New routes to organofluorine compounds based on ketenes and the radical transfer of xanthates†

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New routes to organofluorine derivatives based mostly on the powerful xanthate radical transfer technology are described. A special emphasis is placed on the synthesis of trifluoromethyl-substituted structures, including trifluromethyl ketones and fluorinated aromatic and heteroaromatic substances of interest to the pharmaceutical and agrochemical industries.

The enormous importance of organofluorine derivatives for the pharmaceutical and agrochemical industries and for materials sciences has generated a steep demand for cheap, efficient, and flexible methods for the introduction of fluorine or fluorinated groups into various families of compounds.[1] Countless, and in many cases ingenious, approaches have been devised to cover the needs of academic and industrial chemists interested in organofluorine derivatives.[1,2] Nevertheless, there is still a niche for new reactions allowing the direct introduction of fluorinated groups into the substrate or the synthesis of fluorinated building blocks that can then be incorporated in a given synthetic scheme.

As part of our continuing quest for new chemical reactions, we have occasionally modified our synthetic methods or exploited some aspects of the mechanism to extend the scope of the process to encompass fluorinated structures. For example, as an ancillary study in a broader project on steroids, we described some years ago a simple, efficient route to trifluoromethyl ketones, based on the reaction of a carboxylic acid chloride with trifluoroacetic anhydride and pyridine, as pictured in Scheme 1.[3] Elimination of HCl from the acid chloride leads to the corresponding ketene **1**, which can react reversibly with pyridine to give betaine **2**. Both the ketene and the betaine can be captured by the strongly electrophilic anhydride to give intermediate **3**. This is also a reactive species that combines rapidly with various nucleophiles. Thus, addition of an alcohol provides a trifluoromethyl ketoester **4**. Water reacts to furnish the corresponding trifluoromethyl ketoacid, which undergoes spontaneous decarboxylation to produce trifluoromethyl ketone **5**. Finally, the use of suitable nucleophiles gives rise to a broad range of trifluoromethylated cyclic and heterocyclic structures of interest to medicinal and agrochemical chemists (see below).

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† This paper is dedicated with respect and affection to the memory of Professor Guy Ourisson.

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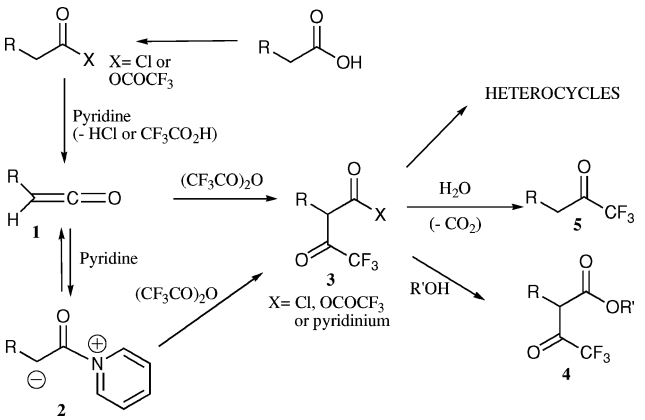
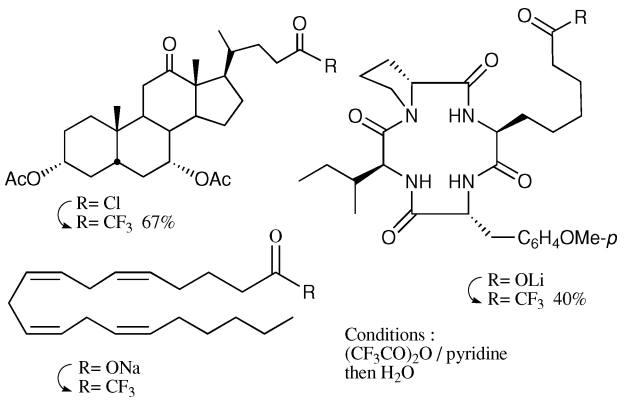
Samir Z. Zard



Scheme 1 Synthesis of trifluoromethyl ketones and derivatives from carboxylic acids.

The acid chloride may be replaced by the corresponding carboxylate salt, as long as an extra equivalent of trifluoroacetic anhydride is employed.[3] In this variant, the source of the ketene is the mixed anhydride formed by reaction of the carboxylate with trifluoroacetic anhydride. The use of pyridine is important since it prevents the undesired dimerisation of the ketene, presumably through the formation of adduct **2** which also has, as an added bonus, an enhanced nucleophilicity in comparison with the ketene

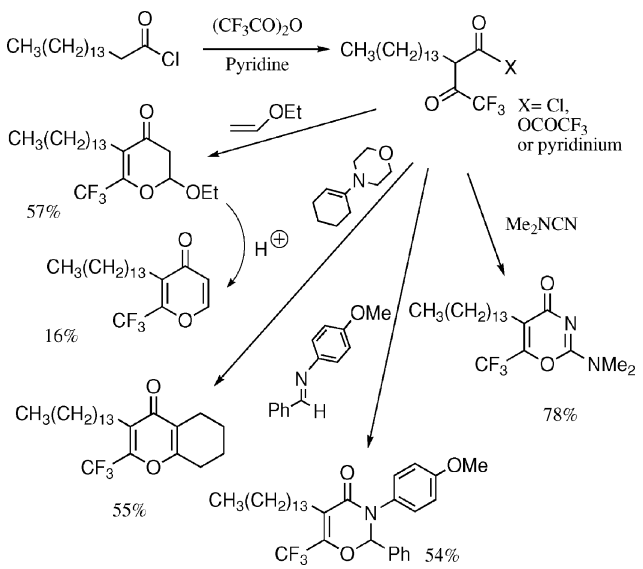
itself. Thus, pyridine acts both as a base and as a promoter and controlling agent for the transformation. The examples displayed in Scheme 2 are representative of the process. Primary carboxylic acids are the preferred substrates, since with secondary analogues the reaction of the intermediate ketene is reversible and cannot be exploited efficiently.



Scheme 2 Examples of trifluoromethyl ketones.

This procedure has been applied by several groups for the synthesis of trifluoromethyl ketones, since these often act as powerful but reversible inhibitors of hydrolytic enzymes such as esterases, lipases, and phosphatases.[4] The readily formed hydrate of the ketone mimics the tetrahedral intermediate involved in the hydrolysis step. Perhaps the most spectacular application is the synthesis by chemists at Merck-Frosst of the trifluoromethyl ketone derived from arachidonic acid (bottom example in Scheme 2).[4] This compound was found to be a slow, tight-binding inhibitor of human cytosolic phospholipase A_2 and all previous synthetic routes to it had failed.

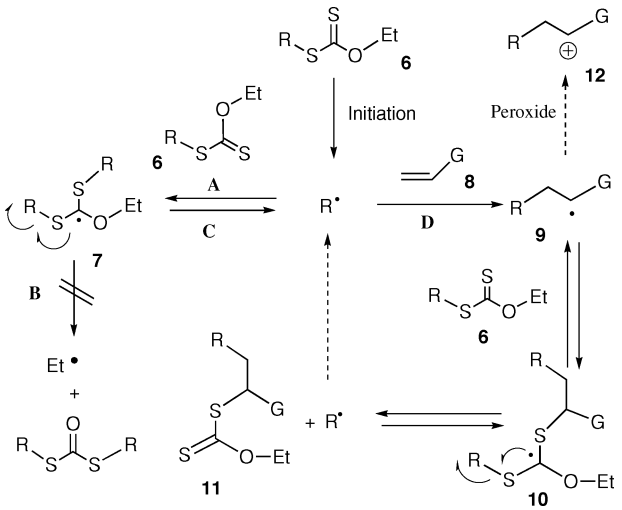
The possibility of capturing the reactive intermediate **3** with various nucleophilic species is illustrated by the examples depicted in Scheme 3 starting with palmitoyl chloride.[2c] Many other variations can be conceived and numerous trifluoromethyl-substituted



Scheme 3 Synthesis of trifluoromethylated heterocycles.

heterocyclic structures could in principle be constructed in this manner.

This first access to trifluoromethyl ketones relies on an ionic mechanism and is sufficiently mild to be applicable to relatively sensitive substrates. A vastly more powerful and general route to fluorinated synthons emerged from another project dealing with the radical chemistry of xanthates and related derivatives of general formula Z–C(=S)S–R. We found that xanthates are capable of undergoing additions to various olefins by way of the radical chain mechanism outlined in Scheme 4.[5] The overall result is the addition of the elements of xanthate **6** across the olefinic bond in **8** to give adduct **11**.



Scheme 4 Degenerative xanthate transfer.

The subtleties of the mechanistic manifold will not be discussed in detail, but three general properties are especially important:

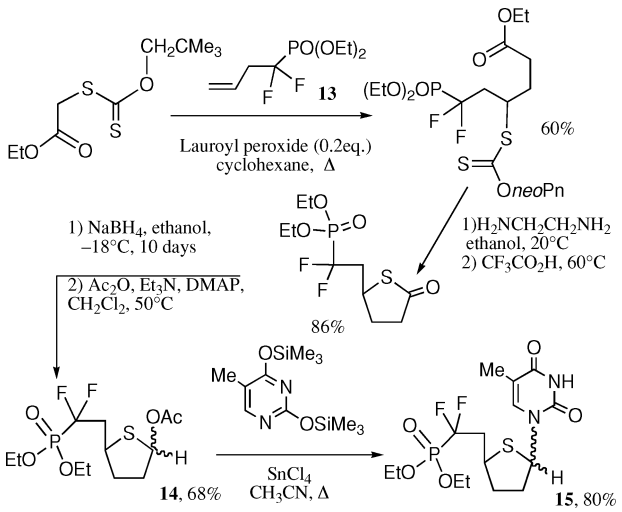
(a) The reaction of radical R• with its xanthate precursor *via* path **A** is degenerate and does not consume the radical, since fragmentation through path **B** is difficult and scission through path **C** returns the starting radical and xanthate. This effective absence of competition provides radical R• with enough lifetime to react with the olefinic trap either in an intra- or intermolecular mode (path **D**). This translates into a unique ability to accomplish *intermolecular* additions to *un-activated* olefins and sets this method apart from essentially all other radical processes.

(b) The adduct **11** is itself a xanthate. Another radical sequence can therefore be implemented, which could, in turn, lead to yet another xanthate, or the xanthate group can be used as an entry into the extremely rich "ionic" chemistry of sulfur. Hence, a large array of synthetic transformations can now be used to introduce further diversity and complexity into the structure.

(c) For the chain process to be efficient, it is important to select the reacting partners in such a way that the adduct radical **9** is less stable than the initial radical R•, in order to favour the fragmentation of intermediate **10** in the desired direction. This consideration is crucial, especially when intermolecular additions are concerned, as it provides a handle for stopping at the mono-adduct in preference to telomerisation. Thermodynamic stability of the radical is implied for simplicity, but polar factors can be important in some cases. It is nevertheless possible, when the adduct radical **9** has a low oxidation potential (*i.e.* G is an

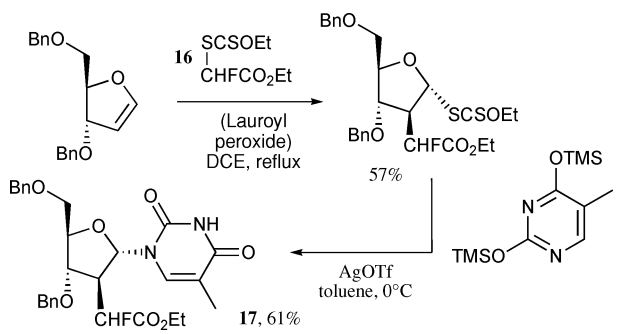
electron-releasing group) and is therefore easily oxidised into the corresponding cation **12**, to use the peroxide both as an initiator and an oxidant. Oxidising the radical throws open a bridge from a radical to a polar reaction manifold and considerably expands the synthetic scope. This aspect will have its importance in the context of a tin-free reductive removal of the xanthate group and in cyclisations involving aromatic rings (*vide infra*).

The utility of this process is that it allows the inter- or intramolecular creation of C–C bonds, even in the case of non-activated alkenes. As far as fluorinated groups are concerned, they can be present in the olefin, in the xanthate, or in both. The convergent synthesis of a difluoro nucleoside analogue **15** detailed in Scheme 5 illustrates the case where the fluorine atoms are located on the olefinic partner **13**.[6] The efficient radical addition is followed by aminolysis of the xanthate, ring-closure to the thiolactone, and mild reduction to give a thiolactol intermediate, which is finally acetylated to provide a substrate, **14**, capable of undergoing a Vorbrüggen type introduction of the thymine base.



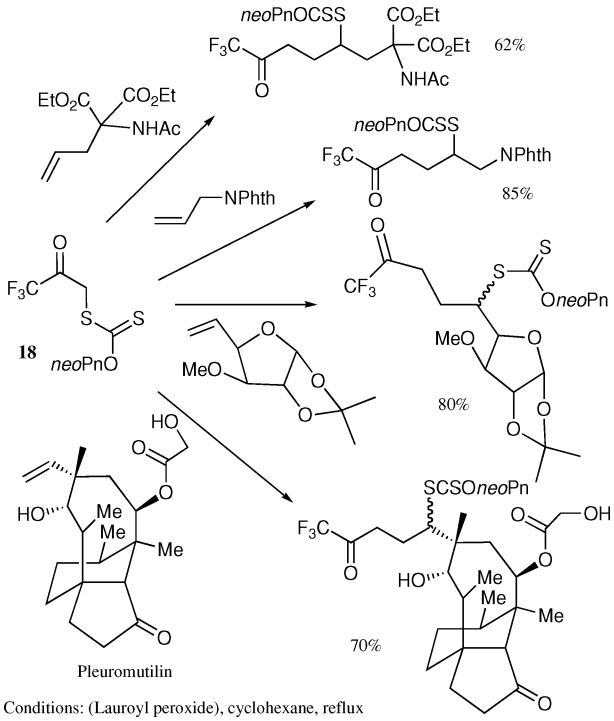
Scheme 5 Synthesis of a difluorinated thymidine analogue.

Alternatively, the fluorinated group can be attached to the xanthate, as in **16**. This variant is again illustrated by a synthesis of a fluorinated nucleoside analogue **17** recently reported by Lequeux and co-workers and displayed in Scheme 6.[7]



Scheme 6 Synthesis of a fluorinated nucleoside.

Numerous fluorinated building blocks can be constructed using the xanthate transfer technology. Trifluoromethyl ketones for instance can now be simply made by addition of xanthate **18** to various olefins as exemplified by the transformations in Scheme 7.[8] Reagent **18** is easily made by reacting a xanthate salt with commercially available 1-bromo-3,3,3-trifluoropropan-2-one. The use of the more hydrophobic *O*-neopentyl instead of the ubiquitous *O*-ethyl xanthate in this case is to limit the (reversible) formation of the hydrate of the trifluoromethyl ketone in **18**. Unlike the ketone itself, the hydrate does not allow stabilisation of the intermediate radical and can be a source of complications. The efficient addition to native, unprotected pleuromutilin, an antibacterial terpenoid, is quite remarkable and worth underlining. Most of these trifluoroketones would otherwise be very tedious to obtain by traditional routes, yet can now be made in one step.



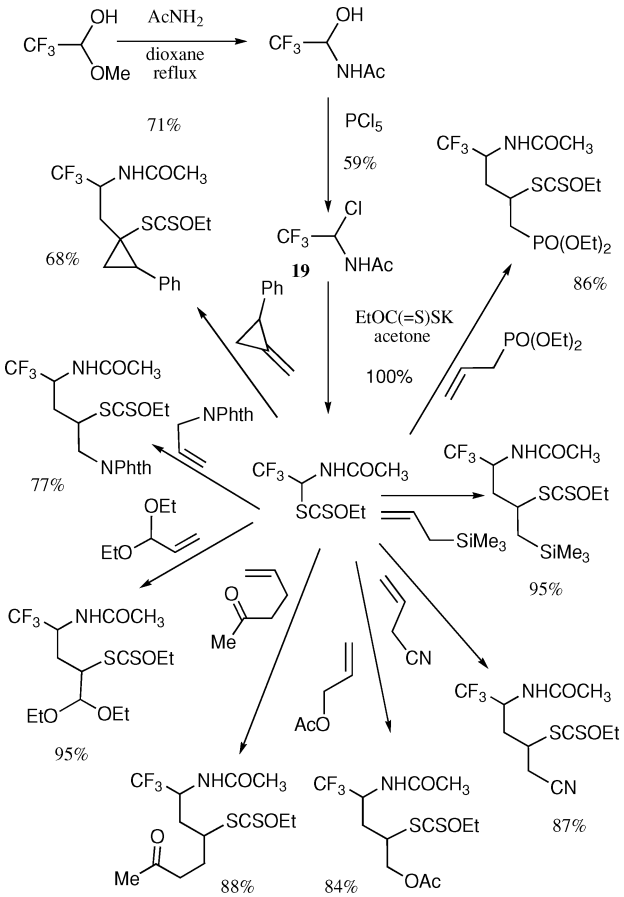
Scheme 7 Synthesis of trifluoromethyl ketones (Phth = phthalimido).

Xanthate **19** is crystalline and can be prepared on a multigram scale starting from the hemiacetal of trifluoroacetaldehyde.[9]

Its addition to variously substituted olefins also proceeds efficiently and cleanly to afford a multitude of structures containing a geminally disposed trifluoromethyl and amido groups. The examples provided in Scheme 8 again highlight the unique compatibility of this synthetic method with a broad diversity of functional groups present on the olefinic partner.[9]

The xanthate group in the addition products can be exploited in many ways. In some cases, another radical addition can be accomplished, allowing the swift assembly of complex and densely functionalised fluorinated structures. This is illustrated by the further conversion of adduct **20** into derivative **21** (Scheme 9).[9]

Addition to vinyl acetate provides an adduct **22** with a masked aldehyde function, since the xanthate is now geminal to the acetoxy group. Heating this adduct with methanol and acid gives acetal **23**, a compound containing an acetylated amine and a protected aldehyde; it thus constitutes a very interesting synthon for the synthesis of trifluoromethyl-substituted heterocycles. The third

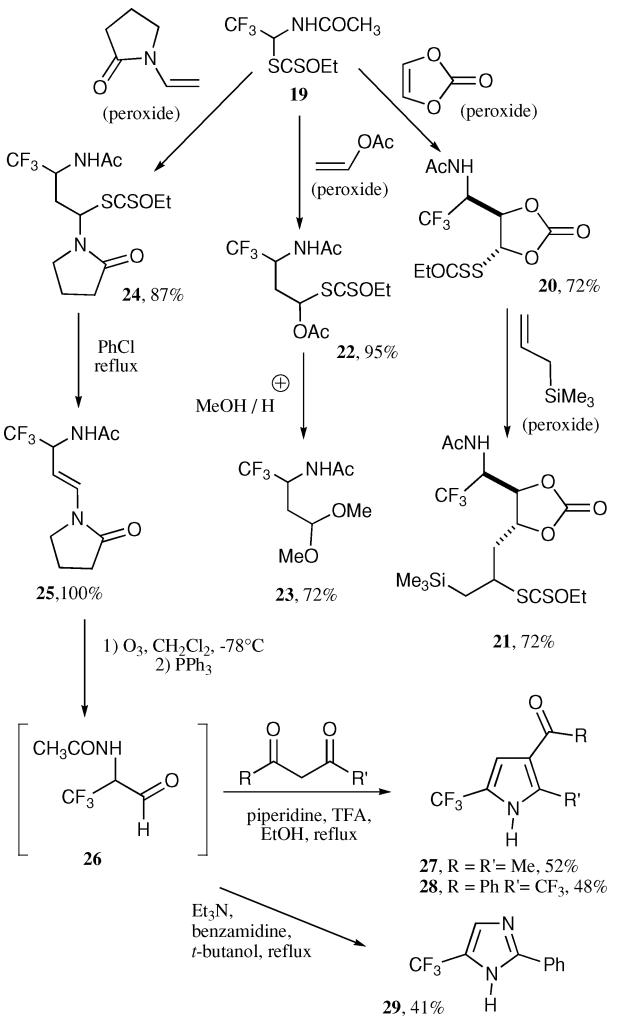


Conditions: Lauroyl peroxide (2-10 mol%), 1,2-dichloroethane, reflux

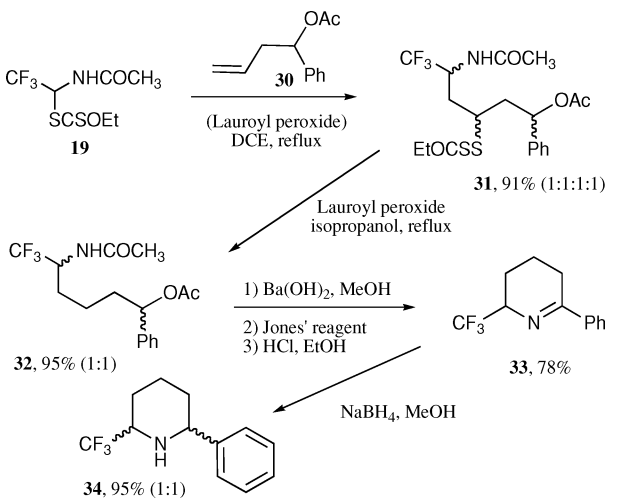
Scheme 8 Synthesis of geminal trifluoromethyl amides.

example in Scheme 9 concerns the addition to *N*-vinyl pyrrolidone, which gives a product, **24**, that can be thermolysed into enamide **25** in essentially quantitative yield. Enamides such as **25** are useful precursors for the synthesis of trifluoroalanine, trifluoroanalinal, and trifluoroalaninol, through ozonolysis of the olefinic bond followed by an appropriate oxidative or reductive work up of the ozonolysis medium.[10] One synthetic application is depicted at the bottom of Scheme 9, where *in situ* condensation of aldehyde **26** with acetylacetone or 1-phenyl-4,4,4,-trifluoro-1,3-butanedione leads respectively to trifluoromethyl pyrroles **27** and **28** through the classical Knorr reaction. In contrast, reaction with benzamidine produces the expected imidazole **29** in moderate yield.[10]

Xanthate **19** can also be used to construct trifluoromethyl-substituted piperidines. One example is displayed in Scheme 10 and relies on the initial radical addition to homoallylic acetate **30**.[10] The adduct, **31**, obtained in high yield, is then subjected to the action of a stoichiometric amount of lauroyl peroxide in refluxing isopropanol to give the reduced derivative **32**. This step is an example of a tin-free reductive de-xanthylation procedure, where the solvent is the hydrogen atom source.[11] In this process, the peroxide acts as both the initiator and oxidant for the ketyl radical generated by removal of the tertiary hydrogen from the isopropanol. Saponification with barium hydroxide in methanol and oxidation followed by acid hydrolysis of the amide gives tetrahydropyridine **33**, which can be reduced to the diastereoisomeric mixture of piperidines **34**.

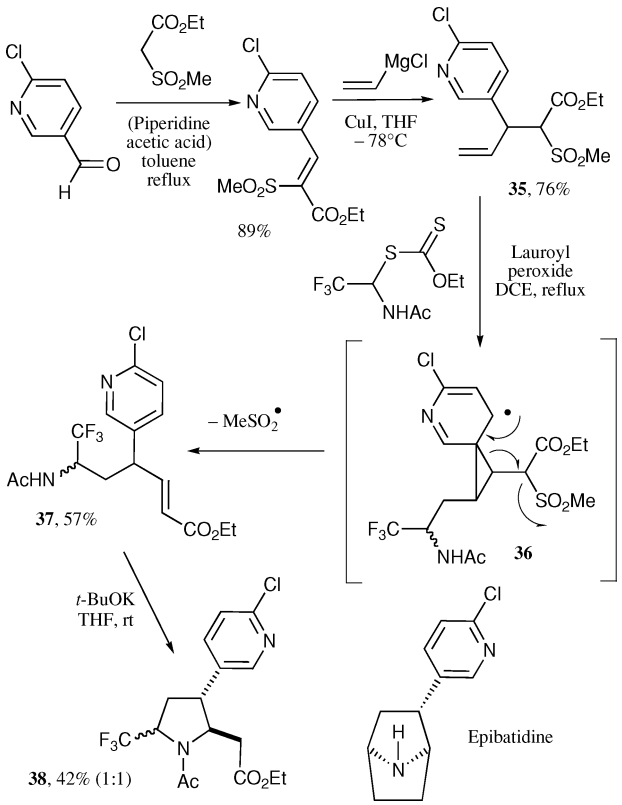


Scheme 9 Some further transformations.

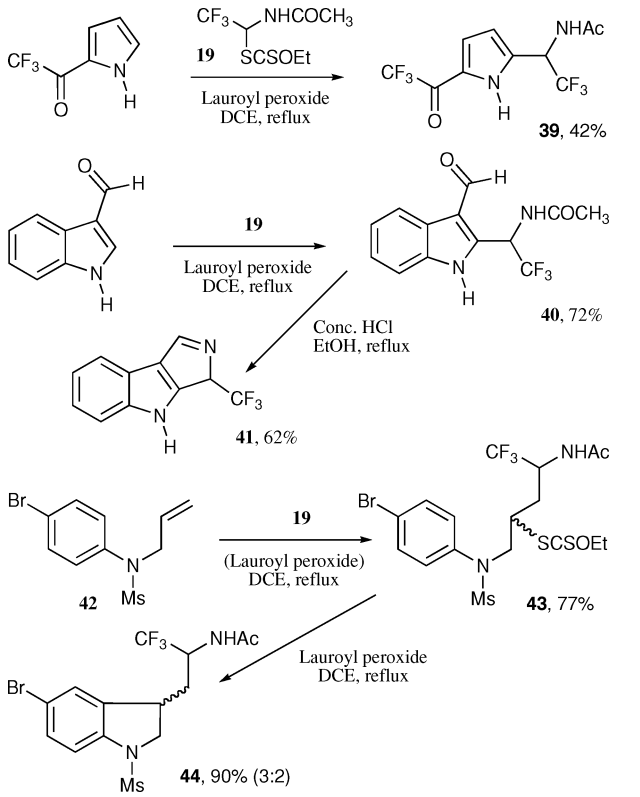


Scheme 10 Synthesis of a trifluoromethyl piperidine.

Aryl pyrrolidines are also important derivatives. A rather unusual, yet powerful approach to trifluoromethyl-substituted aryl pyrrolidines is depicted in Scheme 11.[12] Radical addition of xanthate **19** to the readily prepared olefin **35** results in a sequence whereby the initial addition is followed by a 1,2-shift of the



Scheme 11 Synthesis of a trifluoromethyl arylpyrrolidine.



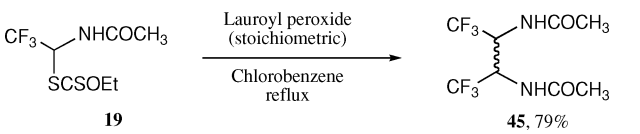
Scheme 12 Synthesis of aromatic derivatives.

pyridine ring *via* spirocyclopropyl intermediate **36** and elimination of a methanesulfonyl radical to finally furnish unsaturated ester **37**. The elimination of the sulfonyl radical ensures that the otherwise reversible neophyl shift is driven in the desired direction. Furthermore, the methanesulfonyl radical expels sulfur dioxide to give a reactive methyl radical that can propagate the chain by reacting with the starting xanthate. Treatment of compound **37** with base causes ring closure by an internal Michael addition to form pyrrolidine **38**, an open chain analogue of epibatidine, one of the most potent analgesic natural products isolated from the skin of the South American "poison-dart" frog.

The comparatively long effective lifetime of radicals generated using xanthates can be exploited to perform intermolecular additions to various heterocyclic systems. The ensuing adduct radical cannot propagate the chain but its oxidation to the cation by electron transfer to the peroxide allows restoration of the initial aromaticity of the heterocyclic ring. As with the reductive dexanthylation in isopropanol discussed above, the peroxide again acts as initiator and stoichiometric oxidant. Two examples of such intermolecular additions of xanthate **19** are pictured in the upper half of Scheme 12. The first takes place on 2-trifluoroacetyl pyrrole to give selectively the 2,5-substituted pyrrole **39**.[10,13] The second involves 3-indolecarboxaldehyde and furnishes, in good yield, an adduct, **40**, that undergoes ring closure into tricyclic derivative **41** upon heating with hydrochloric acid.[10]

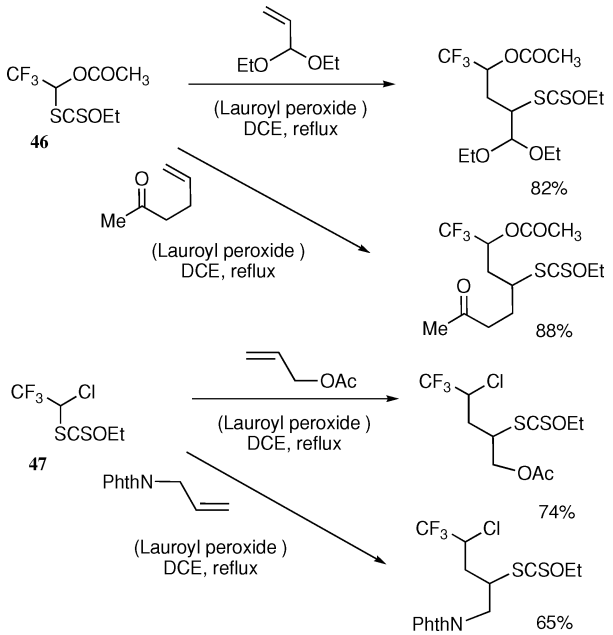
These two examples of *intermolecular* additions to heteroaromatic rings represent only a tiny sample of the very numerous possible combinations that can provide a remarkably concise access to novel fluorinated and non-fluorinated heterocyclic compounds of potential interest to medicinal and agrochemical chemists. Similar, *intermolecular* additions to benzene derivatives are not generally as efficient or regioselective; nevertheless, important aromatic structures can be made by exploiting a combination of an *intermolecular* addition to an olefin, followed by an *intramolecular* closure onto the aromatic ring. This is illustrated by the last sequence in Scheme 12, where addition of xanthate **19** to olefin **42** and cyclisation of adduct **43** using a stoichiometric amount of peroxide gives indoline **44** in good overall yield.[9]

It is interesting to note that in the absence of a trap, xanthate **19** reacts with a stoichiometric quantity of lauroyl peroxide to give homodimer **45**, as 1 : 1 mixture of the *meso* and (+),(−)-diastereoisomers (Scheme 13).[9] The formation of such dimers is not surprising when dealing with radical intermediates; what is astonishing is the high yield, since one would have expected a complex mixture arising from anarchic and statistical recombinations of the various radicals in the medium. The mechanistic implications are exceedingly important and reveal some subtle aspects of the process but these will not be discussed here.[5d] Suffice it to say that this approach represents a unique, practical route to protected 2,3-diamino-1,1,1,4,4,4-hexafluorobutane, a hitherto unknown family of fluorinated vicinal diamines of potential use for the synthesis of unusual ligands for transition metal chemistry or for the construction of fluorinated nitrogen heterocycles.



Scheme 13 Synthesis of a vicinal ditrifluoromethyl diamine.

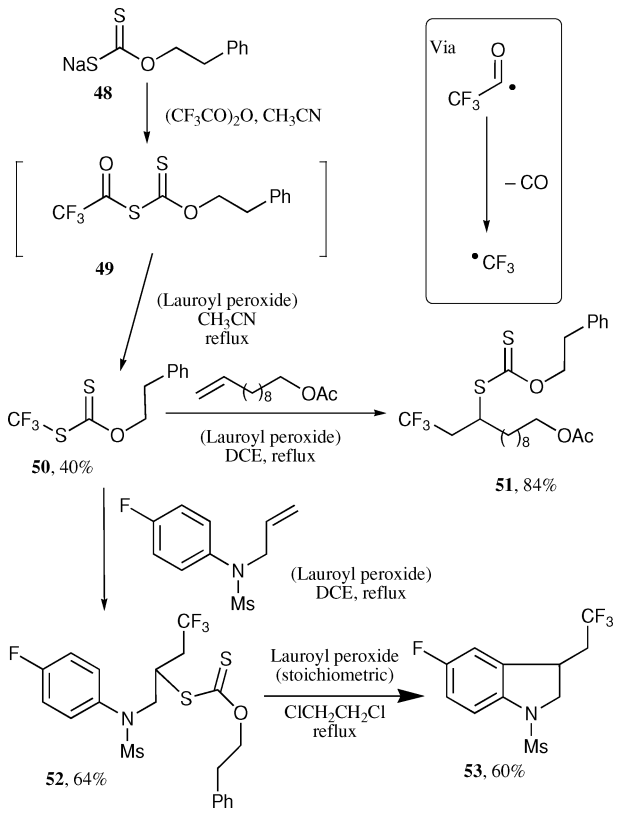
Other useful xanthates can be obtained from the hemiacetal of trifluoroacetaldehyde in a similar manner. Their radical reactions closely mirror those of amide **19**. A few examples of additions of the acetoxy and chloro derivatives **46** and **47** are collected in Scheme 14.[14]



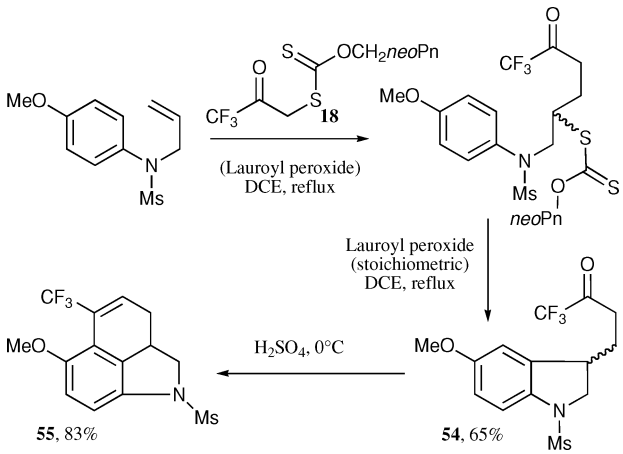
Scheme 14 Synthesis of geminal trifluoromethyl acetates and chlorides.

The generation and capture of a simple trifluoromethyl radical using the xanthate transfer technology is also possible; however, the synthesis of the precursor is less obvious. Direct substitution on trifluoromethyl iodide or bromide by a xanthate is not feasible and an indirect route is needed. The approach outlined in Scheme 15 relies on the *in situ* formation and decomposition of *S*-trifluoroacetyl xanthate **49**.[15] The yellow acyl xanthate **49** produces, through the initiating action of peroxide (or visible light), trifluoroacyl radicals which readily extrude carbon monoxide to give trifluoromethyl radicals. These rapidly react with **49** by the usual reversible addition–fragmentation to give xanthate **50** and trifluoroacetyl radicals that propagate the chain. The use of the *O*-phenethyl xanthate salt **48** instead of the more familiar *O*-ethyl xanthate was dictated by the desire to avoid handling of a potentially volatile *S*-trifluoromethyl xanthate. The two examples of addition displayed in Scheme 15 demonstrate the efficiency of xanthate **50** as a reagent for the direct introduction of the trifluoromethyl group.

The preceding transformations give a glimpse of the variety of fluorinated building blocks that thus become accessible, starting from cheap, readily available starting materials. Synthetic possibilities arising from the subsequent transformations of the highly functionalised adducts represent additional interesting features. One further illustrative example is provided by the sequence in Scheme 16, where the addition of xanthate **18** to *N*-allyl-*N*-methanesulfonyl-*p*-anisidine is followed by a radical ring-closure to give indoline **54** and then by an intramolecular Friedel–Crafts reaction to produce the trifluoromethyl-containing tricyclic indoline **55**, a structure not unrelated to that of the ergot alkaloids.[16]

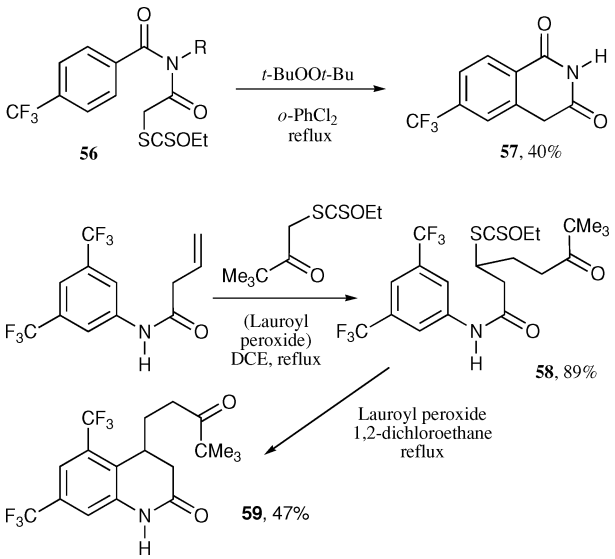


Scheme 15 Addition of trifluoromethyl radicals.



Scheme 16 Synthesis of a fluorinated tricyclic indoline.

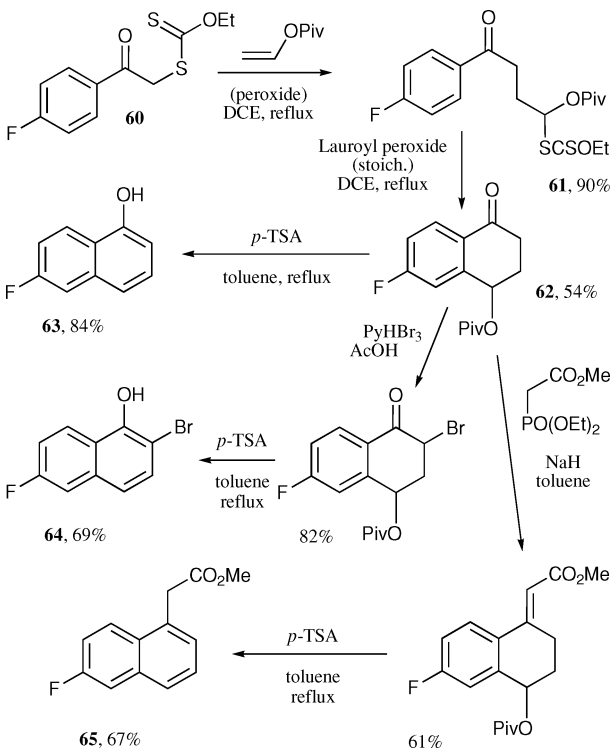
An alternative use of this chemistry is to take advantage of its unique tolerance of functional groups to modify existing fluorinated derivatives in ways not open to other approaches. The synthesis of aromatic compounds constitutes one aspect. The presence of one or more trifluoromethyl groups on an aromatic ring all but completely deactivates it towards electrophilic aromatic substitutions such as the Friedel–Crafts reaction used above in the synthesis of **55**. In contrast, the presence of trifluoromethyl groups does not have a detrimental effect on the corresponding radical cyclisation. For example, the synthesis of trifluoromethyl-substituted homophthalimide **57** is possible by direct cyclisation of xanthate **56** (Scheme 17).[17] The product in this case crystallises upon cooling of the reaction mixture and is simply collected by



Scheme 17 Synthesis of homophthalimides and dihydroquinolones.

filtration. The second example in the same scheme concerns a successful cyclisation on a bis-trifluoromethyl-substituted aromatic ring to give tetrahydroquinolone **59**.[18] Precusor **58** is itself the product of an efficient intermolecular addition of a xanthate. Most remarkably, both of these cyclisations not only lead to six-membered rings, but also take place starting from secondary amides or imides, which are known to be exceedingly difficult to cyclise by other radical processes due to the predominance of unfavourable rotamers.[19]

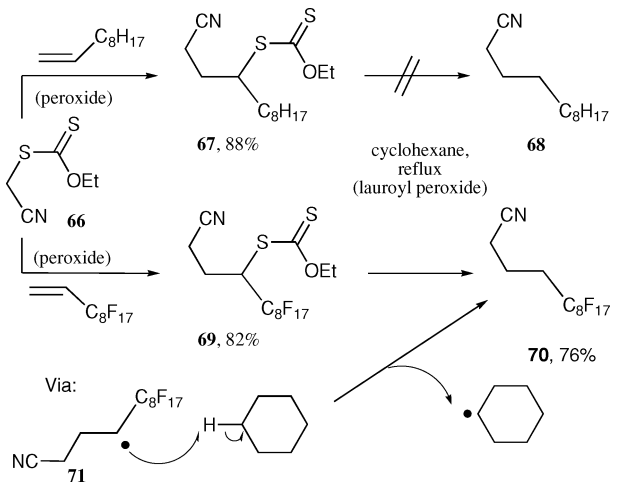
The ease and flexibility with which fluorinated aromatic derivatives can be accessed is further showcased by the synthesis of variously substituted naphthalenes pictured in Scheme 18.[20]



Scheme 18 A divergent approach to naphthalenes.

Radical addition of *S*-*p*-fluorophenacyl xanthate **60** to vinyl pivalate gives the expected adduct **61**, which undergoes ring closure to tetralone **62** upon treatment with stoichiometric quantities of peroxide. Exposure to acid causes elimination of pivalic acid and aromatisation into 6-fluoro-1-naphthol **63**. If a bromination is performed before the aromatisation step, then the sequence leads regioselectively to 2-bromo-6-fluoro-1-naphthol **64**. Finally, a Horner–Wadsworth–Emmons reaction on the ketone and treatment with acid leads to the ethyl (6-fluoronaphthalen-1-yl)-acetate **65**. Thus, from the same tetralone **61**, a host of fluorinated naphthalenes can be obtained rapidly and efficiently.

In many of the above reactions, the effect of the fluorine on the reactivity does not manifest itself. In the transformation outlined in Scheme 19, the presence of the fluorine has a dramatic influence. When an equimolar mixture of xanthates **67** and **69**, derived respectively by addition of **66** to decene and heptadecafluorodecene, was dissolved in cyclohexane and treated with a small amount of lauroyl peroxide, only the fluorinated analogue **69** was converted into **70**.[21] Reductive dexanthylation to give **68** does not take place under these conditions. The powerful electron-withdrawing effect exerted by the fluorine atoms on radical **71** enormously increases the rate of hydrogen abstraction from cyclohexane and an efficient chain can be sustained. Such potent polar effects do not operate with the corresponding non-fluorinated derivative **67**. Such subtle polar factors can therefore be exploited to accomplish a highly effective dexanthylation of adducts to fluorine-containing olefins. It is also interesting to note that a similar situation obtains with carbohydrate xanthates where the hydroxy groups are protected as esters. The electron-attracting ester groups lower the SOMO of the radical without stabilising it, and therefore also accelerate hydrogen abstraction from cyclohexane. Deoxy sugars can thus be prepared in a similar, straightforward manner.[21]

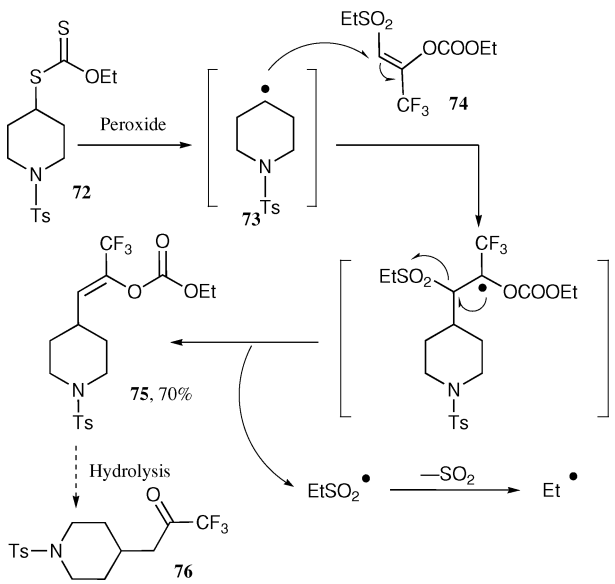


Scheme 19 Reduction by hydrogen abstraction from cyclohexane.

The fact that it is possible to go back to the intermediate radical **9** from the product xanthate **11**, as implicit in Scheme 4, opens up many synthetic opportunities. The preceding examples have illustrated how this property may be exploited to effect successive additions to different olefins, to follow up an intermolecular addition by a ring closure onto an aromatic ring, or to reductively remove the xanthate using isopropanol, or in some cases cyclohexane, as the hydrogen atom donor. There are numerous

other interesting transformations that have not been discussed here simply because they were not performed on fluorinated substrates and for lack of space. One example is the replacement of a xanthate with bromine.[22] Another, perhaps even more important application, is using controlled successive additions on various monomers to obtain block-polymers. Indeed, the mechanistic manifold in Scheme 4 constitutes the basis of the increasingly popular and tremendously powerful RAFT/MADIX controlled polymerisation technology, which, incidentally, can be used to prepare fluorine containing polymers.[23]

It would be appropriate to close this short review, which started with an ionic route to trifluoromethyl ketones from carboxylic acids, with a radical method to replace a xanthate with a trifluoromethyl ketone. The process hinges on the ability of an aliphatic sulfonyl radical to extrude sulfur dioxide and give a reactive alkyl radical to propagate the chain.[24] Thus, taking xanthate **72** as an example, it is possible to capture the corresponding radical **73** with vinyl sulfone **74** to produce, by an addition elimination sequence, enol carbonate **75** and an ethylsulfonyl radical (Scheme 20). The latter fragments into a molecule of sulfur dioxide and an ethyl radical, which propagates the chain by reacting with the starting xanthate. Compound **75** is a masked form of trifluoromethyl ketone **76**.



Scheme 20 A radical approach to enol carbonates of trifluoromethyl ketones.

Conclusions

The transformations discussed in the preceding paragraphs give an overview of the new opportunities now available to chemists interested in organofluorine compounds. The powerful radical exchange of xanthates, in particular, provides an entry into numerous novel fluorinated structures and building blocks. The experimental procedure is quite simple and the reagents are cheap and readily available. Interestingly, the process is essentially self-regulating and the reactions, which often work best in very concentrated media, are easily scaled up.

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References

1 For some recent references, see: (*a*) M. Shimizu and T. Hiyama, *Angew. Chem., Int. Ed.*, 2005, **44**, 214; (*b*) R. D. Chambers, *Fluorine in Organic Chemistry*, Blackwell Publishing, Oxford, 2004; (*c*) P. Kirsch, *Modern Fluoroorganic Chemistry*, Wiley-VCH, Weinheim, 2004; (*d*) *Topics in Current Chemistry—Organofluorine Chemistry: Techniques and Synthons*, ed. R. D. Chambers, Springer, Berlin, 1997, vol. 193; (*e*) *Biomedical Frontiers of Fluorine Chemistry*, ed. I. Ojima, J. R. McCarthy and J. T. Welch, American Chemical Society, Washington D.C., 1996; (*f*) *Fluoroorganic Chemistry: Synthetic Challenges and Biomedical Rewards*, ed. G. Resnati and V. A. Soloshonok, Tetrahedron Symposium-in-Print No. 58, *Tetrahedron*, 1996, **52**, 1–330; (*g*) *Fluorine-Containing Amino Acids*, ed. V. P. Kukhar and V. A. Soloshonok, Wiley, Chichester, 1994; (*h*) *Organofluorine in Medicinal Chemistry and Biochemical Applications*, ed. R. Filler, Y. Kobayashi and L. M. Yagupolski, Elsevier, Amsterdam, 1993; (*i*) G. Resnati, *Tetrahedron*, 1993, **49**, 9385.

2 M. Schlosser, *Angew. Chem., Int. Ed.*, 2006, **45**, 5432.

3 (*a*) J. Boivin, L. El Kaim and S. Z. Zard, *Tetrahedron Lett.*, 1992, **33**, 1285; (*b*) J. Boivin, L. El Kaim and S. Z. Zard, *Tetrahedron*, 1995, **51**, 2573; (*c*) J. Boivin, L. El Kaim and S. Z. Zard, *Tetrahedron*, 1995, **51**, 2585.

4 L. A. Trimble, I. P. Street, H. Perrier, N. M. Trembley, P. K. Weech and M. A. Bernstein, *Biochemistry*, 1993, **32**, 12560; B. F. Cravatt, D. K. Giang, S. P. Mayfield, D. L. Boger, A. E. Lerner and N. B. Gilula, *Nature*, 1996, **384**, 83; J. E. Patterson, I. R. Ollmann, B. F. Cravatt, D. L. Boger and A. E. Lerner, *J. Am. Chem. Soc.*, 1996, **118**, 5938; L. Thommesen, W. Sjursen, K. Gasvik, W. Hanssen, O. L. Brekke, L. Skattebol, A. K. Holmeide, T. Espevik, B. Johansen and A. Laegreid, *J. Immunol.*, 1998, **161**, 3421; O. Provot, H. Moskowitz and J. Mayrargue, *J. Fluorine Chem.*, 1998, **91**, 199; F. Ghomashchi, R. Loo, J. Balsinde, F. Bartoli, R. Apiz-Castro, J. D. Clark, E. A. Dennis and M. H. Gelb, *Biochim. Biophys. Acta*, 1999, **1420**, 45; A. Armstrong and B. R. Hayter, *Tetrahedron*, 1999, **55**, 11119; D. L. Boger, H. Sato, A. E. Lerner, B. J. Austin, J. E. Patterson, M. P. Patricelli and B. F. Cravatt, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 265; A. K. Holmeide and L. Skattebol, *J. Chem. Soc., Perkin Trans. 1*, 2000, 2271; C. Aubert and J. F. Rontani, *Rapid Commun. Mass Spectrom.*, 2000, **14**, 960; C. M. Tice and L. M. Bryman, *Tetrahedron*, 2001, **57**, 2689; R. R. Frey, C. K. Wada, R. B. Garland, M. L. Curtin, M. R. Michaelides, J. L. Li, L. J. Pease, K. B. Glaser, P. A. Marcotte, J. J. Bouska, S. S. Murphy and S. K. Davidsen, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 3443; D. D. Dischino, J. Banville and R. Remillard, *J. Labelled Compd. Radiopharm.*, 2003, **46**, 167; T. H. Masilje, M. P. Hedrick, J. Desharnais, A. Tavassoli, Y. Zhang, I. A. Wilson, S. J. Benkovic and D. L. Boger, *Bioorg. Med. Chem.*, 2003, **11**, 4487; G. Kokotos, S. Kotsovolu and R. Verger, *ChemBioChem*, 2003, **4**, 90; B. Jose, Y. Oniki, T. Kato, N. Nishino, Y. Sumida and M. Yoshida, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 5343; M. Riba, A. Sans, J. Sole, L. Munoz, M. P. Bosch, G. Rosell and A. Guerrero, *J. Agric. Food Chem.*, 2005, **53**, 1158.

5 For general reviews see: (*a*) S. Z. Zard, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 672; (*b*) S. Z. Zard, Xanthates and Related Derivatives as Radical Precursors in *Radicals in Organic Synthesis*, ed. P. Renaud and M. P. Sibi, Wiley-VCH, Weinheim, 2001, vol. 1, p. 90; (*c*) B. Quiclet-Sire and S. Z. Zard, *Top. Curr. Chem.*, 2006, **264**, 201; (*d*) B. Quiclet-Sire and S. Z. Zard, *Chem.–Eur. J.*, 2006, **12**, 6002.

6 J. Boivin, L. Ramos and S. Z. Zard, *Tetrahedron Lett.*, 1998, **39**, 6877.

7 L. Jean-Baptiste, S. Yemets, R. Legay and T. Lequeux, *J. Org. Chem.*, 2006, **71**, 2352.

8 M.-P. Denieul, B. Quiclet-Sire and S. Z. Zard, *Chem. Commun.*, 1996, 2511; E. Bacqué, F. Pautrat and S. Z. Zard, *Chem. Commun.*, 2002, 2312.

9 F. Gagosz and S. Z. Zard, *Org. Lett.*, 2003, **5**, 2655.

10 L. Tournier, *PhD Thesis*, Ecole Polytechnique, Palaiseau, 2005.

11 A. Liard, B. Quiclet-Sire and S. Z. Zard, *Tetrahedron Lett.*, 1996, **37**, 5880.

12 A. Georghe, B. Quiclet-Sire, X. Vila and S. Z. Zard, *Org. Lett.*, 2005, **7**, 1653; X. Vila, unpublished observations.
13 Y. M. Ozornio, R. Cruz-Almanza, V. Jimenez-Montano and L. D. Miranda, *Chem. Commun.*, 2003, 2316.
14 L. Tournier and S. Z. Zard, *Tetrahedron Lett.*, 2005, **46**, 455.
15 F. Bertrand, V. Pevere, B. Quiclet-Sire and S. Z. Zard, *Org. Lett.*, 2001, **3**, 1069.
16 B. Sortais, *PhD Thesis*, Ecole Polytechnique, Palaiseau, 2002.
17 B. Quiclet-Sire and S. Z. Zard, *Chem. Commun.*, 2002, 2306.
18 G. Binot and S. Z. Zard, *Tetrahedron Lett.*, 2005, **46**, 7503.
19 T. Sato, S. Ishida, H. Ishibashi and M. Ikeda, *J. Chem. Soc., Perkin Trans. 1*, 1991, 353; G. Stork and R. Mah, *Heterocycles*, 1989, **28**, 723.
20 A. Cordero-Vargas, I. Pérez-Martin, B. Quiclet-Sire and S. Z. Zard, *Org. Biomol. Chem.*, 2004, **2**, 3018.
21 B. Quiclet-Sire and S. Z. Zard, *J. Am. Chem. Soc.*, 1996, **118**, 9190.
22 F. Barbier, F. Pautrat, B. Quiclet-Sire, B. Sortais and S. Z. Zard, *Synlett*, 2002, 811.
23 For recent reviews, see: (*a*) G. Moad, E. Rizzardo and S. H. Thang, *Aust. J. Chem.*, 2005, **58**, 379; (*b*) S. Perrier and T. Takolpuckdee, *J. Polym. Sci., Part A: Polym. Chem.*, 2005, **43**, 5347; (*c*) For the original patents on MADIX and RAFT, see: P. Corpart, D. Charmot, T. Biadatti, S. Z. Zard and D. Michelet, *Fr. Pat.*, WO 9 858 974, 1998 (*Chem. Abstr.*, 1999, **130**, 82018); (*d*) T. P. Le, G. Moad, E. Rizzardo and S. H. Thang, *Int. Pat.*, 9 801 478, 1998 (*Chem. Abstr.*, 1998, **128**, 115390).
24 F. Bertrand, F. Leguyader, L. Liguori, G. Ouvry, B. Quiclet-Sire, S. Seguin and S. Z. Zard, *C. R. Acad. Sci., Ser. IIc: Chim.*, 2001, **4**, 547; F. Bertrand, B. Quiclet-Sire and S. Z. Zard, *Angew. Chem., Int. Ed.*, 1999, **38**, 1943.