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New Radical Allylation Reaction

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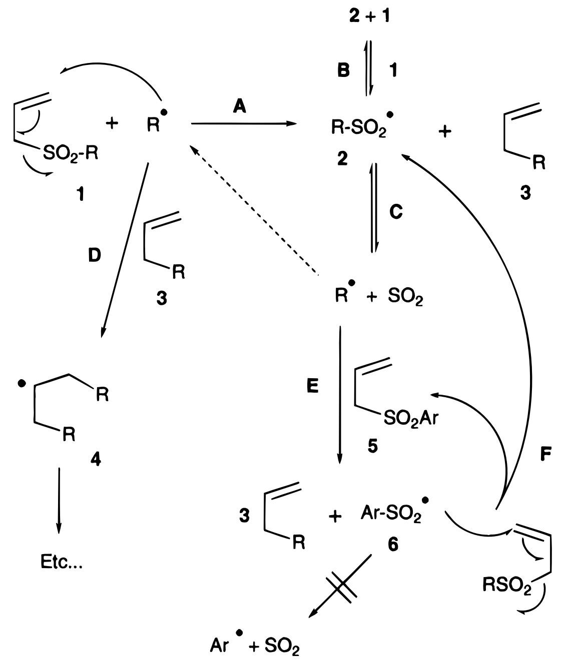
The utility of organotin hydrides, which have dominated the synthetic radical chemistry scene for the past two or three decades,[1] has been significantly increased by the development of allylstannanes and other related tin derivatives. These allow a functional group to be introduced in the last propagation step instead of the usual hydrogen atom transfer.[2] However, the toxicity of organotin residues as well as the perennial purification problems commonly encountered with stannane derivatives[3] has generally precluded large-scale application of stannane-based methodology. We now describe a new allylation process which does not involve heavy metals and which can lead to a number of interesting synthetic transformations.

Our approach relies on the fact that sulfonyl radicals add reversibly to olefins and the little-appreciated observation that *alkyl* radicals can react in a reversible manner with sulfur dioxide.[4] In general, the equilibrium favors the alkylsulfonyl radical, but if the alkyl group represents a stabilized radical (e.g., a benzyl), then extrusion of sulfur dioxide occurs readily.[5] Practically all the synthetic applications of sulfonyl radicals have involved *arylsulfonyls* which do not undergo α-scission,[6] so that this aspect of their chemistry has on the whole been overlooked in the past.[4c]

With these considerations in mind, we contrived a system where a succession of reversible or degenerate steps force the process in the desired direction, even in cases where the extrusion of sulfur dioxide from the alkylsulfonyl radical is not particularly favored. Our conception is outlined in the reaction manifold displayed in Scheme 1. Addition of a radical to the terminal olefin of alkyl allyl sulfone **1** generates an alkylsulfonyl radical **2** (path A) which can only react in a redundant manner with its precursor **1** (path B). The only way for the system to evolve is by extrusion of sulfur dioxide (path C) to give alkyl radical R$^\bullet$, which can now propagate the chain by addition to **1** to give the desired product **3**[7] via path A. This scheme is still flawed, because the product **3** can also serve as substrate for radical additions. As **3** accumulates in the medium, it competes for radical R$^\bullet$ (path D) to give adduct **4** and so on, bringing the system out of control. Since the product **3** is expected to have a reactivity similar to that of the starting allyl sulfone **1**, one solution would be to operate at low conversion, a very serious limitation from a synthetic standpoint. To avoid such an untoward situation, we envisaged the possibility of adding a relay allylating reagent to overwhelm unwanted path D. In principle, this could be accomplished by adding an excess of an *aryl* allyl sulfone **5**. This second allyl transfer reagent, by a sheer concentration effect, will continuously scavenge R$^\bullet$ (path E) to provide the same product **3** and an arylsulfonyl radical **6** which *cannot loose a sulfur dioxide molecule*. The only alternative then is a reversible reaction (path F) with the first allyl sulfone **1** thus regenerating the relay sulfone **5** and producing alkylsulfonyl radical **2** to propagate the chain. Under such conditions, the formation of the desired product **3** will therefore occur principally through path E rather than path A and formation of side products by route D will be largely circumvented.

The following examples demonstrate the validity of the above analysis. Upon heating, a solution of **1a**−**d** with a 5-fold excess

Scheme 1



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[‡] Laboratoire de Synthèse Organique associé au CNRS.

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(6) For radical reactions involving allyl sulfones, see: (a) Phillips, E. D.; Whitham, G. H. *Tetrahedron Lett.* **1993**, *34*, 2537−2540, 2541−2544. (b) Smith, T. A. K.; Whitham, G. H. *J. Chem. Soc., Perkin Trans. 1* **1989**, 313−317, 319−325. (c) Knight, D. J.; Lin, P.; Whitham, G. H. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2707−2713. (d) Padwa, A.; Kline, D. N.; Murphree, S. S.; Yeske, P. E. *J. Org. Chem.* **1992**, *57*, 298−306. (e) Padwa, A.; Bullock, W. H.; Dyszlewski, A. D. *Tetrahedron Lett.* **1987**, *28*, 3193−3196; *J. Org. Chem.* **1990**, *55*, 955−964. (f) Padwa, A.; Bullock, W. H.; Dyszlewski, A. D.; McCombie, S. W.; Shankar, B. B.; Ganguly, A. K. *J. Org. Chem.* **1991**, *56*, 3556−3564. (g) Barre, V.; Uguen, D. *Tetrahedron Lett.* **1987**, *28*, 6045−6048. (h) Baechler, R. D.; Bentley, P.; Deuring, L.; Fisk, S. *Tetrahedron Lett.* **1982**, *23*, 2269−2272.

(7) Thermolysis of alkyl or aryl allyl sulfones at 300 °C was found to lead to rearrangement with extrusion of sulfur dioxide to give compounds of type **3** by what was presumed to be a pericyclic mechanism: Hendrickson, J. B.; Bergeron, R. *Tetrahedron Lett.* **1973**, 3609−3610. Whitham and Phillips (ref 6a) report observing a small amount of a side product in one of their experiments where desulfonative allylation appears to have occurred.

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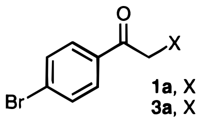
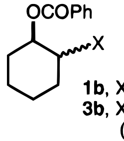
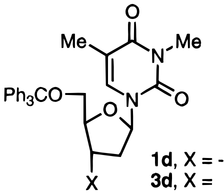
of allyl tolyl sulfone **5** (Ar = *p*-tolyl) in degassed cyclohexane[8] in the presence of a small amount of AIBN (or, sometimes better, in chlorobenzene using di-*tert*-butyl peroxide as initiator as in the case of **3a,b**) afforded the expected allyl derivatives **3a**−**d** in fair to good yields. The carbohydrate and nucleoside examples **3c** and **3d** are noteworthy in illustrating the applicability of the process to complex structures. Moreover, in examples **3b**−**d**, the secondary carbon radical formed by extrusion of sulfur dioxide is not particularly stabilized.



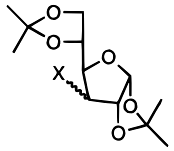
1a, X = $-SO_2$Allyl
3a, X = Allyl (60%)



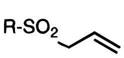
1b, X = trans-SO_2Allyl
3b, X = Allyl (84%);
(cis: trans 1:3)



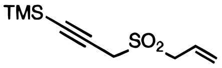
1d, X = $-SO_2$Allyl
3d, X = Allyl (53%)



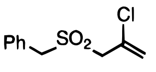
1c, X = β-SO_2Allyl
3c, X = Allyl (60%)
(α:β 2:3)



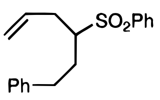
1e, R = $PhCH_2$-
1f, R = 2-thienylmethyl-
1g, R = 1-Adamantyl-
1h, R = Allyl-
1i, R = 2-Chloroallyl-



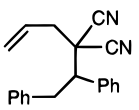
1j



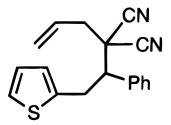
1k



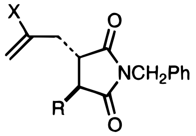
8a (55%)



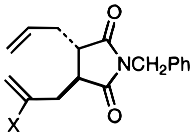
8b (60%)



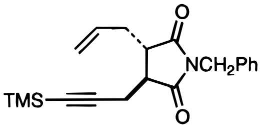
8c (46%)



8d, R = $PhCH_2$-; X = H (56%; 70% based on recovered **7c**)
8e, R = 1-Adamantyl-; X= H (44%)
8 i, R = $PhCH_2$-; X = Cl (55%)

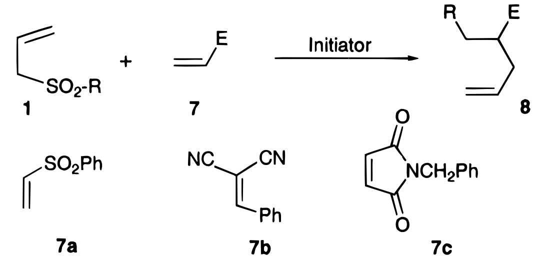


8f, X = H (50%)
8g, X= Cl (64%)



8h (20%)

Scheme 2



The reaction manifold pictured in Scheme 1 can be further expanded to include an addition to an electrophilic olefin **7**, which captures the (normally nucleophilic) carbon radical $R^{\bullet}$ faster than the allyl group. Overall, this modification leads to derivatives **8** as outlined in the greatly simplified Scheme 2. Examples **8a**−**i** illustrate some of the synthetic possibilities, using three representative electron-poor olefins, **7a**−**c**. Since the starting allyl sulfones in these cases are inexpensive, they can be used in excess (5−6-fold) and there is no need to add relay sulfone **5**. Two new carbon−carbon bonds are created in the process, and even two allyl[9] or a propargyl and an allyl group (albeit in modest yield) can be introduced across the electrophilic olefin (examples **8f**−**h**). Clean *intermolecular* additions of the rather unreactive propargyl (and even allyl) radicals are practically unknown,[10] and the products obtained in the present study are potential substrates for various exceptionally useful transition metal based transformations (e.g., alkene metatheses; the Pauson−Khand reaction; etc.).[11] Finally, the allyl group being transferred can be substituted in the 2-position, for example with a chlorine atom as in compound **8i** (in this case the experiment was performed in 1,2-dichloroethane for solubility reasons).

None of the reported yields has been optimized in this preliminary work. We have found for example that, for **3a** and **3b**, a similar yield (60% and 87%, respectively) was obtained with only 3 equiv of relay sulfone **5**. The yield of **8b** (61%) was also comparable when 3 instead of 6 equiv of **1e** was used, but in the case of **8d** it decreased to 34%. The reactions are in many cases nearly complete after the first few percent (5−7%) of initiator has been added; however, as the concentration of the limiting substrate dwindles, the radical chains become relatively short and a further, disproportionate amount of initiator is needed to push the reaction fully to completion.

In summary, this new radical allylation process is simple and flexible and employs readily available starting materials, yet it allows not only the introduction of the highly useful allyl group but also the expedient assembly of complex frameworks. Various modifications and extensions are currently under study.

Supporting Information Available: References to standard methods used in the preparation of starting allyl sulfones as well as a compilation of spectral and analytical data of all new compounds (7 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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[8] A typical experimental procedure is as follows: A solution of alkyl allyl sulfone **1a**−**d** (1 mmol) and allyl tolyl sulfone **5** (3−6 mmol) in a degassed mixture of cyclohexane (3 mL) and toluene (1 mL) was heated under reflux in the presence of AIBN (10−15%, added portionwise over the course of the reaction). For examples **3a** and **3b**, chlorobenzene (3 mL) was used with di-*tert*-butyl peroxide (one drop) as initiator. The reaction, monitored by TLC, took 2−8 h. The solvents were evaporated under reduced pressure, and the residue was chromatographed on a silica gel column to afford the desired allyl derivatives **3a**−**d**. In the case of addition to an external electrophilic olefin **7a**−**c** (1 mmol), the relay sulfone **5** was omitted and an excess of alkyl allyl sulfone **1e**−**k** (6 mmol) was added. Again a mixture of cyclohexane and toluene was used for most examples, except for **8i**, where 1,2-dichloroethane proved a better solvent, and **8c,f**, where the reaction was performed in chlorobenzene (di-*tert*-butyl peroxide as initiator).

[9] It is interesting to note that addition of *p*-tolylsulfonyl radicals to diallyl sulfone at room temperature is reported to lead mostly to a cyclic sulfone. This gives an idea of the rate of β-elimination of a sulfonyl radical, which must be somewhat slower, at least at room temperature, than a *5-exo-dig* cyclization in this case: Serra, A. C.; da Silva Corrêa, C. M. M.; Vieira, M. A. M. S. A.; Gomes, M. A. *Tetrahedron* **1990**, *46*, 3061−3070.

[10] We have found that *S*-allyl or *S*-propargyl xanthates are synthetically useful sources of allyl and propargyl radicals, which can be trapped in an inter- or intramolecular fashion: (a) Mestre, F.; Tailhan, C.; Zard, S. Z. *Heterocycles* **1989**, *28*, 171−174. (b) Boivin, J.; Tailhan, C.; Zard, S. Z. *J. Am. Chem. Soc.* **1991**, *113*, 5874−5876. (c) Denieul, M.-P.; Quiclet-Sire, B.; Zard, S. Z. Unpublished observations. (d) For the intramolecular capture of allyl radicals, see: Stork, G.; Reynolds, M. E. *J. Am. Chem. Soc.* **1988**, *110*, 6911−6913.

[11] For some leading references, see: (a) Grubbs, R. H In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, pp 1115−1127. (b) Negishi, E.-I. *Idem.* Vol. 5, pp 1163−1184. (c) Schore, N. E. *Idem.* Vol. 5, pp 1037−1064, 1129−1162. (d) Schore, N. E. *Org. React.* (*N.Y.*) **1991**, *40*, 1−90. (e) Blagg, J. *Contemp. Org. Synth.* **1994**, *1*, 125−143. (f) Smit, W. A.; Caple, R.; Smoliakova, I. P. *Chem. Rev.* **1994**, *94*, 2359−2382.