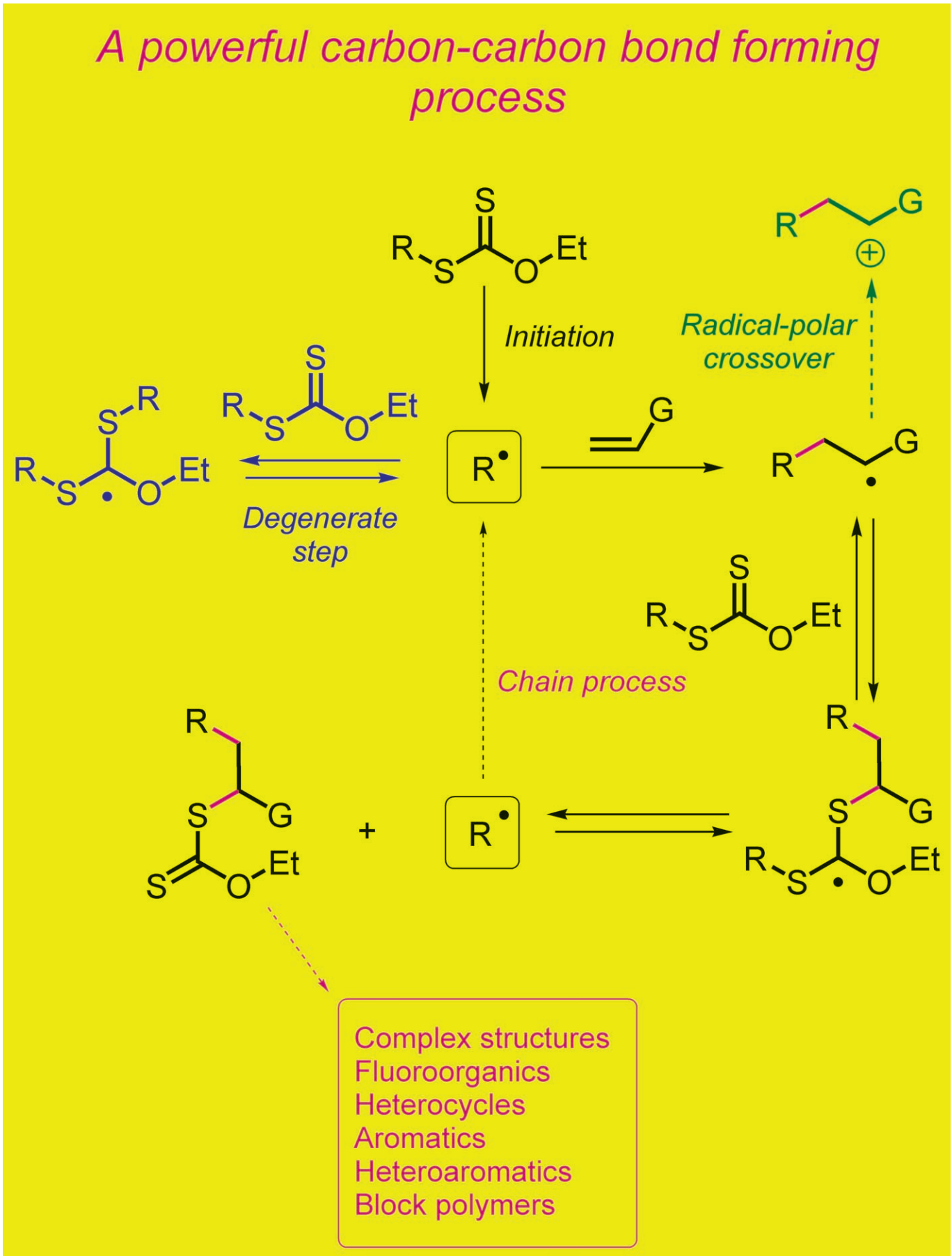

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Powerful Carbon–Carbon Bond Forming Reactions Based on a Novel Radical Exchange Process

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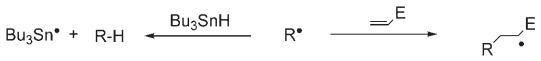
Abstract: Xanthates and related derivatives have proved to be extremely useful for both inter- and intramolecular radical additions. The broad applicability of the intermolecular addition to un-activated olefins opens tremendous opportunities for synthesis, since various functional groups can be brought together under mild conditions and complex structures can be rapidly assembled. The presence of the xanthate in the product is also a powerful asset for further modifications, by both radical and non-radical pathways. Of special importance is the access to highly substituted aromatic and heteroaromatic derivatives and the synthesis of block polymers through a controlled radical polymerisation mediated by various thiocarbonylthio group containing agents (RAFT and MADIX processes).

Keywords: block copolymers · C–C coupling · heterocycles · radical reactions · xanthates

Introduction

There are very few reasonably general reactions capable of creating carbon–carbon bonds in an intermolecular fashion starting with simple, un-activated alkenes. The comparatively low reactivity of ordinary alkenes makes them recalcitrant partners in most bimolecular C–C bond forming processes and the reactive species involved will generally prefer to react with other functional groups present in the molecule. Yet, the formation of C–C bonds is central to organic synthesis, and a broadly applicable, operationally convenient method allowing such a synthetic transformation would be highly desirable. Even though radicals are capable of reacting with simple alkenes, most of the developments and applications in this area have been confined to intramolecular modes or to additions to activated olefins. Allylation reactions based on allyl stannanes and analogous reagents represent a noteworthy exception.[1] Intermolecular additions to un-activated alkenes are simply too slow to compete with other pathways open to the radical intermediate. The difference in rate constants between an intermolecular addition to an ordinary olefin and hydrogen abstraction from a stannane, for instance, is too large and cannot be overcome by playing on concentration effects through high dilution or syringe pump techniques.[1] Thus, in the reaction displayed in Scheme 1, substituent –E has to activate the alkene sufficiently to make the addition faster than premature reduction by the stannane. Group –E cannot therefore be a mere alkyl or some other non-activating group. The same unfavourable situation obtains with all common radical processes, except for Kharasch-type reactions and those benefiting from the persistent radical effect.[1]



Scheme 1. Radical addition to an olefin and competing premature reduction.

A solution to this longstanding problem in chemistry emerged from our work on the degenerative radical exchange of thiocarbonylthio derivatives, and especially xanthates.[2] The main features of the process are summarised in the reaction manifold pictured in Scheme 2. Radicals R•, produced first in the initiation step, rapidly add to the thiocarbonyl group of the starting xanthate **1** (path A). This addition is fast but the stabilised adduct radical **2** is too hindered to dimerise (or does so reversibly) and cannot disproportionate. It can therefore only undergo fragmentation by rupture of either the C–O (path B) or the C–S bonds (path C). The former is quite difficult, for it involves a particularly

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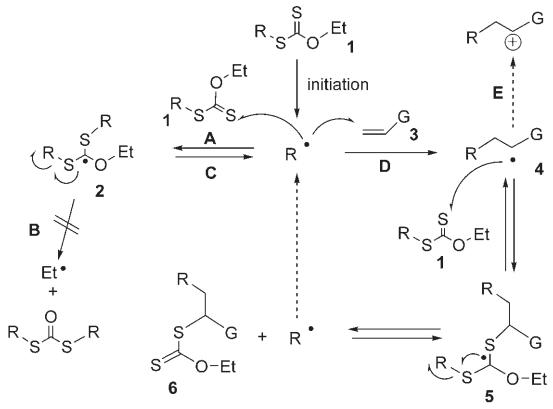


Scheme 2. Reaction manifold for the addition of xanthates to olefins.

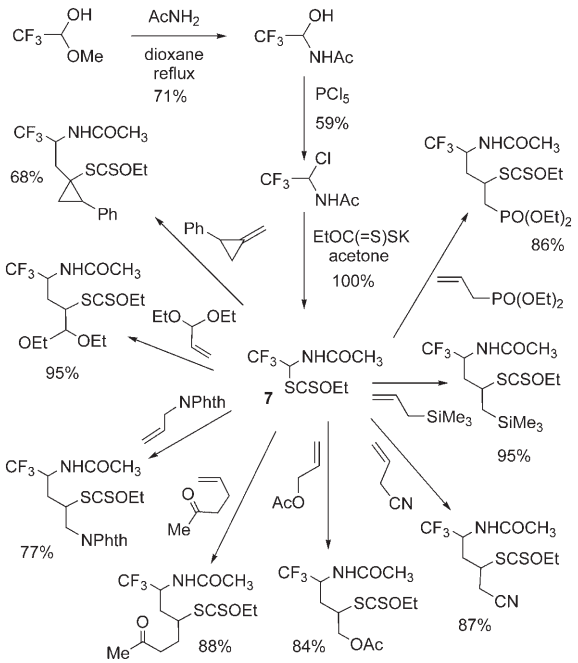
strong bond and generates a high-energy ethyl radical. Scission of the C–S bond (path C) leads simply to the starting xanthate and the same radical R•. Thus, the reaction of the initial radical R• with its xanthate precursor is reversible and degenerate. As a consequence, the effective lifetime of R• in the medium increases considerably, since it is continuously being regenerated. 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 **3** (path D), a new radical **4** is created, which in turn reacts *reversibly* with the starting xanthate to produce intermediate radical **5**. Reversible collapse of this species furnishes finally adduct **6**, as well as the initial radical R• to propagate the chain.

The overall result is relatively straightforward, corresponding to the addition of the elements of the xanthate across the double bond of the olefinic trap. Xanthates are used in this Scheme since most of the transformations discussed below involve this group, but the same applies to other related derivatives of general formula R-S(C=S)-Z, such as dithioesters, dithiocarbamates, trithiocarbonates, even though efficiency and rates can vary significantly depending on substituent Z.[3]

The simplicity of the global transformation should not detract from the mechanistic subtleties of the process, which need to be appreciated. The thiocarbonyl group is vastly more radicophilic than a simple olefin. This means that any reactive radical (namely R•, **4**, and any radical arising from the initiator) is rapidly removed from the medium and stored as stabilised adducts of type **2** and **5**. These adducts fragment to liberate preferentially the most stabilised radical (stabilisation implies thermodynamic effects and this may be used as a rule of thumb, but polar factors speeding up the fragmentation step can also have a significant influence). It is important to bias the fragmentation of intermediate **5** in the desired direction by making adduct radical **4** less "stable" than the initial radical R•; for otherwise the chain will be slowed down causing the appearance of unwanted side reactions. This simple consideration ensures that as long as the starting xanthate **1** is present, product xanthate **6** is "protected" by being, in a sense, prevented from undergoing further radical additions to the olefin resulting ultimately in telomerisation. The greater the difference in "stability" between radicals R• and **4** the better is the dichotomy in the reactivity of the two xanthates and the easier it is to control the process. This is a key point that is important to keep in mind, especially when dealing with intermolecular reactions. As will be seen later in this short overview, it is sometimes possible to oxidise adduct radical **4** by electron transfer to the peroxide resulting in a crossover from the radical to the cationic manifold (path E). This step is favoured when group G is an entity that stabilises the cation.

Xanthates have been used most frequently because they offer the best combination in terms of reactivity, stability, and accessibility. Potassium *O*-ethyl xanthate is commercially available and cheap (it is used on a large scale as a flotation agent in the mining industry). It is an excellent nucleophile and many xanthates can be made trivially by displacement of a suitable leaving group. For instance, xanthate **7** depicted in Scheme 3 is readily made from the hemiacetal of trifluoroacetaldehyde. It adds efficiently to a large assortment of olefins, as demonstrated by the reactions in Scheme 3.[4]

Alternatively, one can consider a given olefin, say allyl trimethylsilane as in Scheme 4, and highlight the great diversity of xanthates that can be added to it. Reagents **8**, **9**, and **10** allow the direct, flexible introduction of a trifluoromethyl containing motif and complement in this respect the amide containing xanthate **7** of the previous scheme. In fact, the xanthate exchange process turns out to be a very powerful



Scheme 3. Formation of α-trifluoromethyl amines. Reaction conditions: reagents, lauroyl peroxide (2–10 mol%), 1,2-dichloroethane, reflux.

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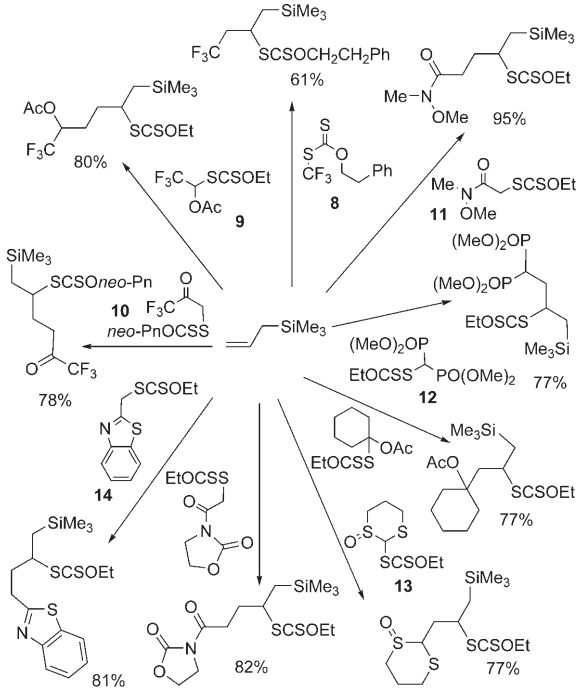
approach to numerous fluorinated synthons.[4,5] Xanthate **11** allows the direct introduction of a Weinreb amide,[6] whereas a geminal bis-phosphonate can be prepared by the use of reagent **12**.[7] Sulfoxide **13** is an interesting one carbon radical equivalent and provides an unusual entry to the very rich chemistry of dithiane derivatives.[8] Heterocycles such tetrazoles, benzothiazoles and imidazoles can be readily obtained by using the corresponding xanthates. A transformation involving a benzothiazole is shown starting with xanthate **14**.[9] Other variants are displayed in the same Scheme[9,10] but an infinite number of combinations can be envisaged.



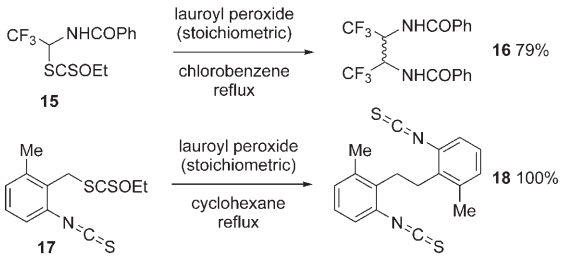
Scheme 4. Radical additions to allyl trimethylsilane.

The examples in Schemes 3 and 4 embody many of the attractive features of the system, and they are indeed numerous.

- The reagents are cheap, generally stable, easy to handle, and readily available.
- The processes are usually convergent and atom economical since all the elements of the xanthate and the olefin end up in the product.
- No heavy metals are involved, even though organotin reagents for instance may be used with xanthates if needed.
- The reactions can be advantageously run under very high concentrations (reduced cost and waste).
- The processes are self-regulating, safe, and easily scalable.
- 1,2-Dichloroethane (DCE) was used as the solvent for convenience but many other solvents, including water, can be used.
- Although peroxides are usually the preferred initiators for triggering the chain reaction, other initiators such as diazo derivatives, a combination of triethylborane and oxygen can also be used. Initiation may equally be performed photochemically.
- There is a remarkable tolerance for many functional groups, allowing an easy access to a very wide diversity of structures and combinations of functional groups.

A classical chain process is not strictly necessary. In some cases, adduct radical **4** can be oxidised by the peroxide causing a crossover from a radical to a polar manifold (path E). This will have its importance for the replacement of the xanthate group by a hydrogen or a bromine and when dealing with the synthesis of aromatic and heteroaromatic derivatives (see below). The peroxide thus behaves both as an initiator and a reagent and needs to be used in stoichiometric amounts.

Going back to Scheme 2, it is important to realise that the xanthate group exerts a powerful regulating influence on the concentration of the various radicals in the medium, scavenging reactive radicals and releasing stabilised radicals. This role can be seen in the selective and high yielding formation of homodimers from xanthates that lead to stabilised radicals, when the xanthate is exposed to stoichiometric amounts of peroxide in the absence of a trap. Two such examples are displayed in Scheme 5. The first involves xanthate **15**, an analogue of xanthate **7** used in Scheme 3. The dimerisation provides a convenient route to hexafluorinated dibenzamide **16**, a compound that would be quite difficult to make by classical routes.[4] The parent diamine and derivatives thereof could be of interest as ligands for transition metals. The second involves the quantitative formation of bis(isothiocyanate) **18** by homocoupling of the corresponding benzylic radicals.[11]



Scheme 5. Selective formation of homodimers. Reaction conditions: reagents, lauroyl peroxide (100 mol%), 1,2-dichloroethane, reflux.

Mechanistically, the clean formation of homodimers, when stabilised radicals are involved, has profound implications, since one would have expected the formation of a complicated mixture resulting from all possible combinations of radicals derived from the peroxide initiator and the xanthate. The simplified reaction sequence in Scheme 6 encapsulates the subtle factors underlying this phenomenon.

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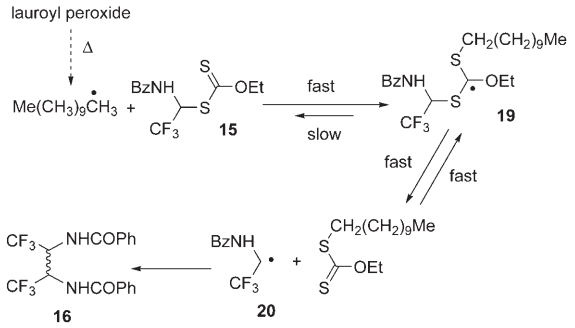


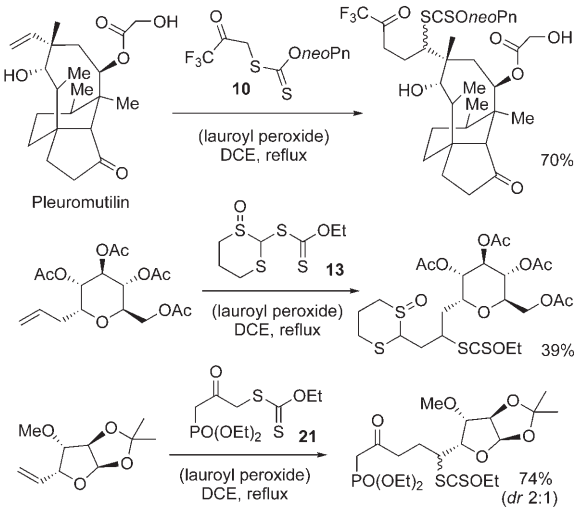
Scheme 6. Selective regulation of the concentration of radicals.

As soon as an undecyl radical is generated, it is rapidly scavenged by the strongly radicophilic thiocarbonyl of xanthate **15** to give adduct **19** (in fact, any xanthate in the medium, and not just starting xanthate **15**). Although this addition is in principle reversible, fragmentation to give the more stable radical **20** is much more facile. Thus, the concentration in undecyl radicals remains extremely low, whereas that of stabilised radical **20** builds up continuously until homocoupling becomes unavoidable, since there is no other reasonable trap in the medium. This observation also means that adduct radical **19** either does not engage in radical-radical interactions with another radical **19** or with stabilised radical **20**, or does so reversibly.

Further Examples

The tolerance of the method may be further underscored by the three transformations pictured in Scheme 7, involving radical additions to relatively complex olefinic partners. The first represents an unusual approach for the modification of pleuromutilin, a terpenic antibacterial, without the need for any prior protection of the existing functional groups.[12] The use of a neopentyl instead of the ubiquitous ethyl group is to render xanthate **10** more hydrophobic and thus to limit the formation of the hydrate of the ketone. Trifluoromethyl ketones readily form hydrates and, in the present case, this would disfavour the generation of the desired trifluoroacetonyl radical because the hydrated radical lacks the stabilisation provided normally by the carbonyl group. Many other xanthates besides **10** can be used for the addition, and novel pleuromutilin derived libraries can be constructed by further modifications of the adducts.

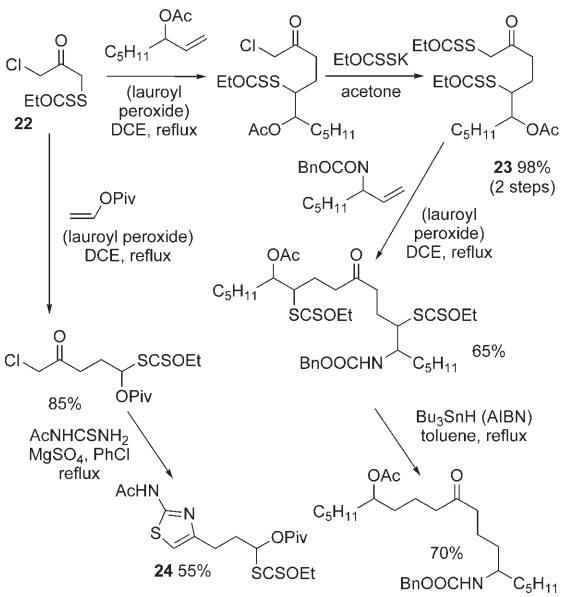
The second example represents the addition of a one carbon equivalent, **13**, to a glucose derivative.[8] Further manipulations can again exploit the rich and now well-established ionic chemistry of dithianes. The last radical addition also involves a sugar derived alkene, as well as an interesting phosphonate reagent **21**, which can be elongated on one side by a radical addition, as shown, and then elaborated on the other side by a classical Wittig–Horner condensation with an aldehyde or a ketone.[13] It is worthwhile noting that the radical carbon–carbon bond-forming step takes place on



Scheme 7. Additions to complex alkenes.

the terminus that bears the least acidic hydrogens in reagent **21**.

Another interesting linchpin reagent is α-chloroketone derived xanthate **22**, which allows the modular elongation of both sides of the ketone by two successive radical additions.[14] This is exemplified in Scheme 8 by a first addition to 3-acetoxy-1-octene, displacement of the chlorine by potassium *O*-ethyl xanthate, then a second addition to a protected allylamine. Note that in the first adduct **23** only the xanthate group vicinal to the ketone and leading to more stabilised radical reacts; the other remains as a spectator since it is more difficult to generate the corresponding unstabilised secondary radical. The final compound now contains two xanthate groups that can be removed by reduction with tributylstannane. More generally xanthate **22** provides



Scheme 8. A linchpin xanthate.

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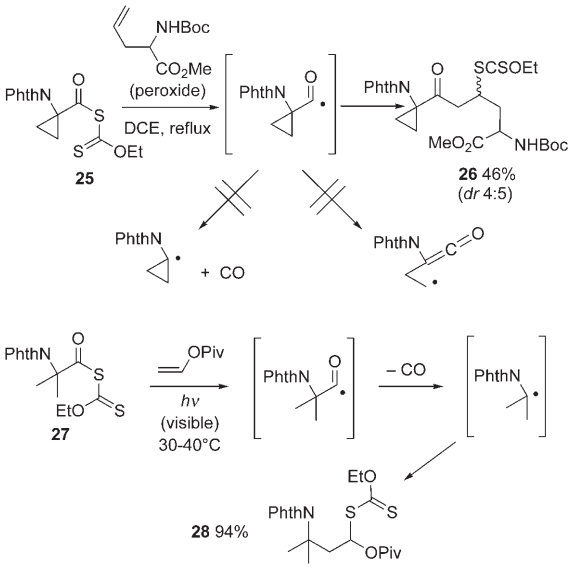
a direct entry into α-chloroketones of unusual structures that are otherwise inaccessible. Many classical heterocyclic syntheses rely on α-chloroketones as key substrates, as they offer two quite reactive electrophilic sites and are ideally suited for condensation reactions. Thus, treatment with a thioamide leads to a thiazole such as **24** through the Hantzsch condensation, as shown in the lower part of Scheme 8.[14]

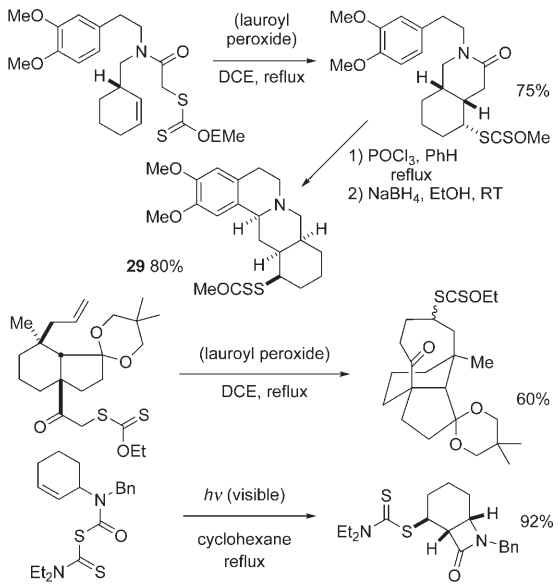
The xanthate transfer technique allows the generation and manipulation of a variety of interesting radicals. For instance, it proved possible to generate and capture cyclopropylacyl radicals in an intermolecular fashion.[15] In the absence of strongly stabilising substituents on the cyclopropyl ring (such as phenyl groups), the extrusion of carbon monoxide and ring opening are too slow to compete with the addition process. The cyclopropyl radical is in fact a high-energy species that is more akin to a vinyl than to an aliphatic radical, because of the particular hybridisation of the cyclopropyl carbons. This difference can be appreciated by comparing the behavior of xanthates **25** and **27**. In the latter, the cyclopropyl motif has been replaced by two geminal methyl groups. In this case, the loss of carbon monoxide cannot be avoided. It is therefore the capture of the tertiary radical that is observed. From a synthetic perspective, both transformations are interesting. The first represents the synthesis of a very unusual protected amino acid **26**, which would be quite difficult to obtain by classical routes. The second corresponds to a general approach to protected tertiary amines, such as **28**, which are also not always easily accessible (Scheme 9).[15]

Synthesis of Rings

If intermolecular additions onto un-reactive olefins are feasible, then obviously the construction of rings by intramolecular additions should also be readily accomplished. This is indeed the case. Furthermore, rings can be assembled not only through radical processes, but also by a combination of radical and ionic processes. Owing to the relatively long effective lifetimes enjoyed by radicals generated through the xanthate exchange process, reputedly difficult cyclisations can be executed under mild conditions and often without the need for high dilution. Ring closures leading to δ-lactams is a case in point. The existence of slow interconverting rotamers hinders the cyclisation, and stannane-based methods are generally unsatisfactory. The key step in the synthesis of the berbane system **29**, summarised in Scheme 10,



Scheme 9. Comparative behavior of cyclopropylacyl and aliphatic acyl radicals.



Scheme 10. Construction of the berbane, pleuromutilin, and β-lactam skeletons.

shows that the xanthate route can indeed overcome this problem.[16] Moreover, the xanthate group survives the somewhat harsh acidic conditions of the subsequent Bishler–Napieralski cyclisation. Even the notoriously difficult four- and eight-membered ring closures can sometimes be effected as indicated by the construction of the bridging ring in a pleuromutilin model[17] and the remarkably efficient β-lactam formation recently reported by Grainger and Innocenti,[18] also displayed in Scheme 10.

Alternatively, cyclic structures can be constructed by combining the radical addition with classical ionic reactions. The bimolecular radical addition serves to bring together various functional groups, which can then be made to react together in an intramolecular fashion by changing the pH or by adding a suitable reagent. This approach is illustrated by the convergent synthesis of cyclohexenes displayed in Scheme 11, where an intramolecular Wittig–Horner condensation is used to install the six-membered ring.[19] Interestingly, in the second sequence leading to **31**, corresponding to the C-D portion of steroids, only one isomer is ultimately obtained: one of the two ketones in precursor **30** reacts pref-

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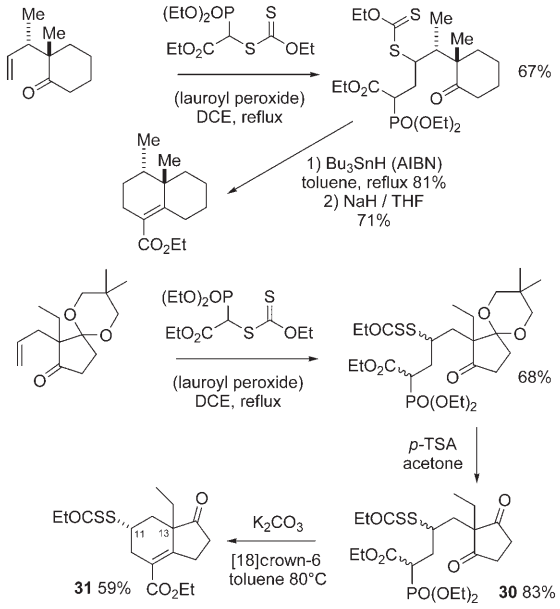
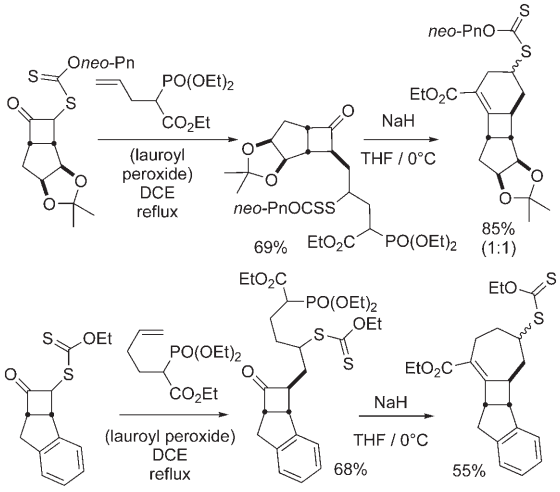


Scheme 11. A convergent construction of cyclohexenes.

erentially to place the xanthate group in the equatorial position in order to avoid a repulsive 1,3-diaxial interaction with the ethyl group. Note that the location of the xanthate group in **31** is that of the important C-11 position (steroid numbering); furthermore, in natural steroids, there is a methyl and not an ethyl group on C-13, but some very potent contraceptives such as desogestrel contain the non-natural ethyl substituent at this position and have to be made industrially by total synthesis.

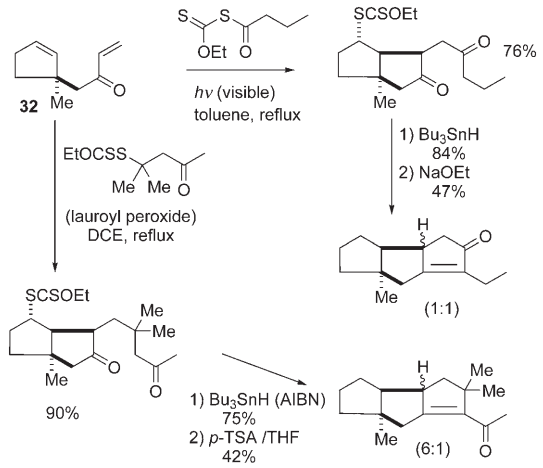
Conversely, the phosphonate group can be part of the olefinic trap, as in the examples shown in Scheme 12.[20] The distance between the olefin and the phosphonate group ultimately determines the size of the new ring, a cyclohexene or a cycloheptene in the present case. It is worth noting that the ease of appending the side chain in the present approach



Scheme 12. Construction of cyclohexenes and cycloheptenes.

contrasts with the general difficulty encountered in alkylating cyclobutanones. Obviously, this strategy is not limited to cyclobutanones: other cyclic or open chain ketones can of course be used.

Another powerful route to polycyclic structures involves a combination of the xanthate addition with a Robinson annelation, because it is quite easy to assemble the desired components. The examples displayed in Scheme 13 start with



Scheme 13. Synthesis of polyquinanes.

enone **32**, a compound made simply from 3-methyl-2-cyclopenten-1-ol in three straightforward steps, including a key Claisen rearrangement which conserves the stereochemistry of the initial allylic alcohol.[21] Intermolecular addition, ring closure, and xanthate transfer using two different xanthates provide the expected bicylic structures in high yield. Reductive removal of the xanthate group and acid- or base-induced Robinson annelation provide the corresponding triquinanes. The stereochemistry of the various chiral centres is either directly controlled by the stereochemistry of the quaternary carbon in the initial enone or may be corrected afterwards through the extended enolate of the enone group in the product. Again, various combinations of rings can be rapidly constructed by altering the starting enone and the xanthate partners.

The sequence depicted in Scheme 14 showcases the possibility of generating and capturing a propargylic radical.[22] Thus, addition of a malonyl radical derived from the corresponding xanthate gives intermediate radical **33**, which ring-closes to furnish ultimately an allene. Reductive removal of the xanthate group simplifies the structure and allows the acid-catalysed rearrangement of the allenyl acetate into a conjugated enone to occur without undue complications. Finally, base-induced internal Michael addition introduces the third ring. Thus, it is possible to elaborate quite complicated structures in very few steps.

For the synthesis of alkaloids, it is advantageous to associate the radical xanthate transfer with the Mannich or the

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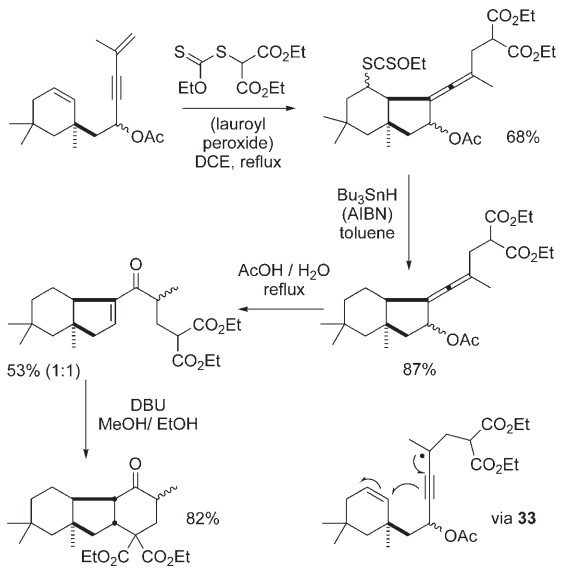
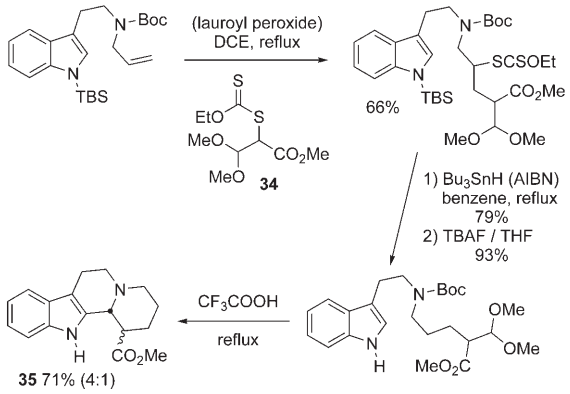


Scheme 14. Formation of an allene by capture of a propargylic radical. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

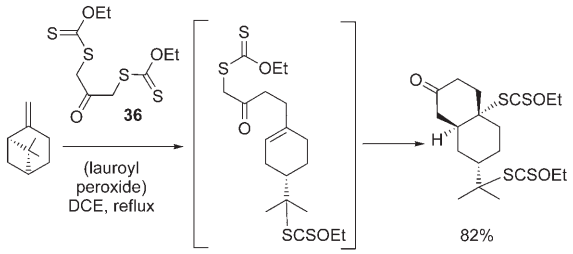
Pictet–Spengler reaction. An example of the latter case is pictured in Scheme 15, illustrating a possible approach to the eburna alkaloids.[23] Addition of xanthate **34** containing



Scheme 15. Synthesis of polycyclic indole derivatives. AIBN = azobis-(isobutyronitrile).

a protected aldehyde onto a protected *N*-allyl tryptamine followed by reductive removal of the xanthate group and deprotection of the indole nitrogen affords the precursor for the ionic cascade. This can be triggered by the action of trifluoroacetic acid to form tetracyclic indole **35** as a mixture of epimers.

The construction of rings can also rely on a double radical addition. This strategy is exemplified by the reaction of bis-xanthate **36** with β-pinene (Scheme 16).[14,24] The first intermolecular addition causes the scission of the cyclobutane ring and places an olefinic bond in a position allowing it to capture the radical produced from the second xanthate. The

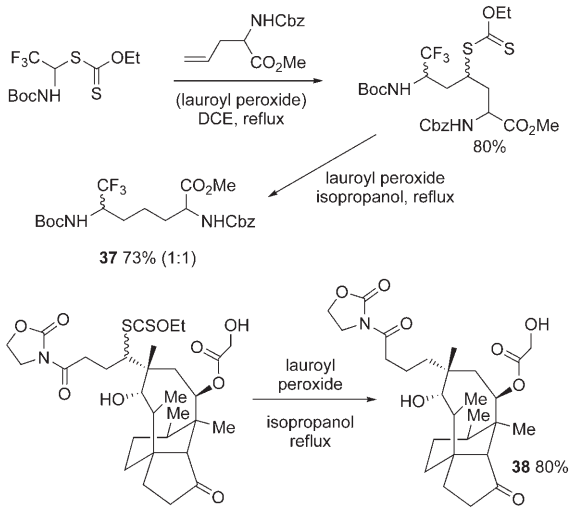


Scheme 16. Synthesis of *cis*-decalins from β-pinene by a radical cascade.

overall result is a highly efficient annelation process that leads to an optically pure *cis*-fused decalin system with a well-defined stereochemistry of the various chiral centres.

Modifications of the Xanthate Group

In the foregoing examples, the xanthate group was either left in the product or reductively removed using tributylstannane. Other, tin-free procedures for the removal of the xanthate are known. Tris(trimethylsilyl)silane or the much cheaper hypophosphorous acid and its salts can be used as the hydrogen atom donors.[25] A combination of a peroxide and isopropanol is also cheap and convenient.[26] The latter system relies on the abstraction of a hydrogen atom from the solvent but a stoichiometric amount of peroxide is required since it is now both an initiator and an oxidant for the ketyl radical generated from the isopropanol. Two examples of the reduction of a xanthate into the corresponding alkane are given in Scheme 17. The first exemplifies an approach to unnatural amino acids such as **37**,[27] and the second shows the synthesis of **38**, a xanthate-free radical addition product of pleuromutilin.[12] Interestingly the isopropanol/lauroyl peroxide combination can also effect a Barton Mc-Combie type deoxygenation, thus avoiding the use of tin-based reagents.[28]



Scheme 17. Tin-free reductive removal of the xanthate group.

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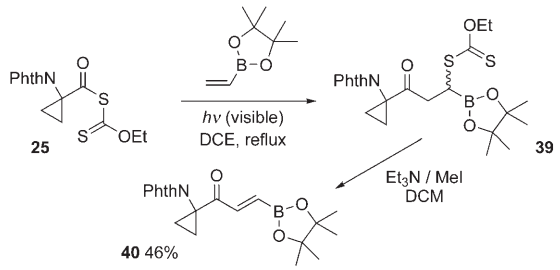
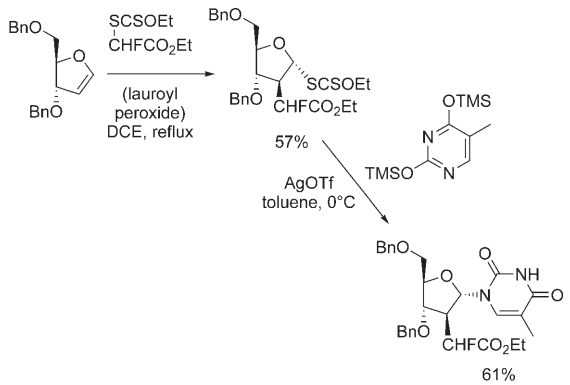
The presence of the xanthate entity in the product is, however, a precious asset. It allows another radical sequence to be implemented and opens, in addition, an entry into the exceedingly rich chemistry of sulfur. The following examples will give an idea of the possibilities, even if they represent only a tiny fraction of what has already been accomplished and of what can actually be done. For instance, depending on its position with respect to other substituents, the xanthate group can sometimes act as a nucleofuge. One such case obtains upon addition of an acyl radical to an olefin, for the xanthate group in the product can now undergo β-elimination with base to give an unsaturated derivative. In the example in Scheme 18, addition of cyclopropylacyl xanthate **25** to a vinyl boronate gives the expected addition product **39** which, upon treatment with triethylamine/methyl iodide, provides a unique unsaturated boronate **40**. This unusual substance could be later used as a substrate in Suzuki–Miyaura couplings or in cycloaddition reactions.[29] Methyl iodide serves to capture irreversibly the eliminated xanthate anion.



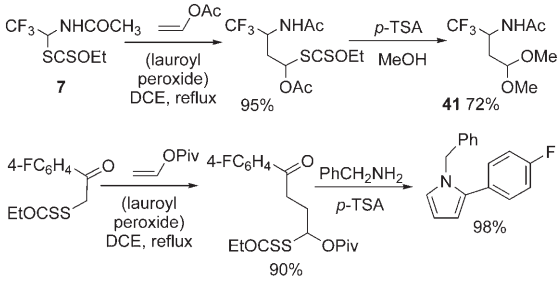
Scheme 18. Synthesis of a vinyl boronate. DCM = dichloromethane.

If an enol ether is used as the radical trap, the xanthate ends up on the same carbon as the oxygen. The C–S bond finds itself weakened by an anomeric-type effect and the xanthate can be made to depart by the action of a Lewis acid or a silver salt. This notion was very recently exploited by Lequeux et al. to expediently construct a fluorinated 2′-α-C-nucleoside as shown in Scheme 19.[30]



Scheme 19. Synthesis of a fluorinated 2′-α-C-nucleoside.

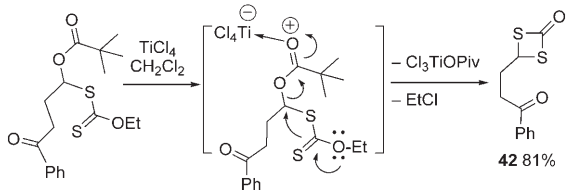
Addition of xanthates to vinyl esters also leads to adducts where the carbon bearing the xanthate group has the oxidation level of an aldehyde. This is demonstrated by the first transformation in Scheme 20 giving rise to an interesting



Scheme 20. Additions to vinyl esters and synthesis of pyrroles. *p*-TSA = *para*-toluenesulfonic acid; Piv = pivaloyl.

synthon **41** for the construction of fluorinated heterocycles.[4] This nicely crystalline compound contains a protected amine and aldehyde groups as well as a trifluoromethyl entity. When the starting xanthate is vicinal to a ketone, the product becomes a convenient substrate for a variant of the Knorr pyrrole synthesis.[31] One example is shown in the same Scheme using vinyl pivalate as the trap. A variety of pyrrole derivatives were expediently prepared, simply by modifying the xanthate and amine components.

Exposure of the adducts with vinyl pivalate to titanium tetrachloride unexpectedly produced dithietanones such as **42**, often in good yields (Scheme 21).[32] Under these conditions, it is the pivaloxy group that behaves as the nucleofuge. Dithietanones are very rare substances and their chemistry is still largely unexplored. They are surprisingly stable to heat but preliminary studies indicate them to be convenient precursors for thioaldehydes through the action of methoxide or DMAP.[33]



Scheme 21. Synthesis of a dithietanone.

It is possible to convert the xanthate into a leaving group by first cleaving it into the corresponding thiol then treating with 1,4-dibromobutane to give the cyclic sulfonium salt. This route was used in a simple synthesis of nine-membered rings.[34] Another more direct pathway takes advantage of the greater radicophilicity of the xanthate as compared with the bromine in ethyl α-bromoisobutyrate.[35] Thus, the radical from the initiator will preferentially attack the xanthate and the resulting radical will then abstract a bromine atom from the bromoisobutyrate. The peroxide has to be used in

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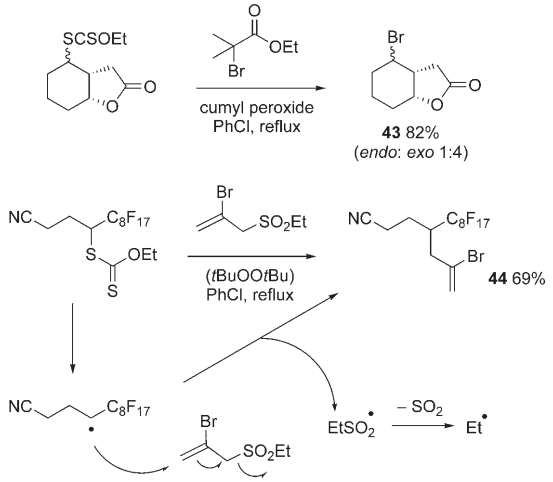
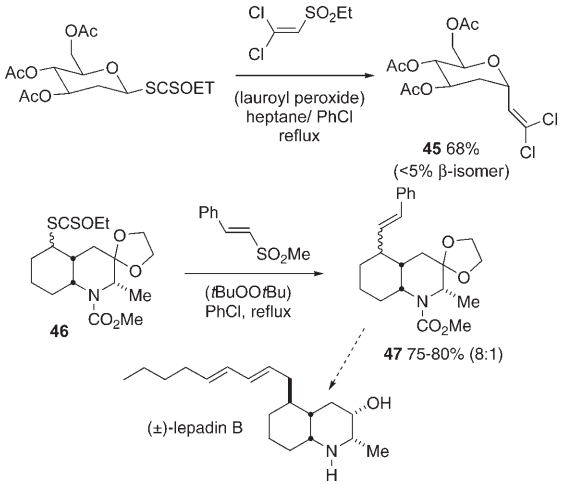
equimolar amounts, because the tertiary isobutyryl radical produced in the bromine transfer step is too stabilised and incapable of propagating the chain. The formation of bromolactone **43** is a representative example of this synthetically valuable functional group exchange.[35]

More impressive transformations can be implemented by exploiting the properties of sulfonyl radicals. For instance, heating a xanthate in the presence of ethyl allyl sulfone and a small amount of a peroxide or a diazo initiator leads to an overall allylation reaction.[36] One example of this allylation procedure, including a simplified mechanistic rationale, is presented in Scheme 22. The key consideration is the fact that the ethylsulfonyl radical extrudes a molecule of sulfur



Scheme 22. Functional group transformations of xanthates.

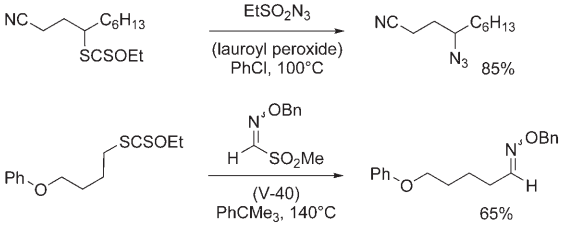
dioxide to give a reactive ethyl radical that is now capable of propagating the chain. The ethyl group in the sulfone reagent can be replaced by a methyl or, for that matter, by any primary aliphatic group, as long as the derived radical is not stabilised. Many substituted allyl groups can be introduced. The fact that the method is tin-free makes it compatible with the presence of halogens. In the transformation shown, a bromoallyl group is introduced with ease. Base-induced elimination of bromide would then lead to an alkyne resulting in an overall indirect radical propargylation. The process can be extended to the introduction of vinyl groups, as illustrated by the two examples in Scheme 23.[37] The first concerns the attachment of a dichlorovinyl motif at the anomeric position of a 2-deoxyglucose derivative, giving rise to compound **45**. The geminal dichlorovinyl entity is especially useful because it can be converted into an alkyne by the Corey–Fuchs reaction or subjected to transition-metal catalysed coupling processes. The second transformation leading to intermediate **47** is a key step in the formal synthesis of lepadine B and involves the appending of a styryl group.[38] The synthesis of the *cis*-perhydroquinoline precursor **46** also relies on an interesting xanthate-mediated cyclisation. Even though no examples are shown, it is worthwhile mentioning that the allylation and vinylation procedures are



Scheme 23. Introduction of vinyl groups.

also applicable to aliphatic iodides.[39] This is an important extension, especially as concerns the vinylation process, since vinyl groups are not easily introduced using traditional transition-metal-based reactions on aliphatic sp^3 centres.

Further, substantial additions to the sulfonyl radical technology were developed in the groups of Renaud and Kim. For instance, Renaud and his co-workers implemented the use a sulfonyl azide to replace a xanthate or an iodide with an azide group, as illustrated by the first example in Scheme 24.[40] This reaction opens up numerous possibilities



Scheme 24. Synthesis of azides and oxime ethers. V-40 = 1,1′-azobis-(1-cyclohexanecarbonitrile).

for the expeditious construction of complex alkaloid structures by combining the easy reduction of azides into amines with the convergence and flexibility of the intermolecular addition of xanthates. Azides have also recently gained high visibility in the context of "click" chemistry. The second transformation in Scheme 24 represents a one-carbon elongation of a xanthate into the homologous aldoxime, devised by Kim and co-workers.[41] As a result of all these efforts, xanthates (as well as iodides and tellurides) can now be considered as springboards to a vast number of structures and functional groups.

Radical–Polar Crossover Reactions

As mentioned in the introduction, the propagation of the chain process depends to a large extent on the difference in

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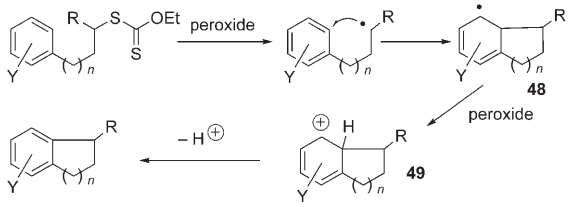
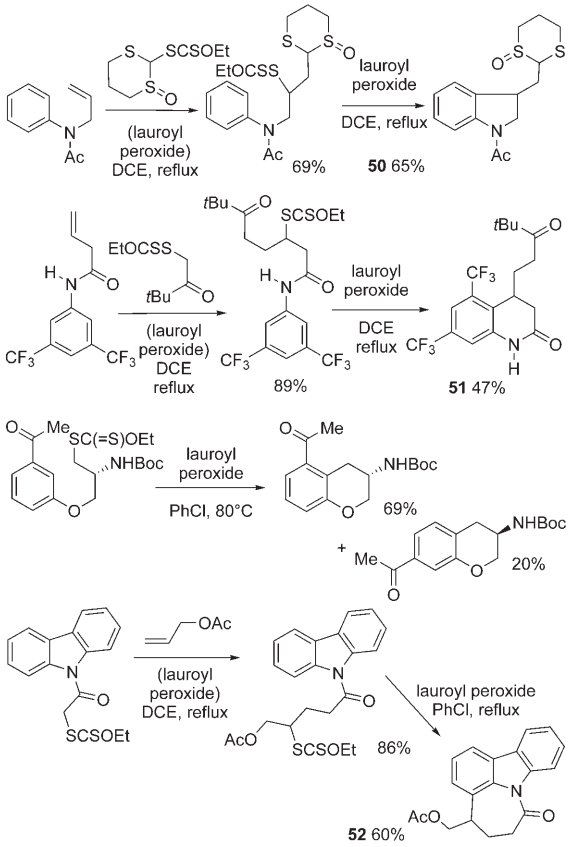
stabilities between the initial and adduct radicals, the former having to be preferably more stable than the latter. It is therefore difficult to establish a chain reaction when the initial radical is of high energy (e.g. vinyl or aromatic radicals) or when the adduct radical is too stable. In the latter situation, if the stabilisation is due to an electron-releasing substituent, then it is possible to imagine oxidation of the adduct radical by a one-electon transfer to the peroxide (path E in Scheme 2). Addition to an aromatic nucleus is a case in point. The resulting cyclohexadienyl radical **48** is too stabilised and not normally capable of propagating the chain, but it can be easily oxidised into the corresponding cation **49**, which then rapidly loses a proton to give back the aromatic system (Scheme 25).



Scheme 25. Radical–ionic crossover in ring closure onto aromatic rings.

This opens a very practical and economical approach to numerous aromatic structures. Some assorted examples are collected in Scheme 26. Five-, six- and sometimes even seven-membered rings can be readily assembled. Oxindoles,[42] indolines (e.g. **50**),[43] dihydroquinolinones (e.g. **51**),[44] dihydroisoquinolinones,[45] homophthalimides,[46] tetralones,[47] aminochromans,[48] can be obtained in a convergent manner from readily accessible precursors. Furthermore, the radical cyclisation step is not usually much affected by the nature of the substituents on the ring. Any variations in the relative rates caused by the substituents are often compensated by the relatively long effective lifetimes of the radical intermediates due to the degenerative exchange of the xanthate group (i.e., if the radical does not cyclise to **48**, it reacts with the starting xanthate in a redundant manner). The tolerance for electron-withdrawing groups is an especially interesting feature because electron-poor aromatics are recalcitrant partners in the traditionally employed Friedel–Crafts and related electrophilic substitutions. Dihydroquinolone **51** is a clear illustration of this advantage, as it contains two trifluoromethyl groups and yet can be obtained in acceptable yield.[44] It is equally noteworthy that the cyclisation occurs despite the absence of a substituent on the nitrogen. Normally a substituent is needed to counteract the unfavourable rotamer distribution. The third example, showing the formation of an aminochroman, also points to a potential drawback regarding the regiochemical control. The generally poor regioselectivity is the price that has to be paid for the high reactivity of the radical species. Finally, it is possible to prepare aromatic structures with fused seven-membered rings such as **52**, possessing a rarely found molecular architecture.[49] The allyl acetate in this



Scheme 26. Examples of ring closures onto aromatic rings.

convergent approach can be replaced by a plethora of other olefins making the synthesis of analogues a trivial matter.

Aza-pyridine derivatives are especially prized by medicinal chemists but are generally less readily available as compared with their benzene analogues. The xanthate transfer approach turns out to be also very useful in this area. The transformations in Scheme 27 summarise some of the possibilities.[50] In the same manner as for the benzene series, five-, six-, and seven-membered rings can be fused to the pyridine nucleus. Most of these derivatives are only tediously accessible by traditional routes. The pyridine ring is often an unwilling participant in the Friedel–Crafts reaction and commercially available functionalised pyridines are somewhat limited in number. The second example nicely demonstrates that an iodo substituent is compatible with the reaction conditions. In this case, the intermolecular addition and ring closure were done directly. The presence of the iodine atom on the pyridine ring in **53** constitutes an especially convenient handle for further transformations based on transition-metal-based couplings. The last sequence shows the formation of aza-benzazepinone **54**, a member of a family that is gaining importance in medicinal chemistry.[50b]

The synthesis of α-tetralones is also particularly convenient, in view of the ready accessibility of the phenacyl halide precursors. Addition of the corresponding xanthate to an olefin followed by peroxide-mediated ring closure gives rise to the expected tetralone in generally good yields. Two ex-

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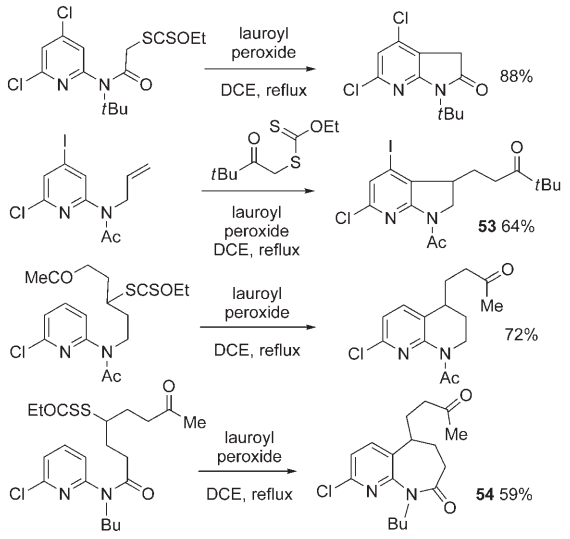
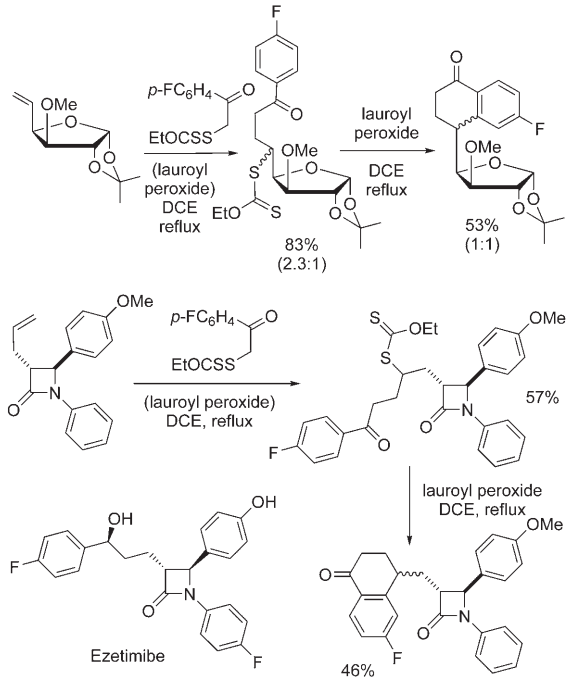


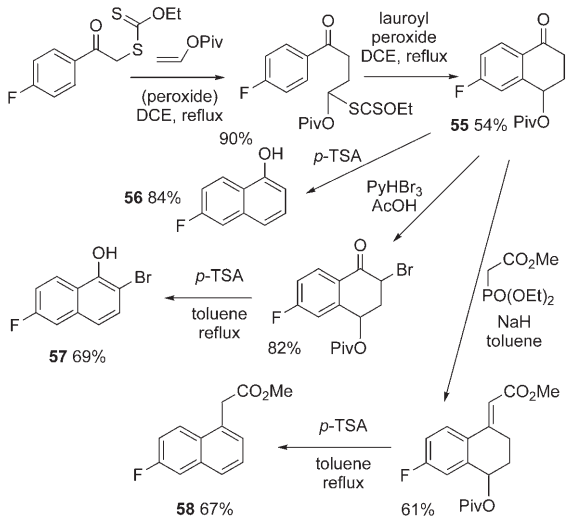
Scheme 27. Examples of ring closures onto pyridines.

amples are provided in Scheme 28 using the same xanthate. In the first, a tetralone containing a sugar side chain is assembled, as a prelude to the C-arylglycoside which can be obtained by aromatisation of the newly formed ring into the corresponding naphthalene.[51] The second represents a synthesis of an analogue of Ezetimibe, a hypocholesteremic drug.[52] In both cases, the motifs are too fragile to be easily introduced in such a direct manner by more conventional routes.

Tetralones are particularly useful structures. They can be converted into naphthalenes, naphthols, naphthylamines (via the Schroeter reaction), or into benzazepinones by ring expansion through a Beckmann rearrangement or other related transformations. Birch reduction of the aromatic ring leads to substituted decalins that can be useful for the synthesis of terpenes or steroids. The synthesis of various naphthalenes is illustrated by the examples in Scheme 29, starting



Scheme 28. Construction of tetralones.



Scheme 29. Synthesis of naphthalenes.

from tetralone **55**.[53] Exposure to acid causes the elimination of the pivaloxy group to give naphthol **56**, a deceptively simple compound which was hitherto unknown. Bromination prior to acid treatment furnishes bromo-analogue **57**, whereas a Wittig–Horner condensation followed by aromatisation leads to 6-fluoro-1-naphthaleneacetate **58**. The pivalate group is sufficiently bulky to permit the selective addition on the ketone of various nucleophilic reagents. This approach can lead to a broad spectrum of naphthalenes with a well-defined and often unusual substitution pattern.

The radical annelation process can be extended to five-membered heteroaromatic rings. In the case of azoles, such as imidazoles and triazoles, it is necessary to neutralise their nucleophilicity either by making a suitably protected derivative or, more simply, by working with their anhydrous salts.[54] Camphorsulfonates are especially convenient because of their general solubility in organic solvents. One example of such a transformation applied to *N*-benzimidazole is given in Scheme 30. Addition and ring closure can be done directly to give tricycle **59**, an interesting template for the synthesis a library of medicinally interesting compounds. This is indicated by the banal conversion into two amides by exposure to cyclopropylamine and to a piperidine derivative. It is also worth mentioning that intermolecular reactions can be accomplished in some cases, as demonstrated by the expedient synthesis of ethyl 2-indole acetate **60**, recently reported by Miranda et al.[55]

Furans often behave differently and their reactions can reveal the reality of the radical–polar crossover.[56] Instead of the expected fused structure, the ring closure leads to a

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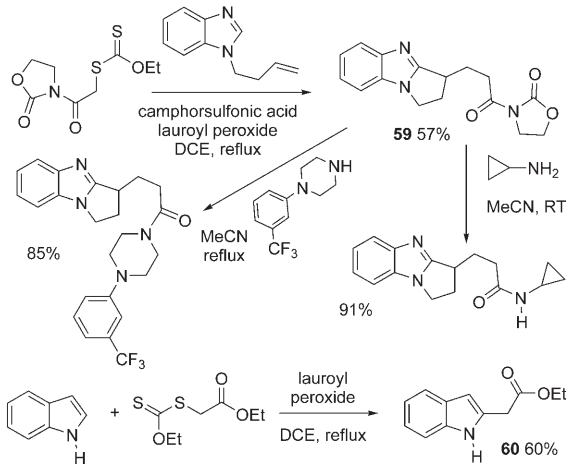
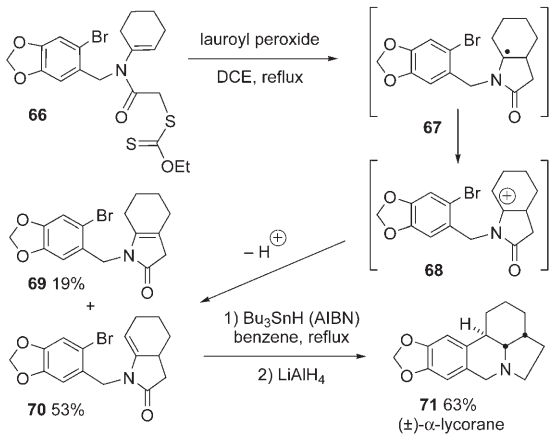
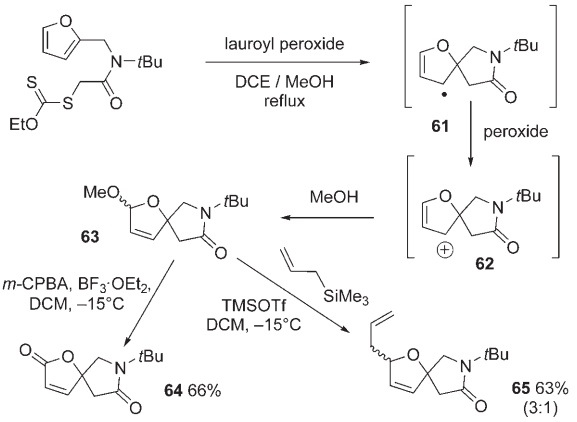


Scheme 30. Additions to heteroaromatics.



Scheme 32. Synthesis of (±)-α-lycorane.

spiro-intermediate **61**, which is oxidised by the peroxide into cation **62**, as delineated in Scheme 31. The use of methanol as the co-solvent allows capture of this cation to afford spirolactam **63** as a mixture of isomers. It is not usually necessary to isolate this rather acid sensitive compound. Its oxidation gives the corresponding lactone **64** whereas a Sakurai-type reaction with allyl trimethylsilane provides **65** in good overall yield.



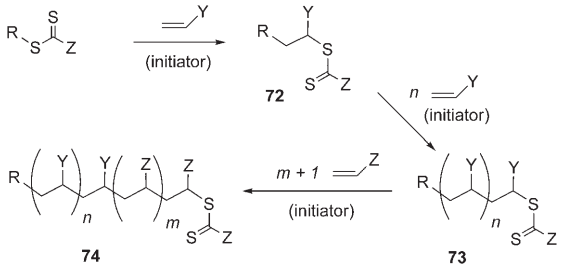
Scheme 31. Spirocyclisation on furans.

Another process where a clear radical–polar crossover can be observed is the ring closure of enamides such as **66** (Scheme 32).[57] The 5-*endo* cyclisation leads to an easily oxidised radical **67**, which readily evolves into cation **68** and from there into isomeric pyrrolidinones **69** and **70** by loss of a proton. A stannane-based 6-*endo* cyclisation of the latter and reduction of the lactam function furnishes (±)-α-lycorane. This very concise synthesis of (±)-α-lycorane highlights the use of two different radical processes to assemble a complex structure. The aromatic bromide is inert under the first, peroxide mediated transformation but can be made to react in the second step by the action of stannyl radicals.

Conclusion

The foregoing examples give a brief overview of the synthetic possibilities attached to the use of the radical xanthate transfer process. Only a small fraction what can be accomplished has been presented. Numerous different types of radicals can be made and captured, including nitrogen-centred radicals,[58] and the products themselves can be modified in infinite ways, by both radical and non-radical reactions. This chemistry represents perhaps the most general solution to the problem of intermolecular carbon–carbon bond formation on un-activated alkenes. This is due to the inherently long life of the intermediate radicals generated using this technique and to the fact that carbon radicals do not react rapidly with many polar groups (such as ketones, esters, amides) commonly encountered in organic synthesis. Most of the potential competing pathways are thus eliminated and clean additions to alkenes can be frequently observed.

In addition to synthesis, the reversible addition fragmentation to the thiocabonylthio motif found in for example xanthates, dithiocarbamates, dithioesters, trithiocarbonates discussed in Scheme 2 for the particular case of xanthates, is now being actively exploited for the synthesis of block polymers.[59] The principle of this approach is summarised in Scheme 33 for the synthesis of a diblock polymer **74**. The first addition to a monomer leads to the usual adduct **72**, which itself can add to further monomer molecules until



Scheme 33. MADIX/RAFT synthesis of block polymers.

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complete consumption of the monomer. Since all the chains can keep growing as long as there is monomer, the polymer obtained, **73**, often has a narrow distribution of molecular weights (or polydispersity). Furthermore, the presence of a capping thiocarbonylthio group in **73** allows a second polymerisation to be performed with a different monomer to give diblock **74**. Triblocks, star polymers, and a multitude of other structures with evocative names (brushes, combs, etc.) can be conveniently assembled. The RAFT and MADIX processes, as they are now called, are set to revolutionise the crafting of polymers with well-defined architectures. This is an extremely effective, cheap technology that can be applied to essentially all commercial monomers and is tolerant of many functional groups. Scientific papers and patents on the topic now number in the hundreds.

Acknowledgements

We are deeply grateful to our students and collaborators, whose names appear in the references, and who made this chemistry possible through their hard work and dedication. We also thank the following organisations and companies who have provided financial support over the years: Ecole Polytechnique, CNRS, DGA, MNRT, the Alfred Kastler Foundation, the Royal Commission for the Exhibition of 1851, CONACyT (Mexico), MECyD (Spain), Rhodia, and Sanofi-Aventis.

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