 1H, H ₉), 4.83 (dddd, <i>J</i> = 4.9, 3.9, 1.2, 0.6 Hz, 2H, H ₅ , H ₈), 4.71 – 4.66 (m, 1H, H ₄), 2.71 (ddd, <i>J</i> = 8.4, 7.3, 0.9 Hz, 1H, H ₇), 2.51 – 2.36 (m, 2H, H ₁₂), 1.98 – 1.67 (m, 4H, H ₁₀ , H ₁₁), 1.50 (d, <i>J</i> = 0.7 Hz, 3H, H ₁), 1.33 (q, <i>J</i> = 0.7 Hz, 3H, H ₂).
¹³C NMR (101 MHz, CDCl ₃)	δ (ppm) = 176.0 (C ₆), 118.7 (C ₁₃), 112.8 (C ₃), 106.0 (C ₉), 84.3 (C ₈), 82.8 (C ₄), 82.2 (C ₅), 46.5 (C ₇), 27.0 (C ₁), 26.9 (C ₂), 26.4 (C ₁₀), 22.9 (C ₁₁), 16.9 (C ₁₂).
IR (neat)	<i>ν</i> (cm ⁻¹) = 2981, 2937, 1766, 1462, 1375, 1212, 1147, 1077, 1019, 899, 838, 734
HRMS (EI ⁺)	[M+H] ⁺ , Calcd for [C ₁₃ H ₁₇ NO ₅ +H] ⁺ : 268.1179; Found 268.1186
M.p.:	103°C

(3aR,3bS,6aR)-2,2-dimethyl-6-(3-(perfluorophenyl)propyl)tetrahydrofuro[2',3':4,5]furo[2,3-d][1,3]dioxol-5(3bH)-one (IV-112d)



Following general procedure A, xanthate **IV-110** (160.2 mg, 0.5 mmol, 1.0 equiv), allylpentafluorobenzene (156.1 mg, 0.75 mmol, 1.5 equiv) and dilauroyl peroxide (5 mol %) were mixed in a tube with neat condition, air in the tube was excluded by nitrogen, then sealed and heated at 85°C. Then additional dilauroyl peroxide (DLP) was added portionwise (5 mol %) every hour, the reaction required 10mol % DLP to consume xanthate completely. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 10/1 to 6/1) afforded radical adduct **IV-111d** as a colorless liquid (247.0 mg, 0.47 mmol, 93% yield).

Following general procedure D, a solution of xanthate **IV-111d** (240 mg, 0.45 mmol, 1.0 equiv) and tris(trimethylsilyl)silane (TTMSS, 124.2 mg, 0.50 mmol, 1.1 equiv) in toluene/cyclohexane (1:1, 0.25 M) was refluxed under nitrogen, then AIBN was added portionwise (10 mol %) every hour, the reaction required 30 mol % AIBN to consume xanthate completely. The reaction mixture was then cooled down to room temperature and volatiles were removed under a nitrogen stream. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 5/1 to 2/1) afforded desired product **IV-112d** as a white solid (160.0 mg, 0.39 mmol, 86% yield).



1H NMR δ (ppm) = 5.94 (d, J = 3.7 Hz, 1H, H₉), 4.84 – 4.78 (m, 2H, H₅, H₈), 4.70 – 4.65 (m, 1H, H₄), 2.79 – 2.68 (m, 3H, H₇, H₁₂), 1.85 – 1.74 (m, 2H, H₁₀), 1.64 (dddd, J = 16.4, 14.1, 8.9, 6.1 Hz, 2H, H₁₁), 1.51 (d, J = 0.8 Hz, 3H, H₁), 1.34 (d, J = 0.7 Hz, 3H, H₂).

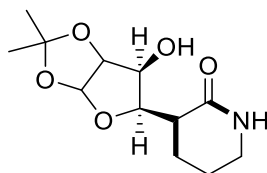
^{13}C NMR δ (ppm) = 176.4 (C₆), 112.7 (C₃), 106.0 (C₉), 84.3 (C₄), 82.8 (C₈), 82.3 (C₅), 47.1 (C₇), 27.5 (C₁), 27.0 (C₂), 26.7 (C₁₂), 26.4 (C₁₁), 21.9 (C₁₀).

IR (neat) ν (cm⁻¹) = 2988, 2953, 1778, 1656, 1521, 1498, 1379, 1213, 1169, 1077, 1029, 953, 902, 830

HRMS (EI ⁺) Calcd for C₁₈H₁₇F₅O₅⁺: 408.0996; Not Found

M.p.: 109°C

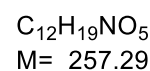
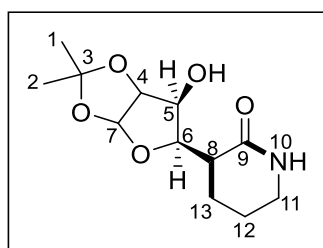
3-((5R,6S,6aR)-6-hydroxy-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)piperidin-2-one (**IV-113**)



Following general procedure A, xanthate **IV-110** (320.4 mg, 1.0 mmol, 1.0 equiv), allylphthalimide (280.7 mg, 1.5 mmol, 1.5 equiv) and dilauroyl peroxide (5 mol %) were mixed in a tube with neat condition, air in the tube was excluded by nitrogen, then sealed and heated at 85°C. Then additional dilauroyl peroxide (DLP) was added portionwise (5 mol %) every hour, the reaction required 10 mol % DLP to consume xanthate completely. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 10/1 to 6/1) afforded radical adduct **IV-111e** as a colorless liquid (447.0 mg, 0.88 mmol, 88% yield).

Following general procedure D, a solution of xanthate **IV-111e** (447.0 mg, 0.88 mmol, 1.0 equiv) and tris(trimethylsilyl)silane (TTMSS, 241.0 mg, 0.97 mmol, 1.1 equiv) in toluene/cyclohexane (1:1, 0.25 M) was refluxed under nitrogen, then AIBN was added portionwise (10 mol %) every hour, the reaction required 20 mol % AIBN to consume xanthate completely. The reaction mixture was then cooled down to room temperature and volatiles were removed under a nitrogen stream. Flash chromatography on silica gel (petroleum ether/ethyl acetate = 5/1 to 1/1) afforded desired product **IV-112e** as a white solid (298.0 mg, 0.77 mmol, 87% yield).

To a solution of compound **IV-112e** (100.0 mg, 0.26 mmol, 1.0 equiv) in 2.6 mL methanol, hydrazine monohydrate (21.5 mg, 0.26 mmol, 1.0 equiv) was added, the reaction mixture was refluxed for 3 hours to consume starting material completely. Then cooled down to room temperature and filtered, the solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 1/1 to 1/4) afforded desired product **IV-113** as a white solid (55.0 mg, 0.21 mmol, 83% yield)



¹H NMR

(400 MHz, CDCl₃)

δ (ppm) = 6.52 (s, 1H, H₁₀), 5.92 (d, J = 3.7 Hz, 1H, H₇), 4.76 (s, 1H, H₅), 4.61 (d, J = 3.7 Hz, 1H, H₄), 4.26 – 4.10 (m, 2H, H₆, OH), 3.32 (td, J = 6.5, 6.0, 2.3 Hz, 2H, H₁₁), 2.84 (dt, J = 10.7, 5.7 Hz, 1H, H₈), 2.02 (tt, J = 9.4, 4.8 Hz, 2H, H₁₂), 1.92 – 1.82 (m, 1H, H_{13a}), 1.76 (dd, J = 11.5, 5.6 Hz, 1H, H_{13b}), 1.48 (s, 3H, H₁), 1.31 (s, 3H, H₂).

¹³C NMR (101 MHz, CDCl ₃)	δ (ppm) = 172.6 (C ₉), 111.2 (C ₃), 104.6 (C ₇), 85.1 (C ₄), 82.2 (C ₆), 75.9 (C ₅), 42.6 (C ₈), 40.9 (C ₁₁), 26.9 (C ₁), 26.1 (C ₂), 24.2 (C ₁₂), 19.5 (C ₁₂).
IR (neat)	ν (cm ⁻¹) = 3236, 2942, 2860, 1638, 1495, 1416, 1373, 1294, 1164, 1065, 1044, 971, 819
HRMS (EI ⁺)	[M-CH ₃] ⁺ , Calcd for C ₁₁ H ₁₆ NO ₅ ⁺ : 242.1028; Found 242.1020
M.p.:	109°C

Titre : Applications des réactions radicalaires pour la synthèse des composés carbonylés et des β -acides aminés

Mots clés : réactions radicalaires, β -acides aminés, cétones, esters

Résumé : Dans cette thèse, nous nous concentrons sur l'application de la chimie des radicaux issus des xanthates pour la synthèse de cétones, d'esters et de dérivés d'acides aminés β^2 . Cette recherche surmonte de nombreux inconvénients associés à l'alkylation des cétones et des esters lors de l'utilisation de méthodes basées sur l'énolate, et complète la dialkylation des cétones insaturées. Le processus de transfert de xanthate offre également une voie convergente vers des acides aminés potentiellement bioactifs.

Nous décrivons une voie convergente vers les dérivés d'acides aminés β^2 en adoptant le processus de transfert du xanthate. Le xanthate peut porter soit un ester, soit un groupe acide carboxylique libre. Lorsque le xanthate portait un groupe acide libre, l'addition sur des

hétérocycles était accompagnée d'une décarboxylation spontanée pour donner des hétéroaryléthylamines N-protégées. Dans certains cas, des produits vinyliques inattendus se sont formés et un mécanisme plausible est discuté.

En remplaçant les énolates et les équivalents énolates par des radicaux α -cétonyle, de nombreux inconvénients de l'alkylation des cétones peuvent être minimisés. Ensuite, nous nous concentrons sur la dialkylation des cétones α , β -insaturées. Pour généraliser l'alkylation des composés carbonylés, l' α -alkylation des esters a également été étudiée. Les réactions utilisant des lactones comme substrats ont également été réalisées dans les mêmes conditions et se sont avérées être tout aussi efficaces.

Title : Applications of radical reactions for the synthesis of carbonyl compounds and β -amino acids

Keywords : radical reactions, β -amino acids, ketones, esters

Abstract : In this thesis, we focus on the application of xanthate based radical chemistry for the synthesis of ketones, esters and β^2 -amino acids derivatives. This research overcomes many drawbacks associated with the alkylation of ketones and esters when using enolate based methods, and complements the dialkylation of unsaturated ketones. The xanthate transfer process also offers a convergent route to potential bioactive amino acids.

we describe a convergent route to β^2 -amino acids derivatives by adopting the xanthate transfer process. The xanthate can bear either an ester or a free carboxylic acid group. When the xanthate was bearing a free acid group, the

addition to hetero-rings was accompanied by spontaneous decarboxylation to afford the N-protected heteroarylethylamines. In some cases, unexpected vinyl products were formed and a plausible mechanism is discussed

By replacing enolates and enolate equivalents with α -ketonyl radicals, many disadvantages of alkylation of ketones can be minimized. Then we focus on the dialkylation of α , β -unsaturated ketones. To generalize the alkylation of carbonyl compounds, α -alkylation of esters was also investigated. Reactions using lactones as substrates were also performed with the same conditions and were shown to be equally efficient.