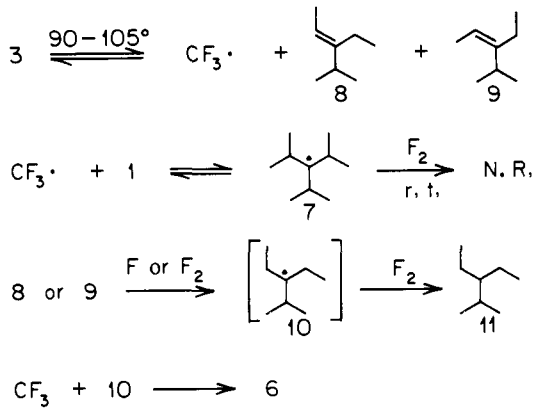
Scheme II



Radical **3** is prepared by bubbling undiluted F_2 into the neat mixture of **1** + **2** in an narrow-mouth Teflon-FEP[13] bottle, at a rate such that most of the F_2 reacts (**HOOD!**); we have had no fires or explosions. Reaction of **1** and **2** and formation of **3** and **4** can be followed by GC;[14] **3** reaches a maximum in 15–20 h and then declines by about 3% per h. alkene **1** reacts faster than **2** and gives a higher yield of **3**.

When dilute (ca. 10^{-3} M) **3** in excess **1** (or **1** + **2**) is heated to 90–100 °C, its spectrum disappears over several hours and is replaced by that of tris-(F-isopropyl)methyl (*F*-2,4-dimethyl-3-isopropyl-3-pentyl) (**7**), $G = 2.003\,02$, shown (recorded at room temperature) in Figure 2. The ESR spectrum of **7** shows splitting by three equivalent β-F's, $a = 2.38$ G, and 18 equivalent γ-F's, $a = 2.65$ G; these small couplings fit a structure in which the β-F's are locked in the nodal plane of the sp^2 carbon but are not consistent with radical **5**, proposed by von Halasz et al.[3] to explain the formation of **6**, since **5** has an α-F that should cause a splitting of about 65 G.[11] Radical **7** fails to react even with 1.3 atm of F_2 over 300 h at room temperature.[15] Inspection of a model shows that both faces of its trivalent central carbon are completely shielded by the close-packed CF_3's. The rate of conversion of **3** into **7** (in excess 1) is indistinguishable from the rate of unimolecular decomposition of **3**. The disappearance of **3** and **7** was followed by ESR in *F*-2-methylpentane solution, using excess I_2 to trap the CF_3's, and showed first-order kinetics, with half-lives of 60 and 110 min, respectively, at 100 °C. The formation of **7** from **3** is necessarily an intermolecular process. While our results do not exclude the intramolecular 1,2-CF_3 shift proposed by von Halasz et al.,[3] we prefer to accept the rule that 1,2-alkyl shifts occur in free radicals only by elimination and readdition[16] and propose that perfluoroalkane **6** arises from **1** or **2** as shown in Scheme II. CF_3 radicals from β-scission of **3** may "park" on **1** while *F*-alkenes **8** and **9** react with F_2 to form the intermediate F-3-isopropyl-3-pentyl (**10**). Radical **10** may then react with F_2 to give **11** or with a CF_3· to give **6**. Alkenes **8** and **9** are formed in an 8:3 ratio when **3** is heated in air, and **11** is a product of the 104 °C fluorination of **1** + **2**.[17] Elimination–readdition of CF_3·'s during the fluorination, without excessive loss by reaction with F_2, is surprising but possible if dissolved [F_2] at 104 °C is low enough and the rates of reaction of F_2 with **10** and CF_3· are comparable to the rates of reaction of CF_3· with **1** and **10**.

(11) Lloyd, R. V.; Rogers, M. T. *J. Am. Chem. Soc.* **1973**, *95*, 1512–1515.
(12) Maletesta, V.; Forrest, D.; Ingold, K. U. *J. Phys. Chem.* **1978**, *82*, 2370–2373.
(13) "Teflon-FEP" is a trademark of E. I. du Pont de Nemours and Co.
(14) Fomblin N-VAC 40/11 (we thank Montedison USA for a sample) or SE-30 stationary phase; for analysis of **3**, use injector and detector temperatures ≥100 °C.
(15) Analysis by ESR; a 10% change might not have been detected.
(16) Beckwith, A. L. J.; Ingold, K. U. "Rearrangements in Ground and Excited States"; de Mayo, P., Ed.; Academic Press: New York, 1980; Vol. 1, Chapter 4.
(17) New compounds, except radicals, have been fully characterized by F NMR and low-resolution NCI-GC/MS; for C_xF_y compounds with $x > 19$, unit resolution is sufficient to assign a unique composition to any ion. Radical **10** has been identified by ESR.

Acknowledgment. We thank the Green Cross Corporation for financial support and G. Millhauser, G. King, Dr. P. Fajer, Dr. E. Fajer, Dr. P. Krusic, and Prof. L. Dalton for some of the ESR measurements.

Registry No. 1, 30320-27-5; **2**, 30320-26-4; **3**, 93683-27-3; **4**, 50285-18-2; **6**, 50285-19-3; **7**, 93683-28-4; **8**, 58621-72-0; **9**, 58621-71-9; **10**, 93683-29-5; **11**, 354-97-2; F_2, 7782-41-4.

Dimethyl(methylthio)sulfonium Tetrafluoroborate Initiated Organometallic Additions to and Macrocyclizations of Thioketals

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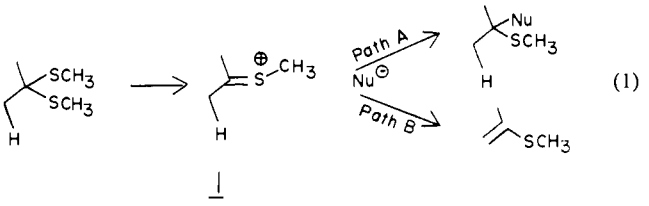
Received July 23, 1984

Thioketals normally provide protection for carbonyl groups against nucleophilic additions. Nevertheless, the ready access of thioketals via lithiated thioacetals makes the notion of their direct reaction for further structural elaboration particularly important.[1-4] In trying to achieve such a goal, two requirements must be met—(1) the initiator used to form a reactive intermediate such as a thionium ion **1** (a thiocarbocation) must be compatible with the nucleophile and (2) the nucleophile must be sufficiently reactive to capture **1** via path A but devoid of basicity to avoid path B (see eq 1). We wish to report that allylstannanes are satisfactory nucleophiles and DMTSF [dimethyl(methylthio)sulfonium fluoroborate (**2**)][2,5,6] is an excellent initiator.



(1)

(1) Trost, B. M.; Vaultier, M.; Santiago, M. L. *J. Am. Chem. Soc.* **1980**, *102*, 7929. Trost, B. M.; Reiffen, M.; Crimmin, M. *J. Am. Chem. Soc.* **1979**, *101*, 257. Pelter, A.; Ward, R. S.; Satyanarayana, P.; Collins, P. *J. Chem. Soc., Perkin Trans. 1* **1983**, 643. Reetz, M. T.; Giannis, A. *Synth. Commun.* **1981**, *11*, 315. Reetz, M. T.; Huttenhain, S.; Walz, P.; Lowe, U. *Tetrahedron Lett.* **1979**, 4971. Kozikowski, A. P.; Ames, A. *J. Am. Chem. Soc.* **1980**, *102*, 860. Brinkmeyer, R. S. *Tetrahedron Lett.* **1979**, 207. Mizyuk, V. L.; Semenovsky, A. V. *Tetrahedron Lett.* **1978**, 3603. Andersen, N. H.; Yamamoto, Y.; Denniston, A. D. *Tetrahedron Lett.* **1975**, 4547. Mukaiyama, T.; Narasaka, K.; Hokonok, H. *J. Am. Chem. Soc.* **1969**, *91*, 4315.
(2) Trost, B. M.; Murayama, E. *J. Am. Chem. Soc.* **1981**, *103*, 6529; *Tetrahedron Lett.* **1982**, *23*, 1047. Kim, J. K.; Pau, J. K.; Caserio, M. C. *J. Org. Chem.* **1979**, *44*, 1544. For reaction with an ortho thio ester, see: Smith, R. A. J.; bin Manas, A. R. *Synthesis* **1984**, 166.
(3) For a few recent examples of generation of thionium ions from sulfoxides and α-chloro sulfides, see: (a) Murayama, E.; Uematsu, M.; Nishio, H.; Sato, T. *Tetrahedron Lett.* **1984**, *25*, 313. (b) Tamura, Y.; Tsugoshi, T.; Annoura, H.; Ishibashi, H. *Synthesis* **1984**, 326. (c) Magnus, P.; Gallagher, T.; Brown, P.; Huffman, J. C. *J. Am. Chem. Soc.* **1984**, *106*, 2105. (d) Hori, M.; Kataoka, T.; Shimizu, H.; Kataoka, M.; Tomoto, A.; Kishida, M. *Tetrahedron Lett.* **1983**, *24*, 3733. (e) Arai, K.; Ohara, Y.; Iizumi, T.; Takakuwa, Y. *Tetrahedron Lett.* **1983**, *24*, 1531. (f) Wada, M.; Shigehisa, T.; Akiba, K. *Tetrahedron Lett.* **1983**, *24*, 1711. (g) Wada, M.; Shigehisa, T.; Kitani, H.; Akiba, K. *Tetrahedron Lett.* **1983**, *24*, 1715. (h) Fleming, I.; Igbal, J. *Tetrahedron Lett.* **1983**, *24*, 327. (i) Lee, T. V.; Okonkwo, J. O. *Tetrahedron Lett.* **1983**, *24*, 323. (j) McKervey, M. A.; Ratananukul, P. *Tetrahedron Lett.* **1983**, *24*, 117. (k) Tamura, Y.; Choi, H. D.; Mizutani, M.; Ueda, Y.; Ishibashi, H. *Chem. Pharm. Bull.* **1982**, *30*, 3574. (l) Khan, H. A.; Paterson, I. *Tetrahedron Lett.* **1982**, *23*, 2399. (m) Tamura, Y.; Maeda, H.; Akai, S.; Ishibashi, H. *Tetrahedron Lett.* **1982**, *23*, 2209.
(4) For some recent reviews on thioacetal anions, see: Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 239. Grobel, B. T.; Seebach, D. *Synthesis* **1977**, 357. Lever, O. W., Jr. *Tetrahedron* **1976**, *32*, 1943.

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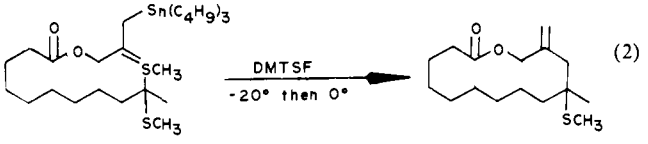
In a typical experimental procedure, a mixture of 1.0 equiv of dimethyl thioketal and 1.1–1.5 equiv of an allylstannane is added to a suspension of 1.05 equiv of DMTSF in methylene chloride at −23 °C. After 1 h, the reaction is quenched by addition of brine and the product is extracted with hexane or ethyl acetate. Final purification is accomplished by flash or thin-layer chromatography. Table I summarizes the examples.

To test the reaction, 2,2-bis(methylthio)heptane (**3**) was employed. Allyl- and methallylstannane reacted smoothly to give excellent yields of the desired adduct at −23 °C. Use of crotylstannane gave the product expected from allyl inversion (see entry 3). Use of an 87:13 *E,Z* mixture of crotylstannanes gave a 1:1 mixture of diastereomers each of which was isolated pure by flash chromatography.

A most striking feature of this reaction is the excellent chemoselectivity. Not only are olefins (entry 9) and acetylenes (entry 4) compatible, but so are esters (entry 8) and even ketones (entries 7 and 10): Indeed the relative order of reactivity of a ketone and thioketal has been totally reversed by this approach. NMR spectroscopy (both ^1H and ^{13}C) as well as chromatography indicate the stereohomogeneity of **5**. The equatorial orientation of the allyl group is assigned on the basis of the expected least hindered attack by the allylstannane.

The reaction depends upon (1) steric factors, (2) the ease of formation of the thionium ion, and (3) the nature of the organometallic. For example, crotylstannane reacts more slowly than methallylstannane and an internal thioketal such as **4** (entry 5) reacts slightly slower than a terminal thioketal such as **3** (entry 1). A thioacetal (as in entry 11) reacts much slower than a thioketal; nevertheless, increasing the ease of formation of the thionium ion by addition of a conjugating group (entry 12) enhances the reactivity of the thioacetal. The poorer Lewis basicity of a phenyl thioacetal compared to an alkyl thioacetal makes the former unsatisfactory. More reactive allylorganometallics were avoided because of the desire for chemoselectivity.[7] Less reactive allylsilanes do react but in less than satisfactory yields.[8] For example **4** gives an 85% yield of 4-allyl-4-(methylthio)heptane with allyltri-*n*-butylstannane at -23 °C but only a 33% yield with allyltrimethylsilane even allowing the reaction to proceed at 0 °C.

The high chemoselectivity of this DMTSF-initiated condensation translates into a facile macrocyclization (0.01 M concentration) in 46-48% yields as shown in eq 2 and 3. Such a strategy

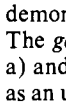
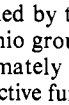


(2)

benefits from the reactivity profile of a *gem*-thio grouping as demonstrated by the synthesis of the macrolide system in eq 3. The *gem*-thio group first facilitates nucleophilic behavior (step a) and ultimately electrophilic behavior (step d) and also serves as an unreactive functionality for intermediary steps b and c. Such control of reactivity should be a powerful tool in synthetic design.

The chemoselectivity of DMTSF as a thiophilic reagent even in the presence of as strong a nucleophile as an allylstannane is remarkable. Most importantly, the higher reactivity of a thionium ion compared to a carbonyl group is established (i.e., a thionium ion may be considered a "super carbonyl equivalent"). The ability to desulfurize the products leads to an equivalent of reductive

Table I. Addition of Allylstannanes to Thioketals and Thioacetals

entry	thioketal or thioacetal	allylstannane	product[e]	isolated yield[a]
1	 **3**			89 (100)
2				78 (90)
3				73 (76)[b,c]
4			**5**	62 (85)
5	**4**			57 (84)[c]
6				86 (91)

entry	thioketal or thioacetal	allylstannane	product[e]	isolated yield[a]
7				53 (56)
8				76
9				87
10			**5**	80 (96)
11				59 (92)[d]
12				76 (100)

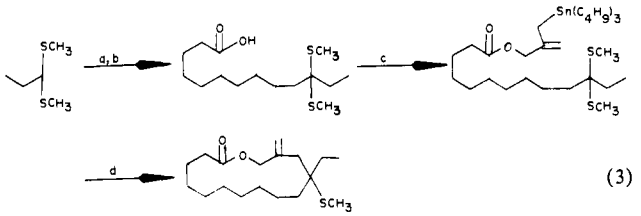
[a] Yield in parenthesis is based upon recovered starting material. [b] The two diastereomers were separated by flash chromatography in 35% and 38% yield, respectively, for a combined yield of 73%. [c] This reaction was performed for 1 day at room temperature. [d] This reaction was performed at 0 °C for 6 h. [e] All new compounds have been fully characterized by spectral means and elemental composition established by high-resolution mass spectrometry and/or combustion analysis.

(5) Smallcombe, S. H.; Caserio, M. C. *J. Am. Chem. Soc.* **1971**, *93*, 5826. Helmkamp, G. K.; Cassey, H. N.; Olsen, B. A.; Pettitt, D. J. *J. Org. Chem.* **1965**, *30*, 933. Meerwein, H.; Zenner, K. F.; Gipp, R. *Justus Liebigs Ann. Chem.* **1965**, *688*, 67.

(6) For triggering nucleophilic additions to olefins, see: Trost, B. M.; Martin, S. J. *J. Am. Chem. Soc.* **1984**, *106*, 4263. Trost, B. M.; Shibata, T. *J. Am. Chem. Soc.* **1982**, *104*, 3225. Trost, B. M.; Shibata, T.; Martin, S. J. *J. Am. Chem. Soc.* **1982**, *104*, 3228. Caserio, M. C.; Kim, J. K. *J. Am. Chem. Soc.* **1982**, *104*, 3231.

(7) Use of allylmagnesium chloride in the case of **3** led to 39% yield of isomeric elimination products (eq 1, path b) in addition to 32% of the desired product (eq 1, path a).

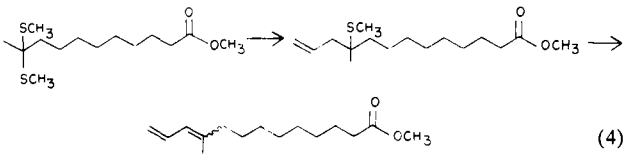
(8) Cf. ref 3g.



(3)

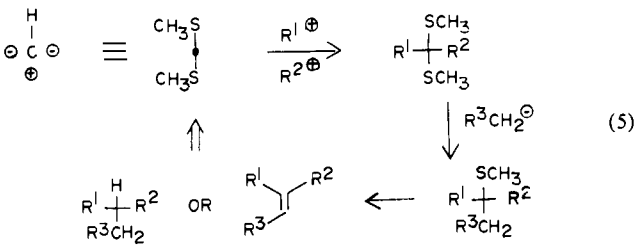
(a) nC_4H_9Li, THF, $Br(CH_2)_8Br$. (b) $LiCH_2CO_2Li$, THF. (c) $(Im)_2CO$, THF $(C_4H_9)_3SnCH_2(C{=}CH_2)CH_2OH$. (d) DMTSF, CH_2Cl_2.

alkylation of a carbonyl group. The ease of elimination by oxidation ($NaIO_4$, CH_3OH, H_2O, room temperature, 87%) and thermolysis ($PhCH_3$, $CaCO_3$, reflux, 97%) as in eq 4 makes the



(4)

overall reaction a convenient procedure for alkylation–elimination. Combined with the ready availability of thioacetals and thioketals by alkylation of lithiated bis(methylthio)methane, the direct and selective DMTSF-induced reactions of the thioketals and -acetals streamlines their application in synthesis (see eq 5).



(5)

Acknowledgment. We thank the National Science Foundation for their generous support of our programs.

Registry No. **3**, 75920-72-8; **4**, 94202-85-4; **5**, 94203-00-6; 7,7-bis(methylthio)-2-octyne, 94202-84-3; 3,3-bis(methylthio)-1-phenyl, 94202-86-5; 11,11-bis(methylthio)-2-dodecanone, 94202-87-6; methyl 10,10-bis(methylthio)undecanoate, 94202-88-7; 11,11-bis(methylthio)-12-methyl-1-tridecene, 94202-89-8; 3,3-bis(methylthio)-5α-androst-17-one, 56253-73-7; 1,1-bis(methylthio)hexane, 82726-67-8; α,α-bis(methylthio)toluene, 14252-44-9; tributylallylstannane, 24850-33-7; tributylmethylallylstannane, 67883-62-9; (*E*)-tributyl-2-butenylstannane, 35998-93-7; (*Z*)-tributyl-2-butenylstannane, 35998-94-8; 4-methyl-4-(methylthio)-1-nonene, 94202-90-1; 2,4-dimethyl-4-(methylthio)-1-nonene, 94202-91-2; 3,4-dimethyl-4-(methylthio)-1-nonene (isomer 1), 94202-92-3; 3,4-dimethyl-4-(methylthio)-1-nonene (isomer 2), 94202-93-4; 7-methyl-(methylthio)-2-decyn-9-ene, 94202-94-5; 4-propyl-4-(methylthio)-3-methyl-1-heptene, 94202-95-6; 4-methyl-4-(methylthio)-6-phenyl-1-hexene, 94202-96-7; 11-methyl-11-(methylthio)-13-tetradecen-2-one, 94202-97-8; methyl 10-methyl-10-(methylthio)-12-tridecenoate, 94202-98-9; 4-isopropyl-4-(methylthio)-1,13-tetradecadiene, 94202-99-0; 4-(methylthio)-1-nonene, 94203-01-7; 1-phenyl-1-(methylthio)-3-butene, 63297-72-3; allyltrimethylsilane, 762-72-1; 2-[(tributylstannane)methyl]-2-propenyl 10,10-bis(methylthio)undecanoate, 94203-02-8; 1-oxa-2-oxo-11-methyl-11-(methylthio)-13-methylenecyclotetradecane, 94203-03-9; 1,1-bis(methylthio)propane, 57093-94-4; 11,11-bis(methylthio)tridecanoic acid, 94203-04-0; 2-[(tributylstannane)methyl]-2-propenyl] 11,11-bis(methylthio)tridecanoate, 94203-05-1; 1-oxa-2-oxo-11-ethyl-11-(methylthio)-13-methylenecyclopentadecane, 94234-88-5; 1,8-dibromooctane, 4549-32-0; lithium lithioacetate, 60419-47-8; methyl 10-methyl-10,12-tridecadienoate, 94203-07-3; 4-allyl-4-(methylthio)heptane, 94203-08-4; DMTSF, 5799-67-7; $(C_4H_9)_3SnCH_2(C{=}CH_2)CH_2OH$, 94203-06-2.

Supplementary Material Available: Detailed experimental procedure for entries 8 and 10 in Table I (1 page). Ordering information appears on any current masthead page.

Chemoselectivity in Palladium-Mediated Cycloadditions of Substituted Trimethylenemethanes

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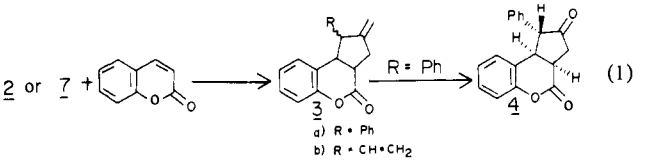
Received August 20, 1984

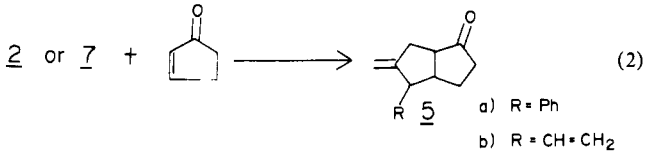
The utility of cycloadditions depends upon the acceptability of diverse substituents on both reaction partners. For Pd-mediated [3 + 2] cycloadditions, we have established a broad base of acceptors.[1,2] The compatibility of functional groups on the donor, i.e., on the trimethylenemethane (TMM) conjunctive reagent, would represent a significant development in the applicability of this strategy in complex synthesis.[3] Because of the established nucleophilic nature of the TMM–Pd complex, we were especially interested in substituents possessing functional groups such as a carbonyl or cyano group which offers an alternative reactivity profile such as self-condensation. In addition, unsymmetrical TMM systems raise the spectre of regioselectivity problems. We wish to report the remarkably diverse array of substituents on the TMM unit cannot only be tolerated but also give highly selective cycloadditions.

2-(Trimethylsilyl)methacrolein[4] (**1**) allows ready access to a wide variety of substituted TMM precursors ranging from cyano to acetoxy as summarized in Scheme I. Initial work focused on the phenyl analogue **2**, which undergoes cycloaddition to coumarin under our usual conditions[1] [9 mol % $(Ph_3P)_4Pd$, $PhCH_3$, 110 °C, 76% yield] to form a 70:30 mixture of cycloadducts **3a**[5] (see eq 1). That the cycloadducts differ only in the stereochemistry of



(1)

the phenyl ring is established by ozonolysis, which gives an isomeric mixture of products. Purification by TLC effects equilibration to a single regio- and stereoisomer **4**[5], mp 174–177 °C, in 98% yield. The structure of **4** is unambiguously established by X-ray crystallography.[6] In employing cyclopentenone as a trap (eq 2),



(2)

a somewhat improved yield arises when the catalyst is switched

(1) Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1983**, *105*, 2315, 2326.

(2) For some other recent [3 + 2] cycloadditions, see: Binger, P.; Brinkmann, A.; Richter, W. J. *Tetrahedron Lett.* **1983**, *24*, 3599. Noyori, R.; Yamakawa, M.; Takaya, H. *Ibid.* **1978**, 4823. Little, R. D.; Stone, K. J. *J. Am. Chem. Soc.* **1983**, *105*, 6976. Fierz, G.; Chidgey, R.; Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 410. Danheiser, R. L.; Carini, D. J.; Basak, A. *J. Am. Chem. Soc.* **1981**, *103*, 1604. Boger, D. L.; Brotherton, C. E. *J. Am. Chem. Soc.* **1984**, *106*, 805.

(3) For reviews, see: Trost, B. M. *Chem. Soc. Rev.* **1982**, *11*, 141. Paquette, L. A. *Top. Curr. Chem.* **1984**, *119*, 1.

(4) (a) Prepared in 71% yield by swern oxidation of 2-[(trimethylsilyl)-methyl]allyl alcohol [Trost, B. M.; Chan, D. M. T.; Nanninga, T. N. *Org. Synth.* **1984**, *62*, 58]. (b) See: Chan, D. M. T. Ph.D. Thesis, University of Wisconsin, Madison, 1982.

(5) All new compounds have been fully characterized spectrally and elemental composition determined by combustion analysis and/or high-resolution mass spectroscopy.

(6) We thank Dr. Ken Haller for aid in this determination.

(7) We assume $n = 2$, 3, or 4 so that 5–7 equiv of triisopropyl phosphite relative to palladium acetate is employed.

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