



# Discovery of the RAFT/MADIX Process. Mechanistic Insights and Polymer Chemistry Implications

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# Discovery of the RAFT/MADIX Process.

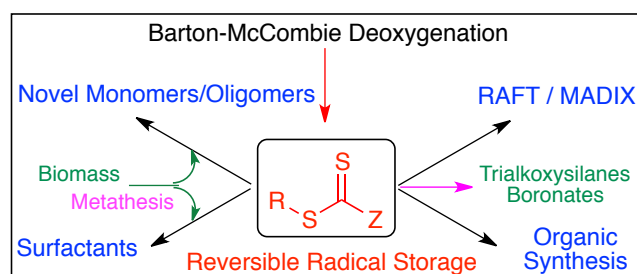
## Mechanistic Insights and Polymer Chemistry

## Implications.

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**ABSTRACT.** This Perspective article outlines the observations leading to the discovery of the degenerative exchange of xanthates and related thiocarbonylthio derivatives. It compares this process with the older Kharasch reaction and discusses the key ability to reversibly store active radicals in a non-reactive form. Implications for the synthesis of polymers beyond the RAFT/MADIX technology are discussed, namely the modification of industrial polymers, the synthesis of novel monomers, oligomers, and surfactants from biosourced feedstocks, especially through an alliance with the powerful metathesis reaction. The synthesis of trialkoxysilanes

crosslinkers for sol-gels and the use of boronates for the construction of well-defined sequences by controlled insertion of single monomers are discussed briefly.

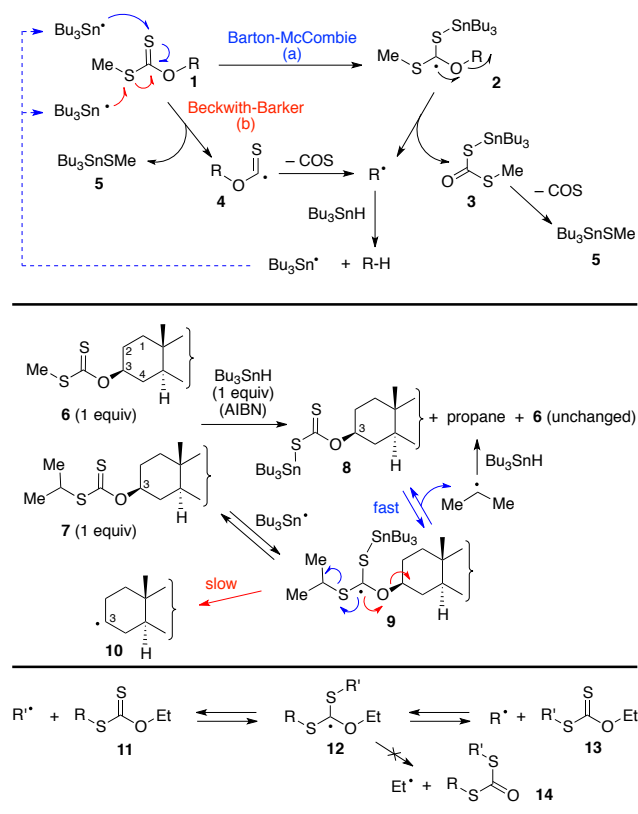
## A BRIEF HISTORY OF A DISCOVERY

The RAFT/MADIX process owes its discovery to a dispute. It was a friendly dispute between two giants of organic chemistry, the late Sir Derek H. R. Barton and Athelstan L. J. Beckwith, who argued about the exact mechanism of the Barton-McCombie deoxygenation of secondary alcohols via the reaction of their *S*-methyl xanthates **1** with tri-*n*-butylstannane (xanthate is the trivial name for an *O,S*-dithiocarbonate). The story has been told elsewhere and only a brief outline will be given here.<sup>1</sup>

In the original Barton and McCombie 1975 article, the stannyl radical was assumed to attack the thiono sulfur to give intermediate **2**, which collapses into radical R• and tin *S,S*-dithiocarbonate **3** (Scheme 1, path **a**).<sup>2</sup> Nearly a decade later, Barker and Beckwith proposed that the attack in fact takes place on the sulfide sulfur (Scheme 1, path **b**) on the basis of ESR experiments (thiocarbonyl radical **4** was detected).<sup>3</sup> In order to distinguish between the two pathways, one equivalent each of cholestanyl derived *S*-methyl- and *S*-isopropyl-xanthates **6** and **7** were made to compete for only one equivalent of stannane.<sup>4</sup> The underlying reasoning was that attack on the thiono sulfur would not be affected by the difference in the steric environment, whereas attack on the sulfide sulfur would be slowed down significantly in the case of the *S*-isopropyl xanthate **7**, if attack indeed occurs on the sulfide sulfur. In the event, *S*-isopropyl-xanthate **7** reacted surprisingly *much faster* than *S*-methyl-xanthate **6** and the product was stannyl xanthate **8** and

propane instead of the expected cholestane resulting from reduction of cholestanyl radical **10** by the stannane.

### Scheme 1. The Barton-McCombie Deoxygenation: Two Alternative Mechanisms

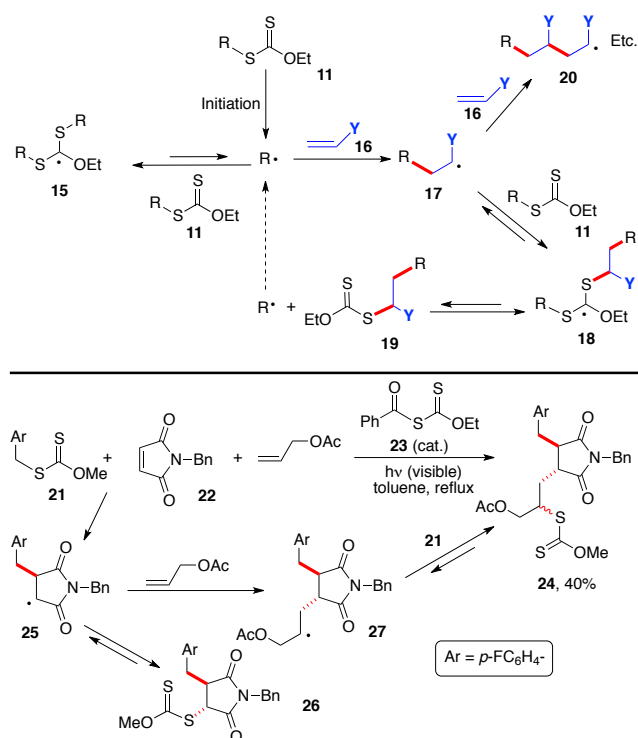


This unexpected result indicated that the stannyl radicals react rapidly and *reversibly* on the thiono sulfur and, importantly, that cleavage of the C-S bond in intermediate **9** is *much faster* than rupture of the C-O bond, when this fragmentation leads to radicals of similar stability (the secondary isopropyl and 3-cholestanyl **10** radicals in this case). By associating this key observation with the known fact that carbon-centered radicals react essentially as fast with thionocarbonyl derivatives as do stannyl radicals,<sup>5</sup> it became obvious that the equilibrium displayed at the bottom of Scheme 1 must be fast and corresponds to the exchange of the xanthate group between radicals  $\text{R}^\bullet$  and  $\text{R}'^\bullet$  (recent theoretical and ESR studies by Coote and

co-workers give an idea of the rates of addition and fragmentation in the case of thionoesters<sup>5b,c</sup>). For the case where  $R = R'$ , the exchange becomes an identity reaction, i. e. a degenerate process. By placing a primary group (such as a methyl or ethyl) on the oxygen, no fragmentation of the C-O bond (à la Barton-McCombie) to give *S,S*-dithiocarbonate **14** takes place.

Incorporating an alkene trap **16** into this system results in the reaction manifold depicted in Scheme 2, whereby a new xanthate **19** is produced by addition of  $R^\bullet$  to the alkene followed by reversible transfer of the xanthate group via intermediate **18**. Because product **19** is also a xanthate, it can revert back to adduct radical **17** and react with another molecule of alkene **16** to give double adduct radical **20**, and so on. As synthetic chemists chiefly interested in small molecules and not in oligomers or polymers, we have striven to limit the sequence to only one addition. To this end, we have selected the partners in such a way that the starting radical  $R^\bullet$  is *more stable* than adduct radical **17**. The collapse of intermediate **18** to give radical  $R^\bullet$  will therefore be more favorable than the return to adduct radical **17** and only little or no oligomer is produced (this aspect is discussed in more detail below). However, if alkene **16** is an easily polymerizable monomer used in excess with respect to the xanthate, then a polymer results that is capped by a xanthate group which can be used to start a second polymerization to another monomer to make a block copolymer. In one experiment, an addition to an excess of methyl acrylate (5 equiv) in cyclohexane as the solvent was attempted that resulted in the precipitation of a beautiful — but at the time unwanted — polyacrylate oligomer bearing a xanthate group at one of its termini. This ability for reversible deactivation and continuous radical additions constitutes the basis of the RAFT/MADIX technology. Indeed, our original work was published in 1988,<sup>6</sup> a decade before the first paper on RAFT appeared in the open literature.<sup>7</sup>

#### **Scheme 2. The Degenerate Addition-Transfer of a Xanthate to an Alkene**



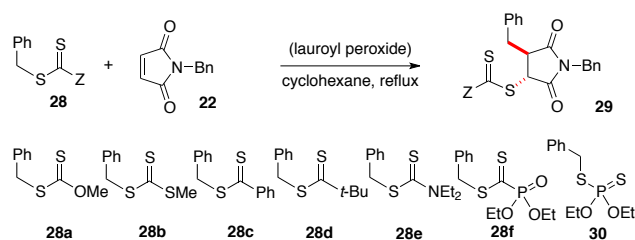
The example shown at the bottom of Scheme 2 is taken from this early study.<sup>6b</sup> Combining *S-p*-fluorobenzyl xanthate **21**, *N*-benzyl maleimide **22**, and allyl acetate, and irradiating the mixture with visible light from a tungsten filament lamp in the presence of a catalytic amount of *S*-benzoyl xanthate **23** gives rise to compound **24** via adduct **26**, which can be isolated or prepared separately (the *O*-methyl xanthate **21** was used instead of the *O*-ethyl congener to simplify the NMR spectra). The *p*-fluorobenzyl radical derived from xanthate has a nucleophilic character and reacts preferentially with the electrophilic maleimide. In contrast, adduct radical **25** has an electrophilic character and adds preferentially to allyl acetate. These polar effects control the sequence of additions. *S*-Benzoyl xanthate **23** absorbs visible light and acts as a photocatalyst (it is regenerated in the process). In later work, we switched to the more practical peroxide initiators, especially DLP (Di-Lauroyl Peroxide, also sold under lauroyl peroxide, Laurox<sup>®</sup> or

Luperox LP®), an industrially available, safe, and inexpensive peroxide, which generates reactive primary undecyl radicals with a half-life of 1-2 h at 80 °C.

## XANTHATES AND OTHER THIOCARBONYLTHIO DERIVATIVES

Inspection of the sequence of steps in Scheme 2 shows that the OEt group is just a spectator and could be replaced by other groups not centered necessarily on oxygen. Indeed, the concluding remark in the 1988 paper stated: “*Although the present preliminary study is confined to xanthates, other analogous thiocarbonyl derivatives should exhibit a similar behaviour*”.<sup>6a</sup> This statement was later confirmed by Hervé Henry within the framework of a Master thesis in 1994 (see supplementary material).<sup>8</sup> This study also provided qualitative information on the relative reactivity of the various types of thiocarbonylthio derivatives through a series of competition experiments. Various *S*-benzyl derivatives **28** were thus reacted with *N*-benzyl maleimide and compared against xanthate **28a** (Scheme 3). The trithiocarbonate **28b** proved best, followed by dithioester **28c**, xanthate **28a**, and dithiocarbamate **28e** (more on dithiocarbamates below).

### Scheme 3. A Study with Various Thiocarbonylthio Derivatives



The difference in reactivity between the first three was modest. Nevertheless, these observations justified the concluding statement made in the first review on the subject, published in 1997: “*In principle, the xanthate functionality can be replaced by other related groups.*”

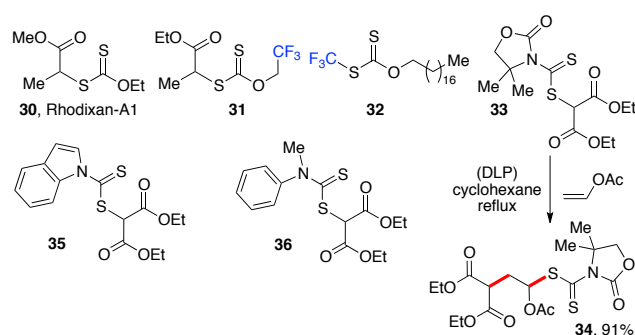
*Preliminary studies thus seem to indicate that trithiocarbonates are equally capable of sustaining the same type of radical chain reactions, but further work is necessary to ascertain whether they offer any special advantages.”*<sup>9</sup> Furthermore, the same year saw the filing of our master patent on the controlled synthesis of block polymers, in collaboration with polymer chemist Dominique Charmot and his team at Rhône-Poulenc Rorer (RPR, part of which later became Rhodia and is now part of Solvay).<sup>10</sup> As a consequence of the above study, this patent protected not only xanthates, but also trithiocarbonates and dithioesters. Incidentally, the unwanted oligomerization of methyl acrylate briefly mentioned above served to induce this fruitful industrial collaboration. Independently, CSIRO colleagues filed a similar patent covering trithiocarbonates and dithioesters but, curiously, not xanthates.<sup>11</sup> For reasons partly practical and partly related to the patent situation, Rhodia chemists decided to develop the xanthates, and not the other derivatives, for the industrial production of block copolymers (the Rhodibloc® line) and came up internally with the acronym MADIX, standing for Macromolecular Design by Interchange of Xanthate. RAFT and MADIX are thus two identical polymerization technologies based on identical mechanisms. The only difference is in the acronyms that the two groups have given to the process. The two master patents cover the same thiocarbonylthio derivatives, with the CSIRO group missing out on xanthates.

As synthetic organic chemists interested primarily in small molecules, we also stayed with xanthates for the vast majority of our later work. So, what are the advantages associated with xanthates as compared with the other thiocarbonylthio congeners? First and foremost, there is the question of cost and availability. Potassium and sodium *O*-ethyl xanthate salts, needed to prepare organic xanthates, are commodity chemicals used chiefly as flotation agents in mineral extraction and produced on a very large scale, with annual global sales for 2019 in excess of US\$

400 million.<sup>12</sup> The bulk cost of these salts is of the order of **two** US dollars per **kilogram**. They are in fact cheaper than most solvents!

The second reason is that, for most purposes, xanthates are sufficiently effective, so there is no need or justification to use the less practical trithiocarbonates or dithioesters. This is certainly the case for small molecule synthesis. Moreover, the reactivity can be modulated by simply replacing the ethyl group with another entity. For instance, *O*-ethyl xanthate **30** (Rhodixan A1) is capable of controlling the polymerization of vinyl esters and vinyl pyrrolidone but is poor at controlling the polymerization of methyl methacrylate (Scheme 4). This is the opposite to dithioesters and trithiocarbonates, which control well the latter but not the former. By replacing the ethyl with a trifluoroethyl group as in **31**, it becomes possible to also control the polymerization of methyl methacrylate.<sup>13</sup> In the case of xanthate **32**, a very convenient reagent for introducing the trifluoromethyl motif,<sup>14</sup> the presence of the long greasy octadecyl side-chain avoids handling a volatile and likely smelly substance. Other substituents could be introduced to increase solubility, crystallinity, ease of purification etc.

#### Scheme 4. Xanthates and Dithiocarbamates



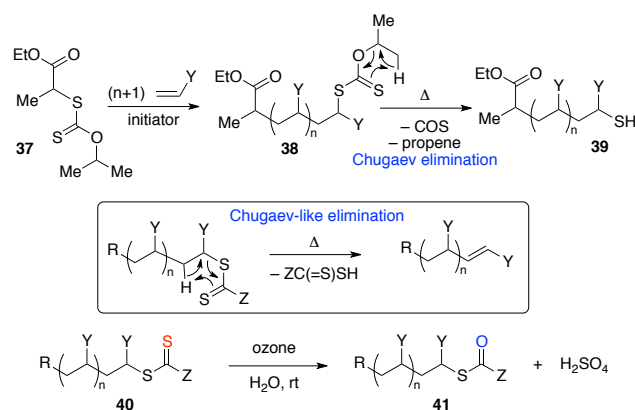
The effect of substituents on dithiocarbamates is also dramatic. The *N,N*-diethyl carbamate **28e** examined above proved relatively inefficient in the addition-transfer process.<sup>8a</sup> Placing an

electron-withdrawing group on the nitrogen changes the situation completely and results in highly efficient reactions, as illustrated by the addition of dithiocarbamate **33** to vinyl acetate to give adduct **34** in high yield.<sup>15</sup> Indole-derived dithiocarbamates such as **35** or even dithiocarbamates such as **36**, where just one phenyl group is attached to the nitrogen atom, become effective at controlling the radical polymerizations.<sup>16</sup> In this respect, it is important to mention the pioneering work of Otsu and collaborators, who used dithiocarbamates as photoiniferters to control the radical polymerization.<sup>16j,k</sup> Their conception hinged on a reversible homolytic photo-dissociation analogous to that of the nitroxides (thermal dissociation) and not on an addition-fragmentation mechanism; they did not therefore examine the influence of the substituents on nitrogen on the reactivity of the thiocarbonyl group and employed mostly poorly reactive *N,N*-diethyl derivatives similar to **28e**.

A third important advantage of xanthates concerns the more varied opportunities for post-modification of the thiocarbonylthio end-group following the radical addition or polymerization. One example will suffice to illuminate this point. By using a xanthate agent **37** bearing a *sec*-propyl group on the oxygen, one obtains polymers **38** which, upon heating to around 160 °C, release propene and carbon oxysulfide through the well-known Chugaev elimination (Scheme 5).<sup>17</sup> This simple operation removes the thiocarbonyl sulfur which is responsible for the eventual liberation of the obnoxious hydrogen sulfide upon exposure of the finished polymer to the elements in later applications.<sup>18</sup> The thiol group remaining in the modified polymer **39** is relatively innocuous (human hair contains an abundance of cysteine residues and thus pendant thiols). The Chugaev retro-ene reaction cannot normally be applied to the other thiocarbonylthio groups, but a Chugaev-like elimination involving rupture of the carbon-sulfur bond and leading to an alkene on the polymer backbone is possible with all thiocarbonylthio derivatives, as shown

by the transformation in the box in Scheme 5. This elimination requires much higher reaction temperatures. Thus, dithiocarbamates of secondary thiols need refluxing in diphenyl ether (bp: 259 °C),<sup>18g</sup> in contrast to the Chugaev elimination of xanthates derived from secondary alcohols which, as noted above, proceed at ca 160 °C, or 100 °C lower. Even for polystyrene derivatives (Y = Ph in the box in Scheme 5) where the carbon-sulfur bond is benzylic and therefore significantly weaker, the thermolysis still requires temperatures of 200 °C.<sup>18h</sup> One interesting case we observed earlier concerns adducts to *N*-vinylpyrrolidone, which undergo this Chugaev-like elimination in refluxing chlorobenzene (bp: 130 °C).<sup>18i</sup>

### Scheme 5. The Chugaev Elimination and Ozonolysis of Xanthates



The thiocarbonyl group is also responsible for the undesirable color imparted to the final polymer. This is especially acute with polymers prepared using dithiobenzoates. We devised an inexpensive, practical solution that can be applied to polymers bearing any thiocarbonylthio end-group. It consists in simply passing a stream of ozone, which rapidly converts the thiocarbonyl group into a carbonyl with concomitant formation of sulfuric acid, as shown by the oxidation of polymer **40** into its oxygen analogue **41** (Scheme 5).<sup>19</sup> The polymer is thus bleached and the main source of possible stench removed (except for trithiocarbonates, **41** Z =  $\text{SR}'$ , when the

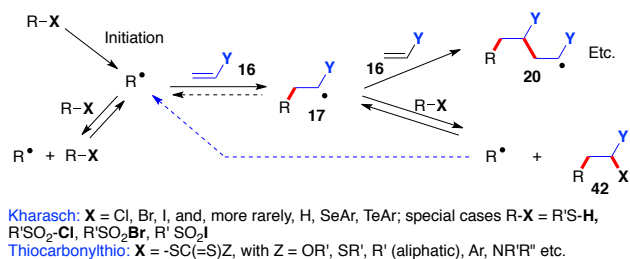
corresponding thiol  $R'SH$  is volatile). Another non-negligible advantage of the small, relatively non-polar, but highly reactive ozone is that it diffuses readily within the polymer lattice and destroys every thiocarbonyl group. It also destroys any residual monomer present in the finished polymer. Most industrial monomers have an unpleasant smell and many are significantly toxic.

## KHARASCH/ATRP AND RAFT/MADIX. A MECHANISTIC COMPARISON

As stated above, the addition of a xanthate / thiocarbonylthio derivative to an alkene gives another xanthate / thiocarbonylthio derivative and the process can be repeated, especially when the alkene is an easily polymerizable monomer. This property underpins the synthesis of block copolymers through the now well-known RAFT/MADIX technology. The older Kharasch addition to alkenes of organic halides, especially bromides and iodides, also furnishes another halide by a similar radical mechanism, as pictured in Scheme 6, and this feature constitutes the basis of the ATRP method to control the polymerization.<sup>20</sup> More recently, tellurides have been applied in an interesting and useful expansion of the Kharasch/ATRP technology.<sup>21</sup>

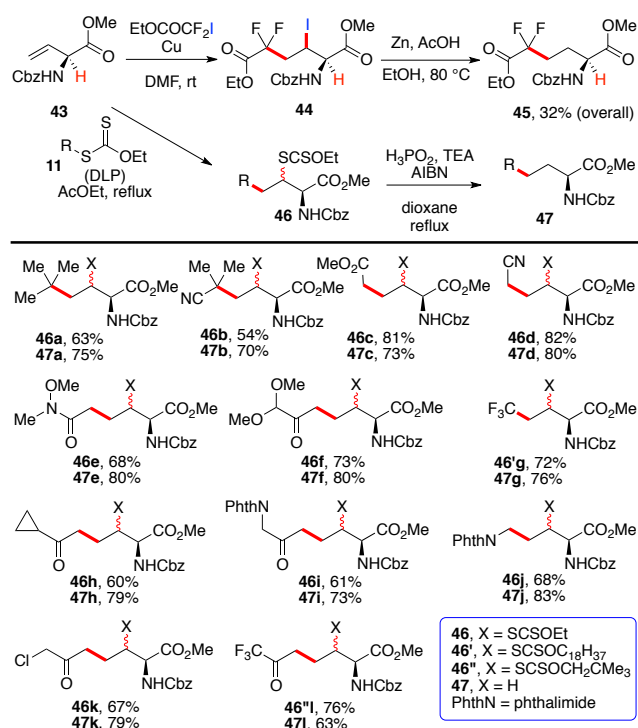
### Scheme 6. The Kharasch Reaction and the Addition-Transfer of Thiocarbonylthio

#### Derivatives



When we discovered the xanthate addition-transfer process, we first thought that we had simply stumbled upon an extension of the Kharasch reaction (X = xanthate in Scheme 6). As we progressed with our studies, we realized that the xanthate-based reaction was in fact vastly more powerful.<sup>22</sup> This observation is illustrated by examining radical additions to protected vinyl glycine **43** as a route to optically pure amino acids (Scheme 7). This vinyl glycine derivative has a rather labile hydrogen, highlighted in red, that is simultaneously tertiary, allylic, and adjacent to both the lone pair on the nitrogen and the carbonyl group of the ester. Its abstraction would generate a particularly stabilized captodative radical, and this could result in serious chain inhibition and the formation of undesired side-products. The addition of ethyl difluoroiodoacetate under typical Kharasch conditions was first reported by Taguchi in 1990<sup>23</sup> and studied in more detail a few years later by Pfizer chemists,<sup>24</sup> who found that ultra-pure DMF was required as the solvent and that, despite extensive optimization efforts, obtained only a modest yield of the final reduced adduct **45**. The problematic step is the radical addition leading to iodide **44**. To quote from their article: *“This reaction is somewhat capricious and the yields are variable. Burton chemistry was attempted with results similar to that described for Taguchi chemistry.”*

#### **Scheme 7. Two Syntheses of Protected Amino Acids**



In stark contrast, the efficient addition of a range of xanthates can be accomplished by merely heating the requisite xanthate **11** with vinyl glycine **43** in refluxing ethyl acetate in the presence of a small amount of DLP.<sup>25</sup> The unoptimized yields of adducts **46** are generally good and the xanthate group can be easily reductively removed using Barton's hypophosphorus method<sup>26</sup> or by heating with stoichiometric amounts of DLP in refluxing isopropanol.<sup>27</sup> In this manner, numerous optically pure protected amino acids **47** bearing a variety of useful functional groups can be expeditiously prepared. Note that trifluoromethyl substituted derivative **47g** was obtained using xanthate **32** presented in Scheme 4.

Why is the addition-transfer of thiocarbonylthio derivatives so much more powerful than the superficially analogous Kharasch reaction? The key to understanding the difference hinges around the unique ability of intermediates **15** and **18** (Scheme 2) to act as *reversible reservoirs* for active radicals.

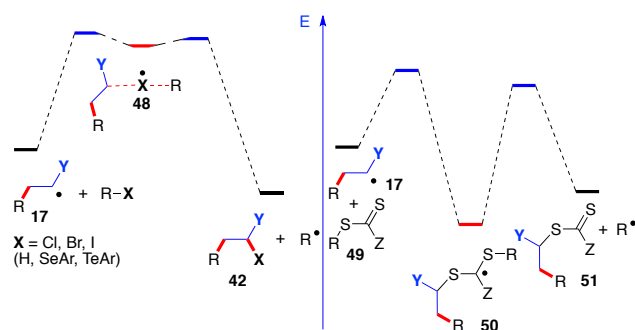
In a radical chain process, it is crucial for the propagation steps to be very fast in order to keep the steady state concentration of the various radicals as low as possible, indeed exceedingly low, for otherwise many side products are formed through uncontrolled radical-radical interactions that diminish the efficacy and lower the yield. Radicals are special species in that they recombine and/or disproportionate at close to diffusion rates (i. e.,  $k_{\text{diff}} \sim 10^{10} \text{M}^{-1} \text{s}^{-1}$ ), so if one of the steps in the sequence is relatively sluggish, it creates a bottleneck and an accumulation of the radicals concerned. Their concentration could then reach sufficiently elevated levels for unwanted radical-radical interactions to become significant. For instance, if the concentration of radicals  $\text{R}^\bullet$  in Scheme 6 reaches  $10^{-6} \text{M}$ , then the pseudo first order rate constant for coupling to form R-R becomes  $10^4 \text{M}^{-1} \text{s}^{-1}$ , so any addition to alkene **16** with a smaller rate constant cannot seriously compete. As a rule of thumb, it is best to keep the steady state concentration of the active radicals at  $10^{-8} \text{M}$  or below.

In the Kharasch process outlined in Scheme 6, both the addition to the alkene *and* the exchange of the halide have to be fast. These constraints have thus limited the range of R-X to polyhalides (e. g.,  $\text{CCl}_4$ ,  $\text{CCl}_3\text{Br}$ ,  $\text{CF}_3\text{I}$ ),  $\alpha$ -bromo- and  $\alpha$ -iodo-esters and nitriles, and  $\alpha$ -bromo- and  $\alpha$ -iodo-malonates. The exchange of chlorine is too slow to be generally useful ( $\text{CCl}_4$ , for example, has to be used as the solvent in vast excess). Exchange of bromine is faster, but effective reactions are still chiefly limited to activated tertiary bromides ( $\alpha$ -bromoisobutyrate has thus dominated ATRP studies) and often require catalysis with transition metal salts and complexes, especially those based on copper. These catalysts act as relays, facilitating and speeding up the exchange process, and also as initiators, through redox generation of the radical species from the halide. Exchange of iodine is very fast, but many iodides (e. g., iodoketones) are not particularly stable, and any molecular iodine and/or hydrogen iodide produced in the medium will behave as

inhibitors. The addition of hexa-*n*-butylditin as a scavenger for I<sub>2</sub> and HI can sometimes alleviate these complications but, despite extensive studies by Curran and co-workers, the iodine based Kharasch additions have remained limited in scope, in particular as regards *intermolecular* reactions.<sup>28</sup> Indeed, these authors have stated in one of their articles that: “*The full potential of bimolecular radical carbon-carbon bond forming reactions has yet to be realized*”.<sup>29</sup>

The exchange of X in the Kharasch reactions is a *one-step* process that proceeds via a very short-lived, high-energy intermediate **48**, which corresponds to a transition state in the case of X = H (Scheme 8). This normally *reversible* exchange step *modulates* the *relative* concentration of radicals R• and **17** (according to their relative stabilities) but *does not reduce* their *absolute combined concentration*. It does not therefore prevent or limit radical-radical interactions in situations where the addition to the alkene step is relatively slow. These observations are encapsulated in the energy profile on the left in Scheme 8, where initial radical R• is assumed to be *more stable* than adduct radical **17**. This arrangement favors the forward process (regeneration of radical R• to propagate the chain) and is normally desirable, and often even mandatory, for both the Kharasch and thiocarbonylthio addition-transfer.

**Scheme 8. Energy Profiles for the Exchange of Halides and Thiocarbonylthio Derivatives**

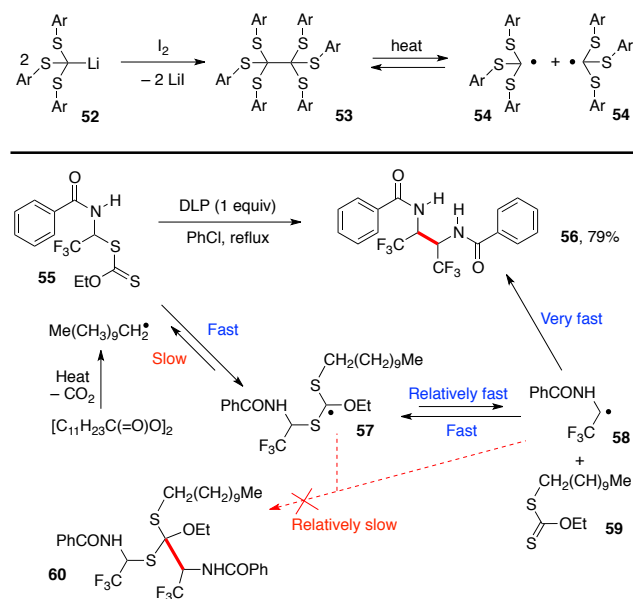


In the case of thiocarbonylthio derivatives **49**, the reversible exchange takes place *over two steps* via a true intermediate **50** that is generally *more stable* than either R• or adduct radical **17**, as shown in the energy profile to the right in Scheme 8. The high radicophilicity of the thiocarbonyl group<sup>5</sup> ensures a rate of capture of radicals that is comparable to that of iodides (this is the reason why the activation barriers for the exchange of the thiocarbonylthio group at right are placed at lower levels than the exchange of **X** in the Kharasch at left). This rate depends obviously on the nature of Z but is nevertheless very fast for most derivatives, even for dithiocarbamates when an electron-withdrawing group is present on the nitrogen. The consequence is that this *readily reversible* exchange step *modulates* the *relative* concentration of radicals R• and **17** and *concomitantly lowers considerably their absolute combined concentration*, since both radicals are most of the time *reversibly stored as dormant* species **50**. Undesirable radical-radical interactions are therefore significantly curtailed so that even when the addition to the alkene is a (relatively) slow step, it can proceed nevertheless. Moreover, the process is self-regulating: the higher the concentration, the more the *bimolecular* formation of dormant intermediate **50** is favored at the expense of radicals R• and **17**, which are regenerated by a *unimolecular* fragmentation. Radical additions based on thiocarbonylthio derivatives are hence quite forgiving and successful with a much broader range of substrates than the Kharasch reactions. It is worth noting that *any* thiocarbonylthio derivative in the medium, be it starting material or product, can capture and reversibly store active radicals in a dormant form. Thus, in the case of xanthates (Scheme 2), both starting xanthate **11** and product xanthate **19** will rapidly intercept active radicals such as R• and **17** to give dormant species **15** and **18**.

How do we know that species such as **15**, **18** and, more generally, **50** are dormant (or lazy), in the sense that they do not react so exceedingly fast with other radicals? Note, first, that these are

bulky, highly stabilized (by at least two heteroatoms) tertiary radicals that *cannot disproportionate* because they lack  $\beta$ -hydrogens. They can therefore react with each other only by dimerization (redox by electron transfer to reactive electrophilic radicals is another reaction pathway that will not be discussed here). However, because of the important steric encumbrance, dimer formation proceeds at rates that are orders of magnitude smaller than diffusion, in contrast to common carbon-centered radicals. This dimer formation is also reversible. Almost 50 years ago, Seebach and Beck found that dimers **53**, prepared by quenching tris(arylthio)methylolithiums **52** with iodine, are indeed in thermal equilibrium with the monomeric free radicals **54** (Scheme 9).<sup>30</sup>

### Scheme 9. Dimer Formation and Mechanistic Implications



More recent observations have further demonstrated that even the coupling of these species with smaller, more active radicals is also much slower than diffusion. In one experiment, heating xanthate **55** with stoichiometric amounts of DLP in refluxing chlorobenzene furnished *selectively*

homo-dimer **56** in 79% yield (Scheme 9). Why is the homo-dimer **56** produced so highly selectively? The half-life of DLP at 130 °C is *less than one minute*<sup>31</sup> yet, despite the high flux of reactive primary undecyl radicals, no significant quantities of compound **60** derived from the coupling of intermediate **57** with radicals **58** were observed. Nor were any cross-dimers (not shown for clarity) generated by capture of the undecyl radical by either intermediate **57** or radical **58** formed. If radical-radical couplings were occurring at diffusion-controlled rates, then a complex mixture of products should have resulted.

There is only one reasonable explanation for the clean formation of homo-dimer **56**. The undecyl radicals produced upon thermolysis of the peroxide are captured extremely rapidly by xanthate **55** to give intermediate **57** (once again a testimony to the extraordinary radicophilicity of the thiocarbonyl group). While this addition is reversible in principle, regenerating a high energy primary undecyl radical is much less favorable when compared to the reversible fragmentation leading to the more stabilized secondary radical **58**. The concentration of undecyl radical therefore remains vanishingly small at any given time, so these radicals are essentially shut out from any interaction with other radicals. This leaves radicals **57** and **58**, as the main radicals in the medium, with the former almost certainly dominating since it is the more stable of the two. The fact that only homodimer **56** is produced means that cross coupling leading to compound **60** is a relatively slow process and *not* diffusion controlled (fast and slow are relative terms in this context). In other words, radicals such as **57** are indeed semi-persistent species that can act as reversible reservoirs for radicals. The actual situation is somewhat more complex but does not change the essence of the argument (for instance co-product xanthate **59** can also participate in the process). The interested reader is directed to ref. 32 for a more detailed discussion.<sup>32</sup>

To summarize, the need for a reversible radical storage mechanism to lower (and keep low) the concentration of active radicals is most acute when one of the steps in the sequence is particularly slow. This is often the case with additions to un-activated, electronically unbiased alkenes (especially for the synthesis of small molecules) and it is here that the advantages of xanthates and related thiocarbonylthio derivatives manifest themselves most visibly. Since radical polymerizations normally involve activated alkenes (styrenes, acrylates, vinyl esters etc.), addition of the macroradical to the monomer is reasonably fast and the concentration of the active radicals remains automatically relatively low. The main role of the RAFT agent is in fact to allow control of the polydispersity index and to provide block copolymers of various architectures through the *reversible* and *rapid* exchange of the thiocarbonylthio group. Nonetheless, while the ability to reversibly store active macro-radicals and keep their concentration low is not strictly needed, this feature endows the polymerization process with a robustness and reproducibility that are very useful from a scale up and manufacturing standpoint.

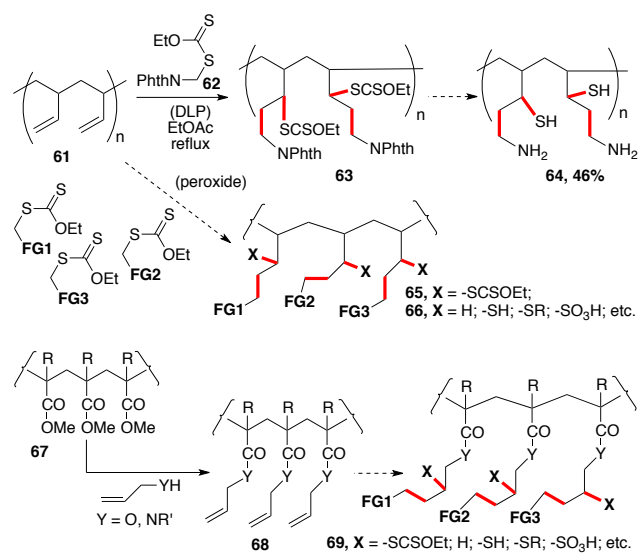
## MODIFICATION OF INDUSTRIAL POLYMERS

The unique ability to reversibly store active radicals in what for all practical purposes is a dormant state, and thus lower automatically their absolute concentration, gives this chemistry of xanthates and related thiocarbonylthio derivatives a decisive edge over the Kharasch and all other radical reactions in terms of overcoming steps with (relatively) slow kinetics and solves an important problem in organic synthesis, namely the *intermolecular* formation of a carbon-carbon bond starting with unreactive alkenes. The dozen examples of additions to protected vinyl glycine **43** displayed in Scheme 7 above represent but a tiny sample of over *two thousand* additions to a variety of alkenes using *hundreds* of different xanthates and related congeners that have been performed by ourselves and by others. The range of functional groups that can be

introduced is enormous and the tolerance for polar groups, both in the xanthate and the alkene partners, is particularly noteworthy.

The possibility of accomplishing *intermolecular* radical additions to both activated and unactivated alkenes offers several interesting opportunities for polymer chemistry, besides the important and now well-established RAFT/MADIX process. These will be discussed in this and the following sections. One first application is to modify existing industrial polymers such as poly-1,2-butadiene **61** (Scheme 10). Reaction with xanthate **62** gives a new polymer **63**, where all the alkenes have been transformed.<sup>33</sup> This polymer is a masked form of polyamino-polythiol **64**. The thiol group can be reductively removed or further modified, if so desired. A non-polar polymer can thus be transformed into a highly polar material.

### Scheme 10. Modification of Industrial Polymers



Only a portion of the pendant alkenes may be modified by employing sub-stoichiometric amounts of xanthate. Furthermore, an appropriate choice of the xanthate partner allows the introduction of almost any desired functionality, or indeed combination of functionalities. The

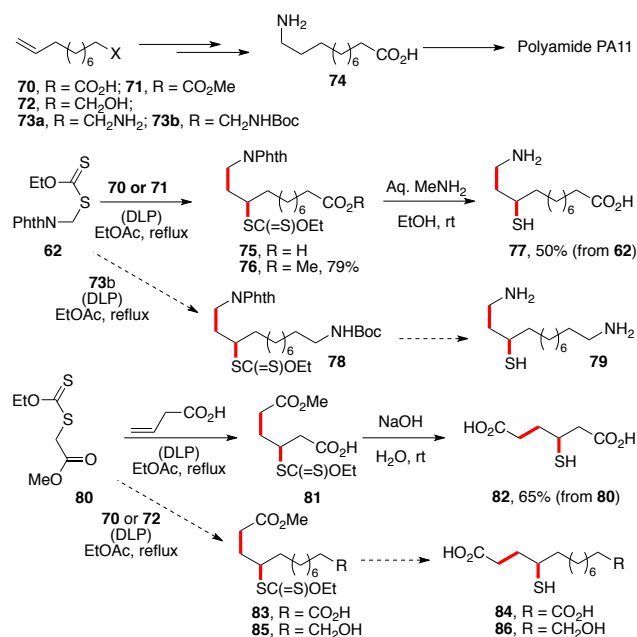
latter could be accomplished by simply reacting poly-1,2-butadiene **61** *simultaneously* with the desired combination of xanthates in any required proportion. In Scheme 10, this is illustrated by reaction with three different xanthates placed in the same reaction flask to give modified polymer **65** (FG = Functional Group), where the xanthate can be further transformed into a plethora of other groups as for polymer **66**. The distribution of the various moieties in the modified polymer will of course be random (shown in succession for clarity), and more than three different xanthates could be used and their relative proportions easily controlled. The functional groups could for example be a boronic acid, a trialkoxysilane, a ketone (aldehyde), an amine (hydrazine or hydroxylamine) and a thiol (from the xanthate). These groups are capable of forming reversible chemical bonding and could result in multi-pronged self-healing polymers and gels. The so-called Constitutional Dynamic Chemistry (CDC) essentially exploits the dynamic and reversible formation of either covalent or non-covalent bonds to heal any cracks that appear and restore the original properties of the polymer or polymer gel.<sup>34</sup> The interaction of these various motifs proceeds at quite different rates, so while the boronic acids, trialkoxysilanes, and amines (hydrazine or hydroxylamine)-ketones (aldehydes) can combine rapidly, the disulfide formation is slower but leads to kinetically stronger linkages. Numerous other potential applications can be envisaged, in particular in adhesives, resins, surface treatments, and precious (or toxic) metal recovery.

For acrylate and methacrylate polymers **67** that do not contain pendant alkenes, it is possible by transesterification with allylic alcohol or by amidation with allylamine to form a modified polymer **68** with pendant alkenes, which then can be used to attach the desired functional groups through addition of the appropriate xanthate(s). The physicochemical properties of the final polymer **69** could thus be easily tailored for a given application.

## NOVEL MONOMERS FROM THE BIOMASS. AN ALLIANCE WITH THE METATHESIS REACTION

Valorization of the biomass is an ongoing challenge that has concentrated much research effort. It has almost become a domain by itself under such denominations as “green” or “sustainable” chemistry.<sup>35</sup> Renewable raw materials certainly constitute attractive starting points for the chemical industry in all its branches, including pharmaceuticals, agrochemicals, cosmetics, surfactants, resins, coatings, and polymers of all kinds. In this respect, bio-sourced 10-undecylenic acid **70** and its derivatives (10-undecylenate ester **71**, 10-undecyl alcohol **72** and amine **73a**) are particularly interesting (Scheme 11).<sup>36</sup> They are obtained from inexpensive castor oil (estimated annual production: 250 000 metric tons), a substance extracted from plants cultivated in dry areas not suitable for other forms of agriculture. It thus constitutes an ideal renewable resource because it does not adversely affect the food supply. From a polymer standpoint, 10-undecylenic acid **70** is converted on an industrial scale into 11-amino-1-undecanoic acid **74**, the monomer needed for the preparation of polyamide PA11.

### Scheme 11. Monomers from Castor Oil

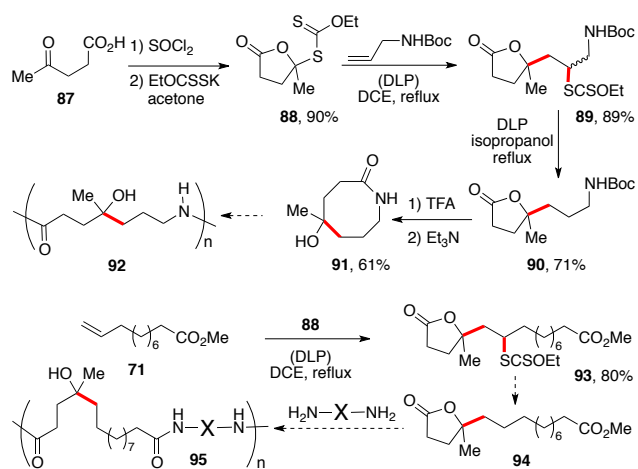


The convenient presence of a terminal alkene allows all the panoply of xanthate additions to be applied. The examples depicted in Scheme 11 illustrate the synthesis of novel monomers for polyamides and, more generally, for polycondensations. Thus, reaction of xanthate **62** with 10-undecylenic acid **70** and its methyl ester **71** furnishes adducts **75** and **76**, respectively.<sup>33,37</sup> Treatment of the former with aqueous methylamine cleaves both the phthalimide and the xanthate groups to give 10-mercapto-12-aminododecanoic acid **77**. Alternatively, addition of the same xanthate to *N*-Boc-10-undecylenamine **73b** would afford protected diamine **78** and thence 4-mercapto-1,12-diamine **79**. Starting with  $\alpha$ -xanthyl ester **80** gives rise to various  $\alpha$ , $\omega$ -dicarboxylic acids. For instance, addition to commercially available 3-butenic acid and saponification of resulting adduct **81** leads to 3-mercaptoadipic acid **82**.<sup>37</sup> Application of the same sequence to 10-undecylenic acid **70** and 10-undecenyl alcohol **72** would result in the synthesis of mercapto-dicarboxylic acid **84** and mercapto-hydroxycarboxylic acid **86**. All these would be useful monomers for the synthesis of novel polyamides and polyesters. They do not need to be polymerized just by themselves; they can be co-polymerized with established

monomers in sufficient proportions to impart the desired properties. The presence of the mercapto group at certain positions along the polymer chain could for example improve the adhesion to metallic surfaces for polyamides used in anti-corrosion coatings. The mercapto group can further serve as handle to introduce other pendant groups (alkylation, conjugate addition, thiol-click, etc.) or as a cross-linking agent through disulfide formation, reaction with bis-epoxides or epichlorhydrin, or thiol click reactions with dienes.<sup>38</sup>

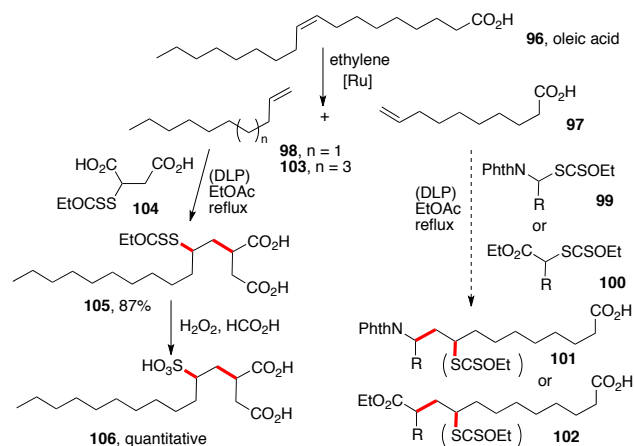
Levulinic acid **87** is another inexpensive raw material that can be obtained from renewable lignocellulosic biomass and starch rich waste.<sup>39</sup> It is readily converted into xanthate **88**, which adds efficiently to a variety of alkenes, including Boc-protected allylamine and methyl 10-undecylenate **71** (Scheme 12).<sup>40</sup> In the case of adduct **89**, reductive removal of the xanthate and deprotection of the amine gives lactam **91** by final ring closure. This compound should be amenable to polymerization into polyamide **92** in the same manner as the well-known caprolactam.<sup>41</sup> As for adduct **93**, which would be the precursor to ester-lactone **94** and eventually to polyamides **95**, it is interesting to note that *all the carbons* derive from the biomass.

### Scheme 12. Monomers and Polymers from Levulinic Acid



In recent times, the metathesis reaction has emerged as a powerful tool for the valorization of renewable unsaturated vegetable oils.<sup>42</sup> The cross-metathesis of unsaturated fatty esters or acids with ethylene is particularly interesting in that it furnishes two terminal alkenes, one of which also bears a terminal carboxylic acid function. In the case of oleic acid **96** (Scheme 13), for example, the cross-metathesis with ethylene results in the formation of 9-decenoic acid **97** and 1-decene **98**.<sup>42c</sup> On the former, addition of xanthates such as **99** or **100** would generate monomers **101** or **102** that are suitable building blocks for the preparation of polyamides, polyesters, etc., containing or not the sulfur of the xanthate or a moiety derived therefrom.

### Scheme 13. An Alliance with the Metathesis Reaction



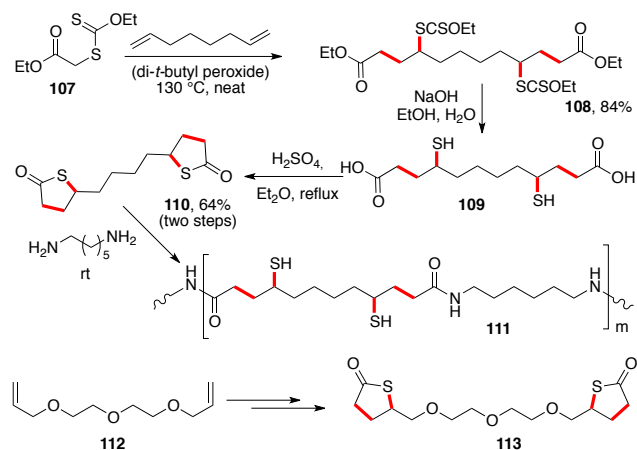
The 1-alkene co-product of the metathesis can serve to prepare surfactants by addition of a xanthate bearing a polar moiety. This is exemplified by addition of succinic xanthate **104** to 1-dodecene **103**, which leads finally to surfactant molecule **106** where the hydrophilicity of the polar succinic head has been reinforced by direct oxidation of the xanthate group in adduct **105** into a sulfonic acid by a combination of hydrogen peroxide and formic acid.<sup>43</sup> The direct introduction of a naked succinic acid motif onto an un-activated alkene is remarkable and could prove valuable for the synthesis of polyimides. Indeed, the ability to perform additions with a

free carboxylic acid is a hallmark of radical chemistry that is not well appreciated by synthetic organic chemists at large. Note furthermore that there is very little waste produced in the sequence. In any case, in this alliance with the cross-metathesis reaction, both products obtained from the unsaturated fatty acids can be exploited and transformed into useful materials.

## BIS-THIOLACTONE MONOMERS

The addition of  $\alpha$ -xanthyl esters to an alkene and saponification of both the ester and the xanthate leads to 4-mercapto carboxylic acids (e. g., **80** and **84**, Scheme 11). Such compounds can be cyclized by the action of acid or upon heating to give thiolactones.<sup>44</sup> In contrast to the ubiquitous lactones, thiolactones have been little studied, principally because of their relative inaccessibility. The radical chemistry of xanthates provides a natural and practical route to these derivatives and allows exploitation of their properties, in particular their greater reactivity towards nucleophiles as compared to their lactone analogues. From the perspective of polymer synthesis, it is the  $\alpha,\omega$ -bis-thiolactones that appear to be the most appealing. These can be obtained by using  $\alpha,\omega$ -dienes as the olefinic trap (Scheme 14).<sup>37</sup>

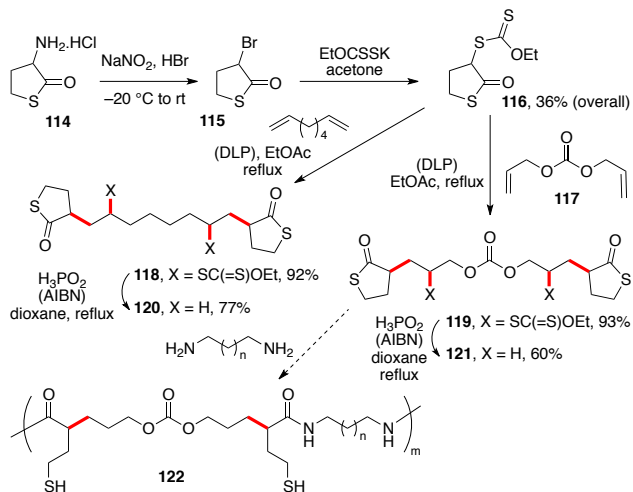
### Scheme 14. Bis-Thiolactones and Polymers Therefrom



A simple example is the addition of xanthate **107** to 1,7-octadiene to give bis-adduct **108**. In this case, the radical reaction is conducted neat (no solvent) using di-*t*-butyl peroxide (DTBPO) as the initiator. This peroxide imposes a higher reaction temperature but allows the removal of almost all side products by passing a stream of nitrogen through the warm mixture. This variation of the usual procedure makes purification easier in large scale work. Saponification of both the ester and xanthate and treatment of mercapto-acid **109** with sulfuric acid furnishes the desired product **110**. This substance reacts with 1,6-hexamethylenediamine even at room temperature to produce polyamide **111**.<sup>37</sup> A similar sequence applied to diethylene glycol derived diene **112** leads to bis-thiolactone **113**.<sup>37</sup> A large array of polyamides bearing thiol groups could be generated by modifying the starting diene, the xanthate, and the diamine partner, allowing a fine tailoring of the desired physicochemical properties.

Xanthate chemistry also allows the direct introduction of a thiolactone motif, as outlined in Scheme 15. Biosourced homocysteine lactone, prepared from methionine<sup>45a</sup> and commercially available as its hydrochloride salt **114**, has itself been used to manufacture polymers,<sup>45b-h</sup> but it can also be readily converted into bromide **115** and thence into xanthate **116**.<sup>46</sup> Double addition to 1,7-octadiene and to diallylcarbonate **117** followed by reductive dexanthylation of the primary adducts **118** and **119** affords bithiolactones **120** and **121**, respectively. Reaction of the latter with a diamine would give rise to polyamide **122**, where the thiol units are not directly attached to the main chain but are tethered by a three-carbon unit.

#### **Scheme 15. A Second Family of Bis-Thiolactones**



The polyamides derived from these various thiolactones are currently under study in collaboration with the group of Dr Laurent Bouteiller at the Institut Parisien de Chimie Moléculaire. As stated above, the thiols could be used to crosslink, reversibly or not, via disulfide bonding (these polyamides may be viewed as models for hair fibers), thiol click reactions, nucleophilic openings of bis-alkylating agents such as epichlorhydrin or di-epoxides. It could be employed to attach bioactive substances for the controlled release of drugs, to improve adherence, and the affinity of sulfur for metals could be harnessed into making more resistant anti-corrosion coatings, etc.

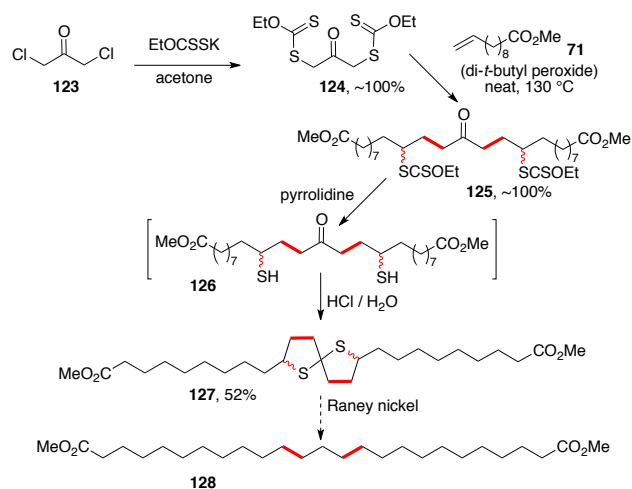
## DITHIOSPIROKETAL MONOMERS

A completely new family of monomers with a globular non-aromatic core can be constructed based on the dithiospiroketal motif (Scheme 16). In contrast to spiroketals, which are quite common entities in natural products, especially pheromones and marine substances, dithiospiroketal, their sulfur analogues, are almost unknown. They are not present in nature and, in the aliphatic series, only the parent compound (**138**, see Scheme 17) has been reported, in 1901!<sup>47</sup> A very convenient access to these structures can be secured through a double radical

addition of bis-xanthate **124**, a nicely crystalline reagent readily prepared from 1,3-dichloroacetone **123**, an inexpensive substance available in bulk from Wacker Chemie as a 50% solution in acetone.<sup>48</sup> Its addition to methyl 10-undecylenate **71**, cleavage of the xanthate in bis-adduct **125**, and acidification completes the synthesis of dithiospiroketal **127**. The ring-closure of the thiols onto the ketone in intermediate **126** is so facile that it occurs spontaneously as soon as the medium becomes acidic. Furthermore, classical desulfurization of dithiospiroketal **127** would furnish the dimethyl ester **128** of the simple 25-carbon linear fatty dicarboxylic acid. It is worth pointing out that all the carbons in monomer **127** (and eventually **128**) are biosourced: from acetone and castor oil derived methyl undecylenate **71**.

Polyamides, and polymers in general, arising from long chain difunctional monomers have received comparatively little attention, despite their interesting properties and potential applications.<sup>49</sup> This appears to be due to their hitherto synthetic inaccessibility. To quote from a recent review on the subject: *“This can be traced to the lack of viable routes to access these monomers in a more practical fashion than the multistep traditional organic syntheses employed for the preparation of these model polymers”*.<sup>49a</sup> The present route is short, inexpensive, and scalable. Indeed, the radical double addition leading to precursor **125** was performed on a 50g scale, *without solvent*.

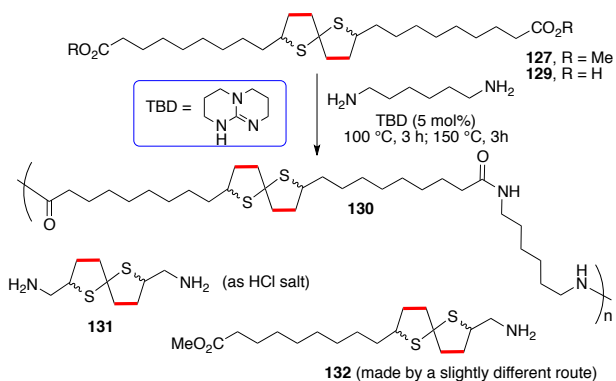
#### **Scheme 16. Novel Dithiospiroketal Monomers from Castor Oil**



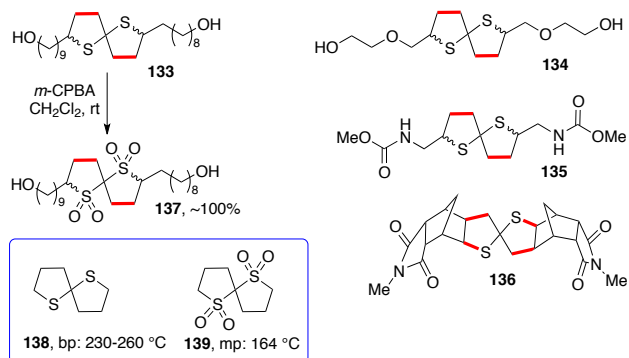
A variety of dithiospiroketal monomers can be prepared by simply modifying the alkene (Scheme 17). The use of 10-undecylenic acid **70** itself leads to diacid **129**. Either diester **127** or diacid **129** can be used to prepare polyamide **130** with hexamethylenediamine as the diamine partner. This polymer, obtained as shown from diester **127**, is currently under study to compare its properties with those of more traditional polyamides. Performing the double radical addition on protected allylamine provides ultimately diamine **131**, which could be used as the diamine component with classic diacids, such as adipic acid, or with the more exotic diester **127** or diacid **129**. Aminoester **132** is another interesting monomer for the manufacture of polyamides; it was prepared by a slightly different route starting with the mono-xanthate derived from dichloroacetone (not shown).<sup>48,50</sup>

### Scheme 17. Further Dithiospiroketal Monomers and Polymers

monomers for polyamides and polyesters



monomers for polyesters, polycarbonates, polyurethanes, polyureas, and polyimides



Diamine **131** and monomers **133-136**, prepared by using the appropriate alkene, would be suitable for the synthesis of polyesters, polycarbonates, polyurethanes, and polyimides, depending on the terminal functionality present. Note that carbamates such as **135** can be converted into polyurethanes and polyureas *without* the need to rely on toxic di-isocyanates.<sup>51</sup>

The dithiospiroketal motif constitutes a globular non-aromatic core that is compact, thermally stable, resistant to acids, bases, and reducing agents. It is non-polar but, like most sulfides, it should exhibit an affinity for metallic surfaces, a property that could be exploited to improve adherence. It can be oxidized to sulfoxides and sulfones, as illustrated by the quantitative conversion of monomer **133** into bis-sulfone **137** using *m*-chloroperbenzoic acid (*m*-CPBA).<sup>48</sup> The corresponding change in polarity, shape, hydrogen bonding ability, affinity for various surfaces, and physicochemical properties in general could be profound. This can be seen by

comparing the only reported aliphatic dithiospiroketal **138** with its bis-sulfone congener **139**. The former is a liquid, whereas the latter is a high-melting solid.<sup>47</sup> Finally, one feature that could have an interesting impact on the final polymer is that the dithiospiroketal unit introduces a kink into the chain, which could influence packing, porosity, and crystallinity.

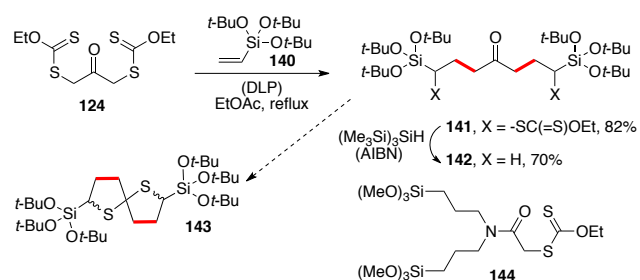
## CONCLUDING REMARKS

Thiocarbonylthio derivatives, and xanthates in particular, offer numerous other possibilities, besides the exceptionally powerful RAFT/MADIX technology and the ability to prepare novel monomers for polycondensations by exploiting, inter alia, biosourced raw materials. The few concluding transformations briefly discussed below are illustrative and represent additional perspectives for polymers and for material sciences.

The first illustrates an example of a convergent route to trialkoxysilanes, as depicted in Scheme 18. It concerns the efficient double radical addition of bis-xanthate **124** to vinyl tris(*t*-butoxy)silane **140** to give adduct **141**, which could be easily dexanthylated into sulfur-free symmetrical bis(trialkoxysilyl) ketone **142**.<sup>52a</sup> Adduct **141** may also be converted in principle into dithiospiroketal **143** and thus connect this chemistry with that described in the previous section. Mono-trialkoxysilanes can be obtained by adding appropriately functionalized mono-xanthates to alkene **140** or to any other suitable alkene bearing the desired alkoxysilane moiety.<sup>52a</sup> Alternatively, the trialkoxysilane motif can be placed on the xanthate, as in compound **144**, which adds to various alkenes in the usual manner. Polymeric vinylorganosilanes have also been briefly studied.<sup>52b</sup> Trialkoxysilanes occupy a central position in material science, surface science, and nanotechnology. They have been used to create nanocomposites and organic-inorganic hybrid materials;<sup>53</sup> to assemble hybrid and supported catalysts;<sup>54</sup> to modify metal oxide and silica

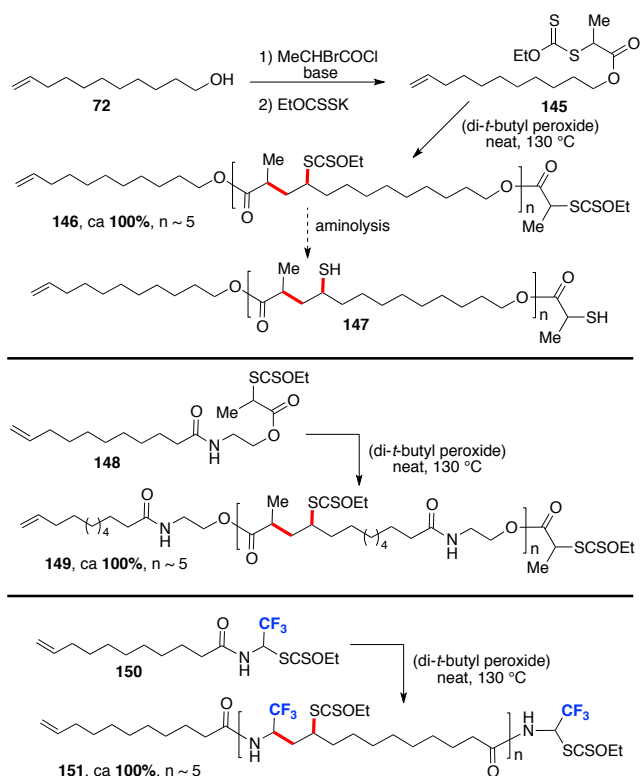
surfaces through the controlled formation of monolayers;<sup>55</sup> and to form sol-gels and organogelators,<sup>56</sup> among numerous other applications.

### Scheme 18. Synthesis of Trialcoxysilane Crosslinkers



In the second application, the unusual ability of xanthates to mediate intermolecular additions to electronically unbiased alkenes is employed to produce a variety of oligomers, as shown by the three preliminary examples in Scheme 19. Compound **145**, trivially prepared from castor oil derived 10-undecenol **72**, contains both a xanthate and a terminal alkene. Simple heating in the presence of a peroxide initiator triggers the oligomerization to give polyester **146** as a viscous resin. Aminolysis would give polymercaptan **147**, which could be crosslinked (“cured”) by oxidation to the disulfide, much in the same way as with the long-known Thiokol elastomers. Under similar conditions, monomers **148** and **150**, obtained from undecylenic acid **70**, furnish oligomers **149** and **151**, respectively. The former is a mixed polyester-polyamide and the latter is a polyamide bearing trifluoromethyl groups. The interesting observation is that polyesters and polyamides have been produced under mild, neutral conditions, without actually making either the ester or the amide bond. This approach represents yet another strategy for exploiting alkenes derived from the biomass and a potential alliance with the metathesis reaction.

### Scheme 19. Synthesis of New Oligomers



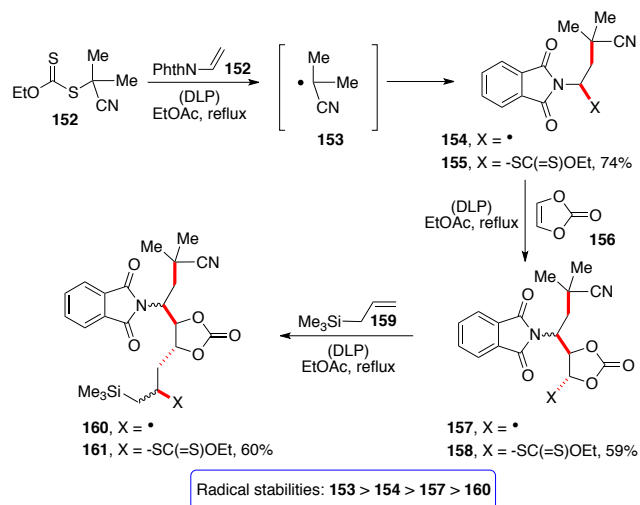
In all the polymers and oligomers described in this Perspective article, the presence of the sulfur scattered across the polymeric network, as mercaptan, sulfide, disulfide, or the more exotic dithiospiroketal motif, could improve adherence properties, dye-ability, increase strength by inter-chain linkages and durability by providing a greater resistance to UV, photo-oxidation, and metal induced oxidative degradation. It could enhance biodegradability and diminish the environmental impact, since most bacteria have the ability to metabolize organosulfur compounds.<sup>57</sup> The thiol and groups derived from it could thus act as suitable points of attack by soil micro-organisms and speed up the biodegradation process.

Finally, there has been in recent times an increasing effort directed towards mimicking, in the polymer field, the ability of Nature to string together hundreds of canonical amino acids or nucleic acids in a precise order. The imitative approach to attach different monomers in a given sequence, from a controlled radical polymerization perspective, has been termed Single Unit

Monomer Insertion or SUMI.<sup>58</sup> Interestingly, much of the current work relies on the use of trithiocarbonates and builds on the early work on xanthates described above, in particular on the transformation in Scheme 2, where three components react in a controlled manner to give product **24**. In this sequence, the order of the additions and the ability to sustain an efficient radical chain depend on both the polarities and the relative stabilities of the radicals involved. Only the polarity aspect was briefly invoked above, since it dictates which alkene, maleimide **22** or allyl acetate, will react preferentially with which radical. However, implicit in the general reaction manifold of Scheme 2, is also the need to have the initial radical  $R^\bullet$  *be more stable* than adduct radical **17**, so that fragmentation of intermediate **18** proceeds mostly in the forward direction, i. e., towards the formation of product **19** and regeneration of  $R^\bullet$  to propagate the chain.<sup>59</sup> In the opposite case, if adduct radical **17** is more stable than  $R^\bullet$ , then it is the one that will be more easily regenerated and the chances of its addition to another alkene molecule to give radical **20** and, ultimately, unwanted oligomers will increase.

This constraint tends to limit the ultimate number and nature of the different alkenes that can be added sequentially. A glance at the example outlined in Scheme 20 will help grasp the key elements.<sup>60</sup> The addition of xanthate **152** to *N*-vinylphthalimide produces a new xanthate **155**, which in turn can be made to react with vinylidene carbonate **156** to give a third xanthate **158**. Finally, this last xanthate undergoes an addition to allyl trimethylsilane **159** to furnish a fourth xanthate **161**. This sequence is successful because, in each step, the initial radical is *more stable* than the adduct radical, as it should be. In the first addition, initial radical **153** is more stable than adduct radical **154**. This latter becomes the initial radical in the second addition and is more stable than new adduct radical **157**, which in turn is the initial radical in the third and last addition and is more stable than last adduct radical **160**.

## Scheme 20. A Four-Component Sequence

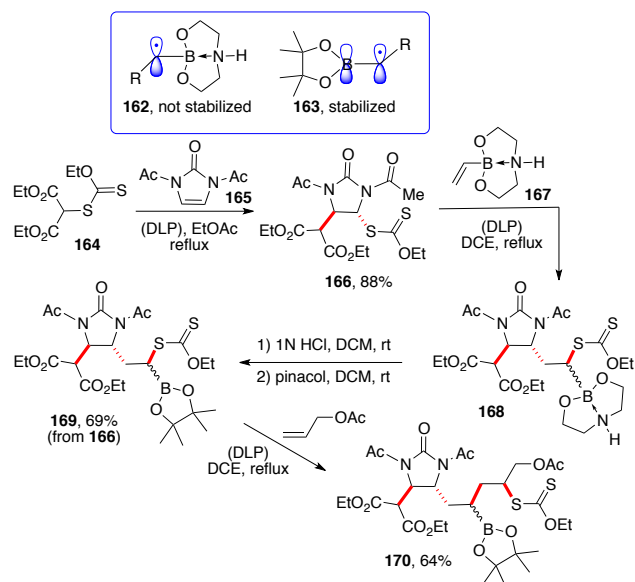


This sequence cannot be easily extended further. The initial radical in a subsequent addition will be non-stabilized secondary radical **160** (the  $\beta$ -trimethylsilyl group does not bring any significant stability) and very few alkene partners would give rise to a radical that is less stable than **160**. The obvious exception is addition to ethylene itself, as this would lead to a primary radical that is less stable than secondary radical **160**, but this is synthetically of rather limited utility.<sup>61</sup>

In these sequential additions, the stability of the successive initial radicals keeps decreasing until, as in the case of **160**, it becomes difficult to implement the requirement that the initial radical be more stable than the adduct radical. One way to circumvent this limitation, apart from exploiting polar effects,<sup>59</sup> is to take advantage of the special properties of boronates to modulate the stability of the intermediate radicals. As pictured in Scheme 21, a radical adjacent to a tetravalent boron, such as diethanoamido boronate or B(DEA) **162**, is not particularly stabilized, in contrast to radical **163** that is adjacent to a trivalent pinacolato boronate or B(Pin). The

unpaired electron in the latter can delocalize into the empty p-orbital on boron and its energy is significantly lowered, by about 6-7 kcal/mole.<sup>62</sup>

### Scheme 21. A Sequence Based on Boronates

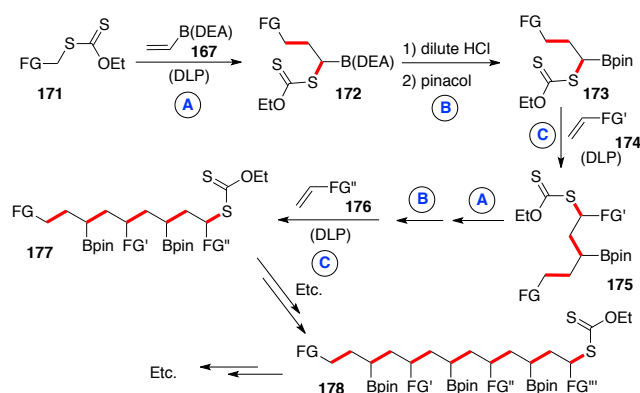


From a xanthate addition perspective, switching from the former boronate to the latter can bring us back to a situation where the initial radical is more stable than the adduct radical. This is exemplified by the sequence in Scheme 21 starting by addition of malonate xanthate **164** to imidazolone **165**.<sup>63</sup> The product, **166**, is in turn reacted with vinylB(DEA) **167** to give a second adduct **168**. Since the B(DEA) moiety does not stabilize the corresponding intermediate adduct radical, the addition proceeds efficiently. By exchanging the B(DEA) in **168** with a pinacolato B(pin) as in **169**, the corresponding radical is now stabilized and capable of participating constructively in a third radical addition to allyl acetate to furnish compound **170**.

This simple but effective strategy of alternating radical stabilities should be applicable for the synthesis of structures with longer well-defined sequences, as outlined in generic form in

Scheme 22. The addition of a functional xanthate **171** (FG = Functional Group) to vinylB(DEA) **167** affords a first adduct **172**. This is followed by exchanging the B(DEA) group with a B(pin), which stabilizes the corresponding radical and allows a second addition to a functional alkene **174**. This three-step sequence, but now using functional alkene **176**, can be reiterated on the resulting product xanthate **175** to give compound **177**, and therefrom to oligomer **178** and so on and so forth.

### Scheme 22. Alternating Boronate Oligomers



The main, rather benign, limitation is for the radicals adjacent to the functional group arising from additions to alkenes **174**, **176**, etc. to be more stable than radicals **162**, so that steps **A** can proceed correctly, but less stable than radicals **163**, so that steps **C** can take place correctly. Post-modification using the incredibly rich chemistry of boronates,<sup>64</sup> as well as that of the various functional groups present in the final oligomeric structures would open access to further diversity. Control of the stereochemistry, in contrast to control of the sequence, remains however a formidable challenge that needs to be solved, possibly by using bulky and eventually chiral, non-racemic, groups on the boron atom.

What started as a friendly mechanistic dispute has evolved into a remarkably powerful carbon-carbon bond forming process that enables the versatile RAFT/MADIX technology, which has become a gigantic area with a life of its own, with over 10 000 publications and 1000 patents.<sup>65</sup> It also allows the valorization of alkenes and other feedstocks, whether derived from the biomass or not. The key feature is the unique ability of thiocarbonylthio derivatives to *rapidly capture* and *reversibly store* active radicals and thus *lower their absolute* concentrations and *regulate their relative* concentrations. This synthetic tool has considerably expanded the possibilities for the creation of carbon-carbon bonds, and numerous molecular structures not hitherto accessible, including novel monomers for polycondensations, can now be assembled in an expedient, convergent manner. Most functional groups, and especially polar entities, are tolerated, and, in the case of xanthates, the requisite reagents are inexpensive industrial commodity chemicals. In view of the large array of accessible architectures and the broad variety in terms of functional group combinations, it is expected that more structures with superior properties will emerge from this chemistry.

## ASSOCIATED CONTENT

**Supporting Information.** Master Thesis (in French) of Mr Hervé Henry (PDF). This document is available free of charge via the Internet at <http://pubs.acs.org>.

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- <sup>59</sup> This requirement can be overcome to a certain extent when particularly favorable polar effects are in play. If, for example, radical **R•** has a highly electrophilic character and alkene **16** is nucleophilic (i. e., substituent Y is electron donating), then the rate of the addition step will be significantly increased, while the step leading to dimer radical **20** will be slowed down because of polarity mismatch (both the alkene and adduct radical **17** are electron rich, since Y is electron donating). Thus, even if fragmentation of intermediate **18** favors adduct radical **17** instead of starting radical **R•**, the fast addition of **R•** to the alkene will pull the system forward and limit complications from the slower step leading to unwanted radical **20**. If, however, adduct radical **17** is too stabilized then it will be regenerated much faster than it is consumed; it will accumulate and its concentration in the medium will eventually reach levels where uncontrolled radical-radical interactions become unavoidable. In these cases, it might be necessary to diminish the flux of initiating radicals so as to decrease the overall concentration of the active radicals in the medium. This could be accomplished, for example, by lowering the temperature to slow down the rate of thermolysis of the initiator.
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## Biography



**Samir Z. Zard** was born in 1955 in Ife, Nigeria. His training as a chemist started at the American University of Beirut, then at Imperial College, London, and finally at the Université Paris-Sud, Orsay, France, where he received his doctorate under the supervision of Professor Sir Derek Barton in 1983. His main research concerns the study and development of new reactions and processes, with a special interest in radicals, organosulfur derivatives, alkynes, and nitro compounds. In addition to a number of academic awards, he received in 2007 the Croix de Chevalier de la Légion d'Honneur.