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Fun with radicals: Some new perspectives for organic synthesis*

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Abstract: The degenerative radical addition-transfer of xanthates onto alkenes allows the rapid assembly of richly functionalized structures. Various families of open-chain, cyclic, and polycyclic compounds can thus be readily accessed. Furthermore, the process can be extended to the synthesis or modification of aromatic and heteroaromatic derivatives by exploiting the possibility of using peroxides both as initiators and stoichiometric oxidants. The modification of existing polymers and the controlled synthesis of block polymers by what is now known as the RAFT/MADIX (reversible addition–fragmentation transfer/macromolecular design by interchange of xanthate) process is described briefly.

Keywords: aromatics; heteroaromatics; heterocycles; radical additions; RAFT-MADIX controlled polymerization; total synthesis; xanthates.

INTRODUCTION

Radical reactions are used to produce polymers on the multimillion-ton scale, yet they are seldom exploited by industry for the manufacture of low-molecular-weight substances. The surge in popularity enjoyed by radicals in academia in the 1980s and early 1990s somehow did not translate into widespread applications within the pharmaceutical and agrochemical sectors. This is in contrast to transition-metal-catalyzed processes, which have witnessed a dramatic development over the past two or three decades, both in academia and in industry.

Transition-metal catalysis is not only powerful and versatile, but many of the problems related to scale up, removal of metal-containing residues, and recovery of the precious catalysts and/or ligands have been largely solved by development chemists. There is, furthermore, a strong and continuous flux of young chemists irrigating the chemical industry, who have been trained in the use of organometallic reactions and who do not hesitate to integrate such processes in their design of new candidates for biological testing. This is paralleled by the emergence of numerous companies offering a wide range of starting materials (e.g., aromatic and heteroaromatic halides and boronates), catalysts, chiral ligands, etc. The downside of this otherwise very favorable situation is that medicinal chemists end up studying and developing similar structures, since they are relying on the same reactions and the same, albeit broad, pool of substrates.

One of the considerable attractions of transition-metal-catalyzed reactions is that a small amount of catalyst can convert a vast quantity of starting material, and asymmetric induction can be readily incorporated into the process by the use of chiral ligands. Even if, in principle, the catalyst can be recov-

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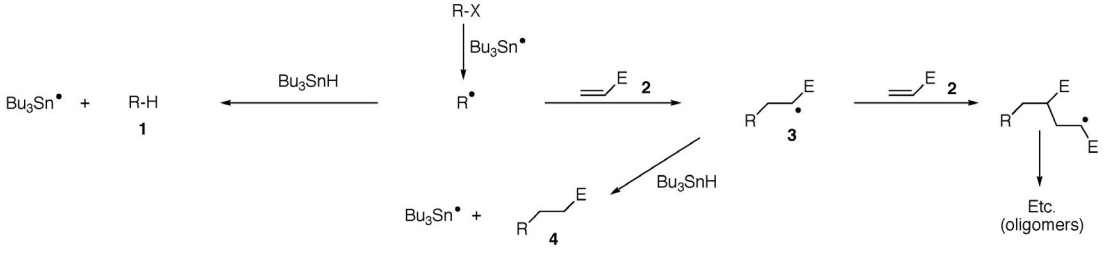
ered, this proves in many cases to be too expensive and uneconomical. In this respect, there is a similarity with radical chain reactions, since a small amount of initiator can induce the formation of a large quantity of product. The initiator is not strictly speaking a catalyst because it is consumed in the process, but common initiators are generally very inexpensive and thus expendable.

This favorable aspect is, unfortunately, countered by a prevalent perception that radical processes are unselective, difficult to control, and difficult to scale up. Radicals seem to conjure up visions of explosions, tars, runaway and irreproducible reactions, vast and unacceptable volumes of solvent, and so on. One can identify several causes for these negative, even if mostly unfounded, impressions. Most can be traced to a gap in the curriculum of chemistry graduates. Only a small fraction of chemistry departments offer complete courses dedicated to teaching the properties and reactivity of radicals and their use in synthesis. This is mirrored by the relatively limited number of groups actively developing radical processes and training Ph.D. students in the art of handling radicals. As a consequence, there are only a few chemists in industry who would naturally consider the incorporation of one or more radical steps in their synthetic designs. This is compounded by the fact that the little radical chemistry (excluding polymers) taught at undergraduate or even graduate levels covers mostly organotin derivatives. The radical chemistry of stannanes is tremendously powerful, but the elimination of organotin residues poses huge problems of purification and effluent management that have not yet been solved adequately. The pre-eminence of stannanes in radical chemistry has thus been both a blessing and a curse [1].

The exceptional efficiency of the hydrogen atom transfer from stannanes, reflected in its exceedingly high rate constant, of the order of 10^6 M^{-1} s^{-1}, introduces another intrinsic and important limitation, as far as capturing the intermediate radicals by internal or external traps is concerned. Except in especially favorable cases, even *intramolecular* reactions often cannot compete with the hydrogen abstraction step without the use of high-dilution or syringe-pump techniques. However, these experimental contrivances, which have generally proved effective in promoting *unimolecular* ring-closures over the *bimolecular* hydrogen abstraction from the stannane, are of very limited applicability when dealing with the *intermolecular* capture of the intermediate radicals, since both competing steps are bimolecular and therefore equally concentration-dependent. Success often requires the combined use of an excess of a highly reactive alkene trap and the slow addition of the stannane component (Giese reactions) [1]. It takes some experimentation and an appreciation of the approximate rate constants of the various steps to secure an acceptable yield of the desired adduct **4** (Scheme 1). If the olefinic trap **2** is not sufficiently radicophilic, premature reduction to give alkane **1** will dominate, whereas the use of too large an excess of olefin **2** or too low a concentration of the stannane (too slow addition) will encourage the formation of oligomers through further additions of intermediate **3** to olefin **2**. These considerations are obviously not limited to stannane-based systems, but apply equally to other radical-based methods where similar competing pathways exist.

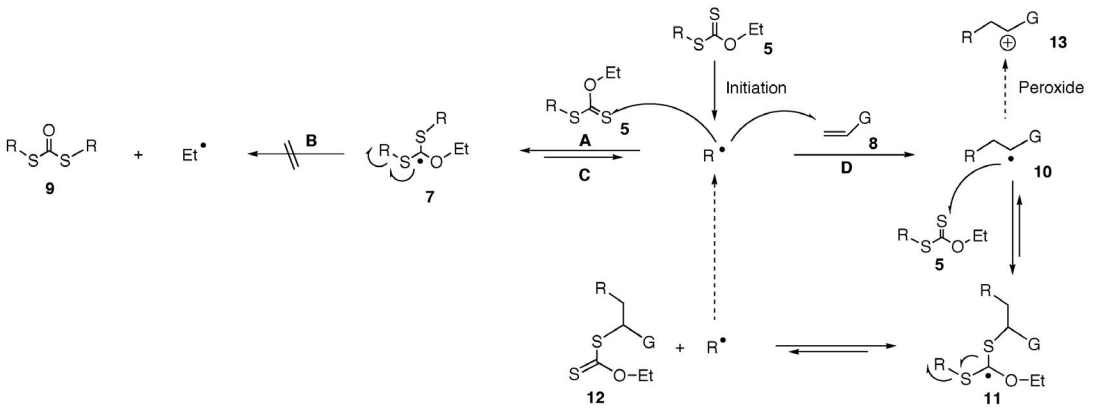


Scheme 1

The creation of carbon–carbon bonds in an *intermolecular* fashion starting with *unactivated* olefins thus remains an important, but as yet an incompletely solved problem in organic synthesis. Indeed, only very few reactions are capable of accomplishing this task, and none is of sufficiently broad generality. It is the purpose of this brief review article to discuss the potential of xanthates and related dithiocarbonyl derivatives in addressing this issue.

DEGENERATIVE TRANSFER OF XANTHATES AND RELATED GROUPS

The mechanism underlying the radical xanthate transfer process is outlined in Scheme 2 [2]. The chemical or photochemical initiation step gives rise to a very small concentration of radicals R•. These are rapidly scavenged by the starting xanthate **5**, since the thiocarbonyl group of the xanthate is generally vastly more radicophilic than the olefinic trap **8**. This very fast addition step results in the formation of a tertiary adduct radical, **7**, which is stabilized by three heteroatoms. It is further too hindered to dimerize, or does so reversibly, and cannot disproportionate; it can therefore only evolve through β-scission, either of the C–O (path **B**) or the C–S bond (path **C**). The former, leading to *S*,*S*′-dithiocarbonate **9**, is difficult, since it involves the breaking of a particularly strong bond to form a high-energy ethyl radical. The latter (path **C**) simply returns the starting xanthate and the same radical R•.



Scheme 2

In other words, *the reaction of the initial radical R• with its xanthate precursor is reversible and degenerate*. This point is crucial to understanding the properties of the system: since R• is continuously regenerated, its effective lifetime in the medium is increased considerably. Now, addition even to simple, non-activated alkenes becomes possible. More generally, the radical is able to undergo comparatively slow inter- or intramolecular processes not easily achievable with other methods. In the case of addition to alkene **8** (path **D**), a new radical **10** is formed, which in turn reacts *reversibly* with the starting xanthate **5** to produce intermediate radical **11**. Reversible collapse of this species furnishes finally adduct **12**, as well as the initial radical R• to propagate the chain.

The general reaction manifold, even in the simplified form displayed in Scheme 2, embodies numerous subtleties that have to be appreciated in order to understand the unique properties of the system and to gain practical mastery of the process. There is strong evidence to suggest that adduct radicals such as **7** and **11**, resulting from the very fast radical addition to the thiocarbonyl of a xanthate, are a fairly persistent species. In contrast to ordinary radicals, where radical–radical interactions take place at near diffusion rates, the reaction of radicals of type **7** and **11** with themselves or with other radicals either does not occur at all or is very much slower than diffusion. These "dormant" species therefore act as "reservoirs" for "active" radicals such as R• and **10**. Furthermore, the equilibrium between the

"active" and "dormant" radicals is generally in favor of the latter. That is to say, for instance, that path **A** dominates path **C**.

These observations have several far-reaching consequences. The first is that the concentrations of the "active" radicals ($R^{\bullet}$ and **10**, and any radicals derived from the initiator) are considerably diminished, resulting in a decrease in the importance of the termination steps and a significant improvement in the efficiency of the radical chain process. The second is that it is now possible to operate under very concentrated conditions, not only because the degenerate reaction of the initial radical $R^{\bullet}$ with its xanthate precursor means that this step does not compete with the desired addition to the olefinic trap **8**, but also because an increase in the concentration favors the *bimolecular* formation of the "dormant" species as opposed to the concentration-independent *unimolecular* fragmentation leading to the "active" radicals. The process is therefore self-regulating, in terms of keeping the concentration of the "active" radicals low, and thus quite forgiving with respect to modifications in the experimental set-up. The third consequence is that the *relative* concentration of all the "active" radicals in the medium is controlled. To a first approximation, and neglecting polar factors, the rate of fragmentation of "dormant" intermediates, such as **7** and **11**, is greater when it leads to more stabilized radicals. Hence, the concentration of the more thermodynamically stable radicals will be higher than that of the less stabilized ones. Indeed, a mere *two* kcal/mol difference in relative stability between two "active" radicals will result in about a *hundred-fold* difference in their relative concentration. So, while the *absolute* steady-state concentrations of the "active" radicals remain very low, their *relative* concentrations can differ by several orders of magnitude.

This last observation represents a key element for controlling the whole radical addition transfer process. It is important for success to design the reaction such that the initial radical $R^{\bullet}$ is more "stable" than adduct radical **10** (with the caveat noted above concerning polar factors), so as to favor the fragmentation of the "dormant" intermediate **11** toward the former. This ensures that the steady-state concentration of $R^{\bullet}$ remains much higher than that of radical **10** and path **D** remains favored over the unwanted oligomerization, which occurs by further addition of radical **10** to olefin **8**. In other words, as long as the starting xanthate **5**, which is the progenitor of the *more stable* radical $R^{\bullet}$, is present in the medium, it will indirectly protect the product xanthate **12**, which is the progenitor of the *less stable* radical **10**, against further undesired oligomerization reactions. The greater the difference in stability between $R^{\bullet}$ and **10**, the better is the dichotomy in the reactivity of the starting and product xanthates, **5** and **12**, and the easier it is to control the process. These crucial considerations have to be kept constantly in mind, especially when dealing with intermolecular reactions.

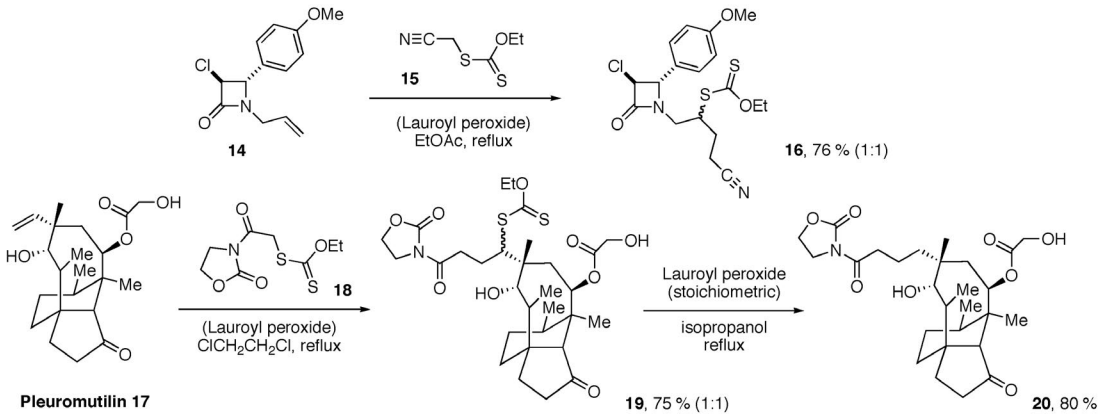
In Scheme 2, an *O*-ethyl xanthate is used since most of the examples we have examined involve such xanthates. Potassium *O*-ethyl xanthate is commercially available and inexpensive (it is used mostly as a flotation agent in the mining industry), and the desired xanthates can often be conveniently prepared by a simple substitution reaction. The ethoxy group, however, remains essentially as a spectator, whose influence is only indirect, and can hence be replaced by other groups. *O*-Neopentyl xanthates are more resistant to degradation by ionic processes and sometimes can be used to advantage. Furthermore, exactly the same reversible addition–fragmentation transfer (RAFT) mechanism can be applied to dithiocarbamates (RSC(=S)NR'R"; it is preferable that at least one of the substituents on the nitrogen be an aryl or an electron-withdrawing group), trithiocarbonates (RSC(=S)SR'), dithioesters (RSC(=S)R'), etc. [3]. Except in a few special applications, these other dithiocarbonyl derivatives do not offer added benefits over the less expensive and more readily available xanthates.

There are many advantages, practical and otherwise, attached to the use of the reversible addition–fragmentation on dithiocarbonyl derivatives: (a) the reagents are inexpensive, generally stable, easy to handle, and readily available; (b) no heavy metals are involved; (c) the radical additions can be run under high concentrations, typically 1 to 2 M, and sometimes even without solvent (reduced waste); (d) while numerous solvents can be used, including water, we have more recently found that the environmentally benign and industrially acceptable ethyl acetate is very convenient for most reactions; (e) the processes are self-regulating, safe, and easily scalable; (f) although peroxides are usually the pre-

ferred initiators for triggering the chain reaction, other initiators such as diazo derivatives, a combination of triethylborane and oxygen, or irradiation with UV or even visible light can be used in some cases; (g) the reactions are atom economical, since all the starting components end up in the product, and highly convergent in the case of the intermolecular variants; (h) the product, being also a xanthate, can act as the starting point for another radical transformation or can be converted into myriad derivatives using the exceedingly rich chemistry of sulfur. One final, very important feature is that a classical chain process is not strictly necessary. If the adduct radical **10** (or more generally any intermediate radical involved in the actual process in hand) is electron-rich, it can often be oxidized by the peroxide, causing a crossover from a radical to a polar manifold. This will be important when dealing with the synthesis of aromatic and heteroaromatic derivatives and when using isopropanol to reduce off the xanthate group. The peroxide thus behaves both as an initiator and a reagent, and needs to be used in stoichiometric amounts.

Some examples and a brief overview

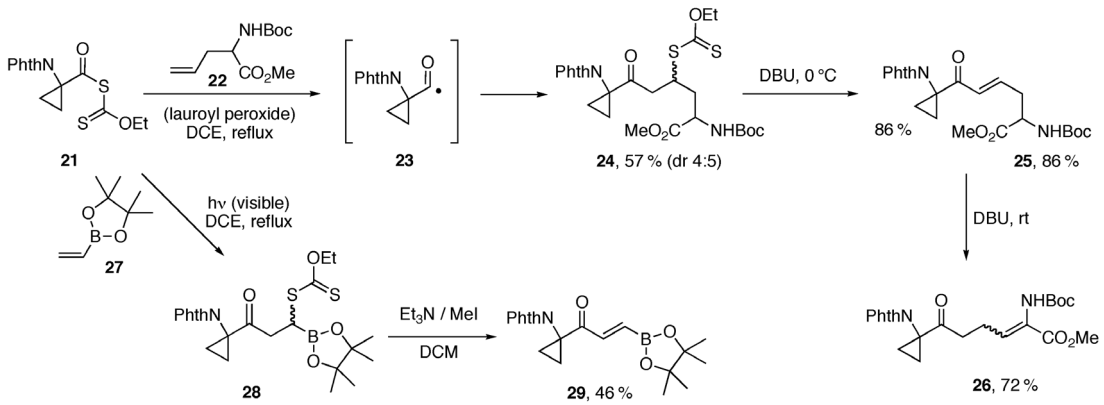
The radical nature of the xanthate addition to alkenes makes it compatible with numerous functional groups. Common polar groups, such as free alcohols, ketones esters, amides, etc., are well tolerated and do not require prior protection. The examples pictured in Scheme 3 illustrate these aspects.



Scheme 3

The first is the addition of *S*-cyanomethyl xanthate **15** to chloroazetidinone **14** to give adduct **16** without harm to the relatively fragile β-lactam ring [4], whereas the second concerns the addition of xanthate **18** to native pleuromutilin, **17**, a natural antibacterial terpene, to furnish the corresponding addition-transfer product **19** in good yield [5]. Dissolving this product in refluxing isopropanol and adding a stoichiometric amount of lauroyl peroxide portion-wise delivers efficiently the reduced compound **20**. In the absence of a better trap, the radical generated from the xanthate abstracts the tertiary hydrogen atom from the isopropanol to give **20** and a ketyl radical, which is oxidized into acetone by the peroxide [6]. The xanthate group can be reductively removed by other reducing agents such as tributylstannane, tris(trimethylsilyl)silane (TTMSS), hypophosphorus acid derivatives [7], Raney nickel, or nickel boride.

The presence of the xanthate may be exploited to introduce additional functional groups, as shown by the transformations in Scheme 4 starting from *S*-cyclopropylacyl xanthate **21**. This xanthate is the precursor of cyclopropylacyl radical **23** which, interestingly, undergoes neither fast ring opening nor loss of carbon monoxide but can be captured intact with either allyl glycine derivative **22** or with

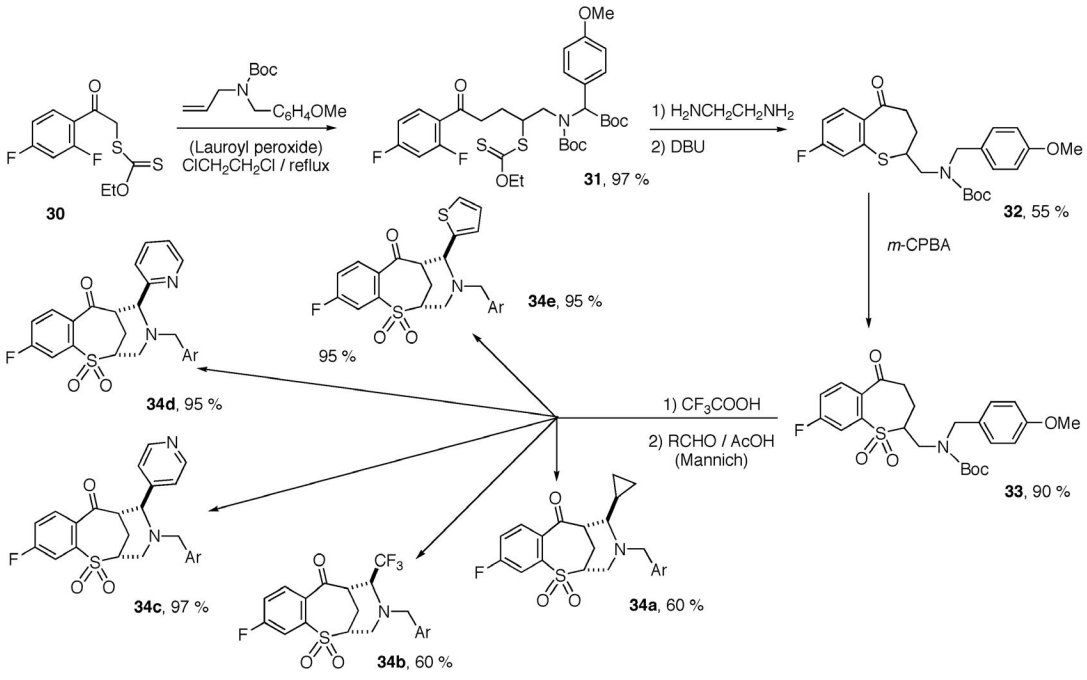


Scheme 4

vinyl boronate **27** to give the corresponding adducts **24** and **28** [8]. The latter is not isolated but immediately treated with triethylamine and methyl iodide to give the rare vinylboronate structure **29** in moderate overall yield. The need for the methyl iodide is to capture irreversibly the eliminated xanthate salt and any nucleophilic sulfur species derived therefrom and prevent their conjugate addition to the quite electrophilic vinylboronate product.

The addition of an alkylating scavenger is not necessary for adduct **24**, where the xanthate group can be cleanly eliminated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). If the reaction is performed at 0 °C, a good yield of unsaturated ketone **25** can be secured. At room temperature, migration of the olefin takes place via the corresponding extended enolate to give finally the thermodynamically more stable enamide isomer **26**. Quite unusual amino acids, which would otherwise be accessible only very tediously, can thus be succinctly prepared.

One or both of the sulfur atoms in the xanthate product may be incorporated into the final structure. One approach is outlined in Scheme 5, where novel, complex morphinane-like scaffolds **34a–e** are rapidly assembled [9]. Thus, addition of xanthate **30** to a protected allylamine provides the expected adduct **31** in high yield. This is followed by aminolysis of the xanthate group with ethylenediamine into the corresponding thiol, which, in the presence of DBU, displaces the *ortho* fluorine of the aromatic ring to produce benzothiepinone **32**. Oxidation with peracid furnishes sulfone **33**, where the Boc group can be easily removed by trifluoroacetic acid and the resulting secondary amine made to react with a number of aldehydes to give rise to the desired tricyclic structures **34a–e** through an intramolecular Mannich reaction. These medicinally interesting scaffolds possess many points of attachment for the synthesis of libraries with a broad diversity of substituents. Apart from modifications in the aldehyde partner, the still activated second fluorine on the aromatic ring may be readily substituted, and the ketone and secondary amine further elaborated through the very rich chemistry of these fundamental groups in organic chemistry.



Scheme 5

It is clear that by modifying the initial xanthate and olefinic trap, an infinite number of adducts can be obtained containing various combinations of functional groups that can be later made to react further. Indeed, over the years, our group has examined more than 100 different starting xanthates and performed over 2000 additions. The broad scope of this reaction and tolerance for functional groups can be gauged by inspecting the selection of 20 xanthates displayed in Fig. 1. The first 3 contain a masked aldehyde associated with a nitrile (**35**), an ester (**36**), or a ketone (**37**) [10]. Xanthate **38** embodies a 1,2-diketone [10], whereas **39** carries an α-amino ketone (PhthN = phthalimido) and **40** an α-chloro ketone [11]. The addition products from all of these xanthates can be converted into an array of heterocyclic and heteroaromatic derivatives through the application of various ionic reactions such as the classical Hantzsch and Knorr condensations. Xanthates **41–43** contain at least one phosphonate group that can be later exploited in typical Horner–Wadsworth–Emmons condensations [12]. Xanthate **41** is especially useful since it allows the introduction of a side-chain on a ketone by a radical addition on one side and by a Horner–Wadsworth–Emmons condensation on the other. It was used in this capacity in a short synthesis of xestamines C, E, and H [12b]. Xanthate **44** furnishes directly a protected α-amino acid function [8a], whereas **45** and **46** introduce a cyanohydrin and a dithiane oxide, respectively [12]. The last two groups are readily converted into the corresponding aldehyde, alcohol, or carboxylic acid. Xanthates **45** and **46** can thus be considered as homologating synthons, allowing the addition of a one-carbon fragment at various levels of oxidation. Xanthate **47** is a representative of the broad class of *S*-acyl xanthates, which are precursors of various acyl or thio acyl radicals ($RC^{\bullet}=O$; $ROC^{\bullet}=O$; $RR'NC^{\bullet}=O$; $ROC^{\bullet}=S$, etc.) [14]. These can behave in various ways depending on the nature of substituents, one illustration being xanthate **21** discussed in Scheme 4. Xanthates **48–52** bear different trifluoromethyl-containing groups and are exceedingly useful for preparing simple or complex fluorinated starting materials [15]. Finally, xanthates **53** and **54** illustrate the possibility of direct introduction of a heteroaromatic ring, pyridine and tetrazole rings in the present case [16].

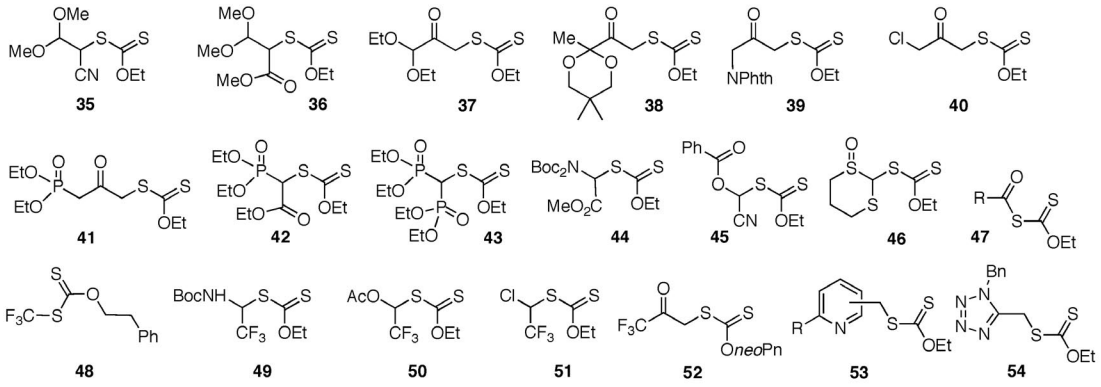
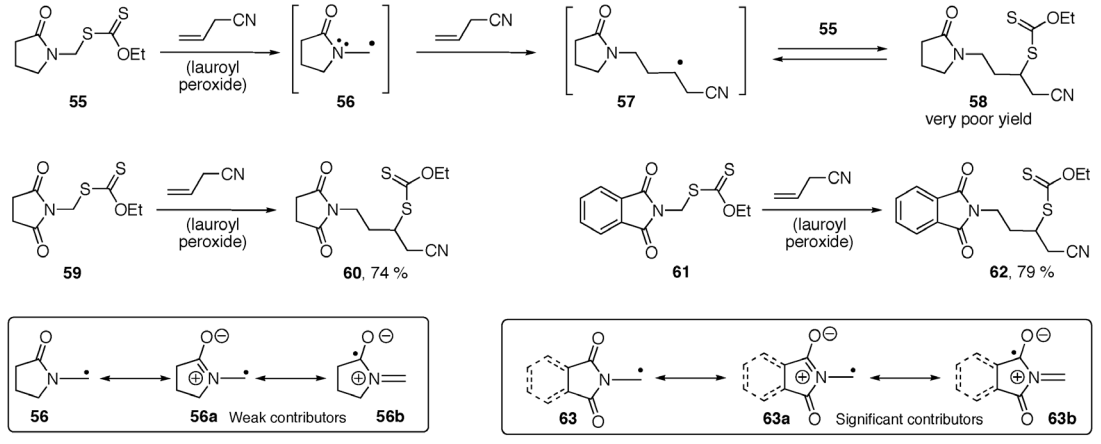


Fig. 1

The remainder of this article will describe how solutions to specific synthetic problems can be devised using this technology.

Aminoalkylation and *N*-arylaminoalkylation of alkenes

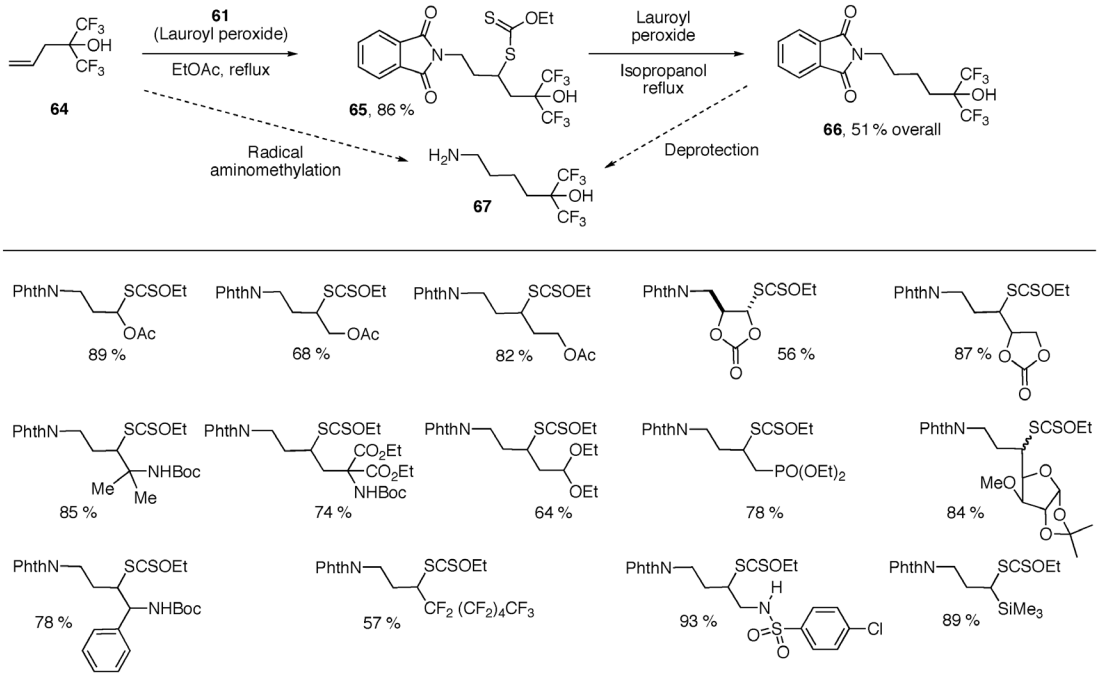
Amines constitute one of the major classes of organic compounds, and their importance cannot be overstated, yet their synthesis is seldom trivial or straightforward and sometimes even quite challenging. From a radical methodology perspective, one obvious route would consist of generating and capturing an aminomethyl radical $RR'NCH_2^{\bullet}$ starting, for example, with the corresponding xanthate $RR'NCH_2SCSOEt$. Such compounds are rather unstable and difficult to handle unless at least one of the substituents on nitrogen is an electron-withdrawing group. However, when the radical addition of xanthate **55** to allyl cyanide was attempted, the result was mostly oligomer formation and very little of normal adduct **58** was produced (Scheme 6). The stabilization of the initial radical **56** by the lone pair on the nitrogen is not sufficient to make it more stable than secondary adduct radical **57**. The key requirement discussed above, namely, that the initial radical has to be more stable than the adduct radical, is clearly not obeyed in this case.



Scheme 6

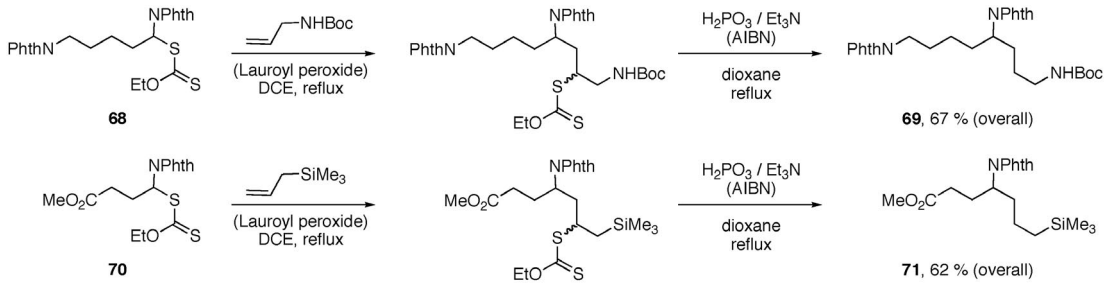
The solution out of this impasse turned out, paradoxically, to be the addition of another carbonyl group and thus to work with the imide instead of the lactam [17]. Indeed, succinimidyl and phthalimidyl xanthates **59** and **61** reacted cleanly with allyl cyanide to furnish the corresponding addition products **60** and **62**, respectively. Intuitively, it would seem that a further attracting group on the nitrogen should diminish the interaction of the lone pair with the unpaired electron and therefore decrease the stability of radicals such as **63**. In fact, these radicals apparently acquire a greater allylic character through resonance structures **63a** and **63b**, and their stability increases sufficiently to allow the desired radical chain to proceed efficiently. The contribution of resonance structures **56a** and **56b** in the case of the lactams is too small to influence positively the outcome of the radical addition.

Xanthate **61** is a nicely crystalline compound, trivially made by reaction of the inexpensive and commercially available chloride (PhthNCH$_2$Cl) with potassium *O*-ethyl xanthate. Its successful addition to alkenes opens an exceedingly powerful route to amines [17a]. Indeed, once the xanthate group in the adduct is reduced off and the PhthN protecting group removed, the overall process would correspond to an aminomethylation of an alkene. This is illustrated by the addition of xanthate **61** to hexafluorinated olefin **64** to give adduct **65** in high yield. This compound need not be isolated but may be reduced directly into **66** (Scheme 7). Deprotection would lead to amine **67**, which results formally from the addition of the elements of methylamine to alkene **64**. A number of additions to variously substituted olefins are collected in the lower part of Scheme 7 to provide an idea of the scope.



Scheme 7

Xanthate **61** is in fact the simplest member of a family of reagents that more generally allow the aminoalkylation of alkenes. For instance, compound **68** can be readily prepared by the radical decarbonylative rearrangement of the *S*-acyl xanthate derived from lysine and represents a 1,5-diamine synthon [17b]. Its addition to alkenes proceeds very effectively, as shown by its addition to Boc-protected allylamine to give differentially protected and unsymmetrical triamine **69** after reductive removal of the

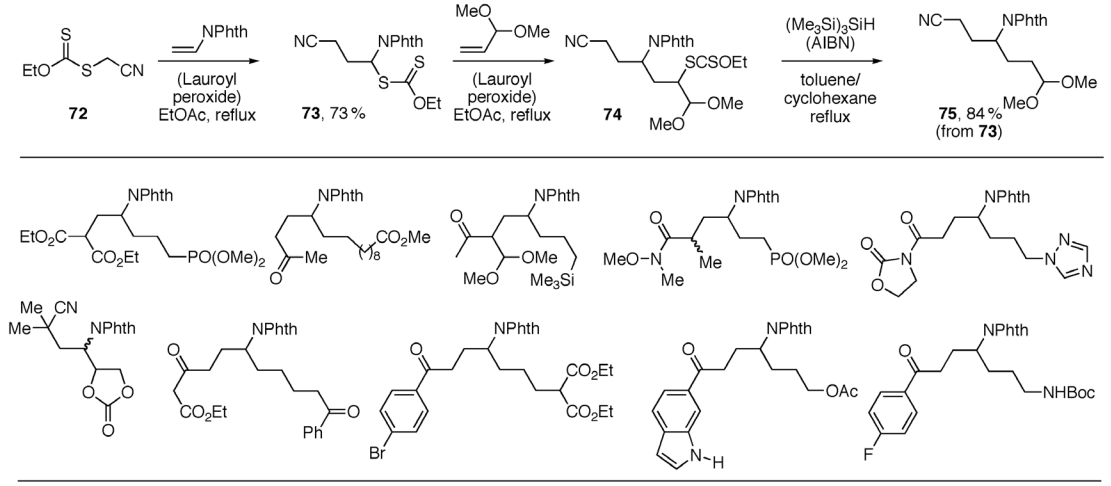


Scheme 8

xanthate group (Scheme 8). Such deceptively simple-looking unsymmetrical triamines are in fact very tedious to assemble by classical approaches.

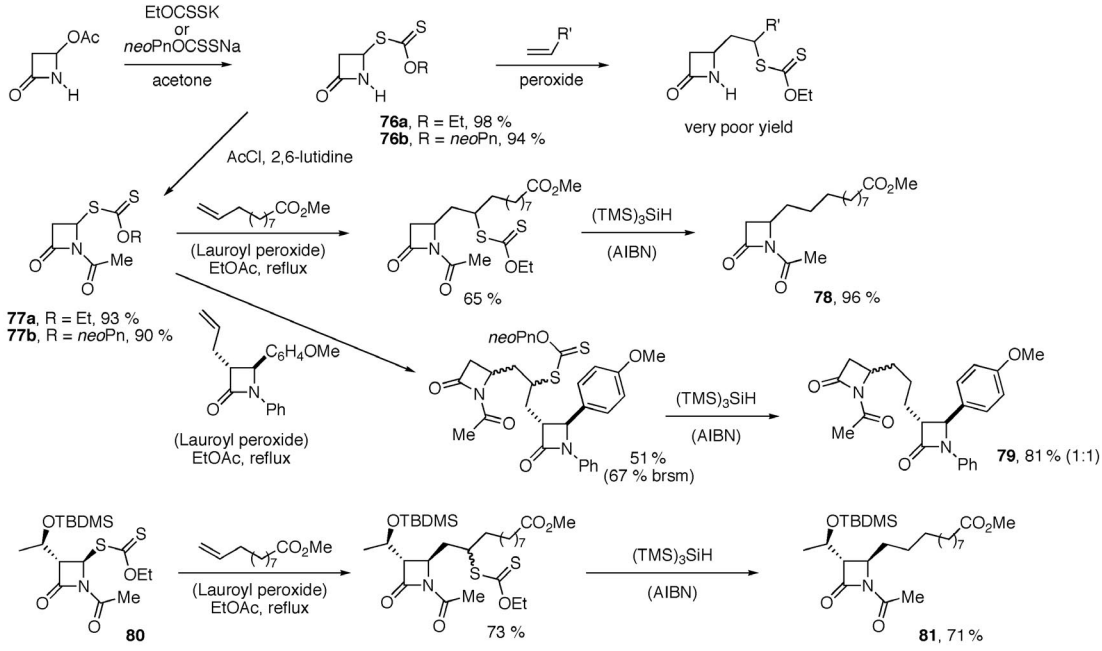
A 1,4-diamine synthon can be similarly prepared from ornithine, and its addition to alkenes furnishes the corresponding PhthN-protected 1,4-diamine adducts. Indeed, starting from various commercially available amino acids, we made a number of xanthates corresponding to functional amine synthons [17b]. The second example depicted in Scheme 8 illustrates the synthesis of a trimethylsilane-substituted protected γ-amino acid **71** by addition of glutamic acid-derived xanthate **70** to allyltrimethylsilane followed by reduction.

Another convenient, highly convergent, and very flexible route to functional amine hinges on the addition of a xanthate to commercially available *N*-vinyl phthalimide [18]. This furnishes directly adducts with a geminal disposition of the xanthate and PhthN groups that are perfectly set to undergo a second radical addition to an alkene. This sequence is showcased by the sequence in Scheme 9, where the addition of xanthate **72** to *N*-vinyl phthalimide is followed by the addition of the resulting xanthate **73** to the dimethyl acetal of acrolein to give **74**, which was not purified but reductively dexanthylated into **75** in order to simplify characterization. In this manner, three molecules—the xanthate, *N*-vinyl phthalimide, and the alkene—are stitched together to produce a highly functionalized protected amine derivative. Numerous combinations can therefore be envisaged, some of which are displayed in the lower part of Scheme 9. In all cases, the xanthate group in the final adduct was reduced off in comparable overall yield.



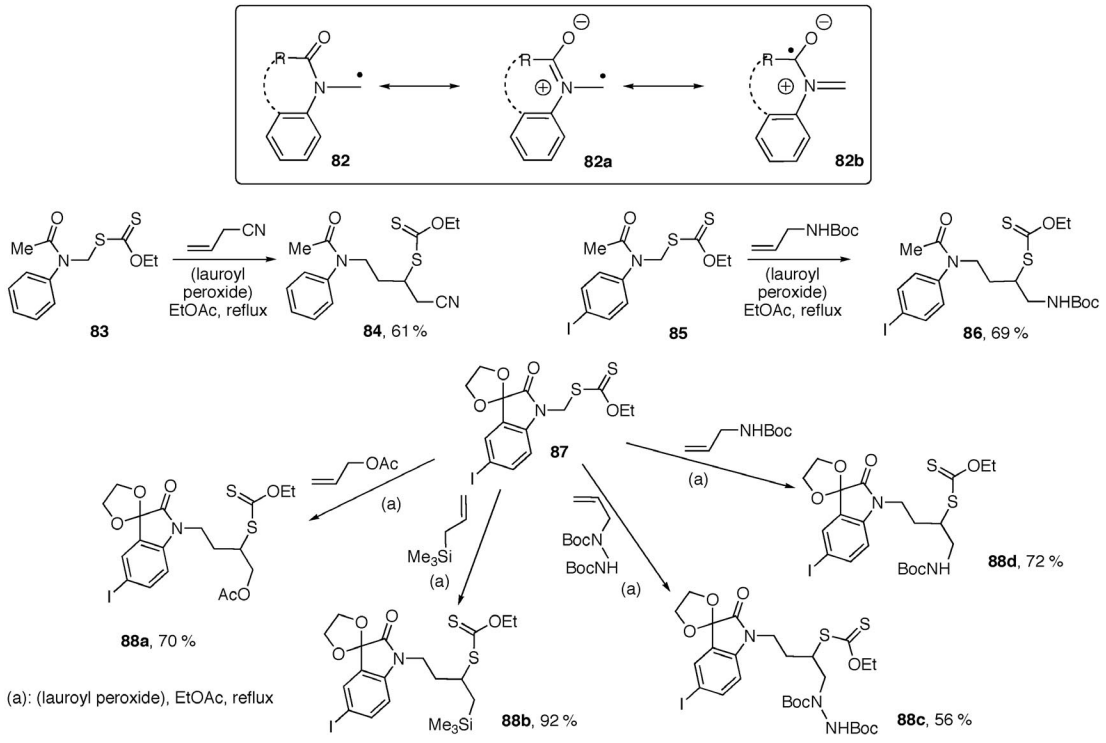
Scheme 9

The stabilization of a radical through an imide structure allowed us to solve another problem related to the modification of β-lactams that frustrated us many years ago. β-Lactam xanthates such as **76** are easily prepared from the commercially available acetoxy analogues, but all our attempts to add **76a** to an unactivated alkene were unsuccessful. In view of our observations related to the aminomethylation process discussed in Scheme 6, a simple solution presented itself; it consisted in acetylating the nitrogen of the azetidinone so that the radical derived from the xanthate could now benefit from the extra stabilization provided by the imide function. Indeed, we were delighted to find that acetylated derivative **77a** underwent a reasonably clean addition to give the normal addition product, which was reduced by TTMSS into **78** to simplify characterization [19]. It proved even possible to perform the addition of **77b** to a β-lactam bearing alkene to give bisazetidinone **79** after dexanthylation. Finally, the more complex azetidinone **80** underwent the addition equally efficiently to give ultimately **81** in good overall yield. An original, convergent, and flexible approach for elaborating β-lactam rings is now in hand.



Scheme 10

Another, possibly more useful extension, of this chemistry, derives from the question of whether one of the carbonyl groups in the imide could be replaced by an aromatic or heteroaromatic ring. In other words, would the stabilization of canonical structures **82a** and **82b**, by conjugation with the aromatic ring be sufficient to tilt the balance in the right direction and promote the desired chain process? In the event, the extra stabilization of the radical, while certainly small in absolute terms, indeed proved decisive, as indicated by the successful additions of xanthates **83** and **85**, as well as isatin xanthate **87**, to give adducts **84**, **86**, and **88a–d** in generally good yield (Scheme 11) [20]. Note the compatibility of the procedure with the presence of an aromatic iodine substituent, as well as the possibility of introducing a hydrazine onto the side-chain of **88c**. Thus, by exploiting subtle, and hitherto under-appreciated, effects for stabilizing the initial radical, it has become possible to access a vast array of highly functionalized primary amines, both terminal and internal, and *N*-substituted anilines. Moreover, these extremely encouraging results are only preliminary, since numerous extensions and variations have yet to be examined.



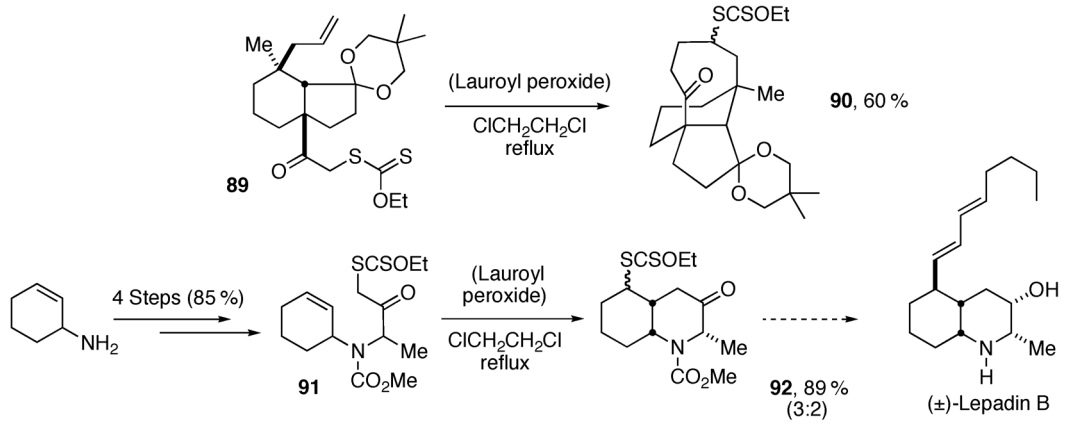
Scheme 11

Synthesis of carbo- and heterocyclic structures

The xanthate transfer process can be readily applied to the construction of cyclic structures, either by direct cyclization, or by using the *intermolecular* radical addition to bring together the elements necessary for an ionic or organometallic ring-closure, or even by applying a combination of both, to access highly complex molecular architectures. Examples of these possibilities will be presented and discussed in this section.

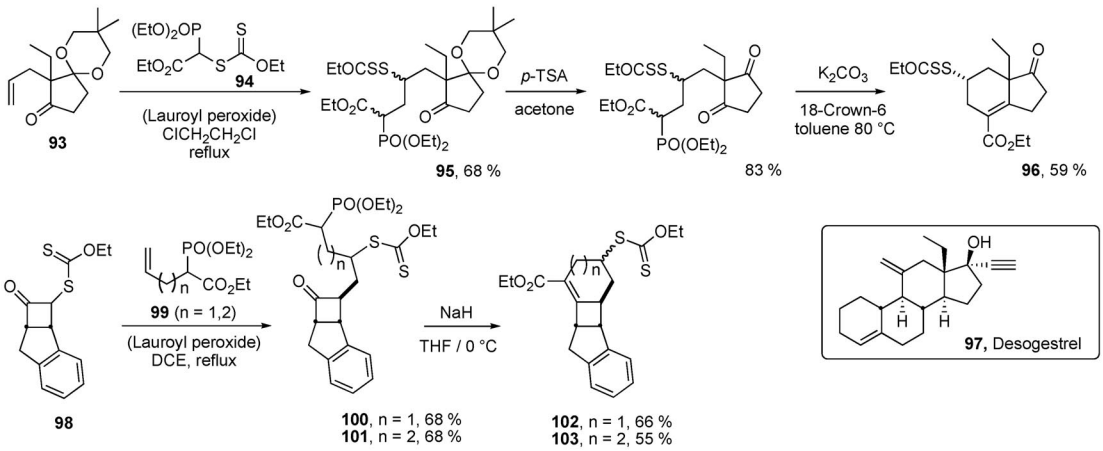
While it is generally easy to construct five-membered rings using almost any of the radical methods so far reported in the literature, it is the routinely simple and direct access to larger rings that sets the xanthate transfer technology apart from other processes. The direct formation of six-, seven-, and eight-membered rings by classical radical approaches is understandably rare due to the need to overcome the intrinsic comparative slowness of the cyclization step with respect to premature capture of the uncyclized radical, and recourse to high-dilution or syringe-pump techniques is usually required [21]. Such limitations do not apply in our case because the degeneracy of the reaction of a given radical with its xanthate precursor extends considerably the lifetime of the intermediate radicals. The two examples pictured in Scheme 12 are representative.

In the first, the 8-*endo* ring-closure of xanthate **89** into **90** allows the rapid installation of the eight-membered ring found in pleuromutilin **17**, solving thus one of the main hurdles in the total synthesis of this natural product [22]. In the second, the cyclization of xanthate **91** occurs readily also under normal concentration conditions to give the *cis*-perhydroquinoline system **92**, which was taken forward in a formal racemic synthesis of lepadin B [23]. The carbon bearing the methyl group equilibrates under the reaction conditions through the easily formed enol to give product with the relative stereochemistry shown.



Scheme 12

The combination of the intermolecular radical addition with an ionic process constitutes another very powerful and versatile approach to polycyclic structures. For instance, addition of xanthate **94** to 2-allyl pentanone **93** furnishes adduct **95**, which, upon deprotection of the second ketone and exposure to base, gives rise to the CD ring subunit **96** found in desogestrel **97**, an exceedingly potent ethylsteroid contraceptive (Scheme 13) [24]. Of the two ketone groups, only the one leading to an equatorial xanthate reacts with the phosphonate. The sequence is therefore highly diastereoselective and provides a xanthate strategically located in the important 11-position.

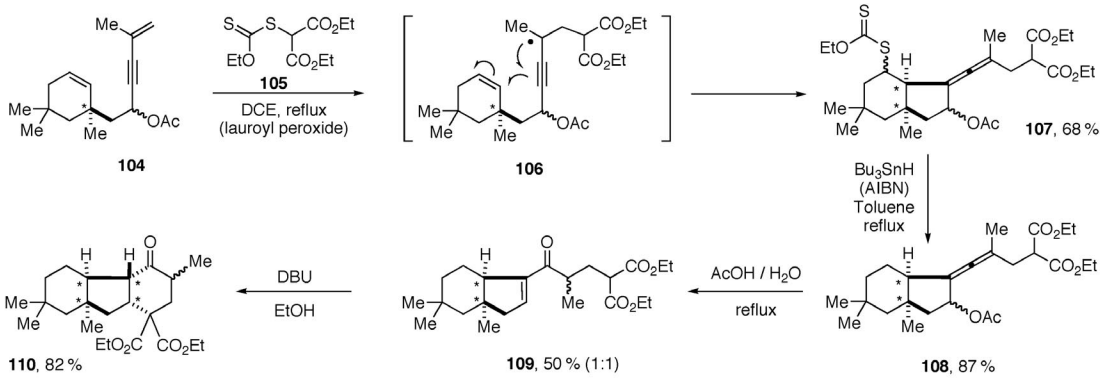


Scheme 13

The components for the Horner–Wadsworth–Emmons reaction may be distributed differently. The transformations in the lower part of Scheme 13 start with reactants **98** and **99**, where the phosphonate is attached to the alkene while the xanthate is placed near the ketone. Depending on the distance between the terminal olefin and the phosphonate, it is possible to construct cyclohexenes such as **102** or cycloheptenes such as **103** by treating the corresponding adducts **100** and **101** with base [25]. While, obviously, the sequence is not limited to cyclobutanones since other cycloalkanones and open-chain ketones may equally be used, it is worthwhile pointing out that the synthesis of *S*-2-oxocyclobutyl xan-

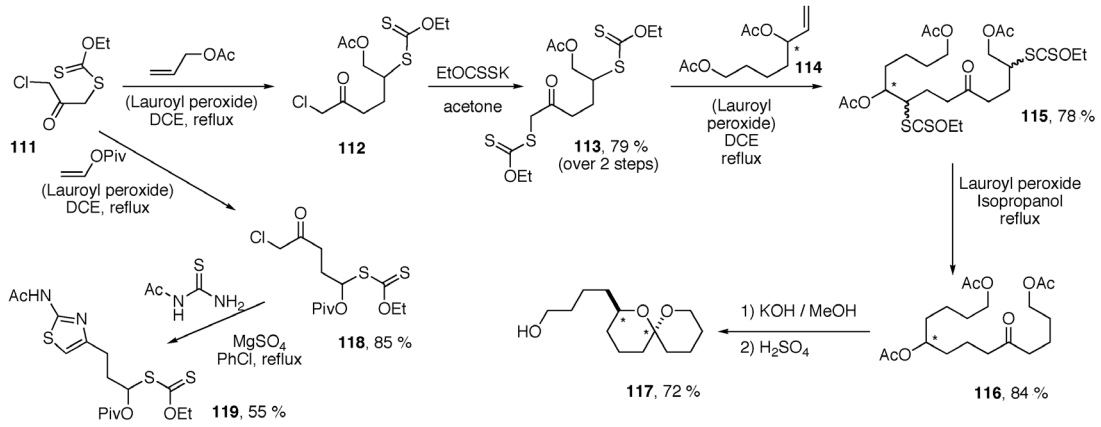
thates such as **98** is not trivial and raises interesting mechanistic considerations outside the scope of this account [26].

The radical addition may be used to put in place the elements needed for a Robinson-type annelation [27] or an internal Michael addition in order to construct complex polycyclic structures. The sequence in Scheme 14 is illustrative and features a rare case of a propargyl radical ring-closing to give an allene [28]. Thus, addition of malonyl xanthate **105** to enyne **104** produces intermediate propargyl radical **106**, which undergoes cyclization and xanthate transfer to give finally bicyclic xanthate **107** containing a tetrasubstituted allene. Reductive removal of the xanthate group leads to **108**, and solvolysis of the allenyl acetate motif by refluxing in aqueous acetic acid gives rise to enone **109**. Finally, treatment with DBU in ethanol induces the intramolecular Michael addition to afford tricylic compound **110**. The configuration of the starred quaternary carbon in **104** ultimately controls the relative stereochemistry of the three other starred chiral centers in the final product **110**. The only uncontrolled asymmetric is the carbon bearing the methyl group adjacent to the carbonyl but which can be corrected through equilibration via the corresponding enol or enolate. Beyond the swift elaboration of polycyclic structures, this approach highlights an unusual synthesis of allenes, which could be of much broader applicability.



Scheme 14

The synthesis of oxygen heterocycles may be readily accomplished by the same general strategy of using the radical process to bring together the required functional groups. In Scheme 15, a unified approach to spiroketals is outlined. Spiroketals are ubiquitous in nature, especially among pheromones and marine products. Our synthesis relies on the use of xanthate **111** to perform two successive radical additions to two different alkenes bearing suitably located protected alcohols which, when finally released, close onto the ketone under acidic conditions [29]. In the example given, the first addition is to allyl acetate to give chloroketone **112** where the chlorine is then substituted by a xanthate group. The new xanthate **113** thus obtained is then made to add to another more complex allyl alcohol **114** to furnish adduct **115**. Notice that of the two xanthate groups in compound **113**, only the one leading to the more stable carbonyl-stabilized radical undergoes the addition. Reductive removal of the xanthate groups and saponification of the acetates in the product **116** followed by acid treatment leads ultimately to 6,6-spiroketal **117**. Other combinations of ring sizes containing, for example, five- and seven-membered rings may be obtained by replacing one or both of the allylic alcohol traps with protected vinylic or homoallylic alcohols. This route is flexible, convergent, and can be made enantioselective by the use of readily available chiral, nonracemic alkenols (e.g., starred carbon in **114**). Furthermore, the xanthate groups need not be removed, allowing in this way access to more highly functionalized spiroketals. The

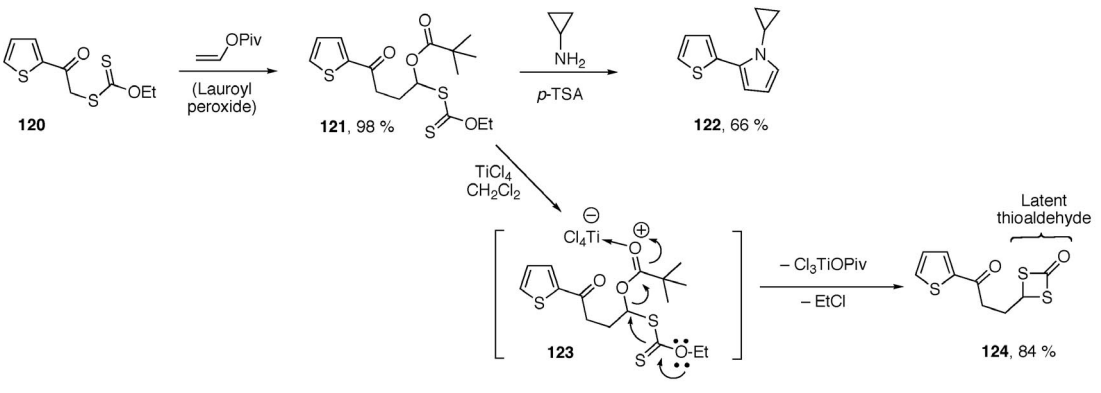


Scheme 15

use of protected allyl- or homoallyl-amines would in principle provide a route to nitrogen-containing analogues [30].

Xanthate **111** is indeed a highly versatile reagent that can be used to introduce various side-chains on both sides of the ketone group. It also underscores the remarkable mildness of the xanthate transfer process since it is possible to create new carbon–carbon bonds without affecting the fragile α-chloroketone moiety. α-Haloketones are starting materials for numerous classical heteraromatic forming reactions, such as the Bischler–Möhlau indole synthesis, the Feist–Benary furan synthesis, the Hantzsch pyrrole and thiazole syntheses, the Tschitschibabin indolizine condensation, etc. The synthesis of thiazole **119** via α-chloroketone **118**, also shown in Scheme 15, is an example where the radical addition is combined with the Hantzsch reaction [11].

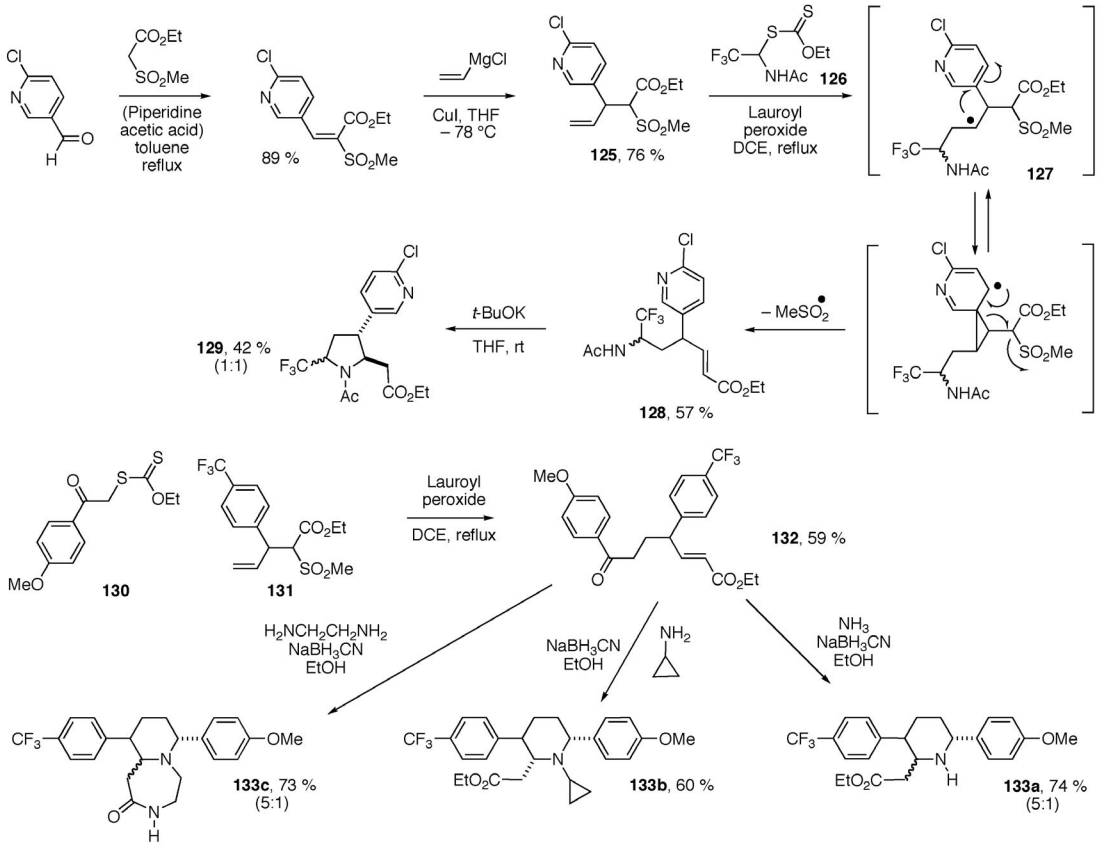
Adduct **118** is interesting in another respect because the terminal carbon is geminally substituted by a xanthate and a pivalate group and has therefore the oxidation level of an aldehyde. Indeed, the addition of α-xanthyl ketones to vinyl acetate or vinyl pivalate furnishes the synthetic equivalents of 1,4-ketoaldehydes, which can be used in a convenient and practical modification of the Paal–Knorr synthesis of pyrroles. This is illustrated by the two-step preparation of 2-thienyl pyrrole **122** from xanthate **120**, vinyl pivalate, and cyclopropylamine (Scheme 16) [31]. Numerous pyrroles can be obtained by simply modifying the starting xanthate and the primary amine (including ammonia).



Scheme 16

Interestingly, treating adduct **121** with titanium tetrachloride converts it smoothly into dithietanone **124** via activated intermediate **123** [32]. Essentially, all of the very few previously reported dithietanones are derived from thiophosgene. The present route is quite general and very convenient, and should allow a better study of the reactivity of this uncommon functional group. Preliminary work indicates dithietanones to be useful masked forms of the highly reactive thioaldehydes [32].

As for the spiroketals and pyrroles, various other heterocyclic and heteroaromatic rings may be constructed by using the xanthate addition to bring together the elements needed for the synthesis. In this manner, substituted pyrrolidines, piperidines, azepines, pyridines, pyrazoles, imidazoles, quinoxalines, pyridazines, thiophenes, etc. may be readily prepared [2b,c]. The synthesis of compounds **34a–e** detailed in Scheme 5 represents indeed an approach to piperidines combining the xanthate addition with an intramolecular Mannich reaction; it also exploits the latent thiol embedded in the xanthate group to construct the benzothiepinone motif. The fact that radical intermediates are involved further opens some unusual pathways to useful derivatives, which otherwise would be difficult to obtain. This is illustrated by the sequences in Scheme 17, implicating a neophilic rearrangement.

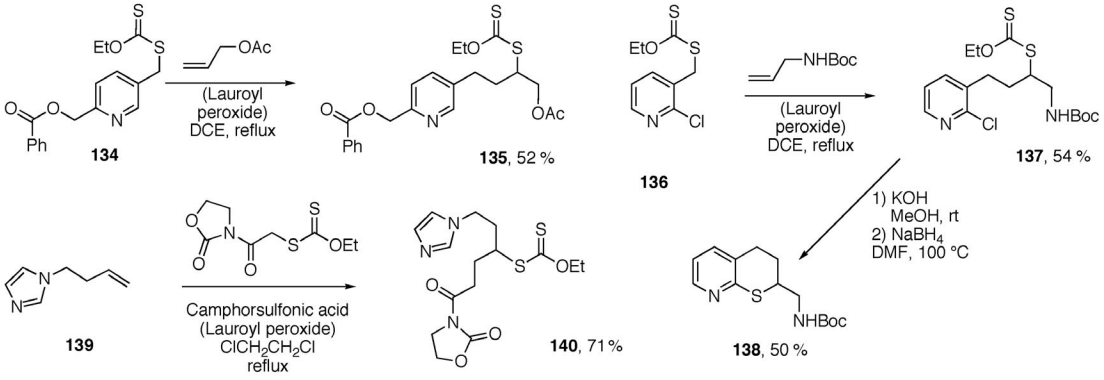


Scheme 17

Thus, addition of xanthate **126** to readily available alkene **125** leads to intermediate adduct radical **127**, which has sufficient lifetime to undertake the relatively slow attack on the neighboring aromatic ring [33]. The reversible neophilic rearrangement is driven forward by the elimination of a methylsulfonyl radical to give finally unsaturated ester **128**. Treatment with base induces an internal conjugate

addition to provide chloropyridine unsubstituted pyrrolidine **129**. In addition to its simplicity, this synthesis further highlights the ease with which it is possible to introduce a trifluoromethyl group into the product. A similar sequence starting with reactants **130** and **131** furnishes compound **132** containing both an unsaturated ester and a ketone [33]. It can therefore react with ammonia or a primary amine to give various piperidines such as **133a–c** following reduction of the corresponding intermediate imine or iminium salt with sodium cyanoborohydride. In the case of ethylene diamine, the second amino group closes onto the ester to create the second lactam ring observed in **133c**. Incidentally, derivatives such as **132** can be easily converted into biaryls by treatment with base under air [34].

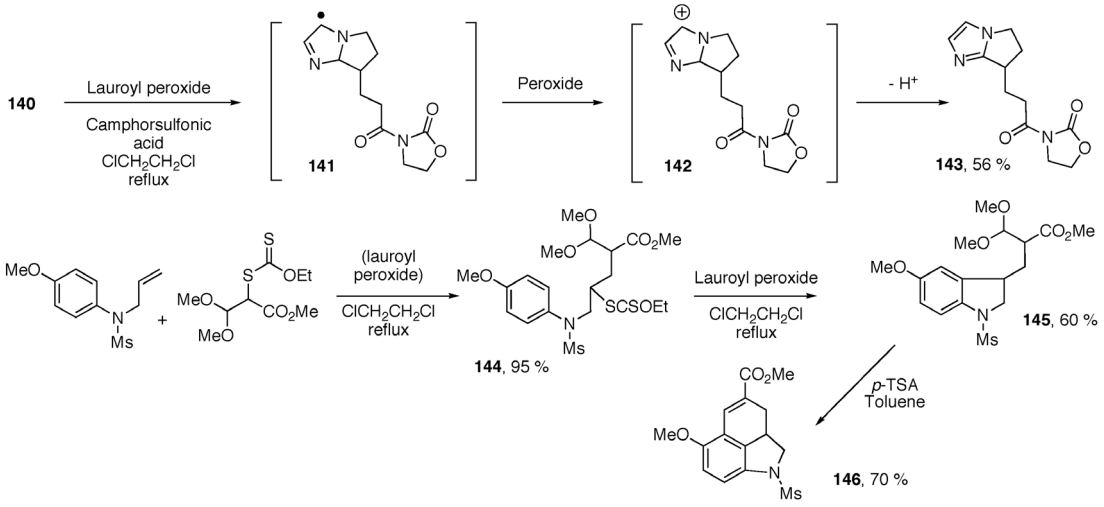
Another route to substituted heterocycles is by using the xanthate addition to modify existing structures. For example, pyridine-derived xanthates **134** and **136** can be added to various olefins to provide adducts **135** and **137** with more complex side-chains (Scheme 18) [16a]. In the case of the latter, liberation of the thiol results in an ionic ring-closure into bicyclic compound **138** possessing the rare 2*H*-thiopyrano[2,3-*b*]pyridine core. An alternative approach is to use the heterocyclic derivative as the alkene component and to modifiy the side-chain by the addition of various xanthates. This variant is illustrated by the conversion of *N*-butenylimidazole **139** into compound **140** [35]. In this instance, it is necessary to add an anhydrous acid, such as camphorsulfonic acid, to neutralize the basicity and potential nucleophilicity of the imidazole ring.



Scheme 18

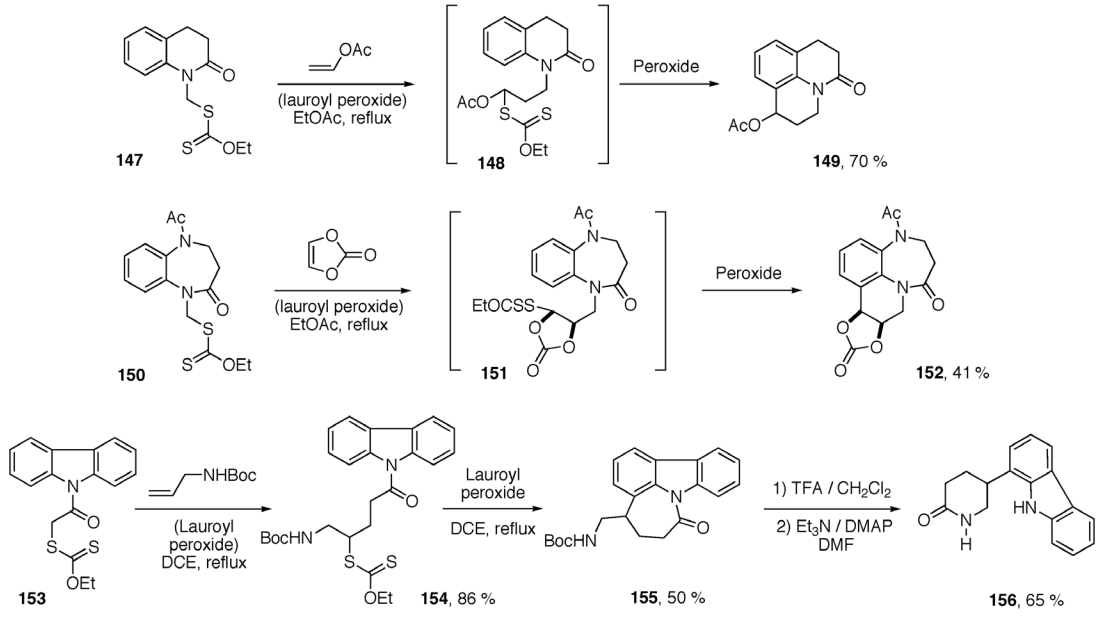
Modification of aromatic and heteroaromatic derivatives

As was explained in the introductory section, one of the main properties of the xanthate transfer process is to provide the intermediate active radicals with more lifetime, thus allowing them to undergo otherwise relatively sluggish transformations. The addition to aromatic rings is one such highly important reaction that is often difficult to accomplish with existing radical-based methods. Access to the xanthate precursors for the radical cyclization is particularly easy. For example, imidazole **140** is obtained in just one step, and its further treatment with peroxide regenerates the intermediate radical and forces it to cyclize onto the imidazole ring (Scheme 19) [35]. This cyclization leading to stabilized radical **141** is normally reversible, but irreversible oxidation by electron transfer to the peroxide leads to cation **142**, where loss of a proton furnishes bicyclic imidazole **143**. The aromatization can also proceed through disproportionation of radical **141**; the relative importance of the two pathways depends on the particular structure of the intermediates and the reaction conditions. The second example in Scheme 19 involves the synthesis of an indoline, **145**, by cyclization of adduct **144** [36]. This indoline contains a masked aldehyde, and heating with a strong acid results in an intramolecular Friedel–Crafts reaction affording the interesting tricyclic compound **146**.



Scheme 19

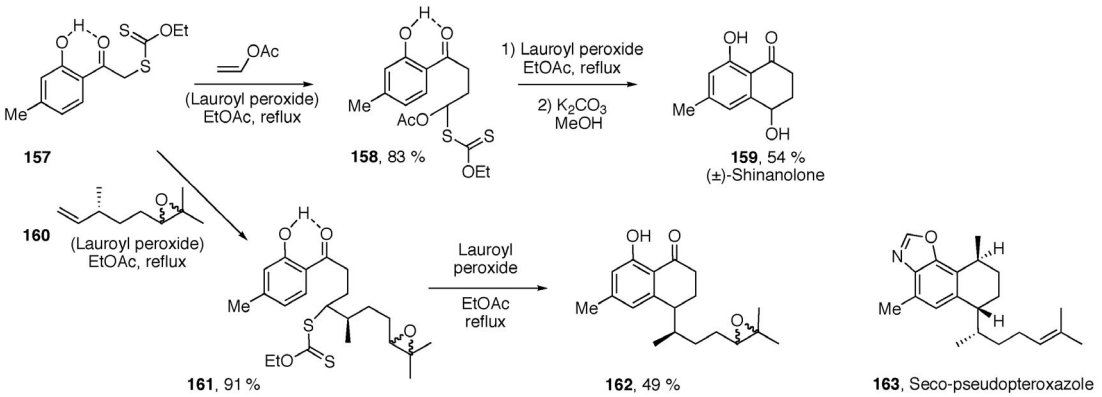
The combination of the intermolecular radical addition of a xanthate and cyclization onto an aromatic or heteroaromatic ring represents an extremely powerful strategy for the swift assembly of a large variety of medicinally interesting structures. The examples that follow are selected from recent studies and only give a pale glimpse of the many possibilities. The versatility of this approach results from the numerous aromatics and heteroaromatics that can be used, the tolerance for many substituents, and the possibility of forming not only five- but often also six- and even seven-membered rings. The creation of six- and seven-membered rings by direct cyclization onto aromatics is generally beyond the scope of most existing radical processes. The three examples in Scheme 20 illustrate this feature.



Scheme 20

Thus, starting with xanthates **147** and **150**, it is possible to perform the radical addition–cyclization to give cyclic structures **149** and **152**, respectively, without the need to isolate intermediate adducts **148** and **151** [20]. In the case of addition product **154** derived from xanthate **153** and *N*-Boc allylamine, further treatment with peroxide induces ring closure to form benzazepinone **155** in moderate yield [37]. Interestingly, removal of the Boc group and exposure to base triggers an intramolecular transamidation to give pyridone **156**. This represents yet another approach to unusual arylpiperidine derivatives (cf. examples in Scheme 17).

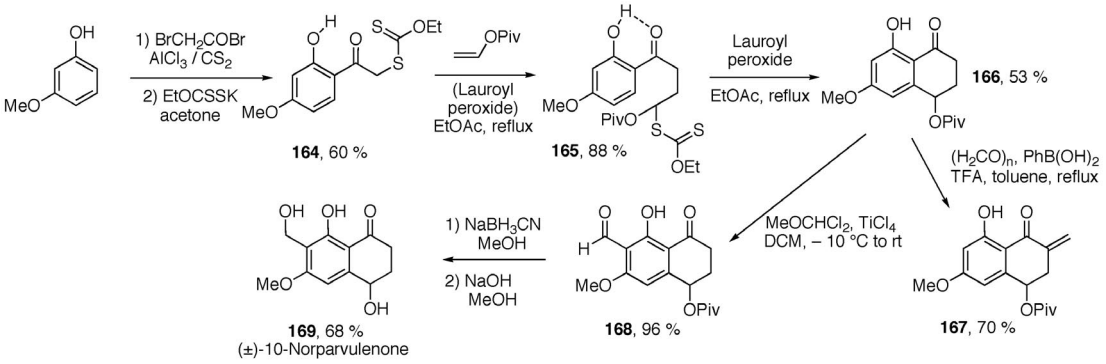
The combination of the intermolecular addition with cyclization to an aromatic ring may be used in the total synthesis of a variety of natural products. For example, shinanolone **159** can be prepared in two steps starting from xanthate **157**, as outlined in Scheme 21 [38]. Thus, addition to vinyl acetate gives adduct **158** in good yield, and this is then subjected to stoichiometric amounts of lauroyl peroxide to induce ring-closure followed by saponification of the acetate group without purification of the intermediate tetralone. It is interesting that the radical reaction could be performed on the free phenol, which are known to be radical chain inhibitors. In fact, the intramolecular hydrogen bonding to the ketone group slows down considerably the rate of the hydrogen abstraction and, in the present case, serves to freeze the intermediate adduct radical in a geometry that is favorable for cyclization. Indeed, earlier work on the *O*-methyl analogue of **157** showed that while the first, intermolecular addition step was efficient, the ring-closure proceeded in very poor yield, in contrast to the case with the free phenol.



Scheme 21

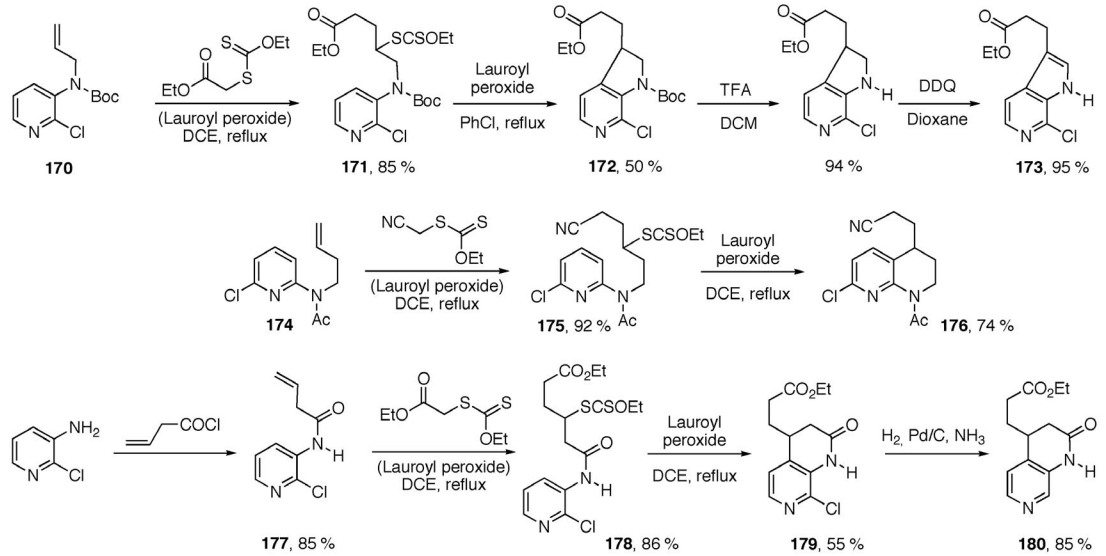
In model studies aimed at the synthesis of pseudopterosines and related substances, tetralone **162** was prepared by a similar approach starting with citronellene-derived epoxy-olefin **160** and the same xanthate **157** via addition product **161** [38]. Tetralone **162** contains most of the elements present in seco-pseudopteroxazole **163**. It is a remarkable testimony to the mildness of the conditions that the sequence could be accomplished without affecting the epoxide ring.

The synthesis of (±)-10-norparvulenone **169** displayed in Scheme 22 hinges upon the same strategy, whereby xanthate **164** is added to vinyl pivalate and the resulting adduct **165** is cyclized by exposure to stoichiometric amounts of peroxide to give key intermediate **166** [38,39]. We initially hoped to introduce the missing hydroxymethyl group by reaction with paraformaldehyde under mild acidic conditions as reported by Nagata and co-workers [40]. Instead, we observed the clean formation of the interesting *exo*-methylene derivative **167**. This unexpected difficulty was resolved by recourse to a modified Reimer–Tiemann reaction, which afforded **168** in high yield, followed by selective reduction of the aldehyde group and saponification of the pivalate ester to give finally the desired natural product.



Scheme 22

One important area where the radical cyclization would be particularly useful concerns pyridine-derived structures. Pyridines are generally recalcitrant partners in Friedel–Crafts and other electrophilic substitution reactions, and the use of organometallic reactions is often hampered by the limited access to the desired substrates, such as halides and boronates. In contrast, the required xanthate precursors are easily obtained, and the radical cyclizations proceed readily in the presence of a variety of substituents. The synthesis of cyclic pyridine derivatives pictured in Scheme 23 is typical of this strategy.



Scheme 23

In the first sequence, radical addition to the terminal alkene in **170** furnishes adduct **171**, which is cyclized by the peroxide into azaindoline **172** [41]. Deprotection and oxidation provides azaindole **173** very efficiently. By a similar addition–cyclization sequence, compound **174** is converted via adduct **175** into tetrahydro-azaquinoline **176** in good overall yield. A tetrahydro-azaquinolinone may be obtained by radical addition to an alkene such as **177** followed by ring-closure to **179**. The chlorine atom may be reductively removed by a controlled catalytic hydrogenation to give **180**. The chlorine atom shields the nitrogen of the pyridine, preventing it from behaving as a nucleophile, and constitutes

an extra handle for the further modification of the end product. It is also worth pointing out that in the case of **178**, the cyclization succeeds even with a secondary amide. This is an extremely rare example of a radical cyclization of an *N*-monosubstituted amide [41b]. Substitution of the amide nitrogen is normally required to increase the population of the rotamers having the correct conformation for cyclization [42].

The examples in Scheme 23 represent only a small fraction of the pyridine derivatives that have been prepared. A better idea of the broad scope of this approach to bicyclic pyridine and pyrimidine derivatives may be obtained by examining the structures collected in Fig. 2, which have been accessed by the xanthate route [41]. Five-, six-, and seven-membered rings can be constructed and the relative position of the nitrogen atoms along the skeleton easily modified. This selection is far from exhaustive, and many more structures could in principle be assembled. Furthermore, the numerous functional groups that can be introduced through the xanthate partner (see Fig. 1) should open access to a vast array of novel and otherwise difficult to obtain pyridine and pyrimidine derivatives of interest to medicinal chemists.

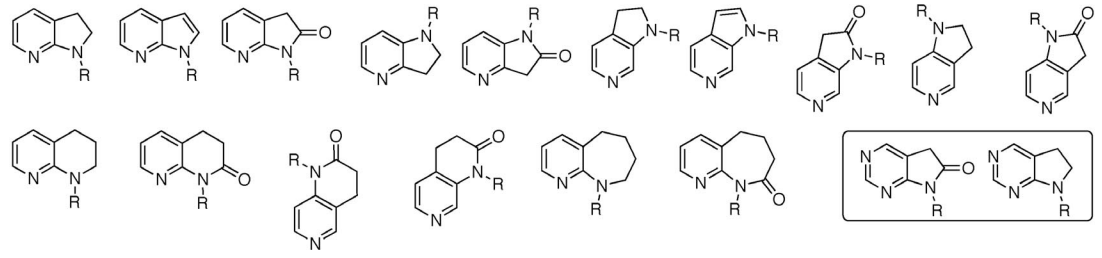
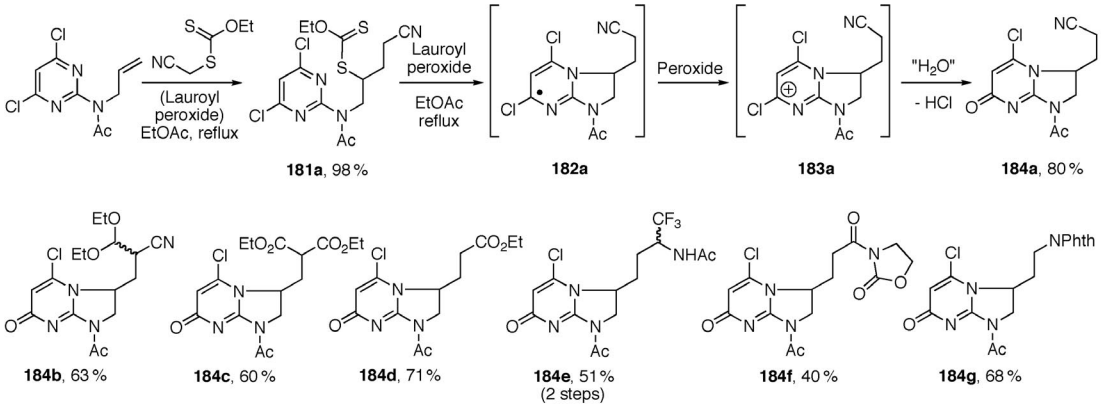


Fig. 2

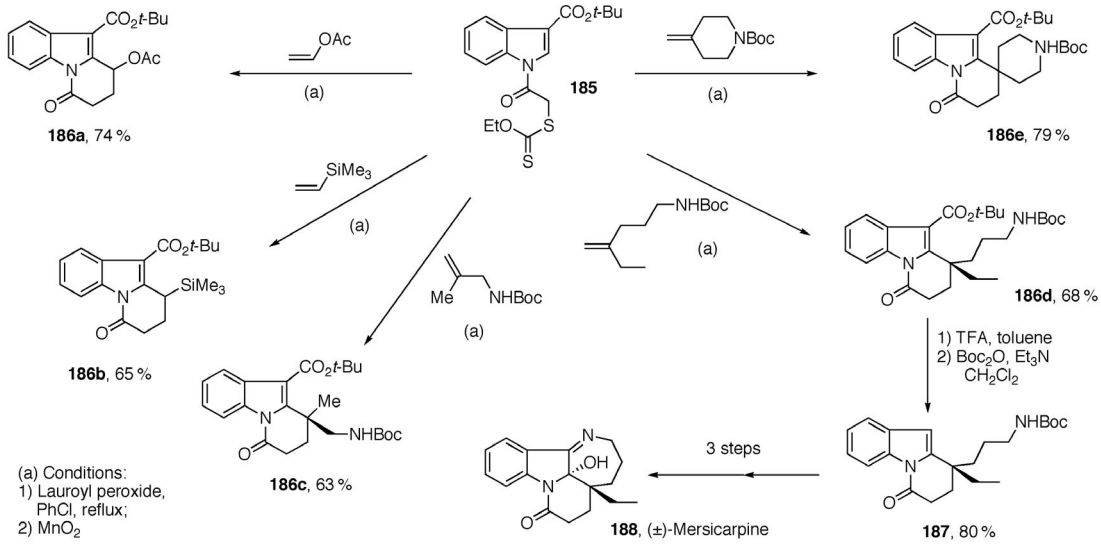
In the course of this study, we stumbled on cases where it was possible to accomplish a hitherto unprecedented radical addition onto the pyridine or pyrimidine nitrogen [43]. This is illustrated by the transformation of the pyrimidine nucleus of adduct **181a** portrayed in Scheme 24 [43b]. The chlorine atom is necessary for this reaction, and, since a normal rearomatization cannot take place following the oxidation of the intermediate cyclized radical **182a** into the corresponding cation **183a**, a hydrolytic pathway is followed that leads to the formation of novel pyrimidinone **184a**.



Scheme 24

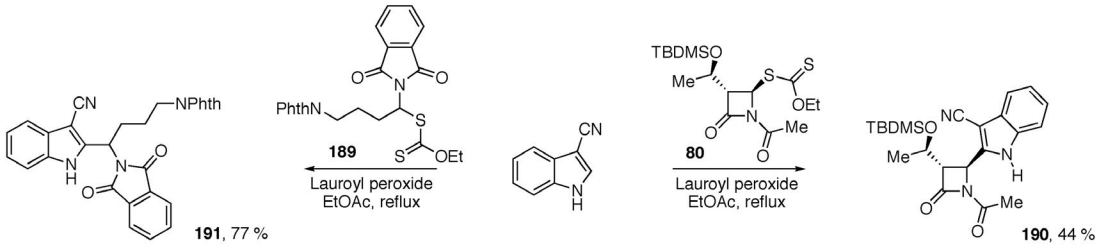
Compounds **184b–g** are other examples of this rather unique transformation. The yields given are for the cyclization step, except for compound **184e**, where the yield is for the combined addition–cyclization. It is worth emphasizing once again the diversity of functional groups that can be introduced and the possibilities for further manipulation. For instance, deprotection of the primary amino group in **184g** could result in an internal displacement of the remaining chlorine atom and the creation of an extra six-membered ring.

The addition–cyclization sequence can be readily applied to other heteroaromatic structures. Indoles, in this respect, are of special importance, in view of the vast number of natural products and pharmacologically useful substances containing intact or modified indole rings. The transformations in Scheme 25 starting with xanthate **185** and leading to polycyclic indole derivatives **186a–e** illustrate nicely this annelation sequence [44]. It was found that because of the presence of an electon-withdrawing ester group on the indole ring and the lower aromatic character of the pyrrole fragment, lauroyl peroxide was not sufficient to completely rearomatize the product. The crude reaction mixture was therefore heated with manganese dioxide before purification. The facile creation of a quaternary center or spirocyclic structures, as in **186c–e**, is noteworthy. Furthermore, in the case of **186d**, cleavage of both the Boc group and the *t*-butyl ester with trifluoroacetic acid gives an intermediate 3-indolecarboxylic acid which undergoes spontaneous decarboxylation. Reprotection of the primary amine affords compound **187**, an advanced intermediate in Kerr's total synthesis of mersicarpine [45], an alkaloid isolated from *Kopsia arborea*, a beautiful indonesian plant. The sequence represents, therefore, a quite short formal synthesis of this substance.



Scheme 25

Intermolecular functionalization of the indole ring by a xanthate is also possible. This is shown by the two examples in Scheme 26, where xanthates **80** and **189** are made to add to 3-cyanoindole to give, respectively, compounds **190** and **191** [18,19,46]. While this extension is limited to certain heteroaromatics, it is nevertheless very useful, as the products are obtained in just one step and often belong to privileged families of heteroaromatics of high value to medicinal chemists.

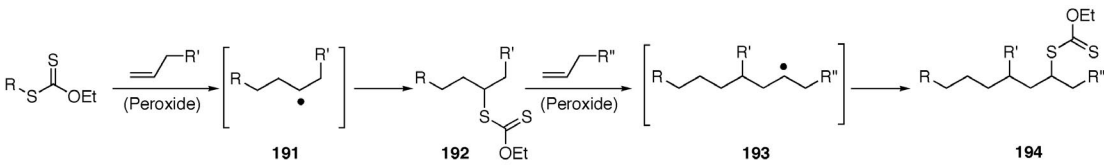


Scheme 26

Synthesis of alkenes

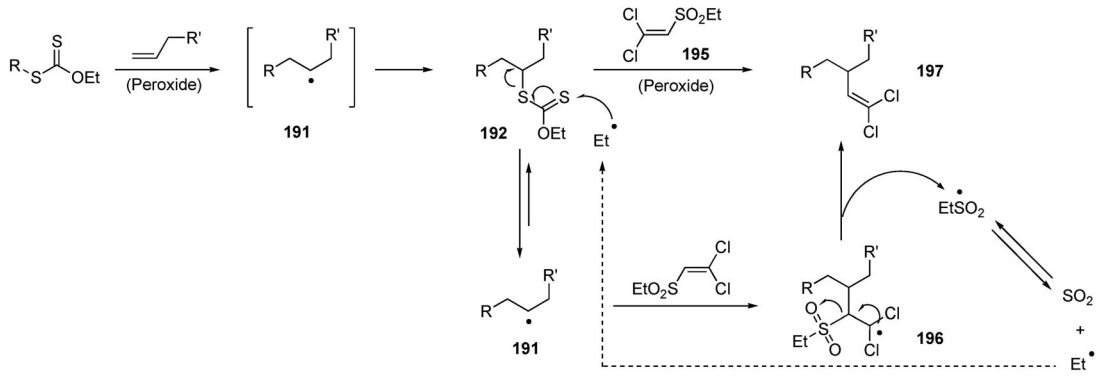
In many of the syntheses of polycyclic aromatic derivatives described in the preceding section, the xanthate group mediates two carbon–carbon-forming steps, the intermolecular addition followed by the ring-closure. Whereas the first is a simple chain process, the second is more complex: it normally requires stoichiometric amounts of peroxide and is driven forward by the final irreversible aromatization process. In the aliphatic series, it is also possible to create two consecutive carbon–carbon bonds when the second event is an irreversible ring-closure. One such example is the sequence in Scheme 14, where intermolecular addition is followed by ring-closure. While the intermediate xanthate could not be isolated in this particular case, it can be in other structures, thus conferring a broad generality to this variant. Introducing consecutively two or more new carbon–carbon bonds in an *intermolecular* fashion is inherently a more difficult problem to solve in a generalized way. The reason derives from the constraint discussed in the introduction, requiring the radical from the starting xanthate $R^{\bullet}$ to be more stable (neglecting polar factors) than the adduct radical **10** (Scheme 2). The sequence displayed in Scheme 9 above is effective precisely because the substituents ensure the correct hierarchy in the stability of the various active radicals involved.

In the more general case involving unfunctionalized terminal alkenes pictured in Scheme 27, accomplishing a second addition will be frustrated by the nearly identical stability of the purely secondary carbon radicals **191** and **193**, corresponding to xanthates **192** and **194**. For the second addition to proceed efficiently, a radical less stable than a secondary radical, such as a primary or a vinylic radical, has to be generated. Thus, addition to ethylene itself would lead to a primary intermediate radical and would represent one, albeit limited, solution.



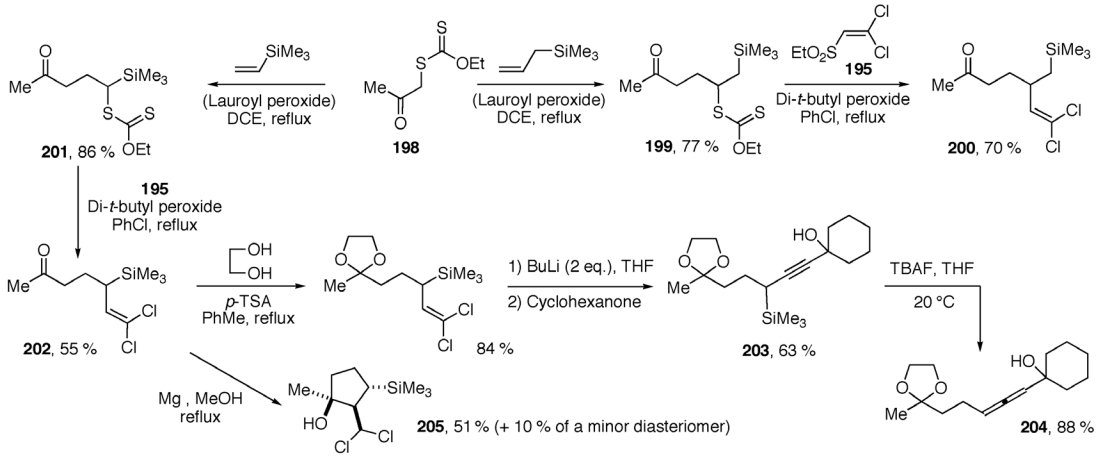
Scheme 27

A more interesting approach is to use as the radical trap an unsaturated alkylsulfone, such as dichlorovinyl ethyl sulfone **195**. As outlined in Scheme 28, the addition of radical **191** to the vinyl group in **195** occurs from the least hindered side, and the resulting intermediate **196** rapidly expels an ethylsulfonyl radical. The latter in turn fragments into sulfur dioxide and the primary ethyl radical, which reacts with xanthate **192** to give the more stable secondary radical **191**, allowing thus propagation of the chain process [47].



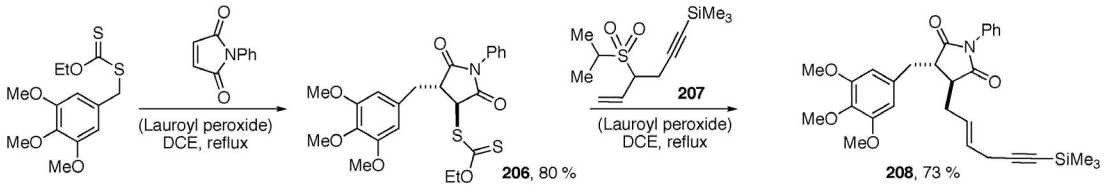
Scheme 28

The synthetic utility of this methodology is illustrated by the transformations set out in Scheme 29. Acetonyl xanthate **198** readily adds to allyl- and vinyl-trimethylsilane to provide the respective addition products **199** and **201** in good yield. In turn, these adducts react with dichlorovinyl ethyl sulfone **195** to furnish compounds **200** and **202**, where the xanthate group has been replaced by a dichlorovinyl moiety. Protection of the ketone group in **202** allows the application of the Corey–Fuchs reaction followed by interception of the lithium acetylide with cyclohexanone to give finally propargyl silane **203**. Cleavage of the silyl group with fluoride anion results in the selective formation of allenol **204** in good yield. By modifying the starting xanthate and the electrophilic trap used to capture the acetylide, a large variety of allenes can be accessed [48]. Furthermore, we found that treatment of dichlorovinyl ketone **202** with magnesium powder in methanol produced cyclopentanol **205** by ring-closure of the ketyl radical [49]. The same transformation could be carried out on derivative **200** in comparable yield and selectivity (product not shown).



Scheme 29

Dichlorovinyl ethyl sulfone **195** is in fact just one representative of a large family of sulfone-based traps that allow propagation of the chain process through the generation of a carbon-centered radical of sufficient reactivity such as an ethyl radical in the case of sulfone **195**. The xanthate group (and incidentally, and very importantly, the iodine atom in aliphatic iodides) can thus be replaced with

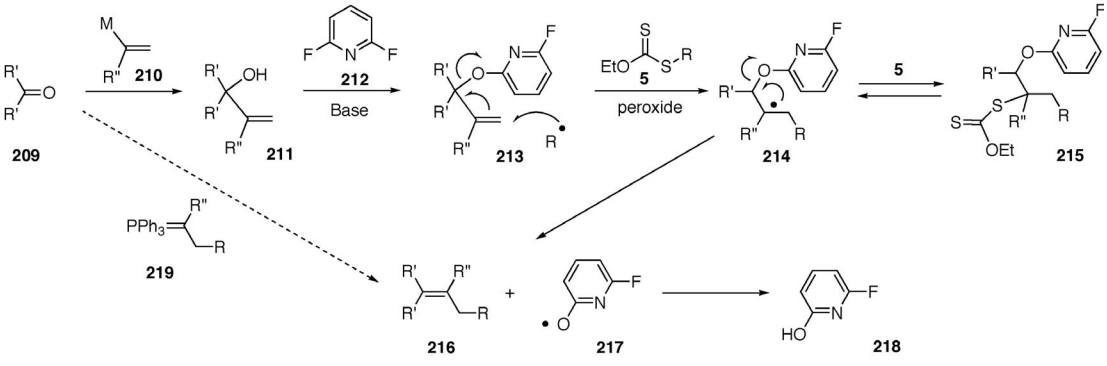


Scheme 30

numerous vinyl and allyl motifs, acyl-, cyano-, and related fragments, as well as with an azide [47,50]. This allows for a staggering array of synthetic possibilities. The example in Scheme 30 illustrates the introduction of an enyne side-chain starting from xanthate **206** and sulfone **207** [50b]. The introduction of the enyne side-chain leading to **208** takes place with retention in this case because the trimethoxybenzyl substituent shields one of the faces of the succinimide ring, forcing radical attack from the other.

In addition to allyl sulfones, the allylation of xanthates can be accomplished with allyl stannanes, allyl silanes, allyl phosphine oxides, and with vinyl epoxides under mediation with triethyl borane [51]. More recently, we discovered a new, very powerful allylation process hinging on the ability to convert a hydroxy group into a leaving group in a radical sense. One of the important advantages of radical processes is that homolysis of strong C–O bonds through β-scission *does not* normally occur; hence the enormous importance of radical methods for the modification of carbohydrates, where C–O bonds are present in abundance. Much synthetic potential would accrue, however, if C–O bonds *could indeed be broken through homolysis in a controlled manner*.

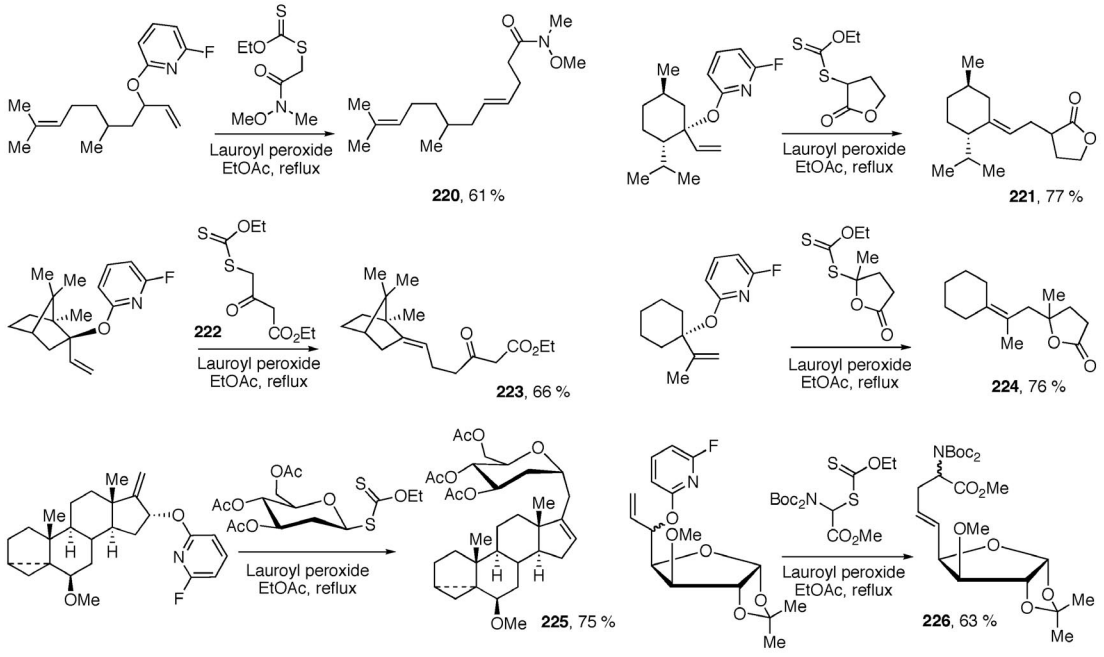
We have found that the easily introduced fluoropyridinyloxy moiety was very suitable for the required task [52]. Furthermore, as indicated in Scheme 31, an overall synthetic equivalent of a Wittig olefination can now be designed by starting with an allylic alcohol **211** made by addition of vinyl metal reagent **210** to aldehyde or ketone **209**. Reaction of the alcoholate with commercially available 2,6-difluoropyridine **212** affords activated substrate **213**, which can undergo radical addition to produce intermediate radical **214**. This species can reversibly exchange a xanthate group with starting xanthate **5** to give adduct **215** but, ultimately, it extrudes a pyridinyloxy radical **217** to furnish the desired alkene **216**. A stoichiometric amount of peroxide is required, and, by a pathway that is still not completely clear, most of pyridinyloxy radical **216** ends up as 2-fluoro-6-hydroxypyridine **218**.



Scheme 31

Alkene **216** formally derives from aldehyde or ketone **209** by condensation with Wittig reagent **219**. The Wittig olefination, despite its tremendous utility, has many limitations due to its sensitivity to steric hindrance (especially when ketones are involved) and the basicity/nucleophilicity of the ylid,

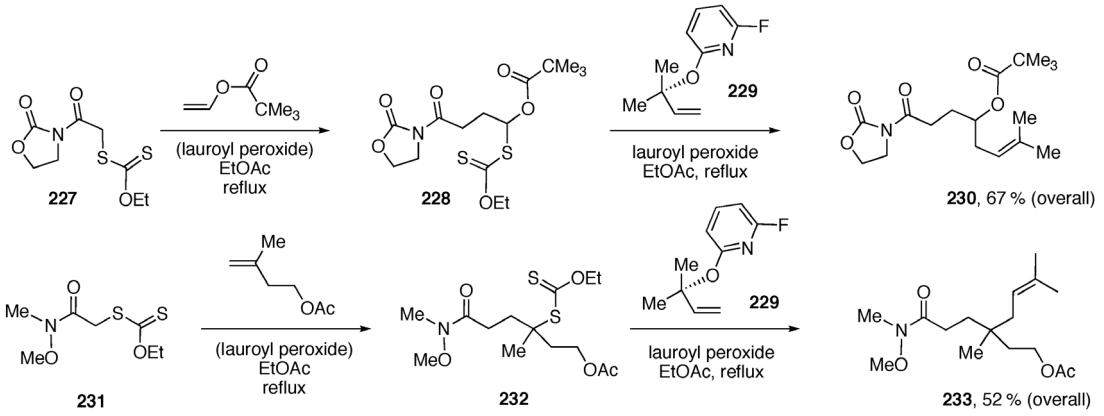
which makes it incompatible with the presence of many polar functional groups that have to be protected. In the present approach, the vinyl metal **210** is a much smaller reagent than the bulky phosphonium ylid on one hand and the radical attack occurs at the unsubstituted terminus of the alkene **213**, away from the hindered core. This allows the ready obtention of tetrasubstituted alkenes, which are very difficult to assemble using the Wittig route. The few allylation reactions displayed in Scheme 32 illustrate some of these features [52].



Scheme 32

Weinreb amide **220** is an example of the synthesis of a disubstituted olefin starting ultimately from an aldehyde, citronellal in this case. Compounds **221** and **223** are examples of trisubstituted olefins starting from ketones, namely, menthone and camphor. In all three instances, only the *E*-isomer is obtained because of the steric bias present in the substrate. It is interesting to note that xanthate **222** allows the formation, under neutral conditions, of a carbon–carbon bond on the terminus of the ketoester bearing the least acidic hydrogens. Lactone **224** illustrates the ease with which a tetrasubstituted alkene is assembled. Finally, steroid and amino acid conjugates with carbohydrates can be readily prepared as represented by compounds **225** and **226**.

A further notable advantage of this approach to alkenes is that it can be made modular and highly convergent. In the first sequence in Scheme 33, addition of xanthate **227** to vinyl pivalate gives adduct **228**, which can be prenylated with reagent **229** to afford ultimately compound **230**. In a similar fashion, xanthate **231** is added to isopentenyl acetate and the resulting product **232** prenylated with the same reagent to furnish alkene **233** containing a new quaternary center.

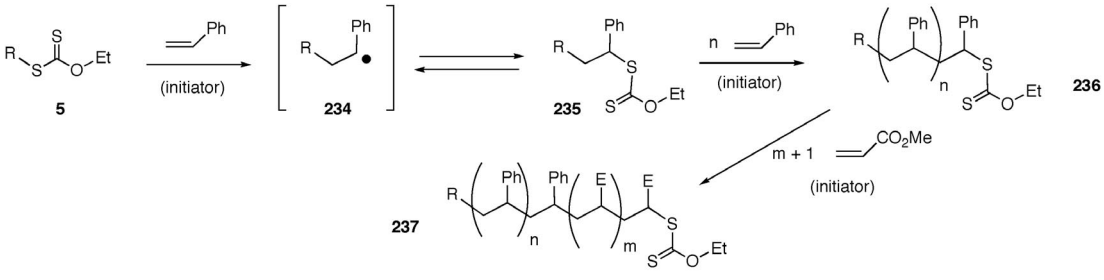


Scheme 33

The work on this new synthesis of alkenes is extremely promising, yet still in its early stages. Numerous aspects remain that need addressing. The scope and exact mechanism, especially the fate of fluoropyridinoxy radical **217**, must be better delineated. The approximate rate of the elimination step and the influence of the substituents have to be determined. Ways to control the geometry of the olefinic bond and to attach thereon diverse functional groups have to be established. Finally, its utility in the total synthesis of natural products has to be highlighted with selected examples.

Applications to polymer chemistry

The fact that both the starting material and adduct are xanthates allows an easy iteration of the addition process in the case of a polymerizable monomer. This leads to a polymer which still has a xanthate group attached to one of its termini, and which can therefore participate in another polymerization sequence, giving rise to a block polymer. This is illustrated by the sequence in Scheme 34, where styrene is used as the first monomer. Thus, addition of xanthate **5** to styrene furnishes the normal adduct **235** via intermediate radical **234**. Since this radical is stabilized by the phenyl group, it is readily regenerated from **235** and, in the presence of excess styrene, can undergo further additions and exchanges of the xanthate group until the monomer is depleted. This produces telechelic polymer **236**, where functional groups initially present in the R-group of the xanthate are attached at one end and the xanthate group itself is at the other. In the presence of an initiator and another monomer, such as methyl acrylate, a second polymerization produces diblock polymer **237**; and the process may be repeated again to give a tri-block or higher polymers or polymers with more complex architectures.

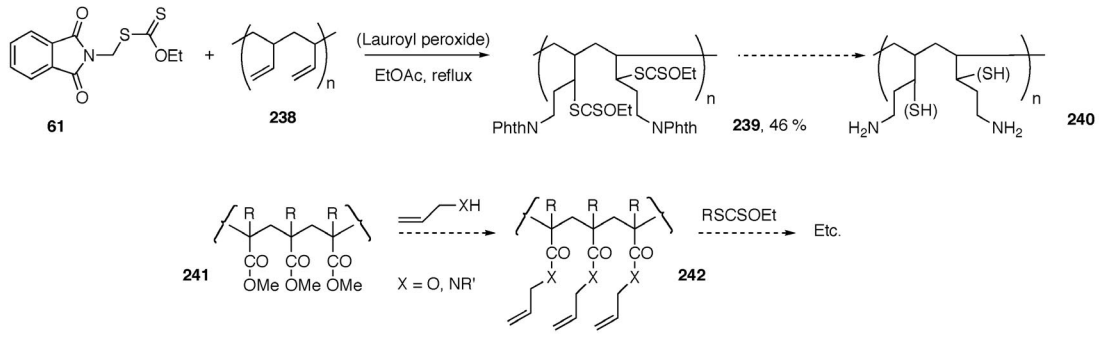


Scheme 34

This polymerization process was developed in collaboration with Rhodia, who coined the acronym MADIX (macromolecular design by interchange of xanthate) [53]. At the same time, polymer chemists at CSIRO in Australia devised an essentially identical system based on dithioesters they termed RAFT. Both processes operate by the mechanism outlined in Scheme 2 we first reported in 1988 [14l]. Indeed, the concluding sentence in this first article pointed to the broader applicability of this key mechanism beyond simply the case of xanthates [141]. As noted in the introductory section, the OEt group in the xanthate is just a spectator with only an indirect influence. Replacing it with other groups modifies the rates of the reversible addition to the thiocarbonyl group and the fragmentation steps but does not modify the basic mechanism. There is in this respect a very significant overlap in the claims of both master patents [53e,f].

The RAFT/MADIX polymerization system has proved to be extremely powerful, because of the mildness of the conditions and compatibility with most functional groups, including polar carboxylic and ammonium groups. In many cases, not only the architecture, but also the distribution of molecular weights (polydispersity) can be finely tuned. Furthermore, the dithiocarbonyl endgroup may be removed or modified in various ways, thus eliminating potential malodorous emanations from the finished product. One practical solution is to pass a stream of ozone, which rapidly converts the thiocarbonyl group into an innocuous carbonyl and cleaves at the same time any undesirable residual monomer [54]. The xanthate-based MADIX technology offers further the advantages of low cost, compatibility with the standard techniques of emulsion polymerization, and ease of scale up. Indeed, Rhodia now produces a di-block polymer on tens of metric tonnes per year.

Another way of applying the xanthate transfer reaction is to modify existing polymers. In the example displayed in Scheme 35, commercial 1,2-polybutadiene **238** is functionalized with xanthate **61** to give polymer **239** with the gross structure shown (possible cyclizations not indicated) [17a]. Deprotection would lead ultimately to a polymeric polyamine **240**, where the xanthate or groups derived therefrom, such as thiols, sulfonic acids, etc., may be retained in the polymer or simply reduced off. Xanthate **61** may be replaced by a plethora of other xanthates bearing a variety of useful functional groups, and the proportion of xanthate to olefin can be easily tailored according to the properties desired in the end-product. Finally, it is quite easy to introduce terminal alkenes into existing commercial polymers, thus expanding considerably the substrate pool. For example, *trans*-esterification of acrylates or methacrylates **241** with allylic alcohol or aminolysis with allylamines would give polymers **242** to which various xanthates could be added.



Scheme 35

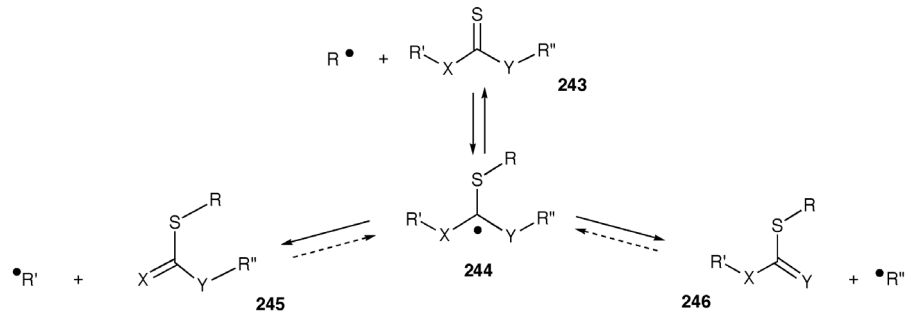
CONCLUSION AND PERSPECTIVES

The degenerative transfer of the xanthate and related groups is based on a unique self-regulating mechanism that solves many of the difficulties normally associated with radical processes. Over the years it has proven to have an extraordinary synthetic potential, since it allows the rapid, convergent assembly of complex structures bearing numerous functional groups that would be very tedious to obtain otherwise. Our efforts in this area, only a very small fraction of which have been discussed in the preceding sections, have focused on exploring and expanding the scope of the process and on developing routes to starting xanthates not readily available by a simple substitution with a xanthate salt, such as tertiary xanthates [55]; on devising new modifications of the xanthate group in the addition product, chiefly reactions leading to yet more carbon–carbon bond formation (cf. the allylations and vinylations described above) [56]; and to examining new chemistry resulting from the unusual association of functional groups that can be created, such as, for example, the serendipitous access to dithietanones detailed in Scheme 16.

The fact that the xanthate transfer provides the intermediate radicals with a relatively long lifetime without the need to resort to high-dilution or syringe pump techniques has revealed some aspects of radical behavior not well appreciated in the past. One instance is the addition to the pyridine and pyrimidine nitrogen exemplified by the reaction in Scheme 24; another is a radical Smiles rearrangement proceeding through a strained azetidininone intermediate, as well as the construction of the azetidinone ring [57a,b] or, more recently, an homolytic *ipso* substitution of a fluorine atom on a pyridine ring [57c].

Numerous applications to the total synthesis of natural products or to the solution of specific synthetic transformations can be envisaged. While a few have actually been realized, more effort in this area is still required. It is worth emphasizing, nevertheless, the fact that the various transformations described in this brief overview allow retrosynthetic disconnections that are not immediately obvious to chemists mostly trained in ionic and organometallic chemistry, yet which could result in a considerable simplification of a given synthetic route. This last point is illustrated by the key step in the total synthesis of (±)-fortucine **255** (Scheme 37 below), which at the same time highlights another dimension of this chemistry related to the generation of nitrogen-centered radicals and places it in a broader mechanistic context.

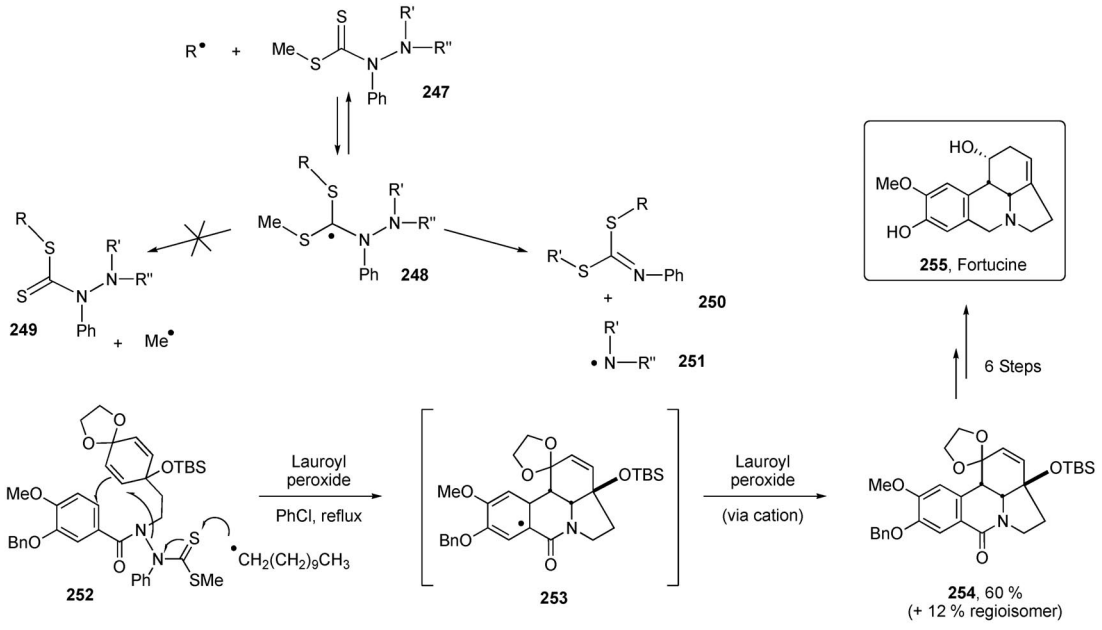
The xanthate transfer is a particular case of the general manifold pictured in Scheme 36, which has its origins in the Barton–McCombie deoxygenation, a formidable reaction invented nearly 40 years ago [1,58]. The key element is the highly radicophilic thiocarbonyl group in **243** which reacts rapidly, and in principle reversibly, with R$^{\bullet}$ (not necessarily a carbon radical) to give adduct **244**. This stabilized intermediate is of paramount importance in controlling the relative concentration of the "active" radicals in the medium and, depending on the nature of X and Y and the substituents, can collapse, often



Scheme 36

reversibly, to give **245** or **246**. There are numerous possibilities for modifying atoms X, Y, and their substituents, and not all have been examined so far.

For the generation of nitrogen-centered radicals, one can start with thiosemicarbazide **247**, where attack on the thiocarbonyl group leads to intermediate **248** (Scheme 37). Unlike the xanthates discussed above, β-scission of the carbon–sulfur bond to give compound **249** is not easy in this case as it would lead to a high-energy methyl radical. In contrast, rupture of the relatively fragile nitrogen–nitrogen bond occurs readily to furnish dithio-imine **250** and a nitrogen radical **251**. This method can be used to generate various nitrogen radicals, the most synthetically useful being iminyls and amidyls [59]. By replacing the N–N bond with an N–O bond, it is possible to produce an oxygen-centered radical, as in the tremendously powerful Barton decarboxylation reaction and its variants [1,60]. For the synthesis of (±)-fortucine **255**, the key step is a cascade starting with hydrazide **252**, which, upon treatment with lauroyl peroxide, furnishes an amidyl that first closes onto the cyclohexadiene fragment and the resulting carbon radical in turn embraces the aromatic ring leading to stabilized radical **253**. Oxidation of the latter by the peroxide and rapid aromatization into **254** completes the sequence. One carbon–nitrogen and one carbon–carbon bond are created in the process as well as two rings. Intermediate **254** can then be processed into (±)-fortucine **255** in 6 steps of a total of 11 steps from inexpensive, commercially available starting materials [61].



Scheme 37

ACKNOWLEDGMENTS

We dedicate this article with respect to the memory of Prof. Athelstan L. J. Beckwith, a great pioneer and master of free radical chemistry, and a wonderful friend. We also wish to express our gratitude to our students and collaborators, whose names appear in the references, for contributing so much to the development of the chemistry described herein.

REFERENCES

1. For recent books on radicals in synthesis, see: (a) P. Renaud, M. P. Sibi (Eds.). *Radicals in Organic Synthesis*, Vols. 1 and 2, Wiley-VCH, Weinheim (2001); (b) S. Z. Zard. *Radicals Reactions in Organic Synthesis*, Oxford University Press, Oxford (2003).
2. (a) S. Z. Zard. *Org. Biomol. Chem.* **5**, 205 (2007); (b) S. Z. Zard. *Aust. J. Chem.* **59**, 663 (2006); (c) B. Quiclet-Sire, S. Z. Zard. *Chem.—Eur. J.* **12**, 6002 (2006); (d) B. Quiclet-Sire, S. Z. Zard. *Top. Curr. Chem.* **264**, 201 (2006); (e) S. Z. Zard. In *Radicals in Organic Synthesis*, Vol. 1, P. Renaud, M. P. Sibi (Eds.), pp. 90–108, Wiley-VCH, Weinheim (2001); (f) B. Quiclet-Sire, S. Z. Zard. *Phosphorus, Sulfur, Silicon* **153–154**, 137 (1999); (g) B. Quiclet-Sire, S. Z. Zard. *J. Chin. Chem. Soc.* **46**, 139 (1999); (g) S. Z. Zard. *Angew. Chem., Int. Ed. Engl.* **36**, 672 (1997).
3. (a) H. Henry. DEA report, Université Paris XI, Orsay (1994); (b) M. Destarac, X. Franck, D. Charmot, S. Z. Zard. *Macromol. Rapid Commun.* **21**, 1035 (2000).
4. B. Quiclet-Sire, S. Z. Zard. Unpublished observations.
5. E. Bacqué, F. Pautrat, S. Z. Zard. *Chem. Commun.* 2312 (2002).
6. A. Liard, B. Quiclet-Sire, S. Z. Zard. *Tetrahedron Lett.* **37**, 5877 (1996).
7. (a) D. H. R. Barton, D. O. Jang, J. Cs. Jaszberenyi. *Tetrahedron Lett.* **33**, 5709 (1992); (b) J. Boivin, R. Jrad, S. Jugé, V. T. Nguyen. *Org. Lett.* **5**, 1645 (2003).
8. (a) M. Heinrich, S. Z. Zard. *Org. Lett.* **6**, 4969 (2004); (b) M. R. Heinrich, L. Sharp, S. Z. Zard. *Chem. Commun.* 3077 (2005); for other xanthate additions to allyl and vinyl boronates, see: (c) H. Lopez-Ruiz, S. Z. Zard. *Chem. Commun.* 2618 (2001).
9. P. Boutillier, B. Quiclet-Sire, S. N. Zafar, S. Z. Zard. *Tetrahedron: Asymmetry* **21**, 1649 (2010).
10. (a) C. Mougin, J. Sançon, S. Z. Zard. *Heterocycles* **74**, 211 (2007); (b) J. A. Wilkinson, N. Ardes-Guisot, S. Duckia, J. Leonard. *Tetrahedron Lett.* **46**, 8053 (2005).
11. O. Bergeot, C. Corsi, M. El Qacemi, S. Z. Zard. *Org. Biomol. Chem.* **4**, 278 (2006).
12. (a) F. Gagosz, S. Z. Zard. *Synlett* 387 (2003); (b) M. Corbet, M. de Greef, S. Z. Zard. *Org. Lett.* **10**, 253 (2008).
13. (a) M. de Greef, S. Z. Zard. *Tetrahedron* **60**, 7781 (2004); (b) S. K. Bagal, M. de Greef, S. Z. Zard. *Org. Lett.* **8**, 147 (2006).
14. (a) S. Ahmed, L. A. Baker, R. S. Grainger, P. Innocenti, C. E. Quevedo. *J. Org. Chem.* **73**, 8116 (2008); (b) R. S. Grainger, P. Innocenti. *Heteroat. Chem*. **18**, 568 (2007); (c) R. S. Grainger, E. J. Welsh. *Angew. Chem., Int. Ed.* **46**, 5377 (2007); (d) R. S. Grainger, P. Innocenti. *Angew. Chem., Int. Ed.* **43**, 3445 (2004); (e) G. Lopez-Valdez, S. Olguın-Uribe, L. D. Miranda. *Tetrahedron Lett.* **48**, 8285 (2007); (f) M. L. Coote, C. J. Easton, S. Z. Zard. *J. Org. Chem.* **71**, 4996 (2006); (g) J. E. Forbes, R. N. Saicic, S. Z. Zard. *Tetrahedron* **55**, 3791 (1999); (h) R. N. Saicic, S. Z. Zard. *Chem. Commun.* 1631 (1996); (i) J. E. Forbes, S. Z. Zard. *Tetrahedron* **49**, 8257 (1993); (j) J. E. Forbes, S. Z. Zard. *J. Am. Chem. Soc.* **112**, 2034 (1990); (k) J. E. Forbes, S. Z. Zard. *Tetrahedron Lett.* **30**, 4367 (1989); (l) P. Delduc, C. Tailhan, S. Z. Zard. *J. Chem. Soc., Chem. Commun.* 308 (1988).
15. (a) F. Gagosz, S. Z. Zard. *Org. Synth.* **84**, 32 (2007); (b) L. Tournier, S. Z. Zard. *Tetrahedron Lett.* **46**, 455 (2005); (c) F. Gagosz, S. Z. Zard. *Org. Lett.* **5**, 2655 (2003); (d) F. Bertrand, V. Pevere, B. Quiclet-Sire, S. Z. Zard. *Org. Lett.* **3**, 1069 (2001); (e) M.-P. Denieul, B. Quiclet-Sire, S. Z. Zard. *J. Chem. Soc., Chem. Commun.* 2511 (1996).
16. (a) Z. Ferjancic, B. Quiclet-Sire, S. Z. Zard. *Synthesis* 2996 (2008); (b) T. Biadatti, B. Quiclet-Sire, J.-B. Saunier, S. Z. Zard. *Tetrahedron Lett.* **39**, 19 (1998).
17. (a) B. Quiclet-Sire, S. Z. Zard. *Org. Lett.* **10**, 3279 (2008); (b) B. Quiclet-Sire, G. Revol, S. Z. Zard. *Org. Lett.* **11**, 3554 (2009).
18. B. Quiclet-Sire, G. Revol, S. Z. Zard. *Tetrahedron* **66**, 6656 (2010).
19. B. Quiclet-Sire, S. Z. Zard. *Heterocycles* (2010). In press.
20. F. Lebreux, B. Quiclet-Sire, S. Z. Zard. *Org. Lett.* **11**, 2844 (2009).

21. A. Srikrishna. In *Radicals in Organic Synthesis*, Vol. 2, P. Renaud, M. P. Sibi (Eds.), pp. 151–187, Wiley-VCH, Weinheim (2001).
22. E. Bacqué, F. Pautrat, S. Z. Zard. *Org. Lett.* **5**, 325 (2003).
23. C. Kalai, E. Tate, S. Z. Zard. *Chem. Commun.* 1430 (2002).
24. N. Cholleton, I. Gillaizeau-Gauthier, Y. Six, S. Z. Zard. *Chem. Commun.* 535 (2000).
25. G. Binot, S. Z. Zard. *Tetrahedron Lett.* **44**, 7703 (2003).
26. R. Heng, B. Quiclet-Sire, S. Z. Zard. *Tetrahedron Lett.* **50**, 3613 (2009).
27. M. E. Briggs, M. El Qacemi, C. Kalai, S. Z. Zard. *Tetrahedron Lett.* **45**, 6017 (2004).
28. (a) C. Alameda-Angulo, B. Quiclet-Sire, S. Z. Zard. *Tetrahedron Lett.* **47**, 913 (2006); (b) M.-P. Denieul, B. Quiclet-Sire, S. Z. Zard. *Tetrahedron Lett.* **37**, 5495 (1996).
29. M. de Greef, S. Z. Zard. *Org. Lett.* **9**, 1773 (2007).
30. M. El Qacemi. Ph.D. Thesis, Ecole Polytechnique, Palaiseau (2005).
31. B. Quiclet-Sire, L. Quintero, G. Sanchez-Jimenez, S. Z. Zard. *Synlett* 75 (2003).
32. (a) B. Quiclet-Sire, G. Sanchez-Jimenez, S. Z. Zard. *Chem. Commun.* 1408 (2003); (b) B. Quiclet-Sire, T. Tétart, S. Z. Zard. Unpublished observations.
33. (a) A. Gheorghe, B. Quiclet-Sire, X. Vila, S. Z. Zard. *Tetrahedron* **63**, 7187 (2007); (b) A. Gheorghe, B. Quiclet-Sire, X. Vila, S. Z. Zard. *Org. Lett.* **7**, 1653 (2005); (c) G. Ouvry, S. Z. Zard. *Synlett* 1627 (2003).
34. B. Quiclet-Sire, G. Revol, S. Z. Zard. *Org. Lett.* **11**, 2832 (2009).
35. F. Gagosz, S. Z. Zard. *Org. Lett.* **4**, 4345 (2002).
36. B. Sortais. Ph.D. Thesis, Ecole Polytechnique, Palaiseau (2002).
37. (a) N. Charrier. Ph.D. Thesis. Ecole Polytechnique, Palaiseau (2008); see also: (b) T. Kaoudi, B. Quiclet-Sire, S. Seguin, S. Z. Zard. *Angew. Chem., Int. Ed.* **39**, 731 (2000).
38. L. Petit, S. Z. Zard. *Chem. Commun.* **46**, 5148 (2010).
39. A. Cordero Vargas, B. Quiclet-Sire, S. Z. Zard. *Org. Lett.* **5**, 3717 (2003).
40. W. Nagata, K. Okada, T. Aoki. *Synthesis* 365 (1979).
41. (a) E. Bacqué, M. El Qacemi, S. Z. Zard. *Org. Lett.* **6**, 3671 (2004); (b) M. El Qacemi. Ph.D. Thesis, Ecole Polytechnique, Palaiseau (2005).
42. (a) R. Yamasaki, A. Tanatani, I. Azumaya, S. Saito, K. Yamaguchi, H. Kagechika. *Org. Lett.* **5**, 1265 (2003) and refs. cited therein; (b) O. M. Musa, J. Horner, M. Newcomb. *J. Org. Chem.* **64**, 1022 (1999); (c) G. Stork, R. Mah. *Heterocycles* **28**, 723 (1989); see also: (d) G. Binot, S. Z. Zard. *Tetrahedron Lett.* **46**, 7503 (2005); (e) B. Quiclet-Sire, S. Z. Zard. *Chem. Commun.* 2306 (2002).
43. (a) M. El Qacemi, L. Ricard, S. Z. Zard. *Chem. Commun.* 4422 (2006); (b) Y. Laot, L. Petit, S. Z. Zard. *Chem. Commun.* **46**, 5784 (2010).
44. A. Biéchy, S. Z. Zard. *Org. Lett.* **11**, 2800 (2009).
45. J. Magolan, C. A. Carson, M. A. Kerr. *Org. Lett.* **10**, 1437 (2008).
46. For earlier examples of intermolecular additions of xanthates to herteraromatics, see: (a) P. E. Reyes-Gutierrez, R. O. Torres-Ochoa, R. Martınez, L. D. Miranda. *Org. Biomol. Chem.* **7**, 1388 (2009); (b) O. Guadarrama-Morales, F. Mendez, L. D. Miranda. *Tetrahedron Lett.* **48**, 4515 (2007); (c) Y. M. Osornio, R. Cruz Almanza, V. Jimenez-Montano, L. D. Miranda. *Chem. Commun.* 2316 (2003); (d) F. Coppa, F. Fontana, F. Minisci, G. Pianese, P. Tortoreto, L. Zhao. *Tetrahedron Lett.* **33**, 687 (1992).
47. F. Bertrand, B. Quiclet-Sire, S. Z. Zard. *Angew. Chem., Int. Ed.* **38**, 1943 (1999).
48. Z. Li, S. Z. Zard. *Org. Lett.* **11**, 2868 (2009).
49. Z. Li, S. Z. Zard. *Tetrahedron Lett.* **50**, 6973 (2009).

50. (a) For a review, see: F. Bertrand, F. Le Guyader, L. Liguori, G. Ouvry, B. Quiclet-Sire, S. Seguin, S. Z. Zard. *C. R. Acad. Sci. Paris* **II4**, 547 (2000); (b) N. Charrier, S. Z. Zard. *Angew. Chem., Int. Ed.* **47**, 9443 (2008); (c) F. Le Guyader, B. Quiclet-Sire, S. Seguin, S. Z. Zard. *J. Am. Chem. Soc.* **119**, 7410 (1997); (d) M. F. Semmelhack, L. Wu, R. A. Pascal Jr., D. M. Ho. *J. Am. Chem. Soc.* **125**, 10496 (2003); (e) B. Quiclet-Sire, S. Seguin, S. Z. Zard. *Angew. Chem., Int. Ed.* **37**, 2864 (1998); (f) S. Kim, S. Kim. *Bull. Chem. Soc. Jpn.* **80**, 809 (2007); (g) J. Y. Lee, S. Kim. *Bull. Korean Chem. Soc.* **27**, 189 (2006); (h) S. Kim. *Adv. Synth. Catal*. **346**, 19 (2004); (i) S. Kim, C. J. Lim. *Angew. Chem., Int. Ed.* **41**, 3265 (2002); (j) S. Kim, H.-J. Song, T.-L. Choi, J.-Y. Yoon. *Angew. Chem., Int. Ed.* **40**, 2524 (2001); (k) S. Cren, P. Schär, P. Renaud, K. Schenk. *J. Org. Chem.* **74**, 2942 (2009); (l) L. Chabaud, Y. Landais, P. Renaud. *Org. Lett.* **7**, 2587 (2005); (m) L. Chabaud, Y. Landais, P. Renaud. *Org. Lett.* **4**, 4257 (2002); (n) P. Panchaud, P. Renaud. *J. Org. Chem.* **69**, 3205 (2004); (o) P. Panchaud, C. Ollivier, P. Renaud, S. Zigmantas. *J. Org. Chem.* **69**, 2755 (2004); (p) C. Ollivier, P. Renaud. *J. Am. Chem. Soc.* **123**, 4717 (2001); (q) C. Ollivier, P. Renaud. *J. Am. Chem. Soc.* **122**, 6496 (2000).
51. (a) H. Fliri, C. P. Mak. *J. Org. Chem.* **50**, 3438 (1985); (b) M. E. Briggs, S. Z. Zard. *Synlett* 334 (2005); (c) G. Ouvry, B. Quiclet-Sire, S. Z. Zard. *Angew. Chem., Int. Ed.* **45**, 5002 (2006); (d) N. Charrier, D. Gravestock, S. Z. Zard. *Angew. Chem., Int. Ed.* **45**, 6520 (2006).
52. (a) N. Charrier, B. Quiclet-Sire, S. Z. Zard. *J. Am. Chem. Soc.* **130**, 8898 (2008); (b) W. Kosnik, M. Michalak, B. Quiclet-Sire, S. Z. Zard. Unpublished observations.
53. A handbook on the RAFT/MADIX technology has recently appeared: (a) C. Barner-Kowollik (Ed.). *Handbook of RAFT Polymerization*, Wiley-VCH, Weinheim (2008); for other reviews, see: (b) G. Moad, E. Rizzardo, S. H. Thang. *Aust. J. Chem.* **62**, 1402 (2009); (c) G. Moad, E. Rizzardo, S. H. Thang. *Aust. J. Chem.* **58**, 379 (2005); (d) S. Perrier, T. Takolpuckdee. *J. Polym. Sci., Part A: Polym. Chem.* **43**, 5347 (2005); for the original patents on MADIX and RAFT, see: (e) P. Corpart, D. Charmot, T. Biadatti, S. Z. Zard, D. Michelet. WO 9858974 (1998) [*Chem. Abstr.*, **130**, 82018 (1999)]; (f) T. P. Le, G. Moad, E. Rizzardo, S. H. Thang. *Int. Pat.* 9801478 [*Chem. Abstr.* **128**, 115390 (1998)].
54. (a) B. Quiclet-Sire, S. Z. Zard. *Bull. Korean Chem. Soc.* **31**, 543 (2010); (b) S. Z. Zard, B. Sire, P. Jost. Int. Pat. WO 2005040233 (2005).
55. (a) S. Fabre, X. Vila, S. Z. Zard. *Chem. Commun.* 4964 (2006); (b) G. Binot, B. Quiclet-Sire, T. Saleh, S. Z. Zard. *Synlett* 382 (2003); (c) G. Bouhadir, N. Legrand, B. Quiclet-Sire, S. Z. Zard. *Tetrahedron Lett.* **40**, 277 (1999).
56. For the direct replacement of a xanthate by a bromine atom or by a 2-chlorophenyl sulfide, see: (a) F. Barbier, F. Pautrat, B. Quiclet-Sire, S. Z. Zard. *Synlett* 811 (2002); (b) M. Corbet, Z. Ferjancic, B. Quiclet-Sire, S. Z. Zard. *Org. Lett.* **10**, 3579 (2008).
57. (a) E. Bacqué, M. El Qacemi, S. Z. Zard. *Org. Lett.* **7**, 3817 (2005); (b) L. Boiteau, J. Boivin, B. Quiclet-Sire, J.-B. Saunier, S. Z. Zard. *Tetrahedron* **54**, 2087 (1998); (c) Y. Laot, L. Petit, S. Z. Zard. *Org. Lett.* **12**, 3426 (2010).
58. D. H. R. Barton, S. W. McCombie. *J. Chem. Soc., Perkin Trans. 1* 1574 (1975).
59. (a) A.-C. Callier-Dublanchet, B. Quiclet-Sire, S. Z. Zard. *Tetrahedron Lett.* **36**, 8791 (1995); (b) M.-H. Le Tadic-Biadatti, A.-C. Callier-Dublanchet, J. H. Horner, B. Quiclet-Sire, S. Z. Zard, M. Newcomb. *J. Org. Chem.* **62**, 559 (1997); (c) A.-C. Callier-Dublanchet, B. Quiclet-Sire, S. Z. Zard. *Tetrahedron Lett.* **38**, 2463 (1997); for a recent review on nitrogen-centered radicals, see: (d) S. Z. Zard. *Chem. Soc. Rev.* **37**, 1603 (2008).
60. (a) D. H. R. Barton, D. Crich, W. B. Motherwell. *J. Chem. Soc., Chem. Commun.* 939 (1983); (b) D. H. R. Barton. *Half a Century of Free Radical Chemistry*, Cambridge University Press, Cambridge (1993).
61. (a) A. Biéchy, S. Hachisu, B. Quiclet-Sire, L. Ricard, S. Z. Zard. *Angew. Chem., Int. Ed.* **47**, 1436 (2008); (b) A. Biéchy, S. Hachisu, B. Quiclet-Sire, L. Ricard, S. Z. Zard. *Tetrahedron* **65**, 6730 (2009).

