160.0553, found 160.0549.

Anal. Calcd for $C_7H_{12}O_2S$: C, 52.50; H, 7.50. Found: C, 52.77; H, 7.56.

(±)-3,3-Dimethyl-2-tetrahydrothiopheneacetic acid (50): 587 mg (3.37 mmol, 75%) from **41**; mp 55–56 °C (hexane–ether); IR ($CHCl_3$) 3500–2300, 1715, 1390, 1370 cm^{-1}; ^1H NMR ($CDCl_3$) δ 11.10 (bs, 1 H), 3.33 (dd, 1 H, J = 10.8, 3.7 Hz), 2.81 (m, 2 H), 2.75 (dd, 1 H, J = 16.5, 3.7 Hz), 2.43 (dd, 1 H, J = 16.5, 10.8 Hz), 1.83 (m, 2 H), 1.11 (s, 3 H), 0.96 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 178.7, 51.8, 44.3, 44.1, 237.4, 28.7, 26.0, 20.9; HRMS m/e for $C_8H_{14}O_2S$ calcd 174.0714, found 174.0709.

Anal. Calcd for $C_8H_{14}O_2S$: C, 55.14; H, 8.09. Found: C, 55.84; H, 8.09.

(±)-2-Thiaspiro[4.5]decane-1-acetic acid (51): 683 mg (3.20 mmol, 71%) from **42**; mp 101–102 °C (hexane–ether); IR (thin film) 3520–2880, 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 12.40–11.60 (bs, 1 H), 3.36 (dd, 1 H, J = 11.4, 3.6 Hz), 2.81 (m, 2 H), 2.76 (dd, 1 H, J = 15.9, 3.6 Hz), 2.40 (dd, 1 H, J = 15.9, 11.4 Hz), 1.93 (m, 1 H), 1.77 (m, 1 H), 1.57–1.25 (cplx, 10 H); ^{13}C NMR ($CDCl_3$) δ 178.5, 64.0, 50.8, 47.8, 38.0, 34.9, 30.6, 28.2, 26.4, 23.3, 23.1; HRMS m/e for $C_{11}H_{18}O_2S$ calcd 214.1022, found 214.1006.

Anal. Calcd for $C_{11}H_{18}O_2S$: C, 61.65; H, 8.47. Found: C, 61.84; H, 8.35.

(±)-4,4-Dimethyl-2*H*-tetrahydrothiopyran-2-acetic acid (52): 662 mg (3.52 mmol, 78%) from **43**; mp 96–97 °C (hexane–ether); IR ($CHCl_3$) 3500–2100, 1720, 1395, 1375 cm^{-1}; ^1H NMR ($CDCl_3$) δ 11.35 (bs, 1 H), 3.31 (m, 1 H), 2.91 (dt, 1 H, J = 13.5, 2.7 Hz), 2.44 (m, 3 H), 1.66 (m, 2 H), 1.44 (dt, 1 H, J = 13.2, 3.9 Hz), 1.24 (t, 1 H, J = 12.6 Hz), 0.93 (s, 3 H), 0.91 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 177.7, 46.8, 40.9, 39.0, 33.7, 33,3, 30.6, 25.4, 23.7; HRMS m/e for $C_9H_{16}O_2S$ calcd 188.0871, found 188.0870.

Anal. Calcd for $C_9H_{16}O_2S$: C, 57.42; H, 8.56. Found: C, 57.35; H, 8.64.

(±)-2-Methyl-2*H*-tetrahydrothiopheneacetic acid (53): 576 mg (3.60 mmol, 80%) from **45**; mp 33–34 °C (pentane–ether); IR ($CHCl_3$) 3700–2200, 1710, 1376 cm^{-1}; ^1H NMR ($CDCl_3$) δ 11.28–10.92 (bs, 1 H), 2.96 (m, 2 H), 2.76 (s, 2 H), 2.11 (m, 2 H), 2.03 (m, 1 H), 1.95 (m, 1 H), 1.56 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 177.2, 53.7, 48.0, 44.0, 33.3, 29.6, 29.5; HRMS m/e for $C_7H_{12}O_2S$ calcd 160.0558, found 160.0557.

Anal. Calcd for $C_7H_{12}O_2S$: C, 52.43; H, 7.55. Found: C, 52.58; H, 7.64.

Reaction Chronology Studies. A. Nitrogen Heterocycles. A 5-mL EtOH solution of 0.57 g (0.62 mL, 5.00 mmol) of ethyl crotonate, 0.54 g (0.55 mL, 5.00 mmol) of benzylamine, 1.06 g (0.74 mL, 5.00 mmol) of 1-iodohexane, and 0.56 g (0.77 mL, 5.50 mmol) of triethylamine was heated at reflux according to the standard heterocyclization procedure. The reaction was monitored by GC analysis of 0.15-μL aliquots removed from the reaction at 30-min intervals during the first 3 h and at 1-h intervals thereafter. After 12 h, all of the benzylamine and 1-iodohexane had been consumed. A significant amount (ca. 75%) of the ethyl crotonate remained unreacted after this time.

B. Sulfur Heterocycles. A mixture of 1.24 g (5.00 mmol) of benzylisothiouronium bromide and 0.88 g (5.00 mmol) of ethyl cinnamate was stirred at 23 °C with 20% KOH in 4:1 water/EtOH. The reaction was monitored by TLC at 15-min intervals for disappearance of the reactants. After 40 min, the ethyl cinnamate had been completely consumed. Benzyl mercaptan and its cinnamate addition product were formed to only a minor extent during this period.

Acknowledgment. Support of this work by the Oklahoma Center for the Advancement of Science and Technology (Nos. HR8-084 and HR1-035) is greatly appreciated. The authors also acknowledge partial support by NSF grants DMB-8603864 and CHE-8718150 in the upgrade of our NMR facility and BSS-8704089 for our mass spectrometry facility.

Supplementary Material Available: High-field ^1H NMR and ^{13}C NMR spectra for **9, 11, 13, 15, 20, 22, 24, 28a, 36, 37, 38, 39, 41, 42, 43,** and **44** (32 pages). Ordering information is given on any current masthead page.

Silyl Group-Transfer-Mediated Serial Michael Additions

Peter G. Klimko[1] and Daniel A. Singleton*

Department of Chemistry, Texas A&M University, College Station, Texas 77843

Received September 26, 1991

Three protocols have been developed for achieving ordered, multiple (serial) Michael reactions initiated by silyl enol ethers or silyl ketene acetals. Anion (fluoride or *m*-chlorobenzoate) catalysis was most effective for reactions of silyl ketene acetal **2** with bis diesters, as in the highly selective formation of **3**. Lewis acid (ZnI_2) catalysis was more general than anion catalysis and afforded stereochemically complementary products with lower selectivity. The use of $SnCl_2$–trityl chloride was effective in reactions of both silyl ketene acetals and silyl enol ethers with bis enones. Very high stereoselectivity was generally observed in the formation of cyclopentanes. The products of serial Michael reactions of bis enones could be regiospecifically cyclized to bicyclic enones. Overall, it was found that the serial Michael reactions initiated by silyl enolates can be used to form efficiently and selectively complex cyclics from simple acyclic precursors.

Introduction

Ordered sequences of Michael reactions, in which each intermediate Michael addition initiates a specific subsequent addition, are a potentially powerful tool for the synthesis of cyclics and polycyclics. The utility of these "serial Michael additions" has been exemplified by the use of sequential inter- and intramolecular Michael reactions in the total syntheses of 3-desmethylaflavinine[2] and dihydronepatolactone,[3] "double Michael" reactions as Diels–Alder equivalents in several syntheses,[4] and the sequencing of up to three intermolecular Michael reactions by Posner.[5] In principle, large and varied arrays of

(1) NSF Pre-doctoral Fellow, 1988–1991.

(2) Danishefsky, S.; Chackalamannil, S.; Harrison, P.; Silvestri, M.; Cole, P. *J. Am. Chem. Soc.* **1985**, *107*, 2474.

(3) Uyehara, T.; Shida, N.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun.* **1989**, 113.

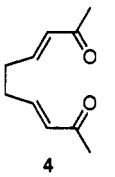
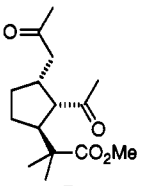
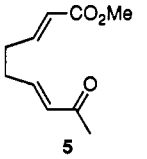
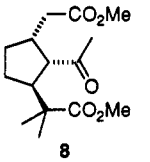
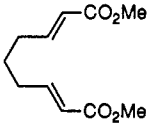
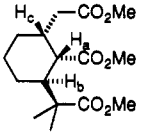
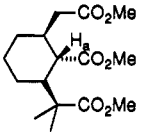
(4) Ihara, M.; Suzuki, M.; Fukumoto, K.; Kabuto, C. *J. Am. Chem. Soc.* **1990**, *112*, 1164, and references cited therein. Roberts, M. R.; Schlessinger, R. H. *J. Am. Chem. Soc.* **1981**, *103*, 724.

0022-3263/92/1957-1733$03.00/0

electrophilic olefins can undergo serial intramolecular Michael additions terminated by protonation or reaction with other electrophiles. However, such sequences are subject to the limitations of Michael methodology. "Traditional" Michael conditions (catalytic amounts of base, protic solvent) have been used in most intramolecular Michael reactions,[6] but are not generally suitable for serial Michael additions due to rapid protonation of intermediate carbanions. "Kinetic" Michael reactions (stoichiometric anions) have been central to the aforementioned serial reactions. However, such sequences must be carefully planned to avoid polymerization, proton transfers, competitive 1,2-addition, and retrograde Michael reactions, and yields have often been low.[7,8]

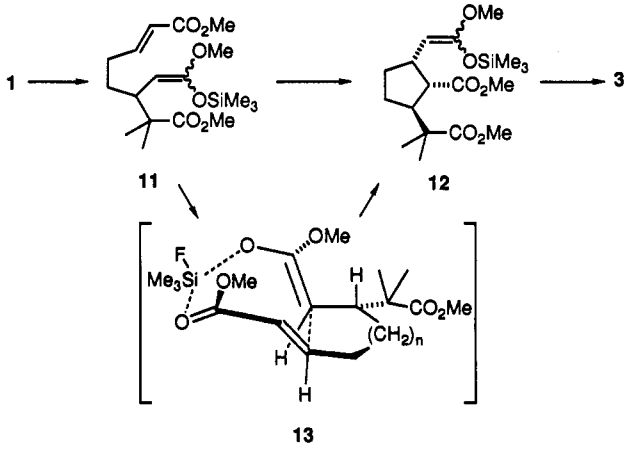
These problems, general to base-promoted Michael reactions, are much less prevalent in Michael additions initiated by silyl enol ethers and silyl ketene acetals. The addition of silyl enolates to activated olefins may be catalyzed by Lewis acids, as in the "Mukaiyama–Michael" reaction,[9] or anions (often fluoride) as in "group-transfer polymerization" (GTP).[10,11] The likely suitability of these reactions for serial Michael additions has been established in recent variations which allow the isolation or subsequent in situ reaction of silyl enol ethers derived from these conjugate additions.[12,13] In this paper, we describe a series of methods for achieving sequential silyl-mediated intermolecular and intramolecular Michael reactions with simple systems containing two activated olefins. We report that these sequences afford simple, efficient, and highly stereoselective methods for the synthesis of cyclopentanes, cyclohexanes, and bicyclics.

Table I. Anion-Catalyzed Serial Michael Additions Initiated by 2

acceptor	procedure[a]	yield	product(s)
 4	B	64%	 7
 5	A	39%[b] (67%)[c]	 8
 6	A B	89%[d] 91%[e]	 9  10

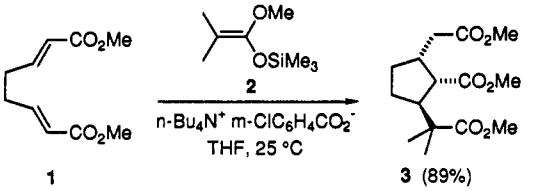
[a] Procedure A: THF, tetrabutylammonium *m*-chlorobenzoate, 25 °C. Procedure B: THF, tris(dimethylamino)sulfonium trimethyldifluorosiliconate, −78 °C. [b] Also recovered were 42% of **5** and 14% of the mono-1,4-addition product. [c] Based on recovered starting material. [d] 1.8:1 ratio of **9**:**10**. [e] 3:1 ratio of **9**:**10**.

Scheme I



Results and Discussion

Anion-Catalyzed Reactions. Our first goal was to achieve serial inter- and intramolecular Michael additions to unsaturated esters analogous to the (completely intermolecular) anion-catalyzed group-transfer polymerizations of acrylates. This was readily accomplished in the reaction of the bis enoate **1** with silyl ketene acetal **2**, a common GTP initiator. Treatment of a mixture of **1** and **2** in THF with either 5 mol % tetrabutylammonium *m*-chloro-



(5) (a) Posner, G. H.; Asirvatham, E. *Tetrahedron Lett.* **1986**, *27*, 663. (b) Posner, G. H.; Webb, K. S.; Asirvatham, E.; Jew, S.; Degl'Innocenti, A. *J. Am. Chem. Soc.* **1988**, *110*, 4754. (c) Posner, G. H.; Shulman-Roskes, E. M. *J. Org. Chem.* **1989**, *54*, 3514.

(6) For examples, see: (a) Stork, G.; Taber, D. F.; Marx, M. *Tetrahedron Lett.* **1978**, 2445. (b) Stork, G.; Shiner, C. S.; Winkler, J. D. *J. Am. Chem. Soc.* **1982**, *104*, 310. (c) Stork, G.; Winkler, J. D.; Saccomano, N. A. *Tetrahedron Lett.* **1983**, 465. (d) Stork, G.; Saccomano, N. *Nouv. J. Chim.* **1986**, *10*, 677. (e) Barton, D. H. R.; Campos-Neves, A. D. S.; Scott, A. I. *J. Chem. Soc.* **1957**, 2698. (f) Alexakis, A.; Chapdlaine, M. J.; Posner, G. H. *Tetrahedron Lett.* **1978**, 4209. (g) Gregory, B.; Bullock, E.; Chen, T. J. *Chem. Soc., Chem. Commun.* **1979**, 1070. (h) Lombardo, L.; Mander, L. N.; Turner, J. V. *J. Am. Chem. Soc.* **1980**, *102*, 6626. (i) Brattesani, D. N.; Heathcock, C. H. *J. Org. Chem.* **1975**, *40*, 2165. (j) Johnson, W. S.; Shulman, S.; Williamson, K. L.; Pappo, R. *J. Org. Chem.* **1962**, *27*, 2015. (k) Trost, B. M.; Suey, C. D.; DiNinno, F. *J. Am. Chem. Soc.* **1979**, *101*, 1284.

(7) An intermolecular Michael addition–intramolecular alkylation or Claisen procedure, termed "Michael-Initiated Ring Closure" by Little, has been used for the synthesis of three- to seven-membered rings, sometimes with excellent diastereoselectivity. (a) Cooke, M. P. *Tetrahedron Lett.* **1979**, 2199. (b) Little, R. D.; Dawson, J. R. *Tetrahedron Lett.* **1980**, 2609. (c) Little, R. D.; Verhre, R.; Monte, W. T.; Nugent, S.; Dawson, J. R. *J. Org. Chem.* **1982**, *47*, 362. (d) Nugent, W. A.; Hobbs, F. W., Jr. *J. Org. Chem.* **1983**, *48*, 5364. (e) Crimmins, M. T.; Mascarella, S. W.; DeLoach, J. A. *J. Org. Chem.* **1984**, *49*, 3033. (f) Yamaguchi, M.; Tsukamoto, M. Hirao, I. *Tetrahedron Lett.* **1985**, 1723. (g) See ref 5a–c.

(8) For a recent review on the intramolecular Michael reaction and other ring-closure methods, see: Thebtaranonth, C.; Thebtaranonth, Y. *Tetrahedron* **1990**, *46*, 1385.

(9) (a) Narasaka, K.; Soai, K.; Mukaiyama, T. *Chem. Lett.* **1974**, 1223. (b) Mukaiyama, T. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 817.

(10) Anion-catalyzed group-transfer polymerization (GTP) of activated olefins: (a) Webster, O. W.; Hertler, Sogah, D. Y.; Farnham, W. B.; RajanBabu, T. V. *J. Am. Chem. Soc.* **1983**, *105*, 5706. (b) Sogah, D. Y.; Hertler, W. R.; Webster, O. W.; Cohen, G. M. *Macromolecules* **1987**, *20*, 1473. (c) Hertler, W. R. *Macromolecules* **1987**, *20*, 2976. (d) Hertler, W. R.; RajanBabu, T. V.; Ovenall, D. W.; Reddy, G. S.; Sogah, D. Y. *J. Am. Chem. Soc.* **1988**, *110*, 5841. (e) Brittain, W. J.; Dicker, I. B. *Macromolecules* **1989**, *22*, 1054. (f) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 994.

(11) Lewis acid-catalyzed GTP of activated olefins: Hertler, W. R.; Sogah, D. Y.; Webster, O. W.; Trost, B. M. *Macromolecules* **1984**, *17*, 1415.

(12) (a) Rajanbabu, T. V. *J. Org. Chem.* **1984**, *49*, 2083. (b) Kita, Y.; Segawa, J.; Haruta, J.; Fujii, T.; Tamura, Y. *Tetrahedron Lett.* **1980**, 3779. (c) Kita, Y.; Segawa, J.; Haruta, J.; Yasuda, H.; Tamura, Y. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1099. (d) Bunce, R. A.; Schlect, M. F.; Dauben, W. G.; Heathcock, C. H. *Tetrahedron Lett.* **1983**, *24*, 4943. (e) Yamamoto, Y.; Maruyama, K.; Matsumoto, K. *Ibid.* **1984**, *25*, 1075.

(13) (a) Kobayashi, S.; Mukaiyama, T. *Chem. Lett.* **1985**, 953. (b) Kobayashi, S.; Mukaiyama, T. *Chem. Lett.* **1986**, 221.

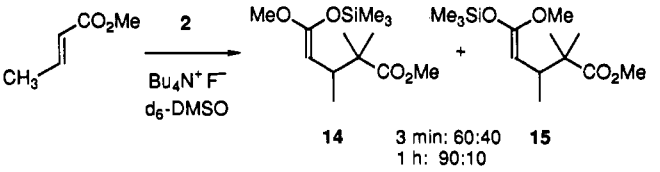
benzoate[14] at 25 °C or 7 mol % tris(dimethylamino)-sulfonium trimethyldifluorosiliconate (TASF)[15] at −78 °C afforded the cyclopentane **3** in 89% and 87% yields, respectively, as the only observable diastereomer. These reactions were conveniently accomplished on multigram scales and were very clean. Small amounts of side products appearing to be oligomers could be minimized using a 50% or greater excess of **2**.

The results of some other anion-catalyzed reactions initiated by **2** are summarized in Table I. The bis enone **4** and the mixed enone/enoate substrate **5** reacted similarly to **1**, except that some starting material was invariably returned due to proton-transfer reactions. Addition of **2** to **5** occurs first at the enone, followed by intramolecular addition of the resulting nucleophile to the enoate. Very high stereoselectivity was consistently observed in the formation of cyclopentanes, but lower stereoselectivity was observed in the formation of cyclohexanes **9** and **10** from **6**.

There are several uncertain points in the mechanism of these reactions (Scheme I). No direct evidence for the presence of **11** could be obtained, and it is unclear whether **11**, a **11**/fluoride complex, or the free enolate anion corresponding to **11** are intermediates. The observation of uncyclized products in the reaction of **5** makes a concerted addition/cyclization unlikely, but no uncyclized products were observed in the reaction of **1**. While silyl ketene acetal **12** could not be isolated, its presence before workup was apparent from the ^{1}H NMR spectrum of a reaction in DMSO-d_6. The major isomer of **12** displayed a characteristic doublet at δ 3.27 and a 3 H singlet at δ 3.38. Varying amounts (20–40%) of a compound displaying a doublet at δ 3.37 and a 3 H singlet at 3.42, consistent with a minor isomer of **12**, were observed. Workup with D_2O gave >96% deuterium incorporation in the expected methylene group of **3**. Interestingly, the protonation of **12** is highly stereoselective; the deuterium specifically replaces only one of the methylene protons.

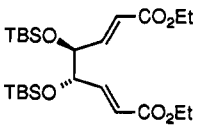
It is appealing to rationalize the stereochemistry of **3**, **7**, **8**, and **9** by a preferred cis substitution of the two reacting centers in the bicyclic transition state **13**, with the large quaternary group trans for steric reasons. A transfer of silicon from nucleophile to electrophile as in **13** was originally proposed for anion-catalyzed group-transfer polymerization.[16] However, the formation of both isomers of **12** casts doubt on a direct transfer of silicon from enolate to enoate, since a cyclic transition state should strongly favor formation of the *Z* silyl ketene acetal. Nonetheless, no conclusion can be reached from this result without excluding equilibration of the isomers of **12** and in the absence of information on the stereochemistry of **11**.

To avoid these complications, the fluoride-catalyzed reaction of **2** with methyl crotonate was carefully examined. In DMSO-d_6, the reaction was complete after 3 min, and complete sets of resonances assignable to a 60:40 mixture of **14** and **15** cleanly appear in the ^{1}H NMR. The equilibration of **14** and **15** was much slower, and the stereochemistries of **14** and **15** were assigned from the expected preference for *Z* silyl ketene acetal in the equilibrium mixture.[17] While incorporation of an s-trans enoate into an eight-membered cyclic transition state leading to **15** may be possible, it seems highly unlikely that such a transition state would compete equally with what should be a much less strained transition state leading to **14**. This result does not exclude a silicon transfer after rate-determining carbon–carbon bond formation.[18]

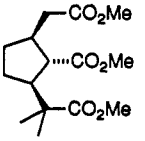


14 3 min: 60:40 **15**
1 h: 90:10

We are left without a simple explanation for the stereoselectivity of these reactions. In recent cuprate-initiated serial Michael additions to **16**, stereoselectivity analogous to that observed in **3** was credited to "rotamer distribution control" by the (*tert*-butyldimethylsilyl)oxy groups.[19] While our results show that rotamer distribution control is not essential for high stereoselectivity in these cyclizations, the silyl group is important in our reactions. Reaction of the lithium enolate of methyl isobutyrate with **1** in THF at −78 °C afforded only a 51% yield of a 64:36 mixture of **17** and **3**, respectively. A similar cyclization of the diethyl ester corresponding to **1** initiated by lithium (trimethylsilyl)benzylamide also afforded a mixture of isomers.[3]

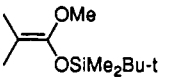


16

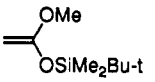


17

Lewis Acid Catalyzed Reactions with Silyl Ketene Acetal Initiators. Although anion catalysis was effective for serial Michael additions initiated by trimethylsilyl ketene acetals, it failed with the *tert*-butyldimethylsilyl ketene acetals **18** and **19** ethyl trimethylsilylacetate, and



18



19

a number of silyl enol ethers. To overcome these limitations and compare the stereochemistry of these reactions under different conditions, we examined Lewis acids as catalysts. The use of the strong Lewis acids $TiCl_4$ and $SnCl_4$ afforded complex mixtures in the reactions of bis enoates **1** and **6** with **2** and **18**. However, use of the mild Lewis acid ZnI_2, an effective catalyst for GTP,[11] afforded good yields of cyclopentanes or cyclohexanes in reactions of **1** or **6** with **2**, **18**, and **19** (Table II). A nice feature of these reactions is that they are stereochemically complementary to the anion-catalyzed reaction, allowing the control of product stereochemistry by choice of reaction conditions. The ZnI_2 catalyzed reactions are unfortunately less stereoselective than the anion catalyzed reactions, but a greater range of silyl ketene acetal initiators may be used.

Initiation with Silyl Enol Ethers. While the above methodology worked well for silyl ketene acetal nucleo-

(14) Dicker, I. B.; Cohen, G. M.; Farnham, W. B.; Hertler, W. R.; Laganis, E. D.; Sogah, D. Y. *Polym. Prepr. (Am. Chem. Soc., Div. Polym. Chem.)* **1987**, *28*, 106.

(15) Varying amounts of tris(dimethylamino)sulfonium bifluoride were present in the samples of TASF used, and it is possible that bifluoride is the active catalyst. No sigificant differences in the stereochemistry or yield of reactions catalyzed by TASF from different sources, or reactions catalyzed by CsF, were observed. For a synthesis of TASF free of the bifluoride, see: Middleton, W. J. In *Organic Syntheses*; Freeman, J. P., Ed.; Wiley: New York, 1990; Collect. Vol. VIII, p 528.

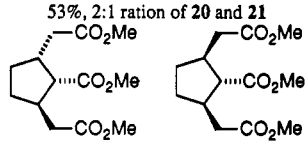
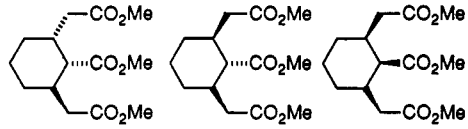
(16) RajanBabu has proposed a similar mechanism for the fluoride-catalyzed addition of silyl ketene acetals to enones. See ref 12a.

(17) Wilcox, C. S.; Babston, R. E. *J. Org. Chem.* **1984**, *49*, 1451.

(18) A similar conclusion has been advanced for certain cases of anion-catalyzed GTP. See ref 8d.

(19) Saito, S.; Hirohara, Y.; Narahara, O.; Moriwake, T. *J. Am. Chem. Soc.* **1989**, *111*, 4533.

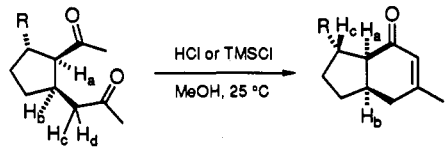
Table II. ZnI_2-Catalyzed Serial Michael Additions[a]

acceptor	initiator	yields and products
1	18	82%, 2:1 ratio of **17** and **3**
1	19	53%, 2:1 ration of **20** and **21**  **20** **21**
6	2	94%, 61:22:17 mixture of **10**, **9**, and 2 other isomers
6	19	76%, 60:30:10 mixture of **22**, **23**, and **24**  **22** **23** **24**

[a] Conditions: 20 mol % ZnI_2, CH_2Cl_2, 25 °C.

philes, it failed for the less nucleophilic silyl enol ethers. A mild and effective alternative was suggested by Mukaiyama's report of $SnCl_2$–trityl chloride catalysis of silyl enol ether or silyl ketene acetal addition to enones.[20] Thus, reaction of bis enone **4** or **25** with 2–5 equiv of **2** or silyl enol ethers **26** and **27** in the presence of ≈1 equiv of $SnCl_2$ and trityl chloride at −78 °C afforded excellent yields of cyclized products (Table III). Outstanding stereoselectivity was again observed in the formation of cyclopentanes, with lower selectivity in the formation of cyclohexanes. The stereochemical similarity of these reactions to the anion-catalyzed reactions is evident, though no explanation is apparent.

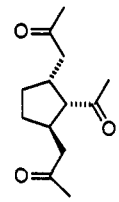
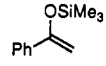
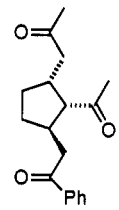
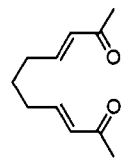
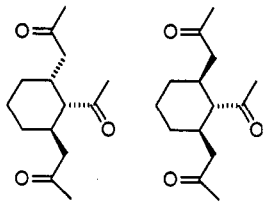
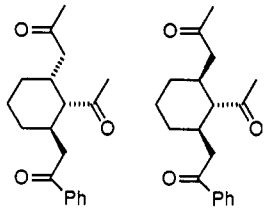
Regiospecific Formation of Bicyclics. Combination of serial Michael additions of bis enones and a subsequent intramolecular aldol/dehydration provides a ready entry into bicyclics. Treatment of **7**, **28**, or **29** with HCl or TMSCl in methanol afforded *regiospecifically* the hydrindanes **34**, **35**, and **36** in excellent yield.[21] Similar cy-



7	R = $MeO_2C(CH_3)_2C$	**34** (99%)
28	R = CH_3COCH_2	**35** (79%)
29	R = $PhCOCH_2$	**36** (79%)

clizations of acyclics are generally only highly selective when there is a quaternary center adjacent to one of the carbonyls.[22] Base-catalyzed cyclization of **7** (KOH, MeOH, H_2O, 73%) also affords **34**, but this procedure was ineffective for **28** and **29**. It is notable than these readily available bicyclic enones are isomerically distinct from those normally available from a Robinson annulation.

Table III. $SnCl_2$/Trityl Chloride-Catalyzed Reactions of Enones

acceptor	initiator	yields and product(s)
4	**2**	**7**, 71%[a]
4	 **26**	 **28**, 79%[a]
4	 **27**	 **29**, 80%[b]
 **25**	**26**	 **30** 3:1 85% **31**
25	**27**	 **32** 2.5:1 88% **33**

[a] Only one diastereomer was detected. [b] >97% one diastereomer.

To gain insight into the origin of the high selectivity of these cyclizations, the DCl-catalyzed reaction of diketone **7** in CD_3OD was studied. The rates of cyclization of **7** and deuterium incorporation into **7** and **34** were conveniently followed by 400-MHz NMR. Surprisingly, there was no appreciable deuterium incorporation into the vinylic position H_v of **34**. This indicates that the cyclization of enol **37** to form **38** is much faster than return to **7**! Incorporation of deuterium into positions L of **7** was competitive with formation of **34**, indicating that the enolization of both ketones of **7** occurred at similar rates, but unlike **37**, **39**, reverts to **7**. Identical results were obtained using TMSCl in place of DCl. A lack of incorporation of deuterium into H_c indicates that no epimerization occurred during the cyclization.

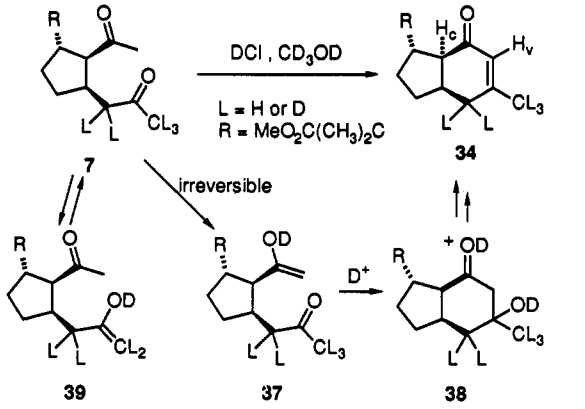
Structure Determination

The stereochemistry of **3** was assigned after a highly selective hydrolysis to form **40**, borane reduction and formation of the crystalline *p*-nitrobenzoate **41**, which was subjected to X-ray analysis. Since vigorous efforts to epimerize **3** at higher temperatures with $NaOCD_3/CD_3OD$ returned **3**, the epimerization of **3** during hydrolysis is unlikely. Extended exposure to epimerization conditions (KO-*t*-Bu, *t*-BuOH) did not interconvert **3** and **17**, and less than 10% of other isomers were formed, which supports

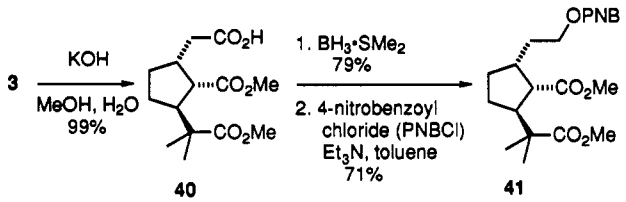
(20) Mukaiyama, T.; Kobayashi, S.; Tamura, M.; Sagawa, Y. *Chem. Lett.* **1987**, 491.

(21) A tandem intermolecular Mukaiyama–Michael addition/regioselective intramolecular aldol reaction has been reported for a chiral (α-silyl)silyl enol ether reaction with several enones, giving chiral cyclohexenones in good yield: Lohray, B. B.; Zimbiniski, R. *Tetrahedron Lett.* **1990**, *31*, 7273.

(22) Begbie, A. L.; Golding, B. T. *J. Chem. Soc., Perkin Trans. 1* **1972**, 602. Harayama, T.; Takatami, M.; Yamanaka, A.; Ikeda, H.; Ono, M.; Inubushi, Y. *Chem. Pharm. Bull.* **1981**, *29*, 766. Kreiser, W.; Below, P. *Tetrahedron Lett.* **1981**, *22*, 429 and references cited therein.



the trans–trans structure of **17**.



The stereochemistry of cyclohexanes **9** and **10** was assigned from ^{1}H NMR coupling constants. Proton H_a of **9**, resolved from overlapping resonances in the homonuclear 2D-J spectrum, appeared as a doublet of doublets with H_a–H_b and H_a–H_c coupling constants of 9.1 and 4.7 Hz, respectively. For compound **10**, proton H_a appeared as a triplet with a J = 10.8 Hz. Compounds **20**, **22**, **28**, and **30** were readily distinguished from symmetrical alternatives from their ^{13}C spectra. The stereochemistry of **32** was expected to match that of **30**, and this was confirmed from coupling constants to the central methine proton of 10.0 and 3.1 Hz. The disposition of methyl and phenyl groups in **32** was confirmed in a homonuclear 2D-COSY experiment which showed the very small but detectable four-bond coupling constants across the carbonyls of the methyl ketones. Compounds **23** and **33** displayed 11.0- and 10.8-Hz triplets, respectively, for their central methine protons, indicative of the trans,trans arrangement of substituents.

The regiochemistry of **34–36** was in each case assigned from the observation of a small coupling between allylic methylene and methyl protons. The assigned stereochemistries of **29**, **7**, **34**, **35**, and **36** are supported by several factors: (1) analogy to the firmly assigned structure of **28**, with regard to the matching stereochemistry of **30** and **32**; (2) the ready cyclization of **7** and **29** to **34** and **36** (without epimerization, vide supra); (3) striking similarities in the ^{1}H NMR spectra of **7**, **28**, and **29** (for example, H_b, H_c, and H_d (see general structure above) display nearly identical coupling patterns and chemical shifts (within 0.03 ppm), and in each case H_a is a triplet with $J \approx 7.5$ Hz); and (4) the H_a–H_b coupling constant in **34–36** ranged from 6.0 to 6.9 Hz. The H_a–H_c coupling constant of each was predicted within 2 Hz by MM2 calculations (MACROMODEL).

Experimental Section

THF, CH_2Cl_2, and CH_3CN were distilled under N_2 from sodium benzophenone ketyl, P_2O_5, and CaH_2, respectively. Tetra-*n*-butylammonium *m*-chlorobenzoate was prepared by a known procedure,[14] TASF was obtained from Aldrich and du Pont,[15] and $SnCl_2$ and trityl chloride were purchased from Aldrich and Lancaster Synthesis, respectively, and were used without purification. Silyl ketene acetals were prepared by known methods.[23] Reactions were generally conducted in oven-dried glassware and under N_2. Flash chromatography was performed using 230–400-mesh Kieselgel 60 silical gel from Merck. The standard workup procedure involved extraction with three 40-mL portions of ether, drying of the combined organic layers over $MgSO_4$, filtration, and concentration on a rotary evaporator. ^{1}H and ^{13}C NMR spectra were observed at 200 and 50 MHz, respectively, in $CDCl_3$ solution unless otherwise noted.

Dimethyl (2*E*,6*E*)-Octa-2,6-diene-1,8-dicarboxylate (1).[24] In a variation of the method of House,[25] 2 equiv of methyl (triphenylphosphoranylidene)acetate was reacted with succinaldehyde to afford 1 in 65% yield after chromatography on silica gel using 20% EtOAc/hexanes as eluent: ^{1}H NMR δ 7.00–6.85 (m, 2 H), 5.84 (d, J = 15.8 Hz, 2 H), 3.72 (s, 3 H), 2.39–2.34 (m, 4 H); ^{13}C NMR δ 166.7, 147.1, 121.9, 51.4, 30.4.

Methyl (1α,2β,3β)-2-(Methoxycarbonyl)-3-[(methoxycarbonyl)methyl]-α,α-dimethylcyclopentaneacetate (3). To a mixture of 591 mg (1.48 mmol) of tetrabutylammonium *m*-chlorobenzoate, 8.00 g (40.4 mmol) of **1**, and 100 mL of THF was added 10.5 g (60.3 mmol) of 1-methoxy-1-(trimethylsiloxy)-2-methylpropene (**2**). After stirring for 1 h, the solution was quenched with 30 mL of water. After the standard workup procedure, the residue was chromatographed on a 6-in. X 56-mm column using 20% EtOAc/petroleum ether as eluent to afford 10.8 g (89%) of **3** as a clear oil: ^{1}H NMR δ 3.75 (s, 3 H), 3.73 (s, 3 H), 3.71 (s, 3 H), 2.87 (dd, J = 6.2, 9.2 Hz, 1 H), 2.74 (ddd, J = 6.3, 7.9, 9.6 Hz, 1 H), 2.50 (m, 1 H), 2.38–2.25 (m, 2 H), 1.88–1.78 (m, 2 H), 1.51–1.39 (m, 2 H), 1.093 (s, 6 H); ^{13}C NMR δ 177.5, 175.9, 172.8, 51.6, 51.5, 51.4, 50.5, 47.9, 44.5, 40.2, 35.5, 31.9, 27.3, 23.3, 22.2; IR (neat) 2955, 1736, 1442, 1381, 1265 cm^{-1}. Anal. Calcd for $C_{15}H_{24}O_6$: C, 59.98; H, 8.05. Found: C, 59.94; H, 8.17.

Preparation of 3 Using Fluoride Catalysis. A mixture of 205 mg (1.03 mmol) of **1** and 330 mg (1.89 mmol) of **2** in 20 mL of dry THF was cooled to −78 °C, and a solution of 20 mg (0.07 mmol, 7%) of tris(dimethylamino)sulfonium difluorotrimethylsiliconate (TASF) in 1 mL of dry CH_3CN was added rapidly. Stirring was continued for 10 min at −78 °C, and the reaction was quenched by the addition of 5 mL of methanol. After the standard workup procedure, the residue was chromatographed on a 6-in. × 10-mm silica gel column using 15% EtOAc/hexanes to afford 271 mg (87%) of **3**.

(3*E*,7*E*)-Deca-3,7-diene-2,9-dione (4). To a mixture of 4.5 g (52.3 mmol) of succinaldehyde and 100 mL of CH_2Cl_2 was added a solution of 40.0 g (126 mmol) of 1-(triphenylphosphoranylidene)-2-propanone. After the mixture was stirred for 5 h, the solvent was removed with a rotary evaporator, the solid residue was rinsed with 300 mL of ether, and filtered, and the filtrate was concentrated on a rotary evaporator. Flash chromatography of the residue on an 8-in. × 56-mm silica gel column using 40% EtOAc/hexanes as eluent afforded 6.0 g (69%) of **4** as a liquid which crystallized upon standing. Samples of **4** were stored in a freezer to minimize decomposition. The spectral properties were as follows: ^{1}H NMR δ 6.85–6.65 (m, 2 H), 6.10 (d, J = 16.7 Hz, 2 H), 2.42–2.32 (m, 4 H), 2.22 (s, 6 H); ^{13}C NMR δ 198.2, 145.7, 131.8, 30.6, 27.0; IR ($CDCl_3$) 2920, 1695, 1675, 1257 cm^{-1}. Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.52; H, 8.72.

Methyl (2*E*,6*E*)-8-Oxonona-2,6-dienecarboxylate (5). The known aldehyde methyl 6-oxo-2(*E*)-hexenoate was prepared in 67% yield from succinaldehyde by the method of House.[25] To a mixture of 2.30 g (16.2 mmol) of this aldehyde in 75 mL of CH_2Cl_2 was added 7.05 g (22.2 mmol) of 1-(triphenylphosphoranylidene)-2-propanone in 25 mL of CH_2Cl_2. The mixture was stirred for 1 d, the solvent was removed with a rotary evaporator, and the solid residue was chromatographed on a 6-in. × 56-mm silica gel column using 40% EtOAc/hexanes to afford 2.25 g (76%) of **5** as a yellow liquid: ^{1}H NMR δ 7.00–6.68 (m, 2 H), 6.08 (d, J = 15.8 Hz, 1 H), 5.84 (d, J = 15.7 Hz, 1 H), 3.70 (s, 3 H), 2.40–2.35 (m, 4 H), 2.22 (s, 3 H); ^{13}C NMR δ 147.0, 145.7, 131.9, 122.0, 51.3, 30.6, 30.5, 27.1; IR ($CDCl_3$) 2953, 1720, 1676, 1277 cm^{-1}. Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 65.91; H, 7.78.

(23) Rathke, M. W.; Sullivan, D. F. *Synth. Commun.* **1973**, *3*, 67.

(24) Williams, J. R.; Lin, C. *J. Chem. Soc., Chem. Commun.* **1981**, 752.

(25) House, H. O.; Cronin, T. H. *J. Org. Chem.* **1965**, *30*, 1061.

Dimethyl (2*E*,7*E*)-Nona-2,7-diene-1,9-dicarboxylate (6).[26] In a variation of the method of House,[25] 2 equiv of methyl (triphenylphosphoranylidene)acetate was reacted with glutaraldehyde to afford **6** in 55% yield after chromatography on silica gel using 20% EtOAc/hexanes: ^{1}H NMR δ 6.90 (dt, *J* = 7.1, 15.6 Hz, 2 H), (5.80 (d, *J* = 15.6 Hz, 2 H), 3.61 (s, 3 H), 2.20 (q of d, *J* = 1.4, 7.9 Hz, 4 H), 1.70–1.52 (m, 2 H); ^{13}C NMR δ 166.9, 148.9, 121.6, 51.4, 31.4, 26.3.

Methyl (1α,2β,3β)-2-(1-Oxoethyl)-3-(2-oxopropyl)-α,α-dimethylcyclopentaneacetate (7). To a mixture of 180 mg (1.08 mmol) of **4**, 283 mg (1.63 mmol) of ketene acetal **2**, and 32 mL of THF at −78 °C was added 36 mg (0.13 mmol) of TASF as a solution in 3 mL of dry acetonitrile. The purple solution was stirred for 10 min, and 3 mL of methanol was added. After the standard workup procedure, the residue was chromatographed on a 10-in. × 22-mm silica gel column using 20% EtOAc/hexanes as eluent to afford 185 mg (64%) of **7**: ^{1}H NMR (400 MHz, C_6D_6) δ 3.31 (s, 3 H), 2.99 (t, *J* = 7.7 Hz, 1 H), 2.76 (q, *J* = 7.7 Hz, 1 H), 2.50 (m, 1 H), 2.21 (dd, *J* = 8.1 Hz, 18.0 Hz, 1 H), 1.95 (s, 3 H), 1.83 (dd, *J* = 6.0 Hz, 18.0 Hz, 1 H), 1.55 (m, 2 H), 1.28 (m, 2 H), 1.02 (s, 3 H), 1.00 (s, 3 H); ^{13}C NMR (C_6D_6) δ 205.1, 201.1, 177.9, 55.3, 51.5, 49.8, 44.8, 39.2, 32.9, 32.1, 29.9, 26.8, 24.0, 22.0, 21.6; IR (neat) 2955, 1724, 1466, 1358, 1192 cm^{-1}. MS *m/e* 268.16746 (calcd for $C_{15}H_{24}O_4$, 268.16744).

Preparation of 7 Using $SnCl_2$/Trityl Chloride. Into a mixture of 220 mg (0.79 mmol) of trityl chloride, 125 mg (0.66 mmol) of $SnCl_2$ and 25 mL of CH_2Cl_2 was added 122 mg (0.73 mmol) of **4**. After the solution was cooled to −78 °C, 470 mg (2.70 mmol) of **2** was added. The reaction stirred for 1 h and was quenched by the addition of 15 mL of 1 N HCl. After the normal workup, the residue was chromatographed on a 7-in. × 26-mm silica gel column using 20% EtOAc/petroleum ether as eluent to yield 140 mg (71%) of **7** as a clear liquid.

Methyl (1α,2β,3β)-2-(1-Oxoethyl)-3-[(methoxycarbonyl)methyl]-α,α-dimethylcyclopentaneacetate (8). To a mixture of 166 mg (0.912 mmol) of **5**, 95 mg (0.24 mmol) of tetrabutylammonium *m*-chlorobenzoate, and 35 mL of THF was added 238 mg (1.37 mmol) of **2**. The mixture was stirred for 15 min, and 2 mL of ethanol was added. The mixture was concentrated on a rotary evaporator, and the residue was chromatographed on a 9-in. × 22-mm silica gel column using 20% EtOAc/hexanes as eluent to give 102 mg (39%) of **8**, 40 mg (14%) of the compound resulting from conjugate addition to the enone alone, and 70 mg of recovered **5**. The spectral properties of **8** were as follows: ^{1}H NMR δ 3.41 (s, 3 H), 3.40 (s, 3 H), 3.12 (t, *J* = 7.3 Hz, 1 H), 2.93–2.87 (m, 1 H), 2.60–2.52 (m, 1 H), 2.37 (dd, *J* = 7.4, 16.3 Hz, 1 H), 2.17 (dd, *J* = 7.8, 16.3 Hz, 1 H), 2.05 (s, 3 H), 1.78–1.58 (m, 3 H), 1.37–1.32 (m, 1 H), 1.12 (s, 3 H), 1.11 (s, 3 H); ^{13}C NMR δ 210.8, 177.9, 173.4, 55.3, 51.5, 51.2, 50.0, 44.8, 40.7, 35.4, 32.6, 32.0, 26.8, 24.2, 21.8; IR (neat) 2950, 1737, 1380, 1150 cm^{-1}; MS *m/e* 284.1616 (calcd for $C_{15}H_{24}O_5$, 284.16235).

Methyl (1α,2β,3β)-2-(Methoxycarbonyl)-3-[(methoxycarbonyl)methyl]-α,α-dimethylcyclohexaneacetate (9). A mixture of 102 mg (0.48 mmol) of **6** and 129 mg (0.74 mmol) of **2** in 10 mL of dry THF was cooled to −78 °C, and a solution of 15 mg (0.05 mmol, 10%) of TASF in 1 mL of dry CH_3CN was added rapidly. Stirring was continued for 30 min at −78 °C, and the reaction was quenched by the addition of 5 mL of brine. After the standard workup procedure, the residue was chromatographed on a 6-in. × 10-mm silica gel column using 20% EtOAc/hexanes to afford 140 mg (93%) of **9**:**10** as a 3:1 mixture of isomers. The spectral properties of **9** were as follows: ^{1}H NMR (400 MHz) δ 3.64 (s, 3 H), 3.62 (s, 3 H), 3.59 (s, 3 H), 2.58 (dd, *J* = 6.1, 16.2 Hz, 1 H), 2.56 (dd, *J* = 9.1, 4.5 Hz, 1 H), 2.45 (m, 1 H), 2.25 (dd, *J* = 16.2, 8.0 Hz), 2.23 (ddd, *J* = 3.9, 9.1, 12.0 Hz, 1 H), 1.66–1.36 (m, 4 H), 1.11 (s, 3 H), 1.08 (s, 3 H); ^{13}C NMR δ 178.0, 174.8, 173.3, 51.7, 51.5, 51.4, 46.4, 45.6, 40.7, 35.0, 32.0, 28.0, 24.2, 23.2, 21.5, 20.0; IR (neat) 2951, 1741, 1733, 1728, 1436, 1194 cm^{-1}; MS *m/e* 314.172 94 (calcd for $C_{16}H_{26}O_6$, 314.172 94).

Preparation of 9 Using Benzoate Catalysis. To a mixture of 204 mg (0.96 mmol) of **6**, 268 mg (1.54 mmol) of **2**, and 20 mL of THF was added 33 mg (0.83 mmol) of tetrabutylammonium *m*-chlorobenzoate in 1 mL of CH_3CN. After being stirred for 2 h, the reaction mixture was quenched by the addition of 20 mL of water. After the standard workup procedure, the residue was chromatographed on a 7-in. × 19-mm silica gel column using 25% EtOAc/hexanes to afford 267 mg (89%) of **9**:**10** as a 1.8:1 mixture of diastereomers.

Methyl (1α,2β,3α)-2-(Methoxycarbonyl)-3-[(methoxycarbonyl)methyl]-α,α-dimethylcyclopentaneacetate (17). To a mixture of 279 mg (1.41 mmol) of **1**, 1.90 g (8.8 mmol) of 1-methoxy-1-(*tert*-butyldimethylsiloxy)-2-methylpropene (**18**), and 50 mL of CH_2Cl_2 was added 130 mg (0.41 mmol) of ZnI_2. After being stirred for 24 h, the mixture was quenched with 40 mL of water. After the standard workup procedure, the residue was chromatographed on a 10-in. × 19-mm silica gel column using 25% EtOAc/hexanes as eluent to give 321 mg (82%) of **17**:**3** as a 2:1 mixture of diastereomers. The spectral properties for **17** were as follows: ^{1}H NMR δ 3.67 (s, 3 H), 3.65 (s, 3 H), 3.62 (s, 3 H), 2.70 (td, *J* = 9.2, 7.3 Hz, 1 H), 2.52–2.43 (m, 2 H), 2.36 (t, *J* = 8.8 Hz, 1 H), 2.28 (dd, *J* = 10.0, 17.2 Hz, 1 H), 1.98–1.90 (m, 1 H), 1.87–1.77 (m, 1 H), 1.58–1.49 (m, 1 H), 1.32–1.23 (m, 1 H). ^{13}C NMR δ 177.4, 176.2, 172.5, 51.8, 51.8, 51.6, 51.5, 50.7, 44.6, 42.2, 38.6, 31.9, 26.8, 23.1, 22.6; IR (neat) 2954, 1741, 1728, 1436, 1265 cm^{-1}. Anal. Calcd for $C_{15}H_{24}O_6$: C, 59.98; H, 8.05. Found: C, 60.22; H, 7.96.

Methyl (1α,2β,3α)-2-(Methoxycarbonyl)-3-[(methoxycarbonyl)methyl]cyclopentaneacetate (20). To a mixture of 162 mg (0.82 mmol) of **1**, 620 mg (3.28 mmol) of 1-methoxy-1-(*tert*-butyldimethylsiloxy)ethene (**19**), and 50 mL of CH_2Cl_2 was added 100 mg (0.31 mmol) of ZnI_2. The mixture stirred for 20 h and was quenched with 20 mL of water. After the standard workup procedure, the residue was chromatographed on an 11-in. × 12-mm silica gel column using 25% EtOAc/hexanes to afford 119 mg (53%) of **20**:**21** as a 2:1 mixture of diastereomers. The spectral properties of **20** were as follows: ^{1}H NMR δ 3.32 (s, 6 H), 3.28 (s, 3 H), 2.82–2.74 (m, 1 H), 2.60–2.55 (m, 2 H), 2.39 (dd, *J* = 3.4, 8.2 Hz, 1 H), 2.18–2.10 (m, 2 H), 2.30 (dd, *J* = 3.6, 7.8 Hz, 1 H), 1.86–1.78 (m, 1 H), 1.66–1.58 (m, 1 H), 1.40–1.30 (m, 2 H); ^{13}C NMR δ 174.9, 173.0, 52.1, 51.4, 39.4, 35.7, 31.5, 31.2; IR (neat) 2954, 1741, 1727, 1437, 1198 cm^{-1}. Anal. Calcd for $C_{13}H_{20}O_6$: C, 57.34; H, 7.4. Found: C, 57.19; H, 7.51.

Methyl (1α,2β,3α)-2-(Methoxycarbonyl)-3-[(methoxycarbonyl)methyl]-α,α-dimethylcyclohexaneacetate (10). To a mixture of 239 mg (1.13 mmol) of **6**, 1.018 g (5.85 mmol) of **2**, and 50 mL of CH_2Cl_2 was added 85 mg (0.27 mmol) of ZnI_2. After being stirred for 2 h, the mixture was quenched with 30 mL of water. After the normal workup procedure, the residue was chromatographed on a 7-in. × 26-mm column using 20% EtOAc/hexanes as eluent to give 332 mg (94%) of **10**:**9**:other diastereomers as a 14:5:4 mixture. The spectral properties of **10** were as follows: ^{1}H NMR (400 MHz, C_6D_6) δ 3.40 (s, 3 H), 3.36 (s, 3 H), 3.28 (s, 3 H), 2.36 (ddd, *J* = 3.2, 10.8, 12.6 Hz, 1 H), 2.31–2.19 (m, 2 H), 2.07 (t, *J* = 10.8 Hz, 1 H), 1.74 (m, 1 H), 1.49–1.41 (m, 1 H), 1.17 (s, 3 H), 1.09 (s, 3 H), 1.08 (m, 1 H), 0.75 (m, 2 H); ^{13}C NMR δ 178.0, 175.5, 172.4, 51.7, 51.4, 51.3, 50.8, 45.5, 45.4, 39.0, 38.0, 31.1, 26.7, 25.0, 22.5, 21.7; IR (neat) 2890, 1742, 1738, 1728, 1436, 1262 cm^{-1}. Anal. Calcd for $C_{16}H_{26}O_6$: C, 61.13; H, 8.34. Found: C, 61.42; H, 8.31.

Methyl (1α,2α,3β)-2-(Methoxycarbonyl)-3-[(methoxycarbonyl)methyl]cyclohexaneacetate (22). To a mixture of 254 mg (1.18 mmol) of **6**, 1.315 g (7.33 mmol) of **19**, and 50 mL of CH_2Cl_2 was added 56 mg (0.18 mmol) of ZnI_2. After being stirred for 8 h at 0 °C the mixture was quenched with 30 mL of water. After the normal workup procedure the residue was chromatographed on a 10-in. × 19-mm silica gel column using 20% EtOAc/hexanes as eluent to give 255 mg (76%) of **22**:**23**:**24** as a 6:3:1 mixture of diastereomers. The spectral properties of **22** were as follows: ^{1}H NMR δ 3.42 (s, 9 H), 2.80–2.70 (br m, 1 H), 2.63 (dd, *J* = 6.0, 17.0 Hz, 1 H), 2.60–2.42 (m, 3 H), 2.33 (dd, *J* = 8, 17 Hz, 1 H), 2.23–2.10 (m, 1 H), 1.95–1.80 (br s, 1 H), 1.70–1.60 (br s, 1 H), 1.35–1.25 (m, 3 H), 1.05–0.9 (br s, 1 H); ^{13}C NMR δ 174.1, 172.7, 51.5, 51.5, 49.9, 34.3, 32.2, 31.0, 30.0, 29.4; IR (neat) 2932, 1736, 1651, 1435, 1165 cm^{-1}; MS *m/e* 286.14307 (calcd for $C_{14}H_{22}O_6$, 286.1416).

(3*E*,8*E*)-Undeca-3,8-diene-2,10-dione (25). To 2.0 g (20 mmol) of glutaraldehyde in 50 mL of CH_2Cl_2 was added 14.0 g (44.0 mmol) of 1-(triphenylphosphoranylidene)-2-propanone. The

(26) Scheffer, J. R.; Wostradowski, R. A.; Dooley, K. C. *J. Chem. Soc., Chem. Commun.* **1971**, 1217.

mixture was stirred overnight, the solvent was then removed with a rotary evaporator, the solid residue was washed with 75 mL of ether and filtered, and the filtrate was concentrated on a rotary evaporator. The residue was flash chromatographed on a 10-in. × 26-mm silica gel column using 40% EtOAc/hexanes as eluent to afford 1.78 g (49%) of **25** as a liquid: ^{1}H NMR ($CDCl_3$) δ 6.77 (d of t, J = 6.8, 16.0 Hz, 2 H), 6.08 (d, J = 16.0 Hz, 2 H), 2.32–2.20 (m, 4 H), 2.24 (s, 6 H), 1.68 (q, J = 7.4 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 198.5 (C), 147.0 (CH), 131.7 (CH), 31.7 (CH_2), 27.0 (CH_3), 26.4 (CH_2); IR (neat) 3007, 2936, 1695, 1678, 1628, 1255 cm^{-1}.

1-[(1α,2α,3β)-2-(1-Oxoethyl)-3-(2-oxopropyl)cyclopent-1-yl]-2-propanone (28). Into a mixture of 225 mg (0.80 mmol) of trityl chloride, 142 mg (0.75 mmol) of $SnCl_2$, and 25 mL of CH_2Cl_2 was added 111 mg (0.67 mmol) of **4**. The mixture was cooled to −78 °C, and 470 mg (3.61 mmol) of 2-(trimethylsiloxy)propene (**26**) was added. After the normal workup, the residue was chromatographed on a 10-in. × 26-mm silica gel column using 40% EtOAc/petroleum ether as eluent to yield 119 mg (79%) of **28** as a light yellow liquid: ^{1}H NMR δ 2.83–2.50 (m, 3 H), 2.46–2.36 (m, 4 H), 2.11 (s, 3 H), 2.08 (s, 3 H), 2.05 (s, 3 H), 2.02–1.76 (m, 2 H), 1.44–1.30 (m, 1 H), 1.26–1.10 (m, 1 H); ^{13}C NMR δ 211.6, 208.0 59.4, 49.4, 44.9, 37.2, 37.1, 32.0, 31.8, 30.7, 30.3, 29.9; IR (neat), 2990, 2900, 1734, 1721, 1712, 1421, 1218 cm^{-1}. Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.72; H, 9.04.

1-Phenyl-2-[(1α,2β,3β)-2-(1-oxoethyl)-3-(2-oxopropyl)-cyclopent-1-yl]ethanone (29). Into a mixture of 668 mg (2.40 mmol) of trityl chloride, 408 mg (2.15 mmol) of $SnCl_2$, and 25 mL of CH_2Cl_2 was added 409 mg (2.46 mmol) of **4**. The mixture was cooled to −78 °C, and 1.31 g (6.81 mmol) of 1-phenyl-1-(trimethylsiloxy)ethylene (**27**) was added. Stirring was continued for 4 h, and the reaction was quenched by the addition of 10 mL of 1 N HCl. After the normal workup, the residue was chromatographed on a 9-in. × 26-mm silica gel column using 20% EtOAc/petroleum ether as eluent to afford 561 mg (80%) of **29** as a white solid: mp 81–83 °C; ^{1}H NMR (400 MHz, C_6D_6) δ 7.85 (dd, J = 8.2, 1.3 Hz, 2 H), 7.13–7.05 (m, 3 H), 2.84–2.80 (m, 1 H), 2.66 (dd, J = 16.2, 6.8 Hz, 1 H), 2.62–2.52 (m, 2 H), 2.43 (dd, J = 16.2, 7.3 Hz, 1 H), 2.22 (dd, J = 18.3, 7.2 Hz, 1 H), 2.03 (s, 3 H), 1.95–1.90 (m, 1 H), 1.86 (dd, J = 18.3, 6.1 Hz, 1 H), 1.72–1.62 (m, 1 H), 1.59 (s, 3 H), 1.36–1.28 (m, 1 H), 1.10–1.05 (m, 1 H); ^{13}C NMR δ 211.7, 208.0, 199.4, 136.7, 133.0, 128.6, 128.0, 59.7, 45.0, 44.3, 37.72, 37.3, 32.0, 31.8, 30.8, 30.4; IR (neat) 2954, 2200, 1710, 1704, 1686, 1215 cm^{-1}. Anal. Calcd for $C_{18}H_{22}O_3$: C, 75.5; H, 7.74. Found: C, 75.64; H, 7.88.

1-[(1α,2α,3β)-2-(1-Oxoethyl)-3-(2-oxopropyl)cyclohex-1-yl]-2-propanone (30). Into a mixture of 310 mg (1.12 mmol) of trityl choride, 203 mg (1.07 mmol) of $SnCl_2$, and 26 mL of CH_2Cl_2 was added 327 mg (1.81 mmol) of **25**. The mixture was cooled to −78 °C, and 756 mg (5.80 mmol) of **22** was added. The reaction was stirred for 3.5 h and was quenched by the addition of 20 mL of saturated NH_4Cl. After the normal workup, the residue was chromatographed on a 10-in. × 26-mm silica gel column using 20% EtOAc/petroleum ether as eluent to afford 333 mg (85%) of **30**:**31** as a 3:1 mixture of diastereomers. The spectral properties of **30** were as follows: ^{1}H NMR δ 2.72–2.60 (m, 1 H), 2.38–2.06 (m, 5 H), 1.90 (s, 3 H), 1.86–1.68 (m, 3 H), 1.66 (s, 3 H), 1.62 (s, 3 H), 1.50–1.39 (m, 3 H), 1.30–1.14 (m, 3 H); ^{13}C NMR δ 211.8, 208.0, 207.4, 57.1, 48.2, 42.8, 30.7, 30.6, 30.5, 30.37, 29.7, 29.4, 20.4; IR (neat) 2932, 1713, 1701, 1357, 1165 cm^{-1}. Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.38; H, 9.27.

1-Phenyl-2-[(1α,2β,3β)-2-(1-oxoethyl)-3-(2-oxopropyl)-cyclohex-1-yl]ethanone (32). Into a mixture of 327 mg (1.17 mmol) of trityl chloride, 434 mg (2.29 mmol) of $SnCl_2$, and 30 mL of CH_2Cl_2 was added 275 mg (1.53 mmol) of **25**. The mixture was cooled to −78 °C, and 665 mg (3.46 mmol) of **27** was added. Stirring was continued for 3 h, and the reaction was quenched by the addition of 20 mL of saturated NH_4Cl. After the normal workup, the residue was chromatographed on an 8-in. × 26-mm silica gel column using 20% EtOAc/petroleum ether as eluent to afford 291 mg (63%) of **32** as a white powder, mp 116.2–118.2 °C, as well as 115 mg (25%) of **33**. The spectral properties of **32** were as follows: ^{1}H NMR (400 MHz, C_6D_6) δ 8.07–8.04 (m, 2 H), 7.10–7.12 (m, 3 H), 2.95 (dd, J = 14.7, 3.4 Hz, 1 H), 2.76–2.70 (m, 1 H), 2.48–2.38 (m, 1 H), 2.26 (dd, J = 18.0, 6.0 Hz, 1 H), 2.20 (dd, J = 14.3, 9.3 Hz, 1 H), 2.20 (dd, J = 10.3, 3.1 Hz, 1 H), 1.92 (s, 3 H), 1.82–1.73 (m, 1 H), 1.77 (dd, J = 18.0, 6.0 Hz, 1 H), 1.60 (s, 3 H), 1.44–1.37 (m, 1 H), 1.30–1.16 (m, 2 H), 1.05–0.95 (m, 1 H), 0.88–0.78 (m, 1 H); ^{13}C NMR δ 211.9, 207.3, 199.6, 137.0, 133.0, 128.6, 128.2, 57.6, 43.3, 42.8, 30.7, 30.6, 30.6, 30.3, 29.8, 28.8, 20.4; IR (neat) 2933, 2254, 1714, 1701, 1685, 1449 cm^{-1}. Anal. Calcd for $C_{19}H_{24}O_3$: C, 75.97; H, 8.04. Found: C, 76.23; H, 7.83.

(1α,3aβ,7aβ)-1-[2-(Methoxycarbonyl)-2-propyl]-5-methyl-2,3,3a,4-tetrahydro-1*H*-7(7a*H*)-indenone (34). To a mixture of 160 mg (0.60 mmol) of **7**, 1 mL of methanol, and 1 mL of water was added 70 mg (1.25 mmol) of KOH. The mixture was heated in a hot water bath for 5 h, and 5 mL of 1 N HCl was added. After the normal workup, the residue was chromatographed on a 9-in. × 22-mm silica gel column using 15% EtOAc/hexanes as eluent to yield 110 mg (73%) of **34** as a light yellow oil: ^{1}H NMR δ 5.82–5.81 (m, 1 H), 3.63 (s, 3 H), 2.76–2.70 (m, 1 H), 2.54 (ddd, J = 2.1, 7.2, 20.0 Hz, 1 H), 2.44 (dd, J = 4.6, 6.5 Hz, 1 H), 2.38–2.29 (m, 1 H), 2.20 (dd, J = 2.8, 20.0 Hz, 1 H), 1.88 (s, 3 H), 1.75–1.60 (m, 2 H), 1.40–1.30 (m, 2 H); ^{13}C NMR δ 201.2, 178.0, 158.5, 125.5, 51.6, 49.2, 49.1, 44.9, 38.6, 32.4, 31.3, 26.6, 24.4, 23.3, 22.8; IR (neat) 2950, 1720, 1650, 1390, 1250 cm^{-1}; MS m/e 250.15662 (calcd for $C_{15}H_{22}O_3$, 250.15688).

Preparation of 34 Using TMSCl. To 238 mg (0.89 mmol) of **7** in 25 mL of methanol was added 136 mg (1.25 mmol) of TMSCl. The reaction was stirred for 3 d, and 10 mL of saturated sodium bicarbonate was added. After the normal workup, the residue was chromatographed on a 6-in. × 26-mm silica gel column using 20% EtOAc/petroleum ether was eluent to afford 221 mg (99%) of **34**.

(1α,3aβ,7aβ)-1-(1-Oxoethyl)-5-methyl-2,3,3a,4-tetrahydro-1*H*-7(7a*H*)-indenone (35). To 97 mg (0.43 mmol) of **28** in 15 mL of methanol was added 111 mg of concentrated HCl. After being stirred for 1 d, the mixture was poured into 20 mL of saturated sodium bicarbonate. After the normal workup, the residue was chromatographed on a 5-in. × 26-mm silica gel column using 40% EtOAc/petroleum ether as eluent to afford 71 mg (79%) of **35** as a light yellow liquid: ^{1}H NMR (400 MHz, C_6D_6) δ 5.84 (d, J = 0.6 Hz, 1 H), 2.72 (dd, J = 17.1, 4.3 Hz, 1 H), 2.65–2.54 (m, 1 H), 2.15–2.02 (m, 2 H), 2.02 (dd, J = 17.1, 9.1 Hz, 1 H), 1.95 (dd, J = 9.5, 6.6 Hz, 1 H), 1.68 (s, 3 H), 1.56–1.51 (m, 2 H), 1.46–1.38 (m, 1 H), 1.32 (s, 3 H), 1.18–1.09 (m, 1 H), 1.14–0.96 (m, 3 H); ^{13}C NMR δ 208.2, 200.7, 160.2, 125.1, 53.7, 49.1, 38.3, 36.6, 33.5, 30.6, 30.5, 30.0, 24.3; IR (neat) 2944, 1713, 1657, 1431, 1377 cm^{-1}. Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.8. Found: C, 75.56; H, 8.72.

(1α,3aβ,7aβ)-1-(2-Oxo-2-phenylethyl)-5-methyl-2,3,3a,4-tetrahydro-1*H*-7(7a*H*)-indenone (36). To 130 mg (0.455 mmol) of **29** in 25 mL of methanol was added 156 mg of concentrated HCl. After stirring for 1 d, the reaction was poured into 20 mL of water. After the normal workup, the residue was chromatographed on a 6-in. × 26-mm silica gel column using 30% EtOAc/petroleum ether as eluent to afford 101 mg (83%) of **36** as a light yellow oil: ^{1}H NMR (400 MHz, C_6D_6) δ 7.90 (dd, J = 6.9 Hz, 1.5 Hz, 2 H), 7.01–7.10 (m, 3 H), 5.85 (d, J = 0.3 Hz, 1 H), 3.52 (dd, J = 16.8, 2.9 Hz, 1 H), 2.82–2.72 (m, 1 H), 2.67 (dd, J = 16.8, 10.2 Hz, 1 H), 2.27–2.14 (m, 2 H), 2.10 (dd, J = 8.2, 6.0 Hz, 6.0 Hz, 1 H), 1.52 (d, J = 7.4 Hz, 2 H), 1.50–1.40 (m, 1 H, 1.32 (s, 3 H), 1.30–1.20 (m, 2 H); ^{13}C NMR δ 200.9, 199.5, 160.4, 136.8, 132.8, 128.4, 128.0, 125.1, 53.9, 44.1, 38.5, 37.2, 33.5, 30.7, 30.6, 24.3; IR (neat) 3100, 2912, 2250, 1684, 1653 cm^{-1}. Anal. Calcd for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.73; H, 7.44.

Methyl (1α,2β,3β)-2-(Methoxycarbonyl)-3-(carboxymethyl)-α,α-dimethylcyclopentaneacetate (40). Into a mixture of 540 mg (1.80 mmol) of **3**, 30 mL of methanol, and 20 mL of water was added 120 mg (2.14 mmol) of KOH. After being stirred for 1 h the reaction was quenched by the addition of 20 mL of 1 N HCl. After the normal workup, the residue was chromatographed on a 4-in. × 26-mm silica gel column using 20% EtOAc/petroleum ether as eluent to give 513 mg (99%) of **40** as a clear oil: ^{1}H NMR (400 MHz) δ 3.64 (s, 3 H), 3.61 (s, 3 H), 2.86 (dd, J = 6.0, 10.0 Hz, 1 H), 2.76–2.69 (m, 1 H), 2.52–2.28 (m, 3 H), 1.86–1.78 (m, 2 H), 1.54–1.34 (m, 2 H), 1.12 (s, 6 H); ^{13}C NMR δ 178.4, 177.6, 175.9, 51.7, 51.5, 50.5, 48.0, 44.6, 39.9, 35.6, 31.9, 27.4, 23.4, 22.3; IR (neat) 2954, 1737, 1713, 1701, 1436, 1196 cm^{-1}.

Methyl (1α,2β,3β)-2-(Methoxycarbonyl)-3-[2-[[(4-nitrophenyl)carbonyl]oxy]ethyl]-α,α-dimethylcyclopentaneacetate (41). Into 1.00 g (3.50 mmol) of **40** in 20 mL THF at 0 °C was added, over a 15-min period, 400 μL (4.0 mmol) of a 10

M solution of borane–dimethyl sulfide complex. The mixture was stirred at 0 °C for an additional 1 h and was then allowed to warm to room temperature over a span of 30 min. The mixture was then poured into 50 mL of ice–water, 40 mL of saturated bicarbonate was added, and the whole was extracted with three 50-mL portions of ether. The combined organic layers were washed with a 50-mL portion of brine, dried over $MgSO_4$, and filtered, and the solvent was removed with a rotary evaporator to give 750 mg (79%) of methyl (1α,2β,3β)-2-(methoxycarbonyl)-3-(2-hydroxyethyl)-α,α-dimethylcyclopentaneacetate as a viscous liquid: ^{1}H NMR δ 3.64 (s, 3 H), 3.60 (s, 3 H), 2.82–2.62 (m, 2 H), 2.20–2.04 (m, 1 H), 1.88–1.14 (m, 9 H), 1.11 (s, 6 H); ^{13}C NMR δ 177.6, 176.4, 61.4, 51.5, 51.2, 50.7, 48.8, 44.5, 40.9, 33.8, 31.7, 27.5, 23.3, 22.1; IR (neat). Anal. Calcd for $C_{14}H_{24}O_5$: C, 61.74; H, 8.88. Found: C, 61.38; H, 8.76. A solution of 1.90 g (6.99 mmol) of this alcohol in 2.20 g (21.8 mmol) of NEt_3 and 25 mL of toluene was added to a solution of 2.00 g (10.5 mmol) of 4-nitrobenzoyl chloride in 75 mL toluene at 0 °C. After being stirred for 75 min at 0 °C and overnight at 23 °C, the mixture was extracted with two 50-mL portions of 0.5 N HCl, the organic layer was washed with two 30-mL portions of saturated sodium bicarbonate, and the organic layer was dried over $MgSO_4$. Filtration and solvent removal with a rotary evaporator was followed by flash chromatography of the residue on a 9-in. × 26-mm silica gel column using 20% EtOAc/petroleum ether as eluent to afford 2.10 g (71%) of 41 as light yellow solid. Recrystallization of the solid by slow evaporation from a solution of absolute ethanol afforded crystals suitable for X-ray analysis: mp 51–53 °C; ^{1}H NMR δ 8.30–8.15 (m, 4 H), 4.36 (t, J = 6.8 Hz), 3.66 (s, 3 H), 3.60 (s, 3 H), 2.85 (dd, J = 9.0 Hz, 6.0 Hz, 1 H), 2.75–2.60 (m, 1 H), 2.20–2.10 (m, 1 H), 1.99–1.30 (m, 6 H), 1.12 (s, 6 H); ^{13}C NMR δ 177.5, 176.1, 164.6, 150.5, 135.6, 130.7, 123.5, 64.9, 51.6, 51.5, 50.9, 48.8, 44.6, 41.2, 31.8, 29.9, 27.6, 23.6, 22.3. Anal. Calcd for $C_{21}H_{27}NO_8$: C, 59.85; H, 6.46; N, 3.32. Found: C, 60.10; H, 6.28; N, 3.26.

Acknowledgement is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research. We also thank Du Pont for a generous sample of TASF.

Supplementary Material Available: X-ray crystallographic data for 41 (16 pages). Ordering information is given on any current masthead page.

Conjugate Addition Reactions of Organosamarium Species via in Situ Transmetalation to Cu(I) Salts

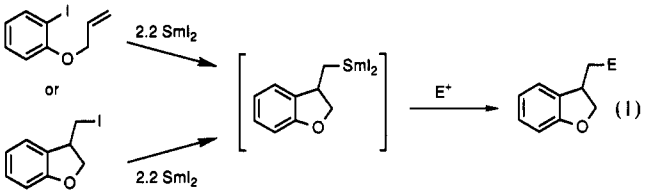
Michael J. Totleben, Dennis P. Curran, and Peter Wipf*

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

Received August 20, 1991

Preformed organosamarium species, available by reduction of aryl or alkyl halides with SmI_2, were treated with copper(I) salts to effect in situ transmetalation and conjugate addition to enones. In a series of copper(I) salts, CuI·P(OEt)$_3$ gave best results in combination with 2 equiv of organosamarium reagent. This new method allows the multiple formation of carbon–carbon bonds through a combination of radical and cuprate chemistry.

Applications of samarium(II) iodide (SmI_2) in synthetic organic chemistry have grown rapidly in recent years.[1] Representative examples include Barbier-type reactions,[2] pinacol couplings,[3] and the preparation of α-ketols[4] and vicinal carbonyl compounds.[5] Recently, samarium(II) iodide mediated radical or ketyl cyclizations have been applied in conjunction with carbonyl addition reactions (eq 1, E^+ = aldehyde, ketone).[6] Experimental observations



(1)

support the intermediacy of solution-stable organosamarium species in this[6a] and probably many other samarium-mediated processes.[2f] These mechanistic observations[6a] led to the development of conditions for the direct reduction of alkyl iodides to alkylsamarium species. These alkylsamarium species then react with a wide variety of electrophiles, including many that are not stable to the SmI_2 reagent used to generate the samarium alkyls (E^+ = PhSSPh, Bu_3SnCl, etc.).[6c]

As expected, alkylsamarium reagents add in a 1,2-fashion to unsaturated ketones.[6a,c] In order to extend the usefulness of these new reagents, we decided to develop conditions to effect 1,4-additions to unsaturated ketones. We now report the first conjugate additions of preformed

(1) (a) Girard, P.; Kagan, H. B.; Namy, J.-L. *J. Am. Chem. Soc.* **1980**, *102*, 2693. (b) Molander, G. A. In *The Chemistry of the Metal–Carbon Bond*; Hartley, F. R., Patai, S., Eds.; Wiley: New York, 1989; Vol. 5, p 319. (c) Kagan, H. B.; Sasaki, M.; Collin, J. *Pure Appl. Chem.* **1988**, *60*, 1725.

(2) (a) Namy, J.-L.; Girard, P.; Kagan, H. B. *Nouv. J. Chim.* **1977**, *1*, 5. (b) Imamoto, T.; Takeyama, T.; Koto, H. *Tetrahedron Lett.* **1986**, *27*, 3243. (c) Molander, G. A.; Etter, J. B.; Zinke, P. W. *J. Am. Chem. Soc.* **1987**, *109*, 453. (d) Otsubo, K.; Kawamura, K.; Inanaga, J.; Yamaguchi, M. *Chem. Lett.* **1987**, 1487. (e) Barner, B. A.; Liu, Y.; Rahman, M. A. *Tetrahedron* **1989**, *45*, 6101. (f) Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1991**, *56*, 4112.

(3) (a) Namy, J. L.; Souppe, J.; Kagan, H. B. *Tetrahedron Lett.* **1983**, *24*, 765. (b) Molander, G. A.; Kenny, C. *J. Org. Chem.* **1988**, *53*, 2132. (c) Molander, G. A.; Kenny, C. *J. Am. Chem. Soc.* **1989**, *111*, 8236.

(4) (a) Souppe, J.; Namy, J.-L.; Kagan, H. B. *Tetrahedron Lett.* **1984**, *25*, 2869. (b) Collin, J.; Namy, J.-L.; Dallemer, F.; Kagan, H. B. *J. Org. Chem.* **1991**, *56*, 3118.

(5) (a) Murakami, M.; Kawano, T.; Ito, Y. *J. Am. Chem. Soc.* **1990**, *112*, 2437. (b) Murakami, M.; Masuda, H.; Kawano, T.; Nakamura, H.; Ito, Y. *J. Org. Chem.* **1991**, *56*, 1.

(6) (a) Curran, D. P.; Fevig, T. L.; Totleben, M. J. *Synlett* **1990**, 773. (b) Curran, D. P.; Wolin, R. L. *Synlett* **1991**, 317. (c) Curran, D. P.; Totleben, M. Manuscript submitted for publication. (d) Molander, G. A.; Kenny, C. *J. Org. Chem.* **1991**, *56*, 1439.

0022-3263/92/1957-1740$03.00/0