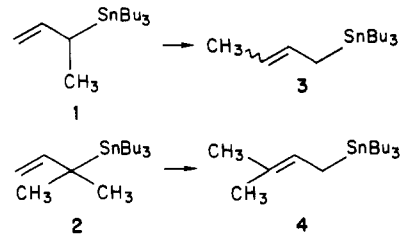
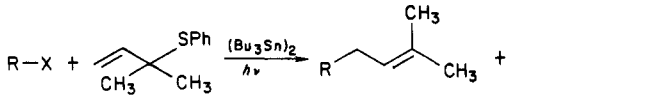
A New "One-Electron" Carbon-Carbon Bond Forming Reaction: Separation of the Chain Propagation Steps in Free Radical Allylation

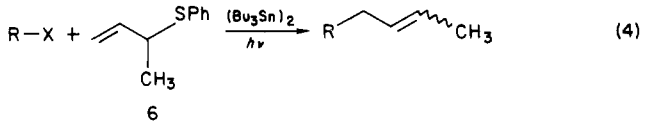
Summary: Certain allylic phenyl sulfides react with alkyl halides or selenides upon irradiation in the presence of hexabutylditin to give formal S_H2' substitution products. The process is successful for the introduction of groups such as prenyl, which cannot be accomplished by using an allylstannane.

Sir: Recently, considerable attention has been devoted to investigations of synthetic applications of free radical or "one-electron" reaction processes.[1] Many of these efforts have involved exploration of various versions of hexenyl radical cyclization[2,3] or investigations of radical additions to electron-deficient or captodative olefins, generally under reducing conditions with the olefinic reactant present in large excess.[4] Our own efforts in this area have focused on free radical carbon–carbon bond forming processes using allylstannanes,[5-7] which can be used in nearly stoichiometric amounts. These reactions have the additional advantage of being conducted under nonreducing conditions. Although this approach to C–C bond formation is very general with respect to tolerance of complex functionality in the substrate, it is quite limited with respect to substitution which can be utilized in the allylstannanes. For example, allylstannanes having methyl substitution at C_3 as in **1** and **2** cannot generally be employed in such reactions since these materials undergo very facile allylic rearrangement (eq 1 and 2) to their thermodynamically more stable isomers **3** and **4** under the reaction conditions.[8] We record herein a solution to this problem.

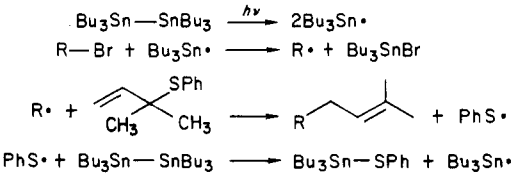


The reaction process for the case of "prenylation" is summarized in eq 3 below. Thus, irradiation of substrates in the presence of 3-methyl-3-(phenylthio)-1-butene[9] (**5**) and hexabutylditin leads to the production of the desired "prenylated" products in fair to good yields.[10] As substrates, alkyl halides, selenides, and mixed thionocarbonates have all been investigated, although best results are obtained with alkyl bromides and iodides.[11] Such reactions have also been accomplished with 3-(phenylthio)-1-butene (**6**); as expected, cis–trans mixtures of olefinic products result in this case, as shown in eq 4 below. Representative results for reactions of **5** and **6** with alkyl halides are tabulated in Table I.





A plausible mechanistic rationale, which in fact served as the working hypothesis for the development of this process, can be written as follows:[12]



Clearly, the success of this reaction depends on a critical balance between relative rates of the chain-carrying steps shown and reasonable alternative reactions which are well precedented. For example, Ueno has demonstrated that sulfides such as **5** react with stannyl radicals in a formal S_H2' process to give allylstannanes.[13] Thus, competition

(1) For a recent and very readable account of radical reactions in organic synthesis, note: Hart, D. J. *Science (Washington, D.C.)* **1984**, *234*, 883.

(2) For recent reviews of hexenyl radical cyclizations, note: (a) Beckwith, A. L. J.; Ingold, K. U. In "Rearrangements in Ground and Excited States"; deMayo, P., Ed.; Academic Press: New York, 1980; pp 162–283. (b) Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073. (c) Surzur, J. M. In "Reactive Intermediates"; Abramovitch, A. A., Ed.; Plenum Press: New York, 1981; Vol. 2, Chapter 3.

(3) For recent examples of various free radical cyclization processes, note: (a) Curran, D. P.; Rakiewicz, D. M. *J. Am. Chem. Soc.* **1985**, *107*, 1448. (b) Burnett, D. A.; Choi, J.-K.; Hart, D. J.; Tsai, Y.-M. *J. Am. Chem. Soc.* **1984**, *106*, 8201. (c) Chuang, C.-P.; Hart, D. *J. J. Org. Chem.* **1983**, *48*, 1782. (d) Stork, G.; Mook, R. *J. Am. Chem. Soc.* **1983**, *105*, 3720. (e) Stork, G.; Baine, N. H. *Ibid.* **1982**, *104*, 2321. (f) Stork, G.; Sher, P. M. *Ibid.* **1983**, *105*, 6765. (g) Stork, G.; Mook, R.; Biller, S. A.; Rynchnovsky, S. D. *Ibid.* **1983**, *105*, 3741. (h) Corey, E. J.; Pyne, S. G. *Tetrahedron Lett.* **1983**, *24*, 2821. (i) Hart, D. J.; Kanai, K. *J. Am. Chem. Soc.* **1983**, *105*, 1225. (j) Bachi, M. D.; Frolow, F.; Hoornaert, C. *J. Org. Chem.* **1983**, *48*, 1841. (k) Clive, D. L. J.; Beaulieu, P. L. *J. Org. Chem.* **1984**, *49*, 1313.

(4) (a) Giese, B.; Groninger, K. *Tetrahedron Lett.* **1984**, *25*, 2743. (b) Giese, B.; Gonzâlez-Gômez, J. A.; Witzel, T. *Ibid.* **1984**, *23*, 69. (c) Giese, B.; Heuck, K.; Lenhardt, H.; Lüning, U. *Chem. Ber.* **1984**, *117*, 2132. (d) Giese, B.; Depuis; *J. Angew. Chem., Int. Ed. Engl.* **1983**, *23*, 896. (e) Giese, B.; Dupuis, J.; Hasskerl, T.; Meirner, J. *Tetrahedron Lett.* **1983**, *24*, 703. (f) Kozikowski, A. P.; Scripko, J. *Tetrahedron Lett.* **1983**, *24*, 2051. (g) Danishefsky, S.; Taniyama, E.; Webb, R. R., II. *Ibid.* **1983**, *24*, 11. (h) Kozikowski, A. P.; Nieduzak, T. R.; Scripko, J. *Organometallics* **1982**, *1*, 675. (i) Burke, S. D.; Fobare, W. F.; Armistead, D. M. *J. Org. Chem.* **1982**, *47*, 3348. (j) Giese, B.; Harler, H.; Zwick, W.; *Tetrahedron Lett.* **1982**, *23*, 931. (k) Giese, B.; Kretzschmar, G.; Meixner, J. *Chem. Ber.* **1980**, *113*, 2787. (l) Giese, B.; Heuck, K. *Ibid.* **1979**, *112*, 3759. (m) Giese, B.; Meister, J. *Ibid.* **1977**, *110*, 2588.

(5) Keck, G. E.; Yates, J. B. *J. Am. Chem. Soc.* **1982**, *104*, 5829.

(6) For applications in the total synthesis of (±)-perhydrohistrionicotoxin and (+)-pseudomonic acid C, note: (a) Keck, G. E.; Yates, J. B. *J. Org. Chem.* **1982**, *47*, 3590. (b) Keck, G. E.; Kachensky, D. F.; Enholm, E. J. *J. Org. Chem.* **1984**, *49*, 1462.

(7) For recent examples of C–C bond forming reactions involving similar radical addition–fragmentation strategies, note: (a) Baldwin, J. E.; Adlington, R. M.; Basak, A. *J. Chem. Soc., Chem. Commun.* **1984**, 1284. (b) Baldwin, J. E.; Kelly, D. R.; Ziegler, C. B. *Ibid.* **1984**, 133.

(8) Keck, G. E.; Yates, J. B. *J. Organomet. Chem.* **1983**, *248*, C21.

(9) Lewis, S. N.; Miller, J. J.; Winstein, S. *J. Org. Chem.* **1972**, *37*, 1478.

(10) (a) A representative experimental procedure for the conversion of **19** to **17** is summarized here. A solution of 0.99 g (3.00 mmol) of **19**, 1.48 g (9.00 mmol) of sulfide **5**, and 2.62 g (4.50 mmol) of hexabutylditin in 5 mL of benzene was placed in a screw-top Pyrex test tube and degassed with argon for 20 min. The tube was sealed and irradiated with a 450-W Hanovia lamp equipped with a Pyrex filter for 13 h, at which time no starting material remained by TLC analysis. The crude reaction mixture was treated overnight with excess $KF{\cdot}2H_2O$ in acetonitrile and then filtered through a pad of alumina, concentrated in vacuo, and chromatographed over silica gel to afford 0.62 g (67%) of pure **17**. (b) Satisfactory C, H combustion analyses or high resolution mass spectra were obtained on all products shown. (c) No reaction was observed in the absence of hexabutylditin. (d) Poor results (very low conversion of starting materials to products) were obtained by using chemical (AIBN, 80 °C) initiation, perhaps due to short chain lengths for the overall process.

(11) Thionocarbonates were found to be quite unreactive. Phenyl selenides do react, but such reactions darken markedly and must be worked up and restarted to achieve complete consumption of starting materials.

(12) A variety of initiation steps are plausible here; only one possibility is shown. For the use of such ditins as initiators for analogous reactions, note ref 3f and 7b.

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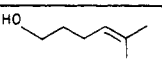
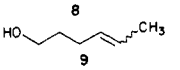
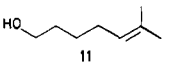
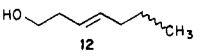
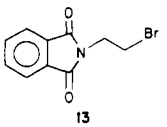
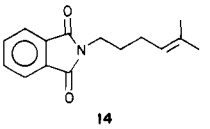
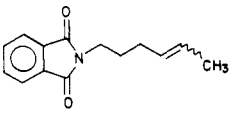
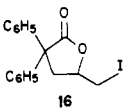
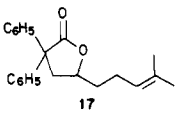
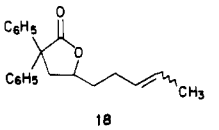
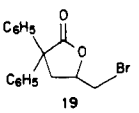
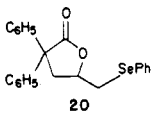
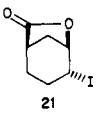
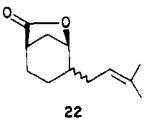
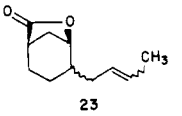
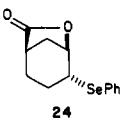
Table I. Isolated Yields for Reactions with Sulfides 5 and 6

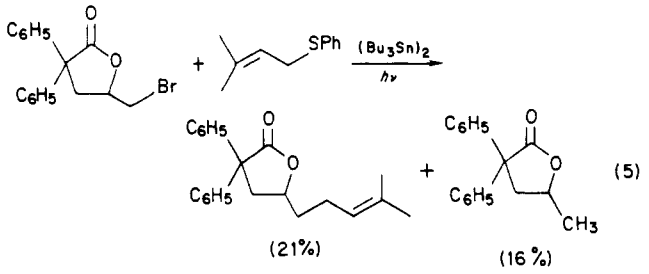
substrate	sulfide	product	yield, % (trans/cis ratio)
bromoethanol (7)	5	 8	74
7	6	 9	60 (3.2)
3-bromopropanol (10)	5	 11	69
10	6	 12	68 (3.8)
 13	5	 14	33
13	6	 15	57 (3.3)
 16	5	 17	58
16	6	 18	68 (2.6)
 19	5	17	59
19	6	18	67 (2.5)
	5	17	28
 20			
20	6	18	36 (2.7)
 21	5	 22	60
21	6	 23	67
 24	5	22	42
24	6	23	64

between pathways involving reaction with substrate (via halogen abstraction) vs. S_H2' reaction with the allylic sulfide is an a priori possibility for stannyl radicals under these reaction conditions. Fortunately, with most substrates examined, halogen abstraction is the preferred pathway. However, if halogen abstraction is slow, as with *aryl* bromides or iodides, then reaction of **5** or **6** with stannyl radicals is apparently the preferred pathway. Thus, only reduction products were obtained upon attempted reaction with *p*-(dimethylamino)bromobenzene and *o*-iodobenzoic acid.[14] Irradiation of hexabutylditin and **5** in the absence of substrate was shown, as expected, to result in the production of stannanes **3** and **4**. These stannanes could presumably react with carbon-centered radicals by transfer of hydrogen,[8] leading to reduced products. Minor amounts of reduction products were also detected with most alkyl substrates examined.

(13) (a) Ueno, Y.; Aoki, S.; Okawara, M. *J. Am. Chem. Soc.* **1979**, *101*, 5414. (b) For other examples of radical reactions involving allylic sulfides, note: (i) Ueno, Y.; Chino, K.; Okawara, M. *Tetrahedron Lett.* **1982**, *23*, 2575. (ii) Barton, D. H. R.; Crich, D. *Ibid.* **1984**, *25*, 2787.

(14) It is at present unclear whether allylically rearranged sulfides, stannanes **3** or **4**, or both are the source of hydrogen in such reductions.

Attempts to extend this process to sulfides bearing alkyl substitution at the allylic terminus have been unsuccessful. For example, if 1-(phenylthio)-3-methyl-2-butene (the allylically transposed isomer of **5**) is reacted with substrate **19**, then no products from direct S_H2' reaction are found: only **17** and the reduction product from **19** are isolable, albeit in poor yield.[15] (Note eq 5).



(5)

Although the yields of this process are not as high as for allylation using allyltri-*n*-butylstannane, the success of this rather complex chain process despite numerous a priori reasonable side reactions is noteworthy, as is the separation of chain-carrying steps[16] in the mechanism. The results described herein demonstrate that the design of complex free radical chains for use in organic synthesis is feasible, and further investigations along such lines are in progress in our laboratories.

Acknowledgment. We thank the National Science Foundation for generous support of this research.

Registry No. **5**, 34043-60-2; **6**, 701-75-7; **7**, 540-51-2; **8**, 42272-94-6; *cis*-**9**, 928-91-6; *trans*-**9**, 928-92-7; **10**, 627-18-9; **11**, 13175-35-4; *cis*-**12**, 50273-95-5; *trans*-**12**, 25143-94-6; **13**, 574-98-1; **14**, 99097-66-2; *cis*-**15**, 99097-67-3; *trans*-15, 99097-68-4; **16**, 53560-49-9; **17**, 99097-69-5; *cis*-**18**, 99097-70-8; *trans*-18, 99097-71-9; **19**, 83160-36-5; **20**, 83160-38-7; **21**, 19914-92-2; **22**, 99097-72-0; **23**, 99097-73-1; **24**, 71404-67-6; hexabutylditin, 813-19-4.

(15) (a) The production of **17** may be rationalized by allylic rearrangement of 1-(phenylthio)-3-methyl-2-butene to give **5**, followed by reaction of **5** with a carbon-centered radical generated from **19**. For leading references on the rearrangement of allylic sulfides, note: Kozikowski, A. P.; Huie, E.; Springer, J. P. *J. Am. Chem. Soc.* **1982**, *104*, 2059 and references therein. (b) Similar results were obtained for reaction of **19** with 1-(phenylthio)-2-butene (the allylically transposed isomer of **6**). In this case, 42% of the reduced product was obtained, along with 7% of **18** and 7% of the product of direct S_H2' substitution.

(16) In free radical allylation using allylstannanes, C–C bond formation and generation of substrate radicals are inevitably linked to one another, since chain-carrying stannyl radicals are generated directly from the C–C bond forming event. In the present process, C–C bond formation and generation of chain-carrying stannyl radicals occur as separate and discrete steps in the chain.

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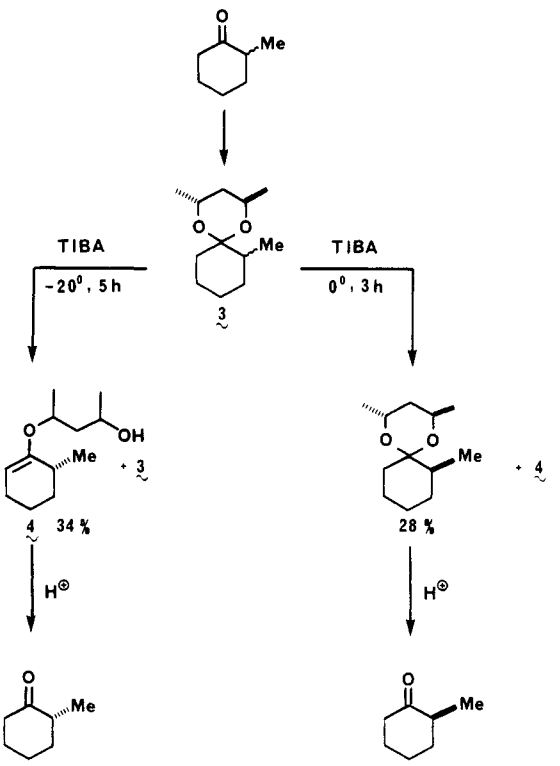
Resolution of Ketones via Chiral Acetals. Kinetic Approach

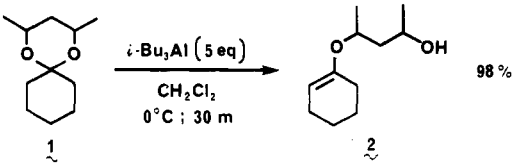
Summary: When a chiral acetal is treated with triisobutylaluminum at low temperature, one diastereoisomer reacts much faster than the other and the resulting enol ether is transformed to optically pure ketone.

Sir: In contrast to the generation of optically active carbonyl compounds by asymmetric alkylation, which is now used with great frequency in synthesis and for which many selective reagents are known,[1] methods for the efficient resolution of carbonyl compounds are still quite limited. Classical approaches to the optical activation of ketones are not always reliable.[2,3] This communication reports the successful development of a new type of resolution for ketones based on a kinetic approach.

Scheme I



We have recently described the nucleophilic cleavage of chiral acetals derived from (–)-(2*R*,4*R*)-2,4-pentanediol using organometallic reagents.[4] By studying this reaction in detail, it was discovered that an enol ether was formed under certain reaction conditions. Thus, treatment of acetal **1** with triisobutylaluminum (TIBA) in dichloromethane at 0 °C for 30 min produced the enol ether **2** in



(1) For reviews, see: "Asymmetric Synthesis", Vol. 2 and 3, Morrison, J. D., Ed.; Academic Press: New York, 1983 and 1984.

(2) For reviews, see: Wilen, S. H. In "Topics in Stereochemistry"; Eliel, E. L., Allinger, N. L., Eds.; Wiley-Interscience: New York, 1971; Vol 6, p 107. See also: Newman, P. "Optical Resolution Procedures for Chemical Compounds"; Optical Resolution Information Center: Manhattan College, New York, 1984; Vol 3, p 479.

(3) Recently Johnson reported an elegant resolution technique of ketone based on the addition of an optically pure sulfoximine: Johnson, C. R.; Zeller, J. R. *J. Am. Chem. Soc.* **1982**, *104*, 4021; *Tetrahedron* **1984**, *40*, 1225.

(4) (a) Mori, A.; Fujiwara, J.; Maruoka, K.; Yamamoto, H. *J. Organomet. Chem.* **1985**, *285*, 83. Mori, A.; Fujiwara, J.; Maruoka, K.; Yamamoto, H. *Tetrahedron Lett.* **1983**, *24*, 4581. Mori, A.; Maruoka, K.; Yamamoto, H. *Ibid.* **1984**, *25*, 4421. See also: (b) Bartlett, P. A.; Johnson, W. S.; Elliott, J. D. *J. Am. Chem. Soc.* **1983**, *105*, 2088. (c) Johnson, W. S.; Elliott, R.; Elliott, J. D. *Ibid.* **1983**, *105*, 2904. (d) Elliott, J. D.; Choi, V. M. F.; Johnson, W. S. *J. Org. Chem.* **1983**, *48*, 2294. (e) Choi, V. M. F.; Elliott, J. D.; Johnson, W. S. *Tetrahedron Lett.* **1984**, *25*, 591. (f) Ghribi, A.; Alexakis, A.; Normant, J. F. *Ibid.* **1984**, *25*, 3083. (g) Lindell, S. D.; Elliott, J. D.; Johnson, W. S. *Ibid.* **1984**, *25*, 3947. (h) Johnson, W. S.; Crackett, P. H.; Elliott, J. D.; Jagodzinski, J. J.; Lindell, S. D.; Natarajan, S. *Ibid.* **1984**, *25*, 3951. (i) Johnson, W. S.; Edington, C.; Elliott, J. D.; Silverman, I. R. *J. Am. Chem. Soc.* **1984**, *106*, 7588.

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