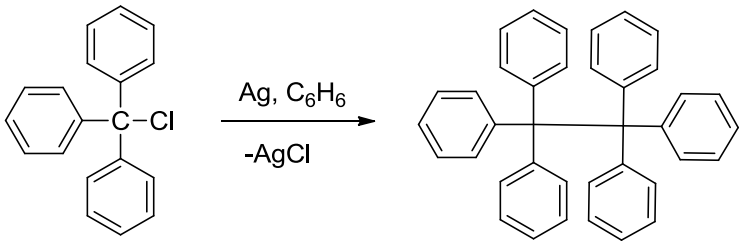
Introduction of Radical Chemistry Associated with Thiocarbonyl Groups

Introduction

Generally, a free radical is an atom, molecule, or ion that bears an unpaired electron. Compared with a bonding or non-bonding electron pair possessing two electrons with opposite spins, +1/2 and -1/2, in one orbital according to Pauli's exclusion principle, a free radical has a single electron, which is alone in one orbital.

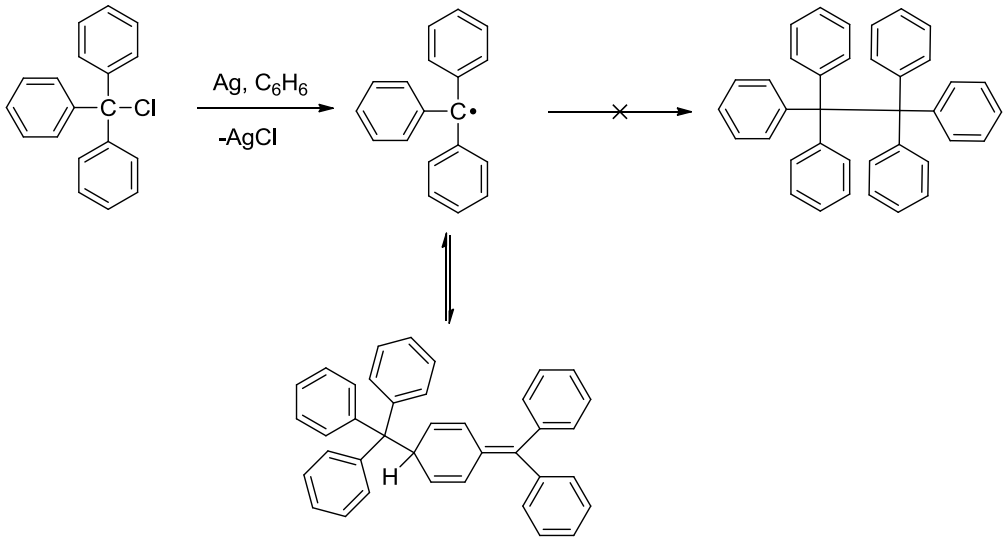
Historically, the first organic free radical triphenylmethyl was found and studied by Gomberg in 1900 at the University of Michigan when he attempted the synthesis of hexaphenylethane.[1] The triphenylmethyl radical is a persistent radical, which could be prepared by homolysis of triphenylmethyl chloride (Scheme 1.1) by silver metal in benzene as the solvent.



Scheme 1.1 Radical reaction of triphenylmethyl chloride

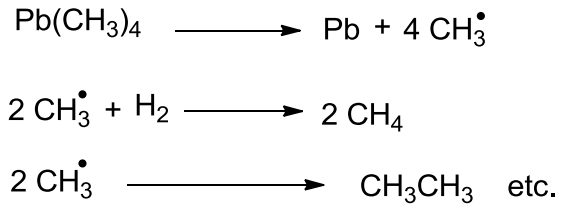
However, hexaphenylethane was in fact never prepared and the correct structure for the dimer was not fully determined until researchers at the Vrije Universiteit Amsterdam published their proton NMR data. Because of steric hindrance the triphenylmethyl radical does not dimerize in the expected manner (Scheme 1.2).[2]

[1] Gomberg. M. *J. Am. Chem. Soc.* **1900**, *22*, 757.
[2] Lankamp, H.; Nauta, W. Th.; MacLean, C. *Tetrahedron. Lett.* **1968**, *9*, 249.



Scheme 1.2

In 1929, the existence of the methyl radical was first demonstrated by Paneth and Hofeditz by thermal decomposition of tetramethyl lead (Scheme 1.3).[3] When the vapours of tetramethyllead mixed with gaseous hydrogen were passed through a hot silica tube at low pressure, the tetramethyl lead was decomposed and a mirror of metallic lead deposited on the internal surface of the tube.



Scheme 1.3 Decomposition of tetramethyl lead

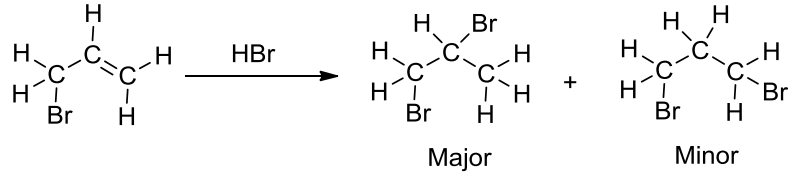
In 1933, a paper entitled "The addition of hydrogen bromide to allyl bromide" was published by Kharasch who for the first time proposed that the anti-Markovnikov addition of HBr to allyl bromide to yield 1,3-dibromopropane was due to the presence of peroxides and proceeded by a radical chain process. This was termed the "peroxide effect".[4] In order to find the direct evidence to support this idea, Kharasch performed

[3] Paneth, F.; Hofeditz, F. *Ber*. **1929**, *62*, 1335.

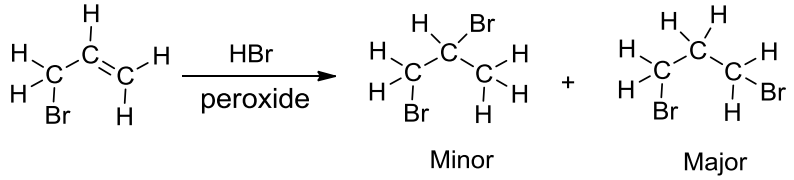
[4] Kharasch, M. S.; Mayo, F. R. *J. Am. Chem. Soc.* **1933**, *55*, 2468.

an adapted version of the thiocyanate test, an analytical test that is often employed to check shelf-stored reagents for their peroxide content. Moreover, by adding the antioxidants to reduce the radicals in the reaction mixture which caused the slow formation of 1,2-dibromopropane, this idea was further supported. Therefore, comparing with ionic Markovnikov process the large bromine atom was more probable to react with the least substituted carbon to produce a stable secondary radical instead of a primary radical, which resulted in the formation of anti Markovnikov product as the major product (Scheme 1.4).

Ionic Markovnikov product



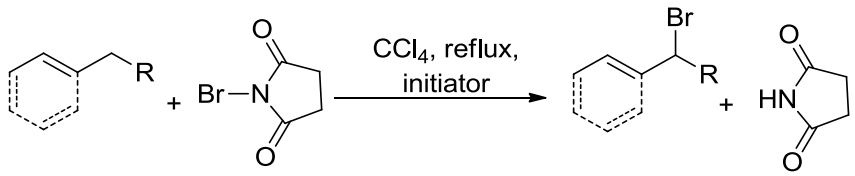
Anti-Markovnikov radical product



Scheme 1.4 Markovnikov and Anti-Markovnikov reactions

The direct introduction of a halogen atom (bromine) in the allylic position of an olefin was first reported by Wohl; however, his papers did not attract much attention. Two decades later, Ziegler extensively studied the allylic bromination of olefins which involved the use of *N*-bromosuccinimide as a more convenient brominating agent (Scheme 1.5).[5] Normally, the best yields were obtained when the reaction was carried out in carbon tetrachloride with *N*-bromosuccinimide.

[5] (a) Wohl, A. *Ber*. **1919**, *52*, 51. (b) Wohl, A.; Jaschinowski, K. *Ber.* **1921**, *54*, 476. (c) Ziegler, K.; Spath, A.; Schaaf, E.; Schumann, W.; Winkelmann, E. *Ann*. **1942**, *551*, 80. (d) Schmid, H.; Karrer, P. *Helv. Chim. Acta* **1946**, *29*, 573.



Scheme 1.5 Wohl-Ziegler reaction

Since the Electron paramagnetic resonance effect was first observed in Kazan State University by Soviet physicist Yevgeny Zavoisky in 1944, scientists could detect radicals directly by this technique which further promoted the development of radical chemistry.[6]

In 1975, the Barton-McComie deoxygenation of alcohols,[7] followed later by the Barton decarboxylation of carboxylic acids[8] and other powerful reactions involving a radical chain process were reported, which opened up numerous possibilities for the application of radical chemistry in organic synthesis. In this chapter, several general concepts of radical chemistry will be mentioned. The Barton radical decarboxylation and the Barton-McCombie radical deoxygenation as two of the most important radical reactions will be briefly introduced. Finally, we will go through other thiocarbonyl related radical reactions and the xanthate chemistry developed in our group.

[6] Schweiger, A.; Jeschke, G. *Principles of Pulse Electron Paramagnetic Resonance;* **2001**. Oxford University Press.
[7] Barton, D. H. R.; Mcombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.
[8] Barton, D. H. R.; Crich, D.; Motherwell, W. B. *J. Chem. Soc., Chem. Commun.* **1983**, 939.

I. General aspects of free radicals

1. Radical types

Generally, organic free radicals are quite reactive and unstable species and can be divided into two kinds, neutral radicals and charged radicals (neutral radical, radical cation and radical anion) (Figure 1.1).

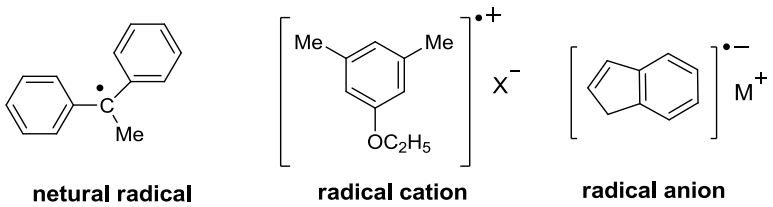


Figure 1.1 Neutral radicals and charged radicals

Moreover, depending to whether the unpaired electron is in sp^x (x=1, 2, 3) σ or in p orbital, two different types of radicals, σ radical and π radical, can be defined. A phenyl radical is a typical σ radical and a *tert*-butyl radical is a typical π radical (Figure 1.2).

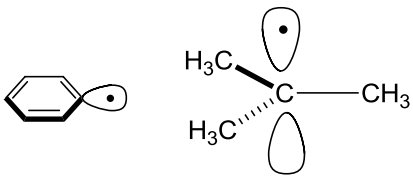
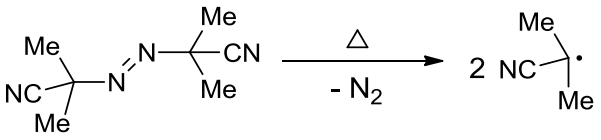


Figure 1.2 σ And π radicals

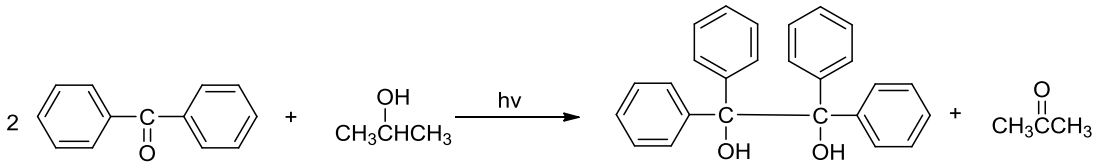
2. Generation of radicals

The radical can be generated by heating, by irradiation or by single electron transfer. As shown in Scheme 1.6, azobisisobutyronitrile, one of the most common radical initiators, generates a molecule of nitrogen gas and two 2-cyanoprop-2-yl radicals upon moderate heating (half-life = 1h at 85 ℃).



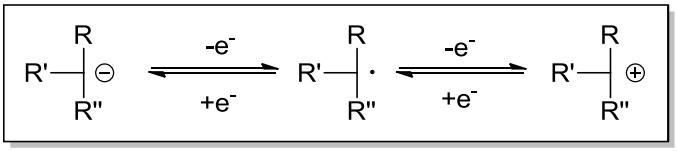
Scheme 1.6. Thermolysis of azobisisobutyronitrile (AIBN)

In the case of the photoinduced radical reaction shown in Scheme 1.7, irradiation causes the homolysis of the carbon-oxygen π-bond and leads to the formation of biradical intermediate which readily abstracts hydrogen from isopropanol to form the corresponding diol product.



Scheme 1.7 Photoinduced radical reaction

As shown in Scheme 1.8, single electron transfer from an electron-rich species (anion) or one electron addition to electron deficient species (cation) is a quite efficient approach to generate radicals (redox processes). [9]

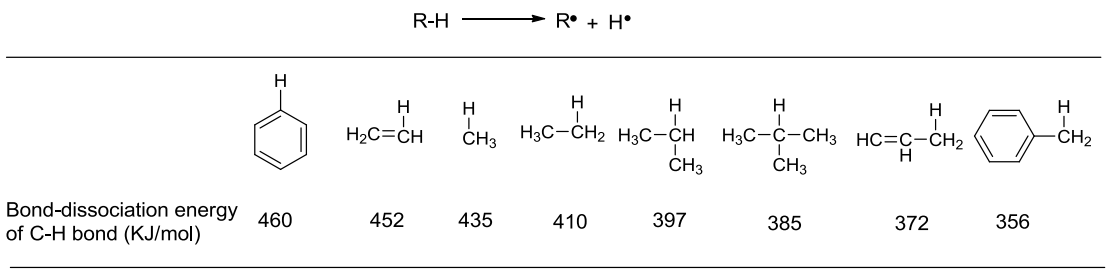


Scheme 1.8 Single electron transfer

3. Radical stability

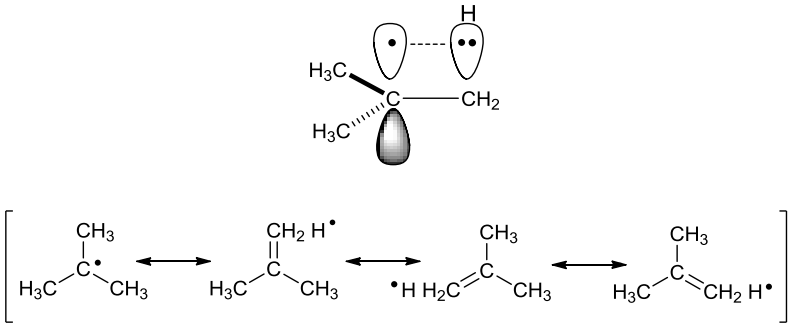
The considerable difference in bond dissociation energies between the starting materials and the products is the main driving force leading to the formation and ratio of products. Therefore, the bond dissociation energy can reflect the different stabilities of radicals. As shown in Scheme 1.9, a lower bond dissociation energy of a carbon-hydrogen bond generally corresponds a more stable carbon radical.

[9] Dalko, P. I. *Tetrahedron* **1995**, *51*, 7579.



Scheme 1.9 Bond dissociation energies

As illustrated in Scheme 10, the resonance structures of *tert*-butyl radical illustrates how hyperconjugation effect stabilizes the *tert*-butyl radical. The overlap between the σ orbital of an adjacent C-H bond with the *p*-orbital holding the single electron results in a stablising 3-electron interaction.



Scheme 1.10 Hyperconjugation effect

Comparing the stability of most common carbon radicals in Figure 1.3, the hyperconjugation effect well explains the reason why higher substituted π-radicals are, in general, more stable than low substituted ones. However, no such stabilizing effect exists for phenyl or vinyl radicals, which leads to their higher bond dissociation energies as shown in Scheme 1.9.

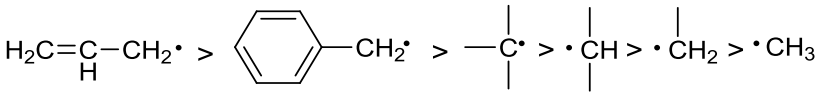
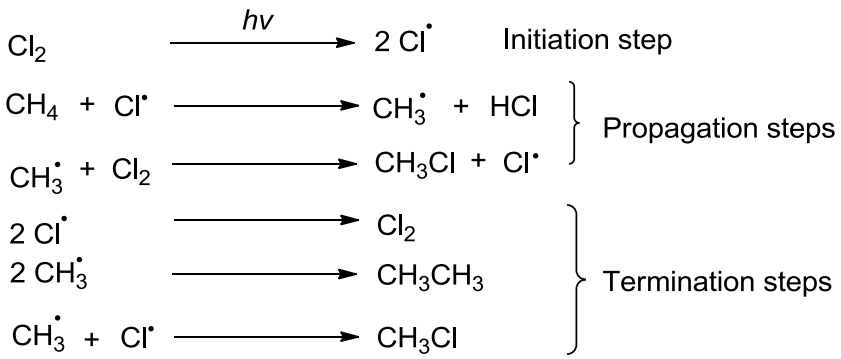


Figure 1.3 Allylic, benzylic > tertiary > secondary > primary > methyl radicals

4. Free radical chain processes

A free radical chain process can be divided into three types: initiation, propagation and termination. The halogenation of methane is one typical example shown in Scheme 1.11 that explains how radicals act in each step.[10] In the initiation step, the homolysis by irradiation of the chlorine-chlorine bond gives two chlorine atoms. In the following propagation step, the chlorine radical abstracts hydrogen from methane to form a methyl radical and this methyl radical readily attacks chlorine to form a new chlorine atom to sustain this radical chain process. Finally, the combinations between different radicals result in the termination of this chain process. This whole process is defined as a free radical chain process.



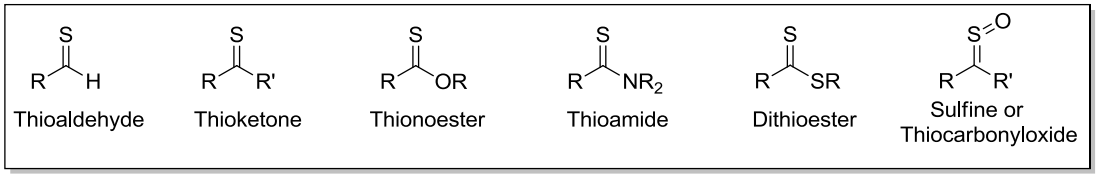
Scheme 1.11 Halogenation of methane

[10] Rossberg, M. et al. *Chlorinated Hydrocarbons in Ullmann's Encyclopedia of Industrial Chemistry*, **2006**, Wiley-VCH, Weinheim.

Π. The Barton radical decarboxylation and the Barton-McCombie radical deoxygenation reaction

1. Thiocarbonyl compounds and their structural properties

The structures and nomenclature of various thiocarbonyl compounds are displayed in Scheme 1.12. Compared with their carbonyl (oxygen) analogs, the larger covalent radius of sulfur vs oxygen (104.9 nm vs 70.2 nm), higher polarizability of sulfur relative to oxygen, less efficient overlap and lower coefficient of S_{3p}-C_{2p} π-bond together lead to the lower dissociation energy of the C=S bond (115 kcal/mol) than the C=O bond (162 kcal/mol). Therefore, thiocarbonyl compounds typically display greater reactivity in either ionic or radical reactions.



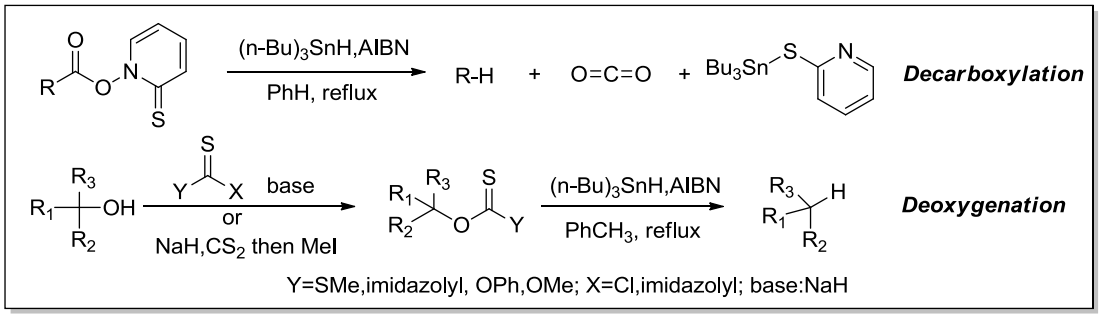
Scheme 1.12 Thiocarbonyl compounds

In radical reactions, thiocarbonyl compounds are generally radicophilic species that efficiently scavenge radical intermediates. This unique structure feature of thiocarbonyl group leads to a rich and varied radical chemistry. Besides the Barton radical decarboxylation and the Barton-McCombie radical deoxygenation, other thiocarbonyl compounds related radical reactions are being studied. In particular, the exchange of xanthates and related dithiocarbonyl derivatives, which will be discussed later, has proved to be especially useful in the context of the general effort to design tin-free processes.

2. Reaction pathway of the Barton radical decarboxylation and the Barton-McCombie radical deoxygenation reaction

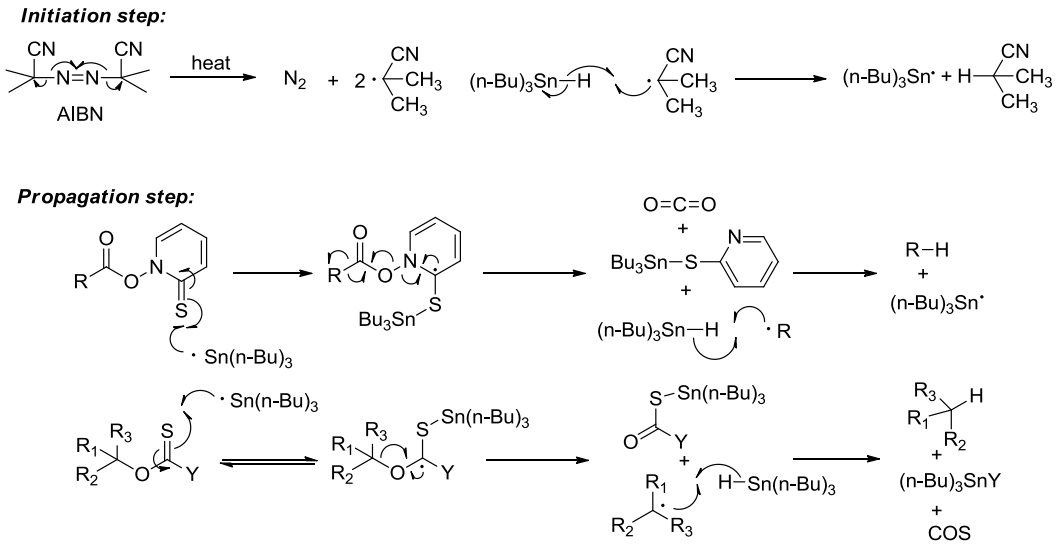
The Barton radical decarboxylation[8] and the Barton-McCombie radical

deoxygenation[7] reactions as two of the most powerful radical reactions, reported by Barton and his co-workers in 1983 and since 1975 respectively. To better understand the similarities and differences of the two reactions, their general equations are pictured in Scheme 1.13. In the Barton decarboxylation, by using tri-*n*-butyltin hydride as the hydrogen atom donor, the reductive decarboxylation product is formed through the thiohydroxamate ester intermediate known as Barton ester. Tri-*n*-butyltin hydride as the hydrogen donor is also used in the Barton-McCombie deoxygenation process which involves reaction with thionoester derivatives of the alcohol.



Scheme 1.13 Barton decarboxylation and Barton-McCombie deoxygenation

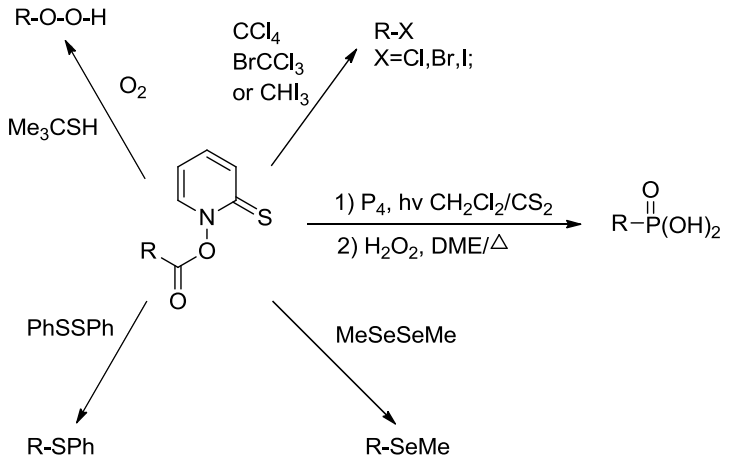
The mechanisms proposed for these transformations are displayed in Scheme 1.14. Both may involve the use of AIBN as the initiator allowing the generation of the starting tri-*n*-butyltin radicals. In their propagation steps, the radicophilicity of the thiono group encourages rapid attack by tri-*n*-butyltin radical to form a strong Sn-S bond. Finally, carbon dioxide is lost in the Barton decarboxylation process to afford the reduced product by abstraction of a hydrogen atom from tri-*n*-butyltin hydride; in the case of the Barton-McCombie deoxygenation, the fragmentation of the intermediate and hydrogen atom abstraction gives the deoxygenated product. .



Scheme 1.14 Mechanism of the Barton decarboxylation and deoxygenation

3. Applications of the Barton radical decarboxylation and the Barton-McCombie radical deoxygenation reaction in organic synthesis

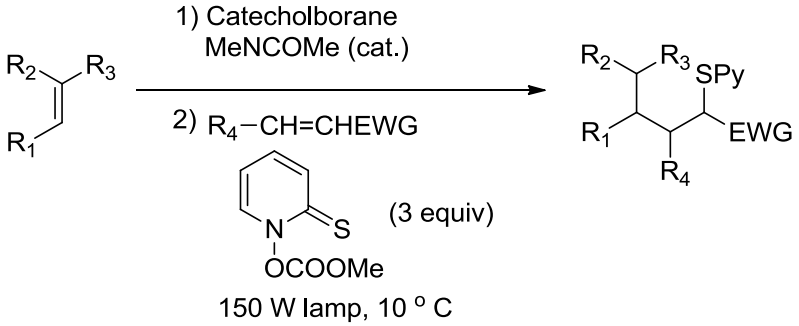
A carboxylic acid group can be converted into various other functional groups via its thiohydroxamate ester intermediate based on the Barton radical decarboxylation reaction. As illustrated in Scheme 1.15, the formation of a carbon-oxygen bond, a carbon-halogen bond, a carbon-sulfur bond, carbon-selenium bond or a carbon-phosphorus can be readily accomplished.[11]



Scheme 1.15 Synthetic variations of the Barton radical decarboxylation

[11] Chimiak, A.; Przychodzen, W.; Rachon, J. *Heteroat. Chem.* **2002**, *13*, 169.

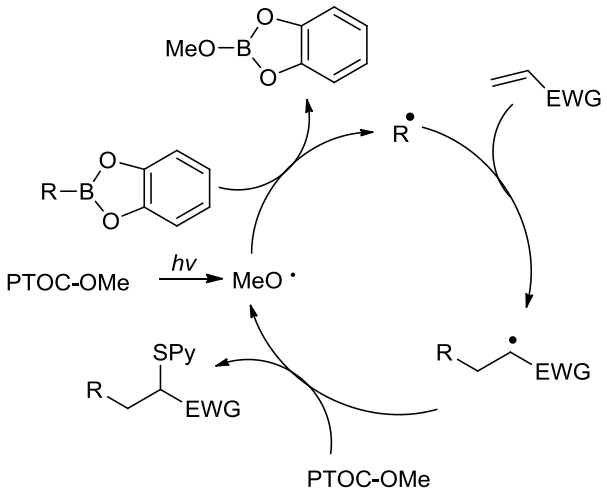
In 2000, a radical conjugate addition process was reported by Renaud and co-workers.[12] As illustrated in Scheme 1.16, the radical addition of an alkylborane to an alkene bearing an electron withdrawing group to furnish the corresponding adduct bearing an *S*-pyridyl group was accomplished through the irradiation of the Barton carbonate PTOC-OMe (PTOC = pyridine-2-thione-*N*-oxycarbonyl) with a 150 W tungsten lamp.



Scheme 1.16 Radical conjugate addition

The reaction pathway is described in Scheme 1.17. The hydroboration of the alkene substrate gives the corresponding alkylborane. In the second step, a methoxyl radical is generated upon photolysis of the Barton carbonate PTOC-OMe with a 150 W tungsten lamp. The methoxyl radical readily reacts with the alkylborane to form an alky radical. As a nucleophilic radical, the alky radical undergoes the radical addition with alkene bearing electron withdrawing group to generate an electrophilic radical. This electrophilic radical intermediate then reacts with another molecule PTOC-OMe to form the desired product bearing an *S*-pyridyl group and another methoxyl radical to sustain this radical chain process. Since the product bearing an *S*-pyridyl group, it can be removed or converted into other functional groups using the rich chemistry of sulfides.

[12] Ollivier, C.; Renaud, P. *Angew. Chem. Int. Ed.* **2000**, *39*, 925.



Scheme 1.17 Mechanism of radical conjugate addition

4. Improvements in the Barton radical decarboxylation and the Barton-McCombie radical deoxygenation reaction

Although the Barton decarboxylation and the Barton-McCombie deoxygenation are widely applied in organic synthesis, the drawbacks still remain in both of the two reactions. For instance, the difficulty in removing the organotin residues from the end products makes the techniques using tin inappropriate for the syntheses of drugs, medicines, and other formulations intended for human consumption.

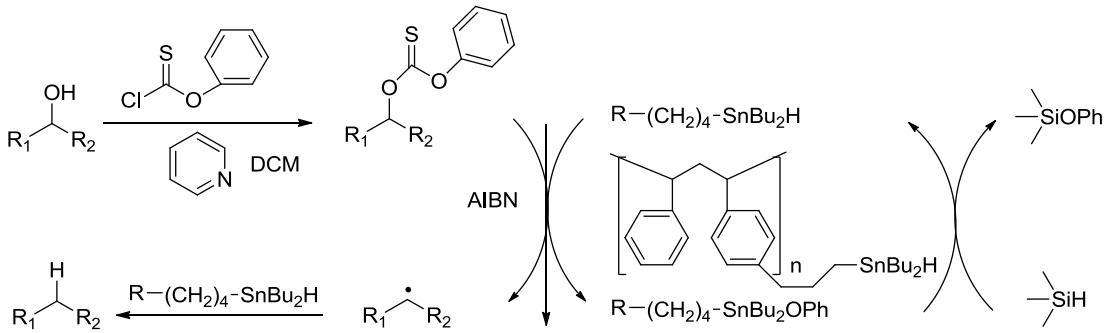
4.1. Modification of organotins and their applications in radical reactions

The tedious purification of reaction mixtures involving stoichiometric tin hydride is a major drawback. In order to easily remove organotin from the desired products, various workup procedures or modification of the structure of the tin hydride have been developed.

For instance, in 2000, Dumartin and co-workers reported a Barton-McCombie process employing a catalytic amount of supported tin hydride in the presence of trimethoxysilane (Scheme 1.18).[13] Since silane rapidly reacts with Sn-OR bonds to give new tin hydride bonds, the regeneration of tin hydride is accomplished via this

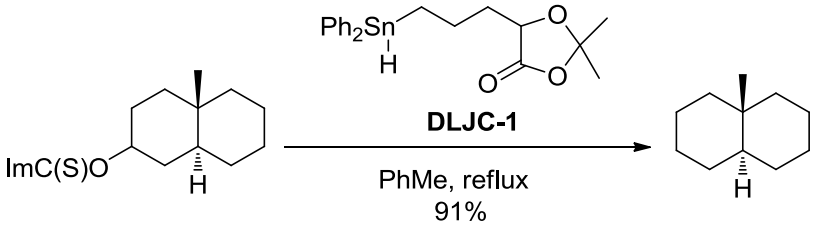
[13] Boussaguet, P.; Delmond, B.; Dumartin, G.; Pereyre, M. *Tetrahedron. Lett.* **2000**, *41*, 3377.

method.



Scheme 1.18 Regeneration of tin hydride

In 2002, the stannane **DLJC-1** was designed as a replacement of tri-*n*-butyltin hydride by Clive and co-workers (Scheme 1.19).[14] The stannane **DLJC-1** can be hydrolyzed by LiOH-water-THF or TsOH-water-THF to form the base-soluble materials which apparently simplifies the separation of desired products from the tin-containing byproducts.



Scheme 1.19 Stannane **DLJC-1** in Barton-McCombie radical deoxygenation reaction

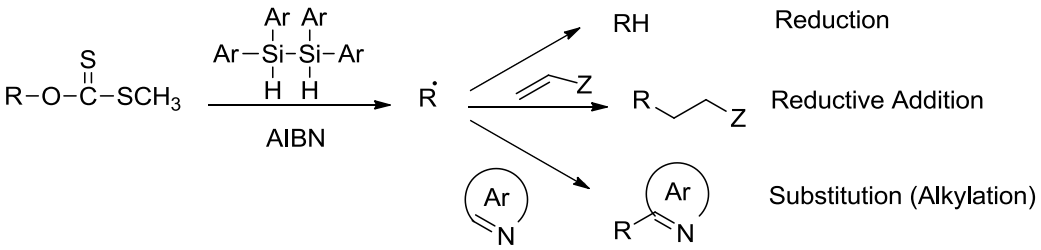
4.2. Tin-free Barton decarboxylations and Barton-McCombie deoxygenation radical reactions

The high toxicity of organotin compounds demands chemists to reduce or even avoid the usage of organotin reagents. In some cases, catalytic amounts of tin hydride are required, so stoichiometric amounts of another reducing agents such as poly(methylhydrosiloxane), sodium borohydride, and cyanoborohydride are employed

[14] Clive, D. L. J.; Wang, J. *J. Org. Chem.* **2002**, *67*, 1192.

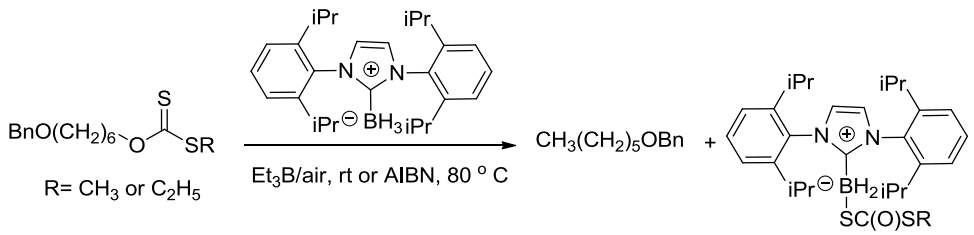
to accomplish this process. However, it is more interesting to avoid the organotin derivatives altogether by devising more acceptable replacements such silanes, dialkyl phosphinates and hypophosporous acid and its salts.

Barton-McCombie deoxygenations involving the utilization of tetraphenyl--disilane instead of organotin were reported by Togo and co-workers in 2000.[15] As shown in Scheme 1.20, the reductive removal of the xanthate group and related reductive additions or alkylations could be accomplished using tetraphenyldisilane as the hydrogen atom donor.



Scheme 1.20 Reductive elimination of xanthate group by using tetraphenyldisilane

Recently, the reduction of xanthate by *N*-heterocyclic carbene boranes (NHC-boranes) hitherto unknown NHC-boryl radicals was reported by Curran and co-workers (Scheme 1.21).[16] Furthermore, they estimated the reaction rate of the reduction step involving NHC-borane to be 2 orders of magnitude slower than with Bu_3SnH and 1 order of magnitude slower than $(TMS)_3SiH$.



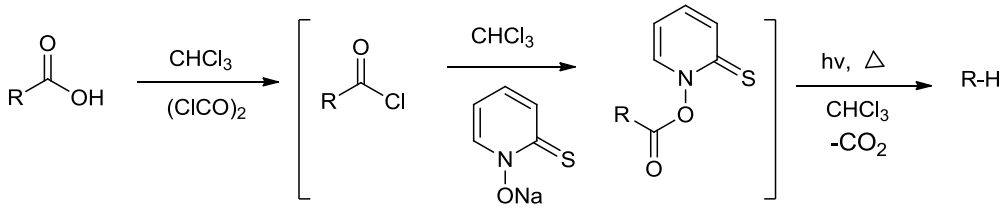
Scheme 1.21 Reductive elimination of xanthate group by using NHC-boranes

Besides tetraphenyldisilane, NHC-borane and their related derivatives,

[15] Togo, H.; Matsubayashi, S.; Yamazaki, O.; Yokoyama, M. *J. Org. Chem.* **2000**, *65*, 2816.

[16] Ueng, S. H.; Solovyev, A.; Yuan, X.; Geib, S. J.; Fensterbank, L.; Lacôte, E.; Malacria, M.; Newcomb, M.; Walton, J. C.; Curran, D. P. *J. Am. Chem. Soc.* **2009**, *131*, 11256.

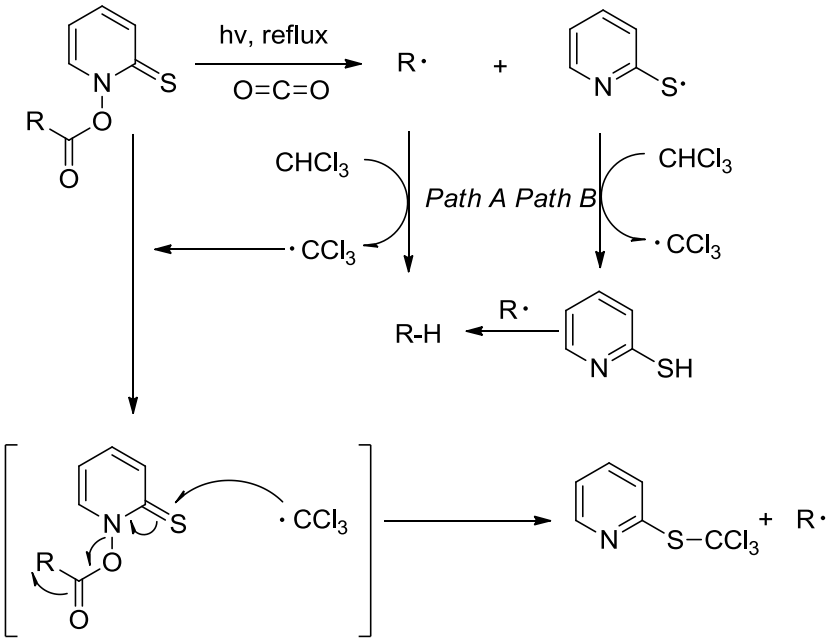
chloroform as solvent can also act as a hydrogen atom donor in the Barton decarboxylation process, as was discovered by Tsanaktsidis and co-workers in 2011.[17] As shown in Scheme 1.22, the irradiation of thiohydroxamate ester in chloroform gave the corresponding reduced product.



Scheme 1.22 Chloroform as a hydrogen atom donor in the Barton decarboxylation

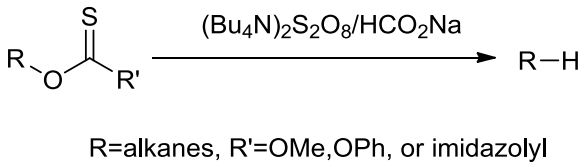
Accordingly, two plausible mechanism pathways A and B were proposed as displayed in Scheme 1.23. The thiohydroxamate ester loses carbon dioxide to generate the alkyl radical. Then, in path A, the alkyl radical abstracts a hydrogen atom from chloroform to form the reduction product. In path B, 2-pyridylthiyl radical as an electrophilic radical prefers to abstract a hydrogen atom from chloroform to form a nucleophilic radical. The hydrogen transfer between 2-pyridylthiyl radical and chloroform in path B is consistent with the concept of polarity reversal catalysis.[18] Both of the reductive reactions in path A or B would result in the formation of a trichloromethyl radical to sustain this radical process.

[17] Ko, J. E.; Savage, G. P.; Williams, C. M.; Tsanaktsidis, J. *Org. Lett.* **2011**, *13*, 1944.
[18] Roberts, B. P. *Chem. Soc. Rev.* **1999**, *28*, 25.



Scheme 1.23 Plausible mechanism

Although the replacements of organotin hydrides by other hydrogen atom donors can improve the applications of related radical reactions, limitations like cost, availability, and toxicity still remain in the above replacements. In 2005, an efficient tin-free Barton-McCombie radical deoxygenation involving a redox process was accomplished by Kim and co-workers.[19] As illustrated in Scheme 1.24, readily available sodium formate and tetrabutylammonium peroxydisulfate were used as the reducing combination.

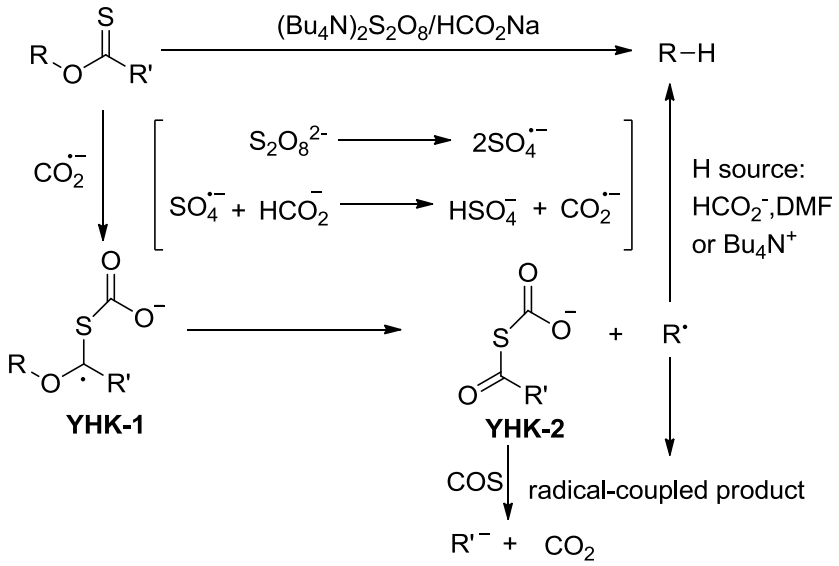


Scheme 1.24 Barton-McCombie radical deoxygenation via a redox process

A plausible mechanism is shown in Scheme 1.25. It assumes that the transfer of a single electron to thiocarbonyl derivatives takes place from carbon dioxide radical anion rather than $SO_4^{\bullet-}$. The radical addition of carbon dioxide radical anion to the thiocarbonyl substrate gives the radical intermediate **YHK-1**. The formation of anion

[19] Park, H. S.; Lee, Y. H.; Kim, Y. H. *Org. Lett.* **2005**, *7*, 3187.

YHK-2 and R radical occur with the loss of COS from **YHK-1**. Finally, the R radical abstracts a hydrogen atom from a hydrogen source to furnish the corresponding deoxygenated product.



Scheme 1.25 Plausible mechanism

III. Degenerative transfer of xanthates

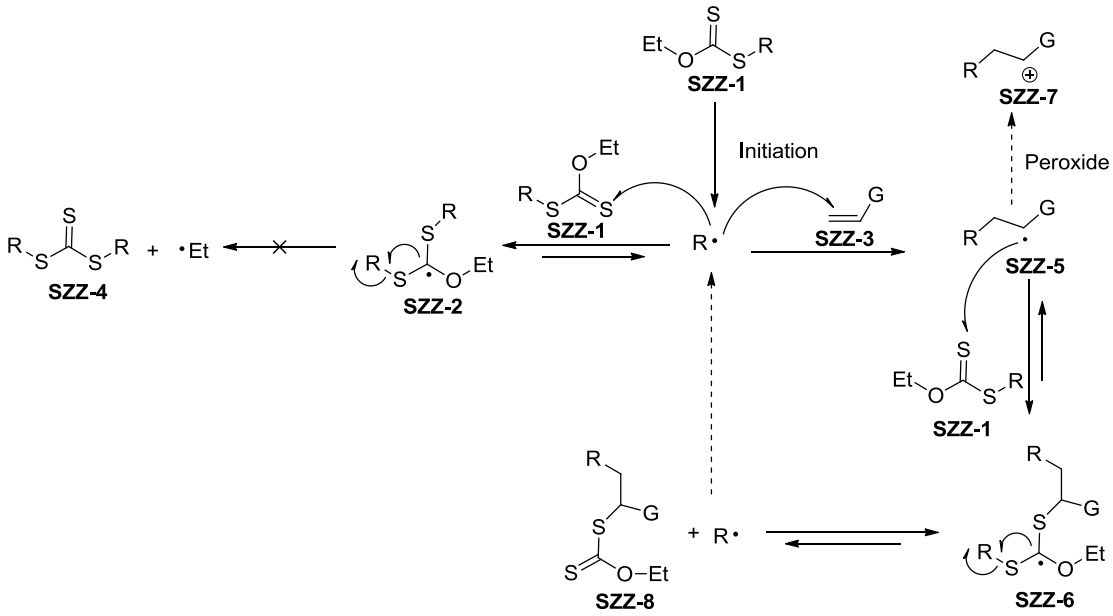
Since the cleavage of carbon-sulfur bond taking place under metal free conditions was found by Zard, the degenerative radical addition transfer of xanthates onto alkenes was systematically investigated by Zard and co-workers during the past decades. This process allows numerous hitherto difficult inter- or intramolecular addition of xanthates to olefins and represents a highly efficient approach to numerous functionalized structures.[20]

1. Mechanism

The mechanistic pathway of the degenerative transfer of xanthates onto alkenes is outlined in Scheme 1.26. In the initiation step, the cleavage of C-S bond of xanthate **SZZ-1** gives an R radical which may either reversibly add to the sulfur atom of another xanthate or add to the alkene. There are two possible pathways in the following steps: either the adduct **SZZ-2** gives **SZZ-4** by generating a high energy ethyl radical or adduct **SZZ-5** attacks the sulfur atom to form another adduct **SZZ-6** in a reversible manner. By contrast, due to the high energy of ethyl radical the former pathway is unlikely. Therefore, radical intermediate **SZZ-6** is formed and then its collapse leads to the formation of corresponding product **SZZ-8** and another R radical to sustain this radical chain process. It is worthwhile to note that the formation of **SZZ-2**, **SZZ-6** or **SZZ-8** is a reversible process. Therefore, even under high concentration of xanthate, the newly formed R radicals could be converted to **SZZ-2** or **SZZ-6** which act as reservoirs for active radicals and lower their concentration in the medium, thus limiting radical-radical interaction. However, we should also notice that excess amounts of peroxide may oxidize the radical intermediate **SZZ-5** to form a cation **SZZ-7** which may be exploited in certain transformations. Finally, a higher

[20] For reviews on the xanthate radical addition-transfer process, see: (a) Zard, S. Z. *Angew. Chem., Int. Ed.* **1997**, *36*, 672. (b) Quiclet-Sire, B.; Zard, S. Z. *Chem. Eur. J.* **2006**, *12*, 6002. (c) Quiclet-Sire, B.; Zard, S. Z. *Top. Curr. Chem.* **2006**, *264*, 201. (d) Zard, S. Z. *Aust. J. Chem.* **2006**, *59*, 663. (e) Zard, S. Z. *Org. Biomol. Chem.* **2007**, *5*, 205. (f) Quiclet-Sire, B.; Zard, S. Z. *Pure Appl. Chem.* **2011**, *83*, 519.

stability of the R radical as compared with the adduct radical **SZZ-5** is an essential to keep the chain process efficient. Otherwise, if the stability of the R radical is lower than that adduct radical **SZZ-5** then oligomers tend to form and process remains difficult to control.

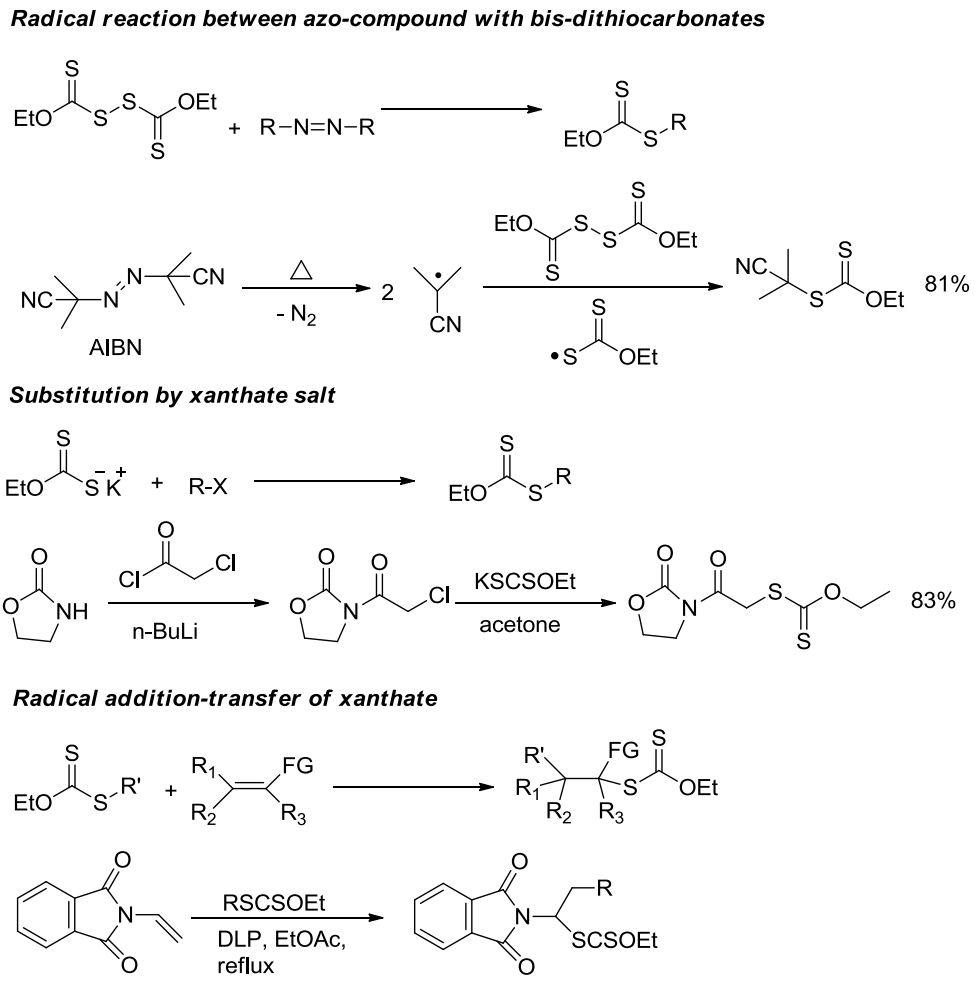


Scheme 1.26 Mechanisms of the degenerative addition transfer of xanthates onto alkenes

2. Preparation

There have been several methods to prepare various types of xanthates, three of them with corresponding examples are presented in Scheme 1.27.[21] Xanthates can be readily obtained by the reaction of a xanthate salt with an alkylating agent, or the reaction of an azo-compound with bis-dithiocarbonates, or by radical addition-transfer of a xanthate onto an alkene.

[21] (a) Bouhadir, G.; Legrand, N.; Quiclet-Sire, B.; Zard. S. Z. *Tetrahedron Lett.* **1999**, *40*, 277. (b) Thang, S.; Chong, Y.; Mayadunne, R.; Moad, G.; Rizzardo, E. *Tetrahedron Lett.* **1999**, *40*, 2435. (c) Maslak, V.; Cekovic, Z.; Saicic, R. N. *Synlett* **1998**, 1435. (d) Tanaka, K.; Tamura, N.; Kaji, A. *Chem. Lett.* **1980**, 595.



Scheme 1.27 Preparation of xanthates

3. Applications of degenerative addition-transfer of xanthate

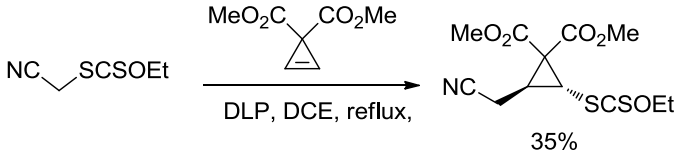
Since the discovery of this degenerative addition-transfer process, Zard and co-workers studied and explored the scope of this process extensively by applying this reaction to the preparation of diversely functionalized compounds. These applications demonstrate the advantages of the xanthate transfer reaction: 1. The xanthate starting material can be readily obtained from cheap potassium *O*-ethyl xanthate salt; 2. The xanthate transfer reaction is easily scaled up; 3. Normally, the reactions take place under mild, neutral reaction conditions and are initiated by the quite cheap dilauroyl peroxide in refluxing ethyl acetate; 4. The reactions are performed under metal-free conditions and are therefore ecologically acceptable

Generally, the degenerative addition-transfer of xanthates onto alkenes is used to bring together various functional groups or to construct complex ring systems via

radical cyclization reactions. These aspects will be described in the following reactions.

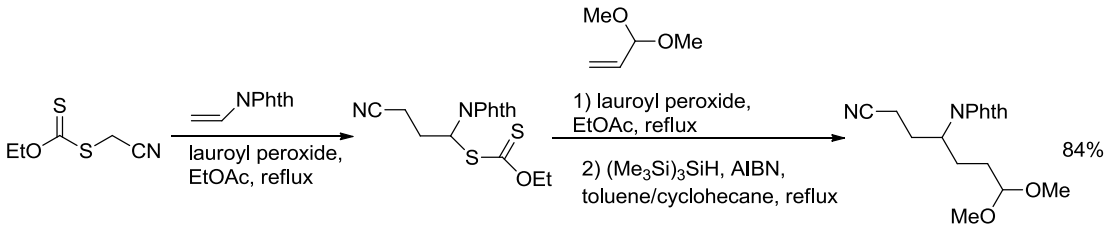
3.1. Radical additions

Radical addition of xanthate to unactivated olefins, inducing various strained olefins such as cyclopropenes, cyclobutenes, azetines and methylenecyclopropanes furnishes the corresponding adducts as shown by the example in Scheme 1.28.[22]



Scheme 1.28. Radical addition of a xanthate to a strained olefin

Another quite interesting application is the synthesis of protected primary amines via radical addition of a xanthate to *N*-vinylphthalimide to give an adduct which can undergo another radical addition to another olefin (Scheme 29).[23] Then the reductive removal of the xanthate group furnishes the corresponding protected primary amine, which can be considered as a radical hydroaminoalkylation process.[24]



Scheme 29. Radical addition of xanthate to *N*-vinylphthalimide

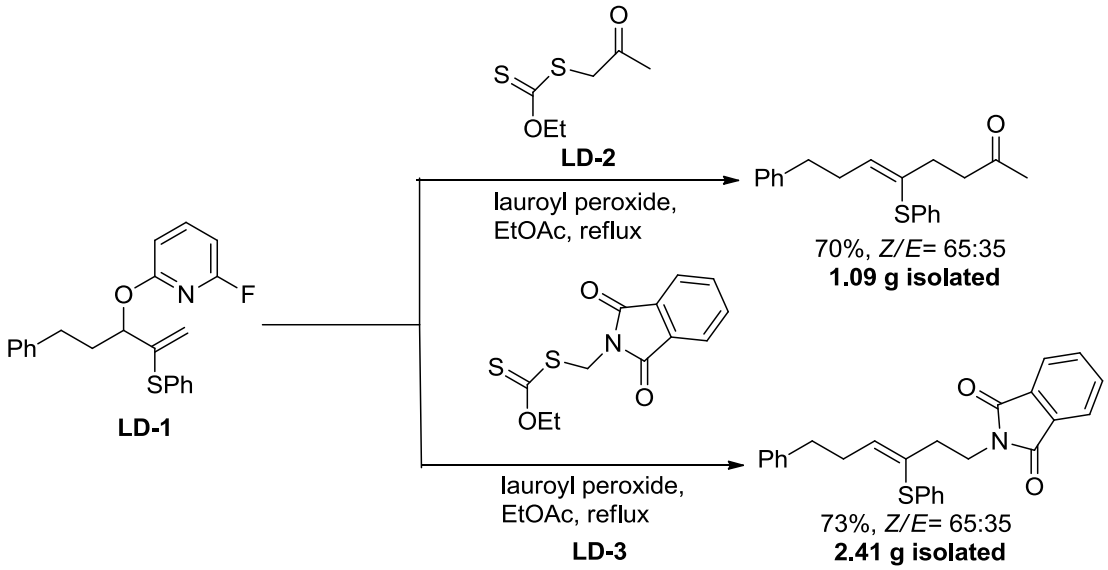
Recently, the group reported a mild and stereoselective synthesis of tri- and tetrasubstituted functionalized vinyl sulfides relying on the radical allylation of xanthates **LD-2** or **LD-3** with vinyl sulfide **LD-1** (Scheme 1.30), which undergoes a

[22] Legrand, N.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **2000**, *41*, 9815.

[23] Quiclet-Sire, B.; Revol, G.; Zard, S. Z. *Tetrahedron* **2010**, *66*, 6656.

[24] (a) Quiclet-Sire, B.; Zard, S. Z. *Org. Lett.* **2008**, *10*, 3279. (b) Quiclet-Sire, B.; Revol G.; Zard, S. Z. *Org. Lett.* **2009**, *11*, 3554. (c) Quiclet-Sire, B.; Lebreux, F.; Quiclet-Sire, B.; Zard, S. Z. *Org. Lett.* **2009**, *11*, 2844. (d) Quiclet-Sire, B.; Zard, S. Z. *Heterocycles* **2010**, *82*, 263.

radical addition elimination process.[25]



Scheme 1.30 Radical addition of xanthate to phenyl vinyl sulfones

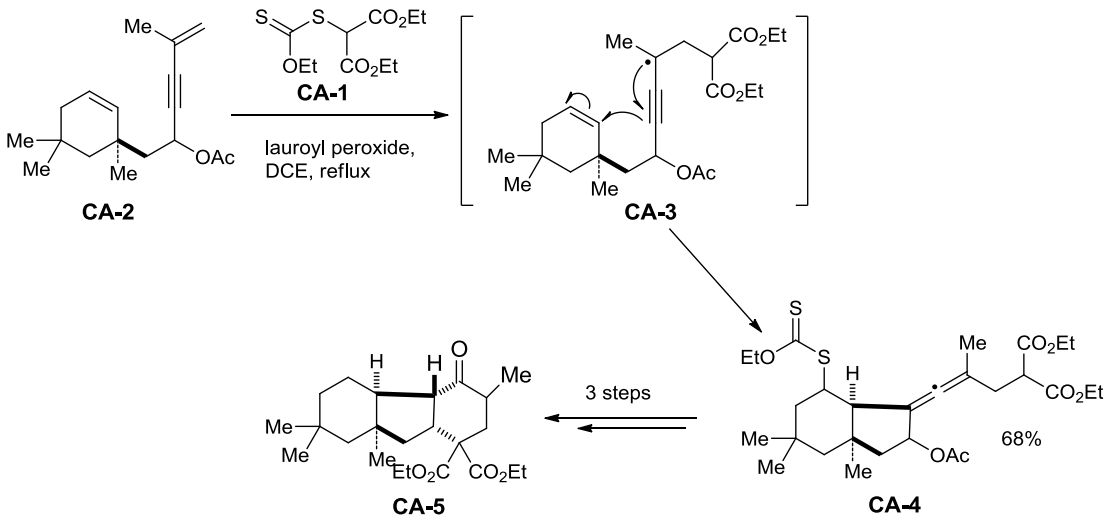
3.2. Radical cyclizations

Since heterocyclic compounds are ubiquitous and highly valuable in the pharmaceutical area and in material science it is more interesting to apply the xanthate technology for the construction of polycyclic structures.[26] As shown in Scheme 1.31, the addition of xanthate **CA-1** to enyne **CA-2** gives intermediate **CA-3** which undergoes cyclization to furnish a tetrasubstituted allene **CA-4** directly in high yield.[27] This allene can be further converted into a complex tricyclic compound bearing five chiral centers via three more steps.

[25] (a) Debien, L.; Braun, M. G.; Quiclet-Sire, B.; Zard, S. Z. *Org. Lett.*, **2013**, *15*, 6250. (b) Braun, M. G.; Quiclet-Sire, B.; Zard, S. Z. *J. Am. Chem. Soc.* **2011**, *133*, 15954.

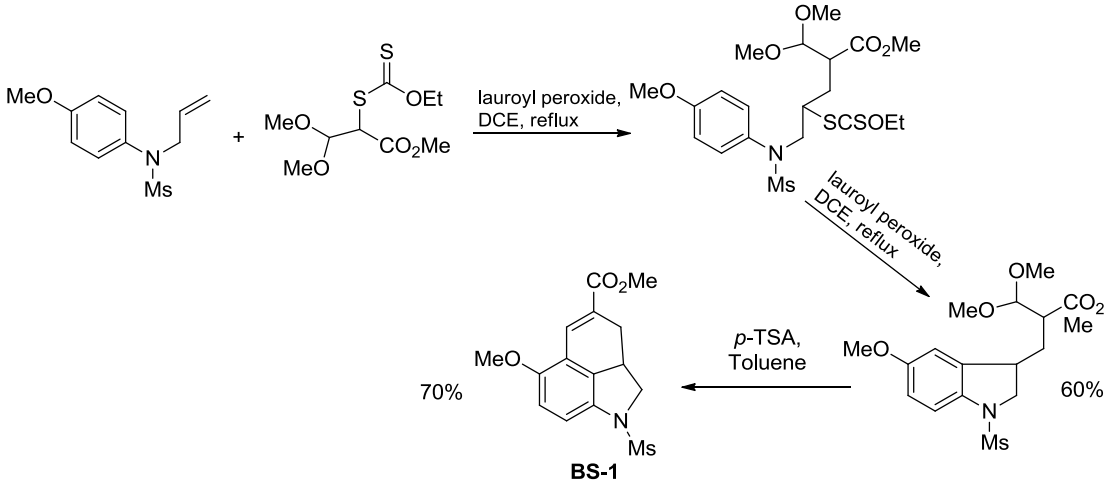
[26] Denieul, M.-P.; Quiclet-Sire, B.; Zard. S. Z. *Tetrahedron Lett.* **1996**, *37*, 5495.

[27] Alameda-Angulo, C.; Quiclet-Sire, B.; Zard. S. Z. *Tetrahedron Lett.* **2006**, *47*, 913.



Scheme 1.31 Synthesis of **CA-5**

The synthesis of tricyclic compound **BS-1** is described by Sortais.[28] It is outlined in Scheme 1.32 and consists in the combination of a radical addition and cyclization flowed by a second ionic ring-closure to finish tricyclic product **BS-1** in high yield.



Scheme 1.32 Synthesis of tricyclic compound **BS-1**

Some unusual heterocyclic compounds or even unknown classes of heterocycles can be prepared via the combination of radical reactions with ionic processes.[29] As shown in Scheme 1.33, the synthesis of both sulfone **PB-1**[30] and dihydrothiazines[31]

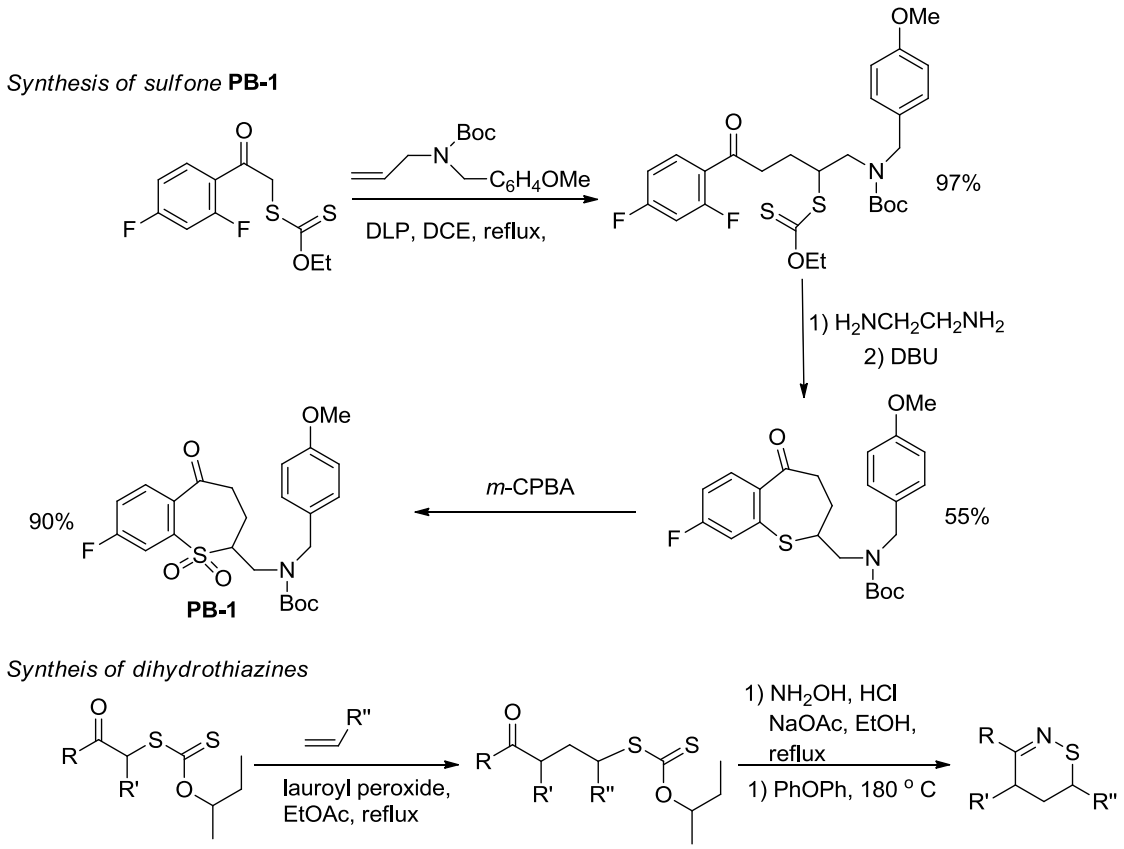
[28] Sortais. B.; Ph. D. Thesis, Ecole Polytechnique, Palaiseau, **2002**.

[29] For a review, see: El Qacemi, M.; Petit, L.; Quiclet-Sire, B.; Zard, S. Z. *Org. Biomol. Chem.* **2012**, *10*, 5707.

[30] Boutillier, P.; Quiclet-Sire, B.; Zafar, S. N.; Zard. S. Z. *Tetrahedron Asymmetry* **2010**, *21*, 1649.

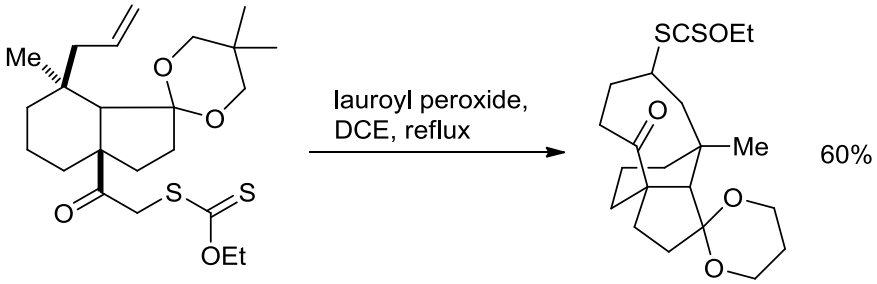
[31] Quiclet-Sire, B.; Zard, S. Z. *Org. Lett.*, **2013**, *15*, 5886.

are accomplished via a radical addition- ionic cyclization process.



Scheme 1.33 Radical addition-ionic cyclization

Besides the preparation of different heterocyclic compounds, this technique was applied to a few total syntheses. As shown in Scheme 1.34, in an approach to the synthesis of the tricyclic skeleton of pleuromutilin, the intramolecular radical addition for the construction of an eight membered ring was accomplished in good yield.[32]



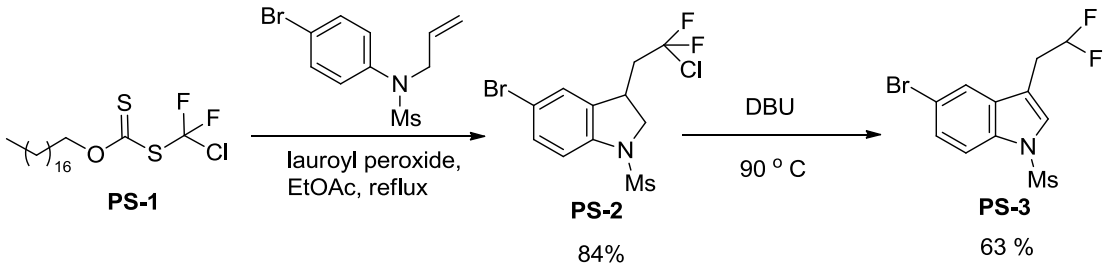
Scheme 1.34 Synthesis of tricyclic skeleton of pleuromutilin

[32] Kalai, C.; Tate, E.; Zard, S. Z. *Org. Lett.*, **2003**, *5*, 325.

3.3. Recent studies of degenerative addition-transfer

3.3.1. The synthesis of *gem*-difluoro compounds

There have been several applications of xanthates for the construction of organofluorine compounds.[33] Recently, Salomon reported the synthesis of *gem*-difluoroalkenes, -dienes and (2,2-difluoroethyl)-indoles, -azaindoles, and -naphthols via the radical addition of xanthate **PS-1** to various olefins followed by radical cyclization.[34] As shown in Scheme 1.35, xanthate **PS-1** can be considered as a convenient source to generate chlorodifluoromethyl radicals which undergo the radical addition cyclization to form adduct **PS-2**. (2, 2-Difluoroethyl)-indole **PS-3** is formed via the elimination of chlorine from **PS-2** by using DBU.



Scheme 1.35 Synthesis of (2, 2-difluoroethyl)-indole **PS-3**

3.3.2. The synthesis of polycyclic aminopyrimidones

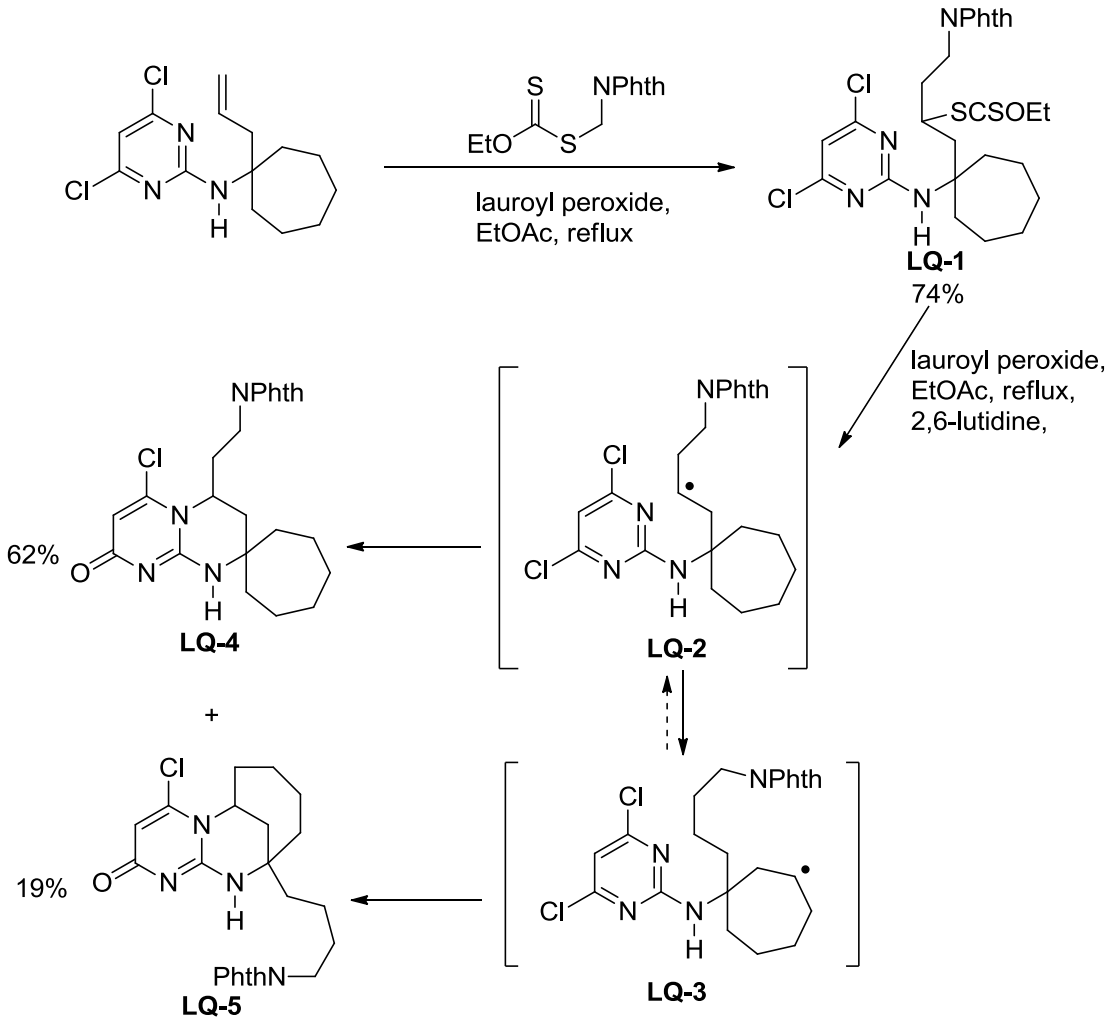
In an ongoing work on the radical cyclization on pyridine and pyrimidine rings,[35] an unexpected observation was recently made. As described in Scheme 1.36, it was found that the cyclization of **LQ-1** gave two different cyclization products, the major being **LQ-4** and the minor **LQ-5.** This represents a synthetically valuable radical ring

[33] (a) Bertrand, F.; Pevere, V.; Quiclet-Sire, B.; Zard, S. Z. *Org. Lett.*, **2001**, *3*, 1069. (b) Li, S.; Zard, S. Z. *Org. Lett.*, **2013**, 15, 5898. (c) Denieul, M.-P.; Quiclet-Sire, B.; Zard, S. Z. *J. Chem. Soc., Chem. Commun.* **1996**, 2511. (d) Gagosz, F.; Zard, S. Z. *Org., Lett.* **2003**, 5, 2655. (e) Gagosz, F.; Zard, S. Z. *Org. Synth.* **2007**, 84, 32. (f) Tournier, L.; Zard, S. Z. *Tetrahedron Lett.* **2005**, 46, 455. (g) Jean-Baptiste, L.; Yemets, S.; Legay, R.; Lequeux, T. *J. Org. Chem.* **2006**, 71, 2352.

[34] Salomon, P.; Zard, S. Z. *Org. Lett.*, **2014.** *ASAP.*

[35] (a) El Qacemi, M.; Ricard, L.; Zard, S. Z. *Chem. Commun.* **2006**, *42*, 4422. (b) Laot, Y.; Petit, L.; Zard, S. Z. *Chem. Commun.* **2010**, *46*, 5784.

closure onto a pyrimidine nitrogen.[36] Radical intermediate **LQ-3** is formed via a 1, 5-hydrogen shift process.



Scheme 1.36 Synthesis of polycyclic aminopyrimidones

4. Radical reactions associated with the xanthates developed in other groups

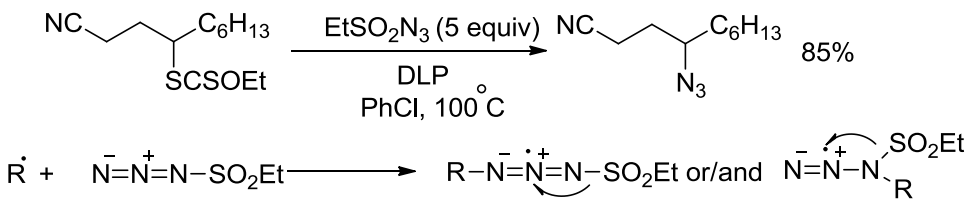
4.1. Radical azidation

In 2000, a radical azidation process was reported by Renaud and co-workers.[37] As illustrated in Scheme 1.37, the R radical generated from the cleavage of the C-S bond in xanthate derivatives was captured by ethanesulfonyl azide to form the

[36] Qin, L.; Liu, Z.; Zard, Z. S. *Org. Lett.*, **2014**, *ASAP.*

[37] Ollivier, C.; Renaud, P. *J. Am. Chem. Soc.* **2000**, *122*, 6496.

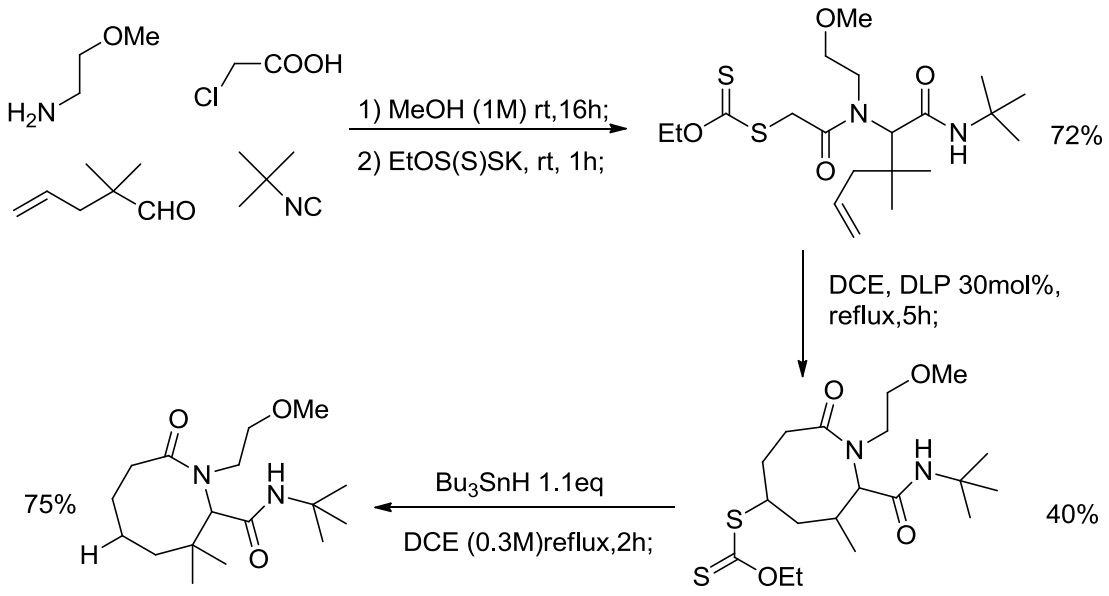
corresponding alkyl azides.



Scheme 1.37 Radical azidation

4.2. Ugi/xanthate cyclization

The Ugi reaction is well known for its rapid combination of multi components in one pot. The combination of Ugi reaction and xanthate radical cyclization onto alkenes was reported by El Ka ïm and co-workers in 2006 (Scheme 1.38).[38] This multi component procedure consists of chloroacetic acid, primary amines, aldehydes and isocyanides, which was then treated with potassium ethyl xanthate to give the xanthate Ugi adducts. Next, the radical cyclization followed reductive elimination of xanthate group afforded the corresponding cyclization product.

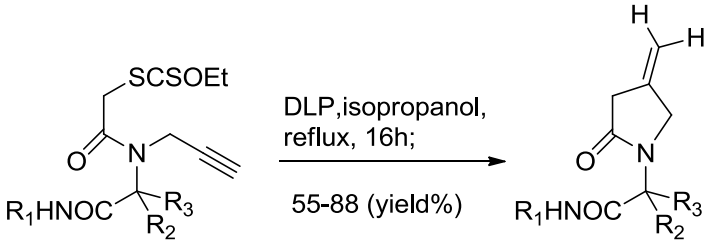


Scheme 1.38 Ugi/xanthate cyclization

[38] El Ka ïm, L.; Grimaud, L.; Miranda, L. D.; Vieu, E. *Tetrahedron Lett.* **2006**, *47*, 8259.

4.3. Xanthate-based radical cyclization onto alkynes

Besides the radical addition or cyclization of xanthate to alkenes, even alkynes can be used to undergo the radical reaction with xanthates. Recently, El Kaïm and co-workers reported the radical cyclization of xanthates to alkynes in generally good yield to form lactams.[39] The xanthate was obtained by the same Ugi reaction, but propargylamine was used as one of the components in this Ugi reaction (Scheme 1.39).



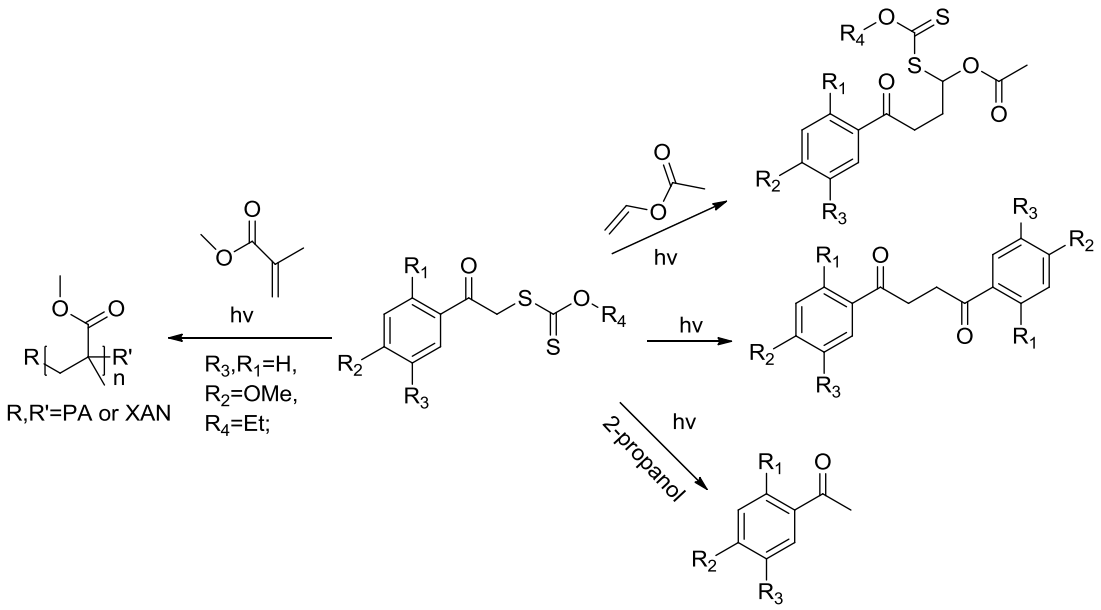
Scheme 1.39 Xanthate-based radical cyclization onto alkynes

4.4. Photoinitiated homolytic scission of C-S bond

Besides lauroyl peroxide, AIBN or other initiators, the homolytic scission of C-S can be accomplished by irradiation in an initiation step. Recently, Klán and co-workers investigated the photochemistry of *S*-phenacyl xanthate.[40] As illustrated in Scheme 1.40, the radical fragments generated via the homolytic scission of C-S could further undergo the radical addition with vinyl acetate or reduction by 2-propanol or polymerization or dimerization.

[39] El Kaïm, L.; Grimaud, L.; Miranda, L. D.; Vieu, E.; Cano-Herrera, M. A.; Perez-Labrada, K. *Chem. Commun.* **2010**, *46*, 2489.

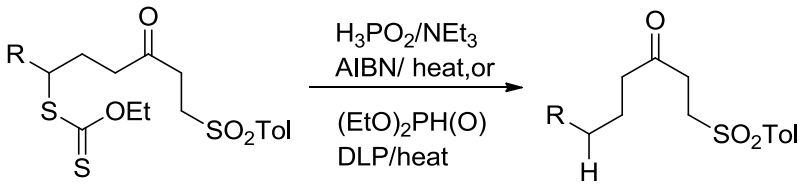
[40] Veetil, A. T.; Šolomek, T.; Ngoy, B. P.; Pavlíková, N.; Heger, D.; Klán, P. *J. Org. Chem.* **2011**, *76*, 8232.



Scheme 1.40 Photoinitiated reactions of *S*-phenacyl xanthate

4.5. Reductive elimination of xanthate groups

There have been numerous studies demonstrating the utility of the xanthate but it is often necessary to remove this group from the resulting adduct. Various tin-free methods for the reductive removal of the xanthate group have been developed in the past few years. One highly efficient procedure to reduce the xanthate group was applied by Boivin and co-workers in 2003 using a procedure described initially by Barton (Scheme 1.41).[41] This process employs a combination of hypophosphorous acid and triethylamine to accomplish the radical reductive dexanthylation in generally high yield.



Scheme 1.41 Reductive elimination of xanthate group by using hypophosphorous acid and triethylamine

[41] (a) Boivin, J.; Jrad, R.; Juge, S.; Nguyen, T. V. *Org. Lett.* **2003**, *5*, 1645. (b) Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. Cs. *Tetrahedron Lett.* **1992**, *33*, 5709. (c) Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. Cs. *J. Org. Chem.* **1993**, *58*, 6838. (d) Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. Cs. *Tetrahedron Lett.* **1992**, *33*, 2311-2314. (e) Barton, D. H. R.; Parekh S. I.; Tse, C.-L. *Tetrahedron Lett.* **1993**, *34*, 2733.

Conclusion

In this chapter, we have presented in general terms radical reactions associated with the thiocarbonyl group. The Barton decarboxylation and the Barton-McCombie deoxygenation are two of the most powerful radical reactions that were briefly introduced along with their later improvements. The degenerative transfer addition of xanthates to alkenes developed largely in our group has demonstrated its highly valuable potential for organic synthesis. This opens up vast possibilities to rapidly assemble complex structures. Various functional groups can be incorporated into the final products, either through the xanthate partner or through the alkene.