Transmetalation Reactions of Organosamarium Reagents. Chlorosilane-Accelerated Copper-Catalyzed Conjugate Additions

Peter Wipf* and Srikanth Venkatraman

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

Received January 29, 1993

TMSCl accelerates the conjugate addition of in situ prepared organosamarium reagents to α,β-unsaturated carbonyl compounds and nitriles in the presence of HMPA and catalytic amounts of Cu(I) salts. Reactions at −78 °C leads to silyl enol ethers which are isolated or cleaved with TBAF to give β-alkylated ketones in 30–90% overall yield. Catalysis is most efficient in the presence of 4 equiv of TMSCl and HMPA. HMPA is also necessary for the in situ preparation of the organosamarium species from alkyl halide and SmI_2. Some functional groups (chloride, ether, alkene, amide) are tolerated in this process. In the absence of Cu(I) salts, 1,2-additions of organosamarium reagents to carbonyl groups are also dramatically accelerated by TMSCl/HMPA and occur within minutes at −78 °C.

The preparation of organocopper reagents by transmetalation protocols has emerged as an attractive new tool for selective C,C-bond formation.[1] The ability to prepare a metal complex which serves as a precursor of another reactive organometallic reagent can significantly enhance the synthetic potential of the individual metal derivatives.[2-4] This concept has already been successfully demonstrated with the development of copper *ate* complexes with lithium as counterion (lithium organocuprates,[5] "Gilman" reagents) or the combination of Grignard reagents with catalytic amounts of Cu(I) salts.[6] It is only very recently, however, that transmetalation schemes that use Al,[7] Mn[8], Sn,[9] Te,[10] Ti,[11] Zn,[12] and Zr[13] derivatives have developed into highly competitive routes to both common and functionalized organocopper reagents.

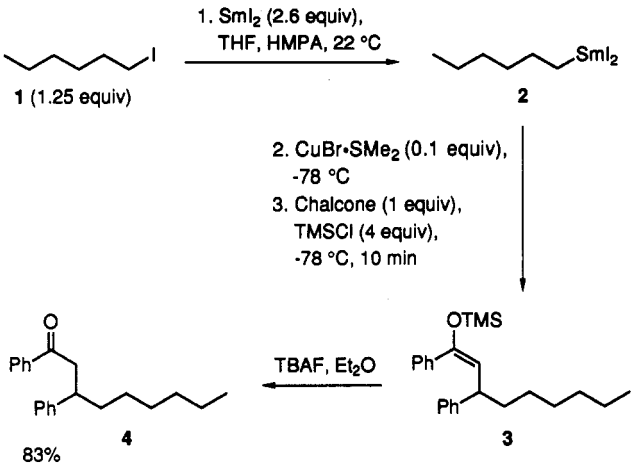
The preparation of alkylsamarium species by reduction of alkyl iodides and bromides with SmI_2 offers a convenient and highly selective entry toward a variety of functionalized organic compounds.[14] Samarium(II) iodide mediated radical or anionic reactions have been applied in conjunction with 1,2-carbonyl addition reactions[15,16] and natural products synthesis.[17-20] Experimental observations support the intermediacy of a solution-stable organosamarium(III) species in many samarium-mediated processes.[21] Transmetalation reactions of alkylsamarium species are especially attractive transformations because they lead to a significant increase in scope and possible areas of applications of these lanthanide derivatives. However, this aspect of organosamarium chemistry has been neglected, undoubtedly because it has only recently been recognized that alkylsamarium derivatives are generated in solution by SmI_2 reductions of halides. Most prominent among the few combinations of samarium reagents with other metals are the palladium-catalyzed reduction of allylic[22] and propargylic[23] acetates and the related formations of allylstannanes[24] and allylic phenyl selenides[25] from allylic acetates/SmI_2 and stannyl chlorides or diphenyl diselenide, respectively, in the presence of palladium catalyst. Furthermore, a report by Inanaga and Yamaguchi discusses the selective reduction of alkynes with SmI_2 and iron, cobalt, or nickel chlorides.[26]

An in situ transmetalation of organosamarium reagents to copper(I) salts combines the unique features of samarium chemistry with the broad scope of organocopper reagents. We have recently disclosed a successful Sm → Cu transmetalation that uses stoichiometric quantities of

(1) For a review, see: Wipf, P. *Synthesis*, in print.
(2) (a) Carr, D. B.; Schwartz, J. *J. Am. Chem. Soc.* **1977**, *99*, 638. (b) Negishi, E. *Pure Appl. Chem.* **1981**, *53*, 2333.
(3) Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1987.
(4) Harrington, P. J. *Transition Metals in Total Synthesis*; John Wiley: New York, 1990.
(5) Gilman, H.; Jones, R. G.; Woods, L. A. *J. Org. Chem.* **1952**, *17*, 1630.
(6) Kharasch, M. S.; Tawney, P. O. *J. Am. Chem. Soc.* **1941**, *63*, 2308.
(7) (a) Wipf, P.; Smitrovich, J. H.; Moon, C.-W. *J. Org. Chem.* **1992**, *57*, 3178. (b) Ireland, R. E.; Wipf, P. *J. Org. Chem.* **1990**, *55*, 1425.
(8) (a) Cahiez, G.; Alami, M. *Tetrahedron Lett.* **1989**, *30*, 3541. (b) Cahiez, G.; Chavant, P.-Y.; Matais, E. *Tetrahedron Lett.* **1992**, *33*, 5245.
(9) Behling, J. R.; Babiak, K. A.; Ng, J. S.; Campbell, A. L.; Moretti, R.; Koerner, M.; Lipshutz, B. H. *J. Am. Chem. Soc.* **1988**, *110*, 2641.
(10) Tucci, F. C.; Chieffi, A.; Comasseto, J. V. *Tetrahedron Lett.* **1992**, *33*, 5721.
(11) Arai, M.; Lipshutz, B. H.; Nakamura, E. *Tetrahedron* **1992**, *48*, 5709.
(12) (a) Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1984**, *106*, 3368. (b) Knochel, P.; Rozema, M. J.; Tucker, C. E.; Retherford, C.; Furlong, M.; AchyuthaRao, S. *Pure Appl. Chem.* **1992**, *64*, 361.
(13) (a) Yoshifuji, M.; Loots, M. J.; Schwartz, J. *Tetrahedron Lett.* **1977**, 1303. (b) Wipf, P.; Smitrovich, J. H. *J. Org. Chem.* **1991**, *56*, 6494. (c) Lipshutz, B. H.; Keil, R. *J. Am. Chem. Soc.* **1992**, *114*, 7919. (d) Wipf, P.; Xu, W. *Synlett* **1992**, 718.
(14) For recent reviews, see: (a) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29. (b) Imamoto, T. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Schreiber, S. L., Eds.; Pergamon: Oxford, 1991; Vol. 1, pp 231-250.
(15) (a) Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693. (b) Curran, D. P.; Fevig, T. L.; Totleben, M. J. *Synlett* **1990**, 773. (c) Molander, G. A.; Kenny, C. *J. Org. Chem.* **1991**, *56*, 1439.
(16) Curran, D. P.; Totleben, M.; Jasperse, C.; Fevig, T. *Synlett* **1992**, 973.
(17) Anguidine: Enholm, E. J.; Satici, H.; Trivellas, A. *J. Org. Chem.* **1989**, *54*, 5841.
(18) Cytochalasin: Vedejs, E.; Ahmad, S. *Tetrahedron Lett.* **1988**, *29*, 2291.
(19) Hypnophilin and coriolin: Fevig, T. L.; Elliott, R. L.; Curran, D. P. *J. Am. Chem. Soc.* **1988**, *110*, 5064.
(20) Desoxystemodinone: White, J. D.; Somers, T. C. *J. Am. Chem. Soc.* **1987**, *109*, 4424.
(21) (a) Molander, G. A.; Kenny, C. A. *J. Org. Chem.* **1991**, *56*, 1439. (b) Curran, D. P.; Totleben, M. J. *J. Am. Chem. Soc.* **1992**, *114*, 6050.
(22) (a) Tabuchi, T.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 601. (b) Hanzawa, Y.; Ishizawa, S.; Kobayashi, Y.; Taguchi, T. *Chem. Pharm. Bull.* **1990**, *38*, 1104.
(23) Tabuchi, T.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 5237.
(24) Tabuchi, T.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1987**, *28*, 215.
(25) Fukuzawa, S.; Fujinami, T.; Sakai, S. *Chem. Lett.* **1990**, 927.
(26) Inanaga, J.; Yokoyama, Y.; Baba, Y.; Yamaguchi, M. *Tetrahedron Lett.* **1991**, *32*, 5559.

0022-3263/93/1958-3455$04.00/0

Scheme I



$CuI{\cdot}P(OEt)_3$ complex for an in situ formation of dialkyl cuprates.[27] The major limitations of this methodology were the requirement for an excess of halide (2–4 equiv vs enone) and the presence of stoichiometric quantities of trialkyl phosphite in the reaction mixture. In this paper, we report a greatly improved catalytic version of this process.

Results and Discussion

Addition of a mixture of TMSCl and chalcone to 1.2–1.5 equiv of the organosamarium species **2** in THF led to a very rapid 1,4-addition at −78 °C in the presence of catalytic amounts of Cu(I) salts (Scheme I). After cleavage of the intermediate silyl enol ether **3** with tetrabutylammonium fluoride (TBAF), ketone **4** was isolated in 83% overall yield. A noteworthy feature of this process is the rate-acceleration over the stoichiometric[27] version, which requires significantly higher temperatures (−20 °C to room temperature) and longer reaction times (2.5 h) to go to completion.[28,29]

This reaction is quite general for a variety of primary alkyl iodides and bromides (Table I). Especially for sensitive substrates, the low reaction temperature and the short reaction time in combination with the trapping of the enolate as the silyl enol ether lead to a significant increase in the overall yield of the conjugate addition. Treatment of iodo ether **5** with 2 equiv of SmI_2 followed by addition of catalytic $CuBr{\cdot}SMe_2$ and a mixture of TMSCl and methyl vinyl ketone at −78 °C leads, via 5-*exo-trig* radical cyclization, formation of an alkylsamarium reagent, copper-catalyzed conjugate addition, and cleavage of the silyl enol ether with TBAF in THF, to methyl ketone **6** in 92% overall yield (entry 1). Due to the ease of polymerization of methyl vinyl ketone in the presence of Lewis acids such as SmI_3, ketone **6** was obtained in only 30% yield from the stoichiometric transmetalation protocol.[27] Similarly, the catalytic, chlorosilane-accelerated process allows the use of cyclopentenone (entry 8) and amide- or chloro-functionalized substrates (entries 6 and 8).

The copper(I)-catalyzed addition of samarium reagents to γ-substituted enones occurs stereospecifically in accordance with the general reactivity of organocuprates. With tyramine derivative **11**,[30] for example, a single isomer **12** was isolated in 59% yield from the reaction mixture (entry 5). The stereochemistry of **12** was tentatively assigned based on molecular mechanics calculations of the conformation of **11** and steric arguments. The exclusive β-attack of the samarium cuprate on the sterically more accessible face of the enone is in accordance with stereochemical studies of Corey and Boaz on the conjugate addition of Gilman reagents to γ,γ-disubstituted enones.[31]

Earlier attempts for copper(I)-mediated coupling of organosamarium species to α,β-unsaturated nitriles had been unsuccessful.[27] With the present methodology, acrylonitrile addition product **8** was accessible in 34% yield (entry 3). The use of secondary halides such as cyclohexyl iodide, however, is still problematic, as only 31% of cyclohexenone addition was observed (entry 9). The stability of secondary alkylsamarium species in THF/HMPA solutions is probably too low to result in a high-yielding stepwise reaction protocol.

The presence of TMSCl and HMPA in the reaction mixture not only accelerates 1,4-additions to carbonyl compounds, it also dramatically increases the rate of 1,2-additions. A mixture of hexylsamarium(III) and acetophenone at −78 °C provided only 7% of carbonyl addition product after 30 min at −78 °C. In the presence of 4 equiv of TMSCl, however, 1,2-addition product **18** was isolated in 65% yield after 10 min reaction time (Scheme II).

Whereas this effect is potentially very useful for carbonyl additions according to the samarium–Grignard protocol, it is a potential concern in conjugate addition reactions. Due to the relatively low concentration of the active copper species in reaction mixtures with catalytic $CuBr{\cdot}SMe_2$, the increase in the reaction rate for 1,2-addition of the organosamarium reagent can lead to the formation of product mixtures with sterically hindered substrates. The reactions of phenethyl iodide and pulegone illustrate the competition between 1,2- and 1,4-additions, which are both accelerated by TMSCl. Treatment of phenethylsamarium reagent **19** with (*R*)-(+)-pulegone at −78 °C did not lead to any reaction product after 1 h, even in the presence of 10 mol % Cu(I) salt (Scheme III). With TMSCl, however, a rapid reaction to the tertiary alcohol **20** was observed. In the presence of both TMSCl and catalytic amounts of $CuBr{\cdot}SMe_2$ complex, an approx. 2:1 mixture of 1,4- and 1,2-addition products **21** and **20** was formed.

The level of steric hindrance of the tetrasubstituted double bond in pulegone is sufficient to allow a successful competition of the TMSCl-accelerated 1,2-addition process with the copper-catalyzed conjugate addition to the enone.

(27) Totleben, M. J.; Curran, D. P.; Wipf, P. *J. Org. Chem.* **1992**, *57*, 1740.

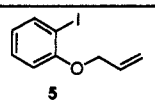
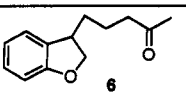
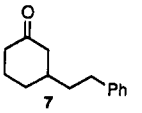
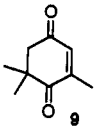
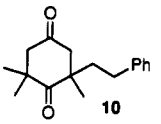
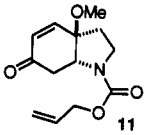
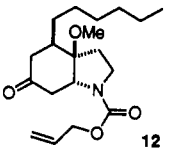
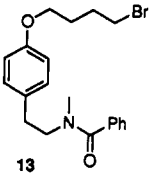
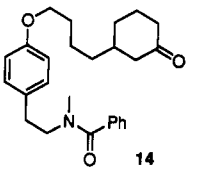
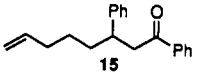
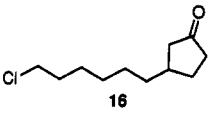
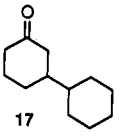
(28) For a discussion of chlorosilane-accelerated conjugate additions of organocopper reagents, see: (a) Matsuzawa, S.; Horiguchi, Y.; Nakamura, E.; Kuwajima, I. *Tetrahedron* **1989**, *45*, 349. (b) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6019.

(29) In control experiments, we have found that the catalytic reaction is most favorable in the presence of 4 equiv of TMSCl vs enone. Four equiv of HMPA should be present in the reaction mixture from the SmI_2 reduction of the halide starting material. If the amount of HMPA vs halide is decreased significantly below this level, the initial reduction of the halide, e.g., the formation of the organosamarium reagent, becomes very sluggish. We have therefore not been able to investigate the efficiency of the catalytic transmetalation protocol at low HMPA concentrations. However, there was no increase in yield or reaction rate at HMPA concentrations above the 4 equiv ratio. For a discussion of possible effects of HMPA in transmetalation to Cu(I), see ref 28. Interestingly, addition of TMSCl was of no consequence in our earlier[27] stoichiometric transmetalation/conjugate addition sequence.

(30) Prepared according to: Wipf, P.; Kim, Y. *Tetrahedron Lett.* **1992**, *33*, 5477.

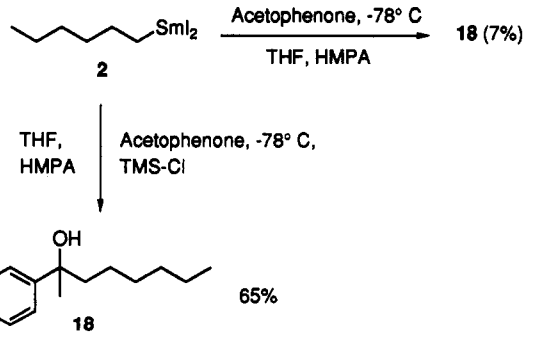
(31) In the presence of TMSCl, the sterically more favorable copper d,π*-complex is rapidly trapped: Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6015 and references cited therein.

Table I. TMSCl-Accelerated Cu(I)-Catalyzed Conjugate Additions of in Situ Prepared Organosamarium Reagents to α,β-Unsaturated Ketones and Nitriles

entry	RX	enone	product[a]	% isolated yield[b]
1	 5	methyl vinyl ketone	 6	92[c]
2	phenethyl iodide	2-cyclohexen-1-one	 7	68[d]
3	phenethyl iodide	acrylonitrile	$Ph(CH_2)_4CN$ (8)	34
4	phenethyl iodide	 9	 10	72
5	*n*-hexyl iodide	 11	 12	59
6	 13	2-cyclohexen-1-one	 14	60
7	5-bromo-1-pentene	chalcone	 15	55
8	1-bromo-6-chlorohexane	2-cyclopenten-1-one	 16	59
9	cyclohexyl iodide	2-cyclohexen-1-one	 17	31

[a] After cleavage of the intermediate silyl enol ether with TBAF in THF. [b] Based on enone. [c] The stoichiometric procedure[27] resulted in a 30% yield starting with 2.2 equiv of **5**. [c] The stoichiometric procedure[27] resulted in a 67% yield starting with 2.2 equiv of phenethyl iodide.

Scheme II

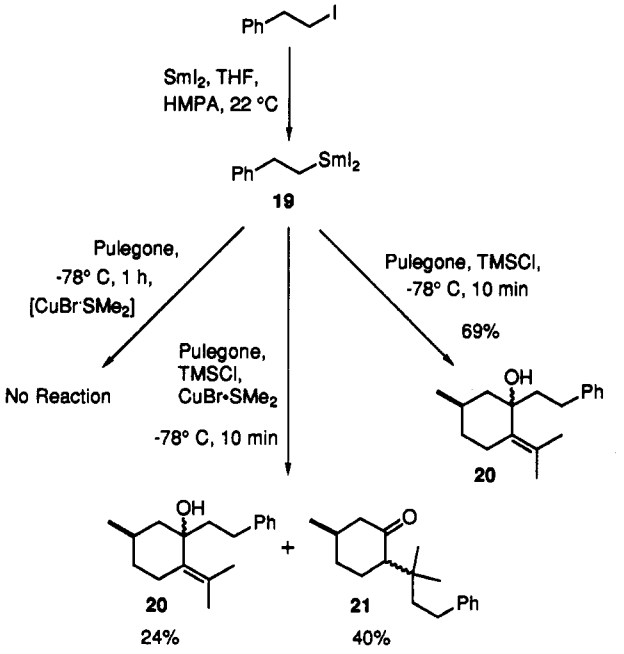


These parallel reaction pathways result in the formation of a mixture of allylic alcohol and ketone.

Conclusions

Alkylsamarium reagents are easily prepared by SmI_2 reduction of alkyl halides. A free radical is formed as an intermediate in this process and is synthetically useful especially for C,C-bond formations via intramolecular alkene or alkyne additions. Further reduction with excess SmI_2 provides a nucleophilic organosamarium derivative which can be transmetalated to Cu(I). The chlorosilane-accelerated conjugate addition of organosamarium reagents allows a rapid in situ conjugate addition to α,β-unsaturated carbonyl compounds and nitriles in the presence of catalytic amounts of $CuBr{\cdot}SMe_2$. Reaction at −78 °C leads to silyl enol ethers which are isolated or cleaved with TBAF to give β-alkylated ketones and nitriles in 30–90% overall yield. Compared to the earlier stoichiometric transmetalation protocol, this methodology is considerably milder and faster and results in significantly improved yields, especially with Lewis-acid sensitive substrates. Some functional groups (chlorides, alkenes, amides, carbamates, ethers, ketones) in the starting halide as well as in the enone are tolerated. In the absence of Cu(I) salts, 1,2-additions of organosamarium reagents to carbonyl groups are also dramatically accelerated by TMSCl/HMPA and occur within minutes at −78 °C.

Scheme III



Experimental Section

General. Anhydrous solvents were freshly distilled from either sodium benzophenone ketyl, P_2O_5, or CaH_2. HMPA was distilled from CaH_2 and stored under argon. CuBr·DMS was commercially available and used without further purification. Chlorotrimethylsilane was distilled from CaH_2 under N_2. All reactions were performed in oven-dried glassware under an argon or nitrogen atmosphere.

Preparation of 0.1 M SmI_2 in THF. A suspension of samarium powder (1.84 g, 12 mmol) and I_2 (2.54 g, 10 mmol) in dry THF (100 mL) was stirred vigorously at 22 °C overnight, during which time the color changed from purple to rust-brown to green and finally to prussian blue. This procedure gave a 0.1 M solution of SmI_2. The concentration of SmI_2 was checked by titration with a 0.1 M solution of I_2 in THF (the endpoint is reached when the solution turns yellow and SmI_3 precipitates out).

General Procedure: 3-(2-Phenethyl)cyclohexanone (7). To a solution of 16 mL (1.6 mmol) of a 1.0 M solution of SmI_2 in THF was added 1.25 mL (7.3 mmol) of HMPA (1.25 mL, 7.3 mmol). The deep purple solution was stirred at 22 °C for 5 min and treated with a solution of 175 mg (0.75 mmol) of 2-phenethyl iodide in 2 mL of THF. The resulting yellow mixture was stirred for 10 min and cooled to −78 °C, and 15 mg (0.075 mmol) of CuBr·DMS was added. The mixture was stirred vigorously for 5 min, and a solution of 49 mg (0.5 mmol) of 2-cyclohexen-1-one and 0.25 mL (1.96 mmol) of TMSCl in 2 mL of THF was added. After 5 min, 100 mL of Et_2O was added and the resultant solution was filtered through a plug of basic Al_2O_3. The filtrate was extracted with water (3 × 30 mL), dried ($MgSO_4$), concentrated under reduced pressure, and treated with 0.6 mL (0.6 mmol) of a 0.1 M solution of TBAF in THF. To this solution was added 1.5 g of silica gel, and the solvent was evaporated. The free flowing powder was loaded on top of a SiO_2 column and chromatographed (EtOAc/hexanes (1:4)) to give 68 mg (68%) of **7** as a pale yellow oil: R_f = 0.58 (EtOAc/hexanes (1:4)); identical by NMR analysis to an earlier prepared sample.[27]

1,3-Diphenyl-1-nonanone (4). According to the general procedure, 159 mg (0.75 mmol) of hexyl iodide and 104 mg (0.5 mmol) of chalcone afforded 122 mg (83%) of **4** as a colorless solid: R_f = 0.64 (EtOAc/hexanes (1:4)); mp 54.5–55 °C; identical by NMR analysis to an earlier prepared sample.[13b]

5-[3-(2*H*,3*H*-Benzofurfuryl)]-2-pentanone (6). According to the general procedure, 175 mg (0.67 mmol) of **5** and 31.5 mg (0.45 mmol) of methyl vinyl ketone afforded 84 mg (92%) of colorless **6** as an oil: R_f = 0.29 (EtOAc/hexanes (1:4)); identical by NMR analysis to an earlier prepared sample.[27]

5-Phenylpentanenitrile (8).[32] According to the general procedure, 174 mg (0.75 mmol) of 2-phenethyl iodide and 26.5 mg (0.5 mmol) of acrylonitrile afforded 27 mg (34%) of **8**: R_f = 0.57 (EtOAc/hexanes (1:3)); ^{1}H NMR δ 7.33–7.28 (m, 2 H), 7.25–7.03 (m, 3 H), 2.66 (t, 2 H, J = 7.0 Hz), 2.34 (t, 2 H, J = 7.0 Hz), 1.85–1.60 (m, 4 H).

2-(2-Phenethyl)-2,6,6-trimethylcyclohexane-1,4-dione (10). According to the general procedure, 170 mg (0.75 mmol) of 2-phenethyl iodide and 75 mg (0.5 mmol) of **9** afforded 97 mg (72%) of **10** as a white crystalline solid: R_f = 0.27 (EtOAc/hexanes (1:4)); mp 61–61.5 °C; IR ($CDCl_3$) 2965, 2932, 1707, 1458, 1385, 1242, 1043, 1007, 912, 748 cm^{-1}; ^{1}H NMR δ 7.30–7.25 (m, 2 H), 7.20–7.14 (m, 3 H), 2.89, 2.59 (AB, 2 H, J = 18 Hz), 2.64 (s, 2 H), 2.51–2.45 (m 2 H), 2.08–1.98 (m, 1 H), 1.72–1.61 (m, 1 H), 1.22 (s, 3 H), 1.22 (s, 3 H), 1.20 (s, 3 H); ^{13}C NMR δ 215.7, 208.4, 141.3, 128.6, 128.3, 126.2, 50.5, 48.2, 47.1, 43.6, 41.1, 30.9, 26.9, 26.4, 25.7; MS (EI) m/z (relative intensity) 258 (M^+, 1), 185 (2), 154 (100), 139 (20), 112 (40), 91 (50), 69 (20), 55 (20); HRMS m/z calcd for $C_9H_{14}O_2$ (M − $PhCHCH_2$) 154.0993, found 154.0997.

(3a*SR*,4*RS*,7a*RS*)-*N*-[(Allyloxy)carbonyl]-4-hexyl-3a-methoxy-1,2,3,3a,4,5,7,7a-octahydroindol-6-one (12). According to the general procedure, 159 mg (0.7 mmol) of hexyl iodide and 105 mg (0.5 mmol) of **11** afforded 87 mg of **12** as a yellow viscous oil: R_f = 0.5 (EtOAc/hexanes (1:1)); IR ($CDCl_3$) 2928, 2858, 1705, 1408, 1340, 1267, 1225, 1199, 1093, 1116 cm^{-1}; ^{1}H NMR (DMSO-d_6, 385 K) δ 6.06–6.00 (m, 1 H), 5.42–5.29 (m, 2 H), 4.65 (d, 2 H, J = 5.1 Hz), 4.36 (t, 1 H, J = 7.4 Hz), 3.56–3.51 (m, 2 H), 3.25 (s, 3 H), 2.88–2.81 (m, 1 H), 2.61–2.45 (m, 2 H), 2.36–2.28 (m, 2 H), 2.00–1.90 (m, 1 H), 1.80–1.70 (b, 1 H), 1.55–1.30 (b, 9 H), 1.25–1.19 (m, 1 H), 1.00 (t, 3 H, J = 6 Hz); ^{13}C NMR (DMSO-d_6, 385 K) δ 206.4, 153.3, 132.9, 116.1, 84.8, 64.3, 57.5, 48.2, 43.5, 43.2, 41.3, 34.2, 30.4, 29.0, 28.4, 28.0, 25.7, 21.2, 12.9; MS (EI) m/z (relative intensity) 337 (M^+, 11), 305 (10), 296 (10), 264 (10), 252 (12), 236 (20), 220 (15), 205 (15), 193 (15), 149 (15), 97 (30), 69 (30), 55 (40); HRMS m/z calcd for $C_{19}H_{31}O_4N$ 337.2253, found 337.2235.

***N*-Benzoyl-*N*-methyl-O-[4-(1-oxo-3-cyclohexyl)butyl]-tyramine (14).** According to the general procedure, 340 mg (0.75 mmol) of **11** and 48 mg (0.4 mmol) of 2-cyclohexenone afforded 124 mg (61%) of **14** as a viscous oil: R_f = 0.18 (EtOAc/hexanes (1:1)); IR ($CDCl_3$) 2932, 2862, 1709, 1633, 1512, 1448, 1400, 1302, 1244, 1176, 1070, 1026 cm^{-1}; ^{1}H NMR (DMSO-d_6, 385 K) δ 7.42–7.38 (m, 3 H), 7.27–7.24 (m, 2 H), 7.06 (d, 2 H, J = 8.1 Hz), 6.85 (d, 2 H, J = 8.4 Hz), 3,98 (t, 2 H, J = 6.4 Hz), 3.55 (t, 2 H, J = 7.2 Hz), 2.93 (s, 3 H), 2.81 (t, 2 H, J = 7.1 Hz), 2.34–2.22 (m, 3 H), 2.10–2.02 (m, 1 H), 2.02–1.90 (m, 1 H), 1.90–1.67 (m, 4 H), 1.67–1.54 (m, 1 H), 1.44–1.35 (m, 5 H); ^{13}C NMR (DMSO-d_6, 385 K) δ 209.2, 169.8, 156.9, 136.6, 130.2, 128.9, 128.3, 127.4, 125.8, 114.3, 67.3, 49.8, 46.7, 37.4, 34.8, 32.0, 29.7, 28.3, 23.7, 22.0; MS (EI) m/z (relative intensity) 407 (M^+, 4), 272 (90), 237 (10), 231 (20), 220 (20), 205 (30), 120 (50), 105 (100); HRMS m/z calcd for $C_{26}H_{33}O_3N$ 407.2460, found 407.2445.

1,3-Diphenyl-7-octen-1-one (15). According to the general procedure, 111 mg (0.75 mmol) of 5-bromo-1-pentene and 104 mg (0.5 mmol) of chalcone afforded 76 mg (55%) of **15** as a pale yellow oil: R_f = 0.48 (EtOAc/hexanes (1:5.7)); IR ($CDCl_3$) 2930, 2856, 1682, 1597, 1495, 1448, 1265, 1207, 1001, 910, 750, 700 cm^{-1}; ^{1}H NMR δ 7.75–7.73 (m, 2 H), 7.41–7.30 (m, 1 H), 7.30–7.24 (m, 2 H), 7.16–7.00 (m, 5 H), 5.64–5.51 (m, 1 H), 4.82–4.73 (m, 2 H), 3.22–3.15 (m, 1 H), 3.12–3.06 (m, 2 H), 1.90–1.81 (m, 2 H), 1.62–1.45 (m, 2 H), 1.20–1.08 (m, 2 H); ^{13}C NMR δ 199.0, 144.8, 138.7, 137.2, 133.0, 128.5, 128.0, 127.6, 126.3, 114.5, 45.9, 41.2, 35.8, 33.7, 26.8; MS (EI) m/z (relative intensity), 278 (M^+, 6), 235 (3), 221 (4), 209 (40), 158 (40), 117 (50), 105 (100), 91 (30), 77 (50); HRMS m/z calcd for $C_{20}H_{22}O$ 278.1670, found 278.1665.

3-(6-Chlorohexyl)cyclopentanone (16). According to the general procedure, 160 mg (0.75 mmol) of 1-bromo-6-chlorohexane and 41 mg (0.5 mmol) of 2-cyclopentenone afforded 59 mg (59%) of **16** as an oil: R_f = 0.45 (EtOAC/hexanes (1:4)); IR ($CDCl_3$) 3854, 2928, 2856, 1741, 1456, 1406, 1280, 1159, 725, 650 cm^{-1}; ^{1}H NMR δ 3.51 (t, 2 H, J = 6.8 Hz), 2.37–2.20 (m, 2 H), 2.18–2.07 (m, 3 H), 1.81–1.70 (m, 3 H), 1.47–1.23 (m, 9 H); ^{13}C NMR δ 219.9, 45.3, 45.1, 38.6, 37.2, 35.6, 32.6, 29.5, 29.0, 27.7, 26.8; MS (EI) m/z

(32) Jovanovic, J. J.; Boberg, F.; Schultze, G. R. *Ann. Chem.* **1966**, *696*, 55.

(relative intensity), 202 (M^+, 7), 173 (8), 158 (2), 112 (12), 97 (40), 91 (20), 83 (100), 55 (50); HRMS (EI) m/z calcd for $C_{11}H_{19}OCl$ 202.1124, found 202.1135.

3-Cyclohexylcyclohexanone (17). According to the general procedure, 146 mg (0.6 mmol) of cyclohexyl iodide and 48 mg (0.5 mmol) of 2-cyclohexenone afforded 33 mg (31%) of **17** as a pale yellow oil: R_f = 0.54 (EtOAc/hexanes (1:4)); identical by NMR analysis to an earlier prepared sample.[27]

2-Phenyl-2-octanol (18).[33] According to the general procedure, 116 mg (0.5 mmol) of *n*-hexyl iodide and 60 mg (0.5 mmol) of acetophenone afforded 67 mg (65%) of colorless **18** as an oil: R_f = 0.47 (EtOAc/hexanes (1:5.7)); IR ($CDCl_3$) 3568, 3399, 2932, 2856, 1655, 1458, 763, 700 cm^{-1}; ^1H NMR δ 7.46–7.45 (m, 2 H), 7.43–7.37 (m, 2 H), 7.35–7.20 (m, 1 H), 1.90–1.79 (m, 3 H), 1.56 (s, 3 H), 1.40–1.05 (broad s, 8 H), 0.86 (t, 3 H, J = 6.4 Hz); ^{13}C NMR δ 148.1, 128.1, 126.5, 124.8, 74.8, 44.3, 31.6, 30.1, 26.7, 24.0, 22.6, 14.1.

(1*RS*,5*R*)-5-Methyl-2-(1-methylethylidene)-1-(2-phenylethyl)cyclohexanol (20) and (2*RS*,5*R*)-2-(1,1-dimethyl-3-phenylpropyl)-5-methylcyclohexanone (21). According to the general procedure, 176 mg (0.75 mmol) of phenethyl iodide and 72 mg (0.5 mmol) of pulegone afforded 29 mg (24%) of **20** and 53 mg (40%) of **21**.

20 (mixture of diasteromers): R_f = 0.54 (EtOAc/hexanes (1:4)); IR ($CDCl_3$) 3470, 2920, 1600, 1540, 1482, 1400, 1180, 1000, 770, 710 cm^{-1}; ^1H NMR δ 7.31–7.15 (m, 5 H), 2.85–2.70 (m, 2 H), 2.58–2.54 (m, 1 H), 2.17–2.11 (m, 1 H), 2.08 (s, 3 H), 1.88–1.75 (m, 1 H), 1.74 (s, 3 H), 1.74–1.64 (m, 3 H), 1.42–1.34 (broad s, 1 H), 1.27–1.23 (m, 2 H), 1.00–0.98 (m, 4 H); ^{13}C NMR δ 143.2, 133.6, 128.5, 128.4, 125.6, 125.2, 78.3, 52.3, 41.5, 35.2, 30.4, 30.0, 28.9, 23.6, 22.5; MS (EI) m/z (relative intensity) 258 (M^+, 1), 240 (10), 225 (21), 197 (4), 175 (3), 153 (100), 149 (30), 135 (30), 121 (10), 107 (20), 91 (35).

21 (mixture of diastereomers): R_f = 0.69 (EtOAc/hexanes 1:4)); IR ($CDCl_3$) 2955, 2870, 1709, 1496, 1454, 1385, 1363, 1120, 698; ^1H NMR δ 7.30–7.15 (m, 5 H), 2.57–2.47 (m, 2 H), 2.32–2.26 (m, 2 H), 2.19–2.02 (m, 2 H), 2.02–1.75 (m, 4 H), 1.72–1.50 (m, 2 H), 1.47–1.26 (m, 1 H), 1.20–0.90 (m, 8 H); ^{13}C NMR δ 213.0, 212.1, 143.4, 128.7, 128.4, 125.7, 57.5, 52.6, 50.5, 42.6, 36.5, 34.9, 34.5, 32.3, 31.7, 31.5, 30.5, 28.3, 25.2, 25.0, 24.6, 24.2, 22.7, 22.5, 14.2; MS (EI) m/z (relative intensity) 258 (M^+, 10), 240 (4), 225 (12), 153 (100), 146 (40), 112 (80), 91 (70), 69 (20), 55 (20); HRMS m/z calcd for $C_{18}H_{26}O$ 258.1983, found 258.1976.

According to the general procedure, but in the absence of any Cu(I) salts, 176 mg (0.75 mmol) of phenethyl iodide and 72 mg (0.5 mmol) of pulegone afforded 84 mg (69%) of oily **20** as a mixture of diastereomers.

(33) Braun, J. V. *Ber.* **1910**, *43*, 2837.

Acknowledgment. We thank Professors D. P. Curran and E. Hasegawa for stimulating discussions.

Supplementary Material Available: ^1H and, in most cases, ^{13}C NMR spectra of compounds described in the Experimental Section (22 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.