

## Riding the tiger: Using degeneracy to tame wild radical processes

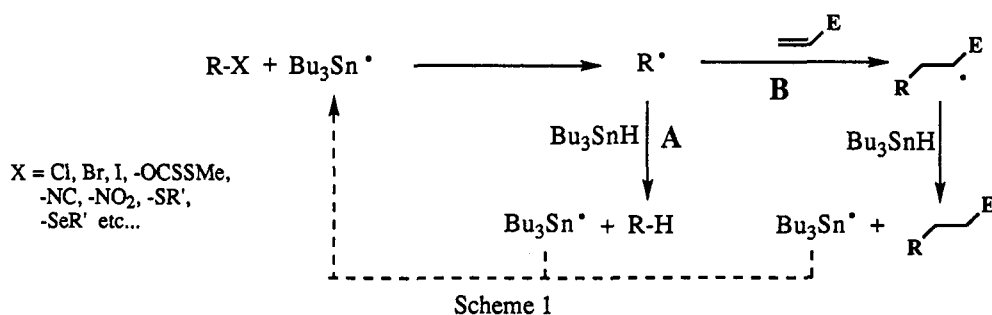
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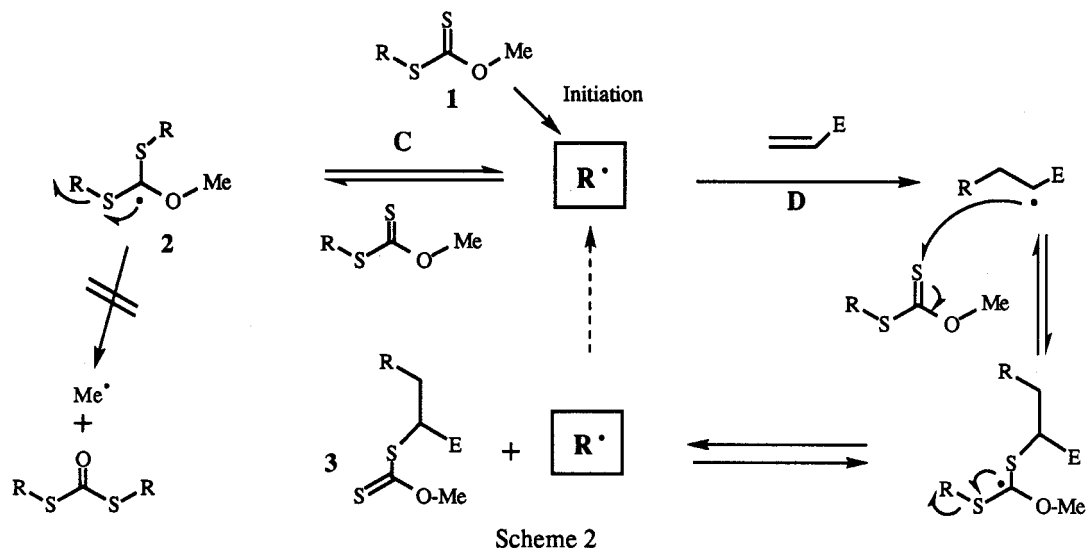
**Abstract:** Xanthates are convenient precursors of a variety of radicals that can be captured in an inter- or intramolecular fashion. Overall, the process involves rupture of the sulfide C-S bond and addition of the elements of the xanthate to the olefinic trap. The xanthate in the product can be reductively removed in some cases simply by heating in isopropanol with stoichiometric amounts of dilauroyl peroxide. A new radical allylation reaction based on allyl sulfones has also been devised where, in a manner similar to that with xanthates, a number of degenerate steps force the reaction in the desired direction.

Over the past decade or so, the use of free radical processes in organic synthesis has witnessed an extraordinary development. Radical reactions offer in fact many of the properties desired by synthetic organic chemists in terms of mildness, variety, and potential for C-C bond formation as well as for functional group interchange. The main difficulty with radicals, one which has given them their bad reputation for decades, is that they interact with themselves (dimerisation, disproportionation) with extremely fast rates that are practically diffusion controlled. It is therefore essential that the desired reaction sequence be made of very fast steps in order to keep the steady-state concentration of radical species very low and thus "tame" their wild behaviour by limiting radical-radical reactions. "He who rides a tiger is afraid to dismount" is a Chinese proverb; as long as the tiger is moving (fast), one is safe. Whence the title of this contribution. This notion is illustrated by the typical and now extremely popular chain process based on tributylstannane where the propagating steps are quite fast, as in scheme 1 below:



A serious competition problem arises however when several steps have to be performed in a given order in the same pot. In the scheme above, it is more challenging to proceed cleanly through the synthetically much richer path **B** than to accomplish merely a reduction (i. e. only  $R-X \rightarrow R-H$  via path **A**). It is because of the tough competition between paths **A** and **B** that most applications involve intramolecular processes (e. g. cyclisations) where the importance of path **A** can be effectively curtailed by the use of high dilution, syringe pump addition of the stannane etc. (ref. 1).

One way to control a complex situation of fast elementary steps is to design a radical process where redundant or degenerate loops force the radical in the desired direction. We have devised several such systems based on sulfur chemistry, which do not involve the use of heavy metals such as tin or mercury, and which allow not only functional group inter conversions but also the creation of new inter- or intramolecular carbon-carbon bonds under mild conditions.

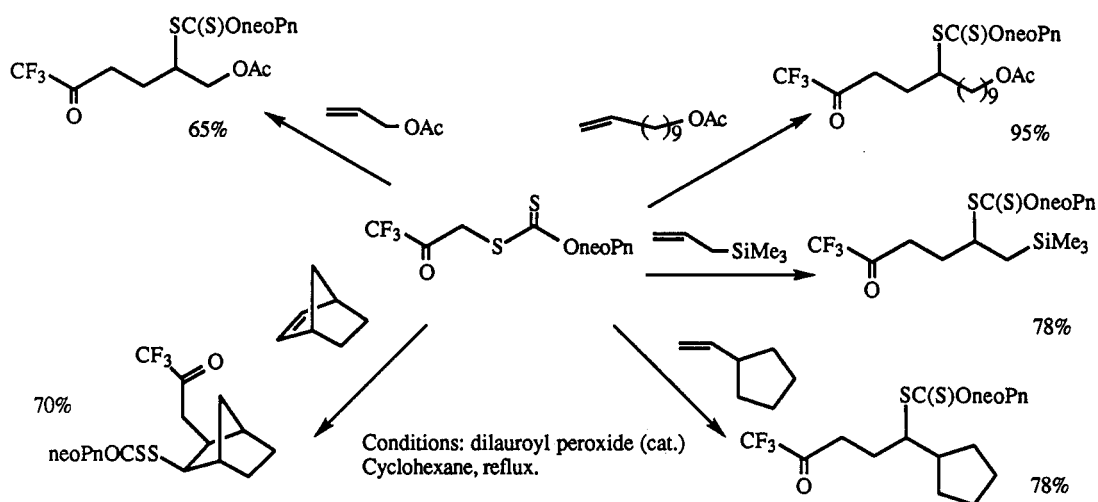


The first and most general system involves xanthates **1**. The mechanistic manifold underlying our approach is set out in Scheme 2 (ref. 2). Following a chemical or photochemical initiation step, a radical  $R^\bullet$  thus generated has the choice of either reacting with the starting xanthate (path C) or with a given trap, say an olefin, placed in the medium (path D). The former possibility leads to an adduct **2** where  $\beta$ -scission of the strong carbon-oxygen is very unfavourable since it would produce the thermodynamically less stable methyl radical (in comparison to  $R^\bullet$ ). Rupture of either of the carbon-sulfur bonds on the other hand leads back to the  $R^\bullet$  and the starting xanthate **1**. The same will apply if the methyl group on the oxygen is replaced by another group, as long as the corresponding radical is of comparable, but preferably of lower stability with respect to  $R^\bullet$  (in most applications a primary substituent is sufficient). The properties of this radical generating method are thus analogous to those of atom transfer processes, also known as Kharasch reactions (ref. 1).

In other words, paths C and D are not in competition with each other, unlike the situation prevailing with tributylstannane shown in Scheme 1. Because  $R^\bullet$  is not irreversibly quenched by its precursor, its effective lifetime in the medium becomes longer; it is therefore possible to use relatively unreactive traps that cannot normally be employed with other radical generating systems or to work with "lazy" radicals such as benzyl, allyl, or even propargyl radicals. Another, non negligible practical advantage is that the reactions can be run in a quite concentrated medium since the kinetic constraints imposing high dilution no longer apply. Overall, following two reversible steps, another xanthate **3** is finally produced whereby a new carbon-carbon bond and a new carbon-sulfur bond have been formed.

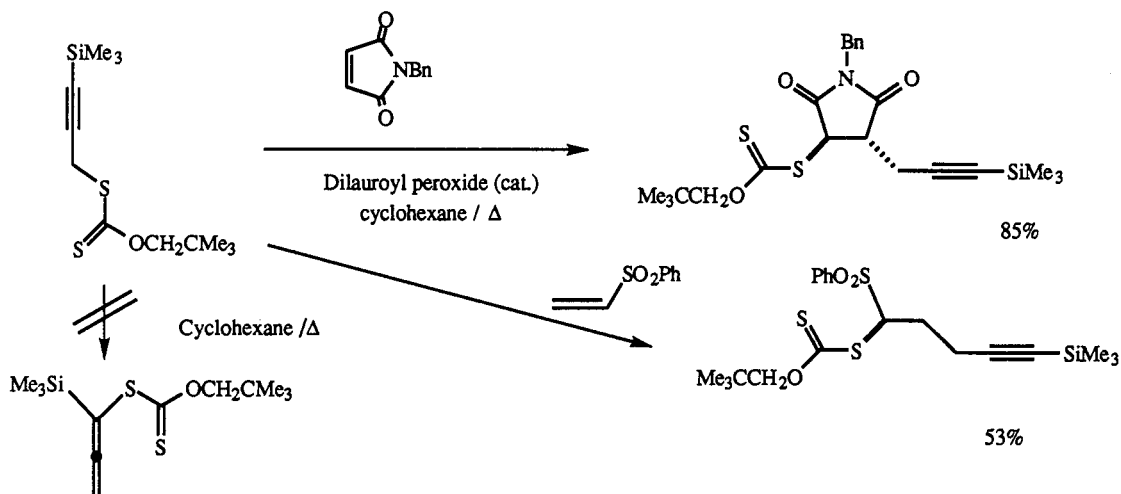
The examples displayed in Scheme 3 provide an idea of the synthetic possibilities (ref. 2, 3). These are the first cases involving the generation and capture of trifluoroacetyl radicals. Terminal olefins are usually the best substrates but unhindered or especially reactive internal olefins (e. g. norbornylene) can sometimes be used. It is worth pointing out that many of these olefinic radical traps are too unreactive to be useful with the tributylstannane method. Thus a great diversity of structures is now readily accessible through modification of the starting xanthate or the substitution pattern of the trap. Many functional groups are tolerated and, since the adducts themselves contain a xanthate group, a great number of further ionic or radical based

transformations become possible. Intramolecular reactions are of course especially favoured and many highly functionalised mono or polycyclic systems can be easily constructed (ref. 2).



Scheme 3

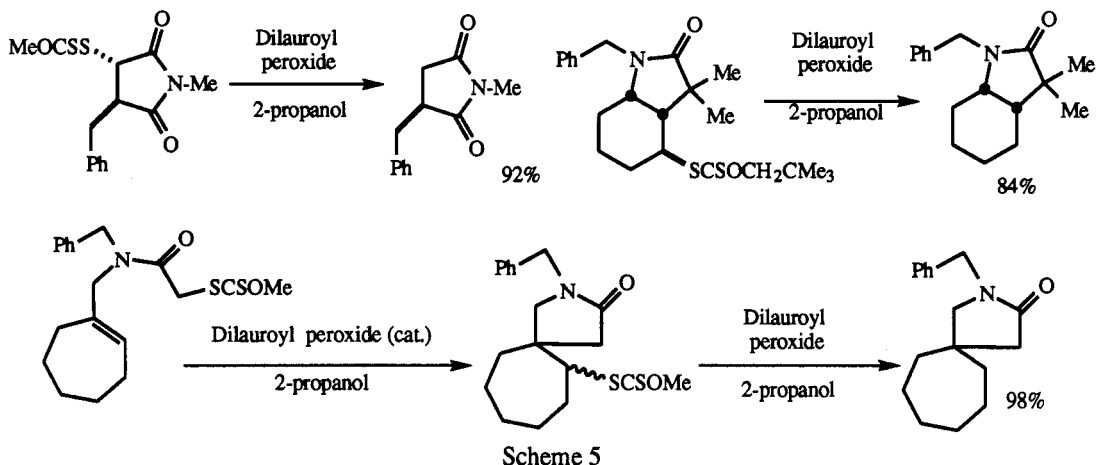
The case of propargylic radicals, a class of relatively stabilised and little studied species, is illustrated by the transformations pictured in scheme 4. They represent, as far as we know, the first high yielding examples of inter- or intramolecular capture of a propargylic radical to give alkynes (ref. 4). It is important in our case that the terminus of the triple bond opposite the xanthate group be substituted, even with a simple methyl group, to slow down an alternative non-radical pathway involving a [3,3] sigmatropic rearrangement to give an allene, as shown for the trimethylsilyl substituted derivative. This aspect of S-propargyl xanthates is very interesting in its own right (ref. 5) but will not be discussed here.



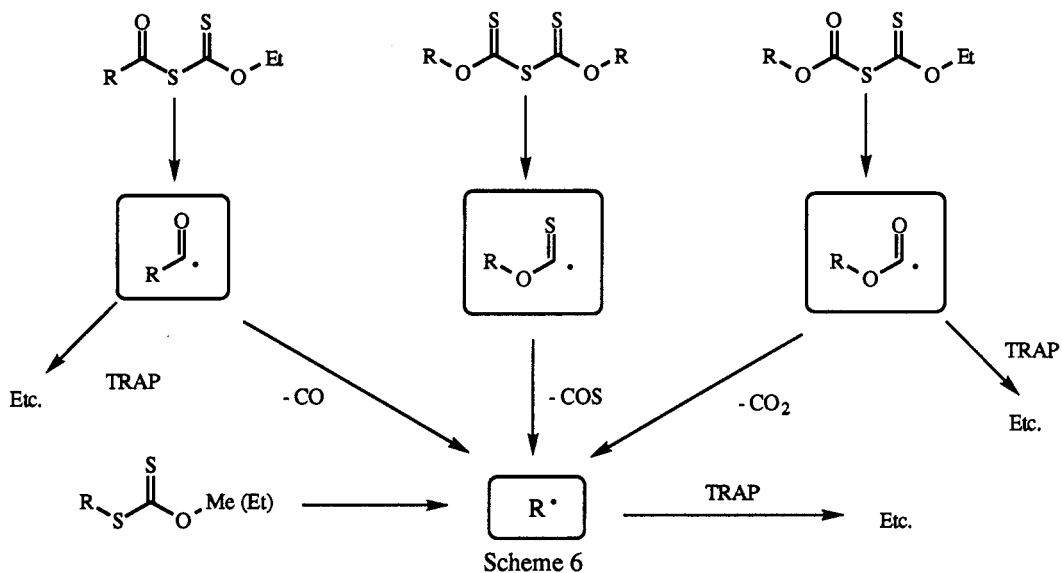
Scheme 4

The presence of the xanthate group in the end product may be considered as a synthetic asset, but many targets do not contain sulfur and it is necessary sometimes to perform a reductive cleavage with tributylstannane or with Raney nickel or nickel boride. It seemed however that the very degeneracy of the reaction of a radical with its xanthate precursor (path C in Scheme 2) may in fact be exploited to accomplish the replacement of the xanthate group with a hydrogen atom abstracted from isopropanol. The process is not a chain reaction any more and consists in the portion wise addition of stoichiometric amounts of dilauroyl

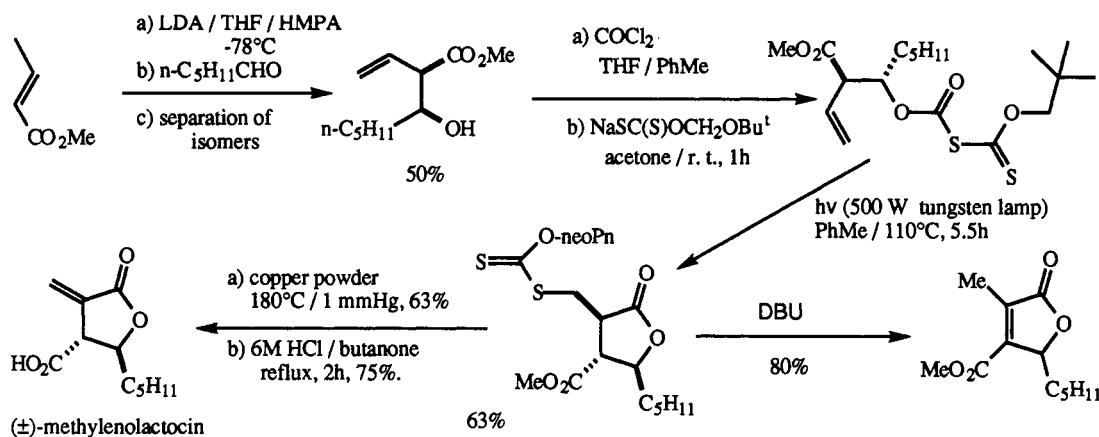
peroxide to a refluxing solution of the xanthate in isopropanol alone or in mixture with another solvent. This generally high yielding transformation is limited in practice to secondary cases (Scheme 5) but these are synthetically the most interesting; moreover, a cyclisation step can be incorporated as shown by the third example in the same scheme (ref. 6).



One very important advantage of xanthates is that a variety of carbon centered (and even tin centered) radicals can be easily generated and captured. By employing the appropriate precursor, a variety of highly functionalised structures thus become easily accessible. The top three xanthates are a little special in that they are yellow coloured and the radical process may be triggered by simply irradiating with visible light. Discoloration indicates completion of the reaction. Acyl or alkoxy carbonyl radicals may be captured to give ketones or esters (or lactones), or allowed to extrude carbon monoxide or dioxide respectively to produce an alkyl type radical.

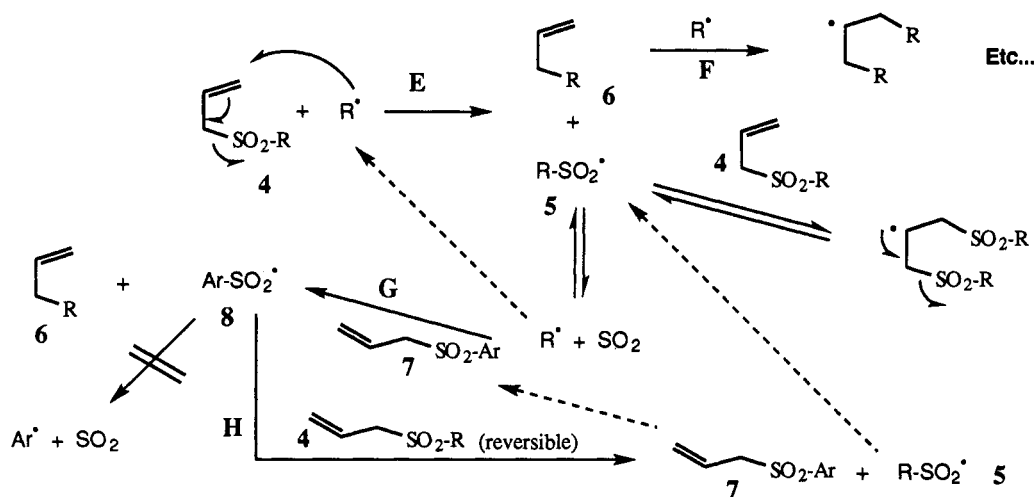


The formation of lactones by interception of an alkoxy carbonyl radical is exemplified by the short synthesis of ( $\pm$ ) methylenolactocin outlined in Scheme 7 (ref. 7). The xanthate group in the adduct is in the  $\beta$ -position with respect to the carbonyl group and is easily eliminated. In this case, however, this must be done by heating with copper powder since the use of a base such as DBU results in the migration of the double bond to give the undesirable isomer.



Scheme 7

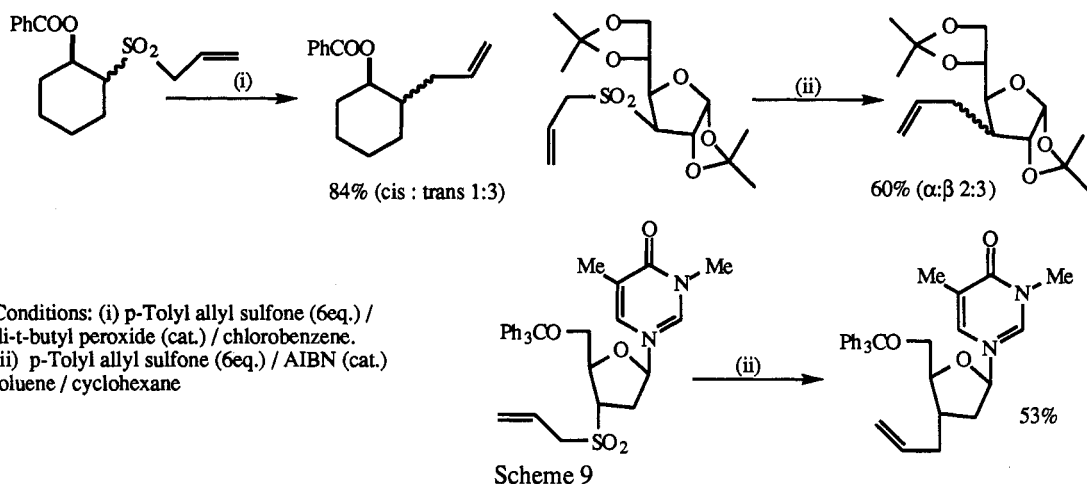
The principle of using degenerate steps to guide a radical process in a given direction may be applied to the case of allyl sulfones (ref. 8). Our aim was to develop a radical allylation method not involving tin chemistry and thus set out to reduce to practice the reaction manifold pictured in Scheme 8. The whole proposition hinges upon the hitherto little appreciated observation that an alkylsulfonyl radical *reversibly* extrudes sulfur dioxide to give an alkyl radical. This is not the case with arylsulfonyl radicals, at least at the refluxing temperature of commonly used solvents.



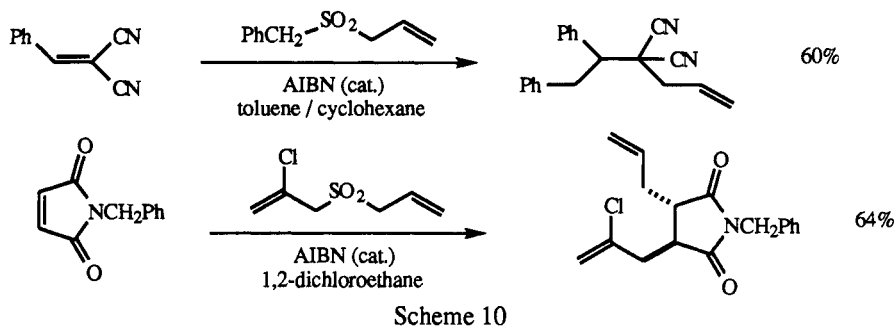
Scheme 8

Starting from alkyl allyl sulfone **4**, an alkylsulfonyl radical **5** may be generated which can lose sulfur dioxide in a reversible manner to give an alkyl radical  $R^\bullet$ . In turn this radical can react with the starting allyl sulfone leading to the desired C-allyl derivative **6** and propagating the chain at the same time (path E). There is however a major difficulty that arises from the fact that product **6** has a similar reactivity towards radicals as the starting allyl sulfone **4**. As the reaction progresses and the concentration of the latter diminishes, the probability of forming unwanted side products through path F increases. One not very satisfactory solution is to work at low conversion. Another, conceptually more pleasing remedy is to add an excess (4-6 equivalents) of an *aryl* allyl sulfone **7**. By a sheer concentration effect, this additive will preferentially scavenge radical  $R^\bullet$  to give the same C-allyl derivative **6** and an arylsulfonyl radical **8** (path G). Since **8** does not extrude sulfur dioxide, its only alternatives are to react with its precursor **7** in a degenerate way, to add reversibly to the product **6** or, more constructively, to the alkyl allyl sulfone (path H). The latter process propagates the chain by producing an alkyl sulfonyl radical and regenerates at the same time *aryl*

allyl sulfone **7** which in fact is not consumed but acts as a relay for transferring the allyl group. This contrivance prevents to a large extent the formation of unwanted side reactions.



This new allylation method was successfully applied to a number of substrates as shown by the three examples in Scheme 9. In addition, an electrophilic olefin may be incorporated into the system and, if the starting allyl sulfones are readily available and cheap, they can be used in excess to act as their own relay in these cases. In this manner, two new C-C bonds are created across the electrophilic olefin as can be seen in the examples in scheme 10. The second case involves the introduction of two different allyl groups.



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