***exo*-Benzo[6,7]bicyclo[3.2.1]oct-6-en-2-yl Chloride (25).** This chloride has been previously reported[33] (though not characterized) and is obtained admixed (1:1) with *exo*-benzobicyclo[2.2.2]oct-5-en-2-yl chloride by treatment of *exo*-benzobicyclo[2.2.2]oct-5-en-2-ol with thionyl chloride in dry ether at room temperature. The chlorides are resolved analytically by VPC on column C at 150 °C (17.4 and 19.2 min for **25** and its isomer, respectively) but cannot be resolved by preparative VPC.

Photolyses of *exo*-BBOC and *endo*-BBOC in Methanol. Typically, 4 mL of the chloride (0.01 M) was degassed with argon for 20 min and irradiated in a quartz tube in the Rayonet reactor with the 254-nm lamps. Photolysis times were of the order of 2.5 h for exo and 15 min for endo chloride. Analysis by column C (150 °C) gave the products as: **20** (6.53 min), **10** (7.30 min), **21** (8.45 min), **12** (10.96 min), **22** (12.16 min), **23** (13.65 min), **24** (12.34 min), **14** (14.03 min), **25** (17.38 min) and **16** (19.28 min), with *exo*- and *endo*-BBOC at 18.10 and 27.91 min respectively. *exo*-BBOC gave unidentified[34] peaks at 5.40 and 24.38 min while *endo*-BBOC gave additional peaks at 5.16, 5.40, 6.16, 7.19, 14.17, and 14.38 min.

For the (*E*)-2-heptene quenching studies, a stock solution of *endo*-BBOC (1.18×10^{-2} M) and hexadecane (1.77 mg/mL) in methanol was prepared and 3.6 mL was transferred to each of four quartz tubes. The four solutions were degassed simultaneously with argon for 20 min, and two tubes were sealed. To the other two tubes was added 29.8 mg (0.11 M) and 41.8 mg (0.12 M) (*E*)-2-heptene, and all four tubes were then photolyzed for 35 min in a turntable using the Rayonet reactor and the 254-nm lamps. The four solutions as well as an unphotolyzed solution were analyzed on column C at 150 °C. An average of 31.3% loss of starting material was found in the control tubes and 31.2% found in the tubes containing quencher. There was only one observable difference in the product fingerprint between the two sets of tubes; i.e., the ratio of alkene (**21**) to di-π-methane product (**12**) was greatly increased in the tubes containing the triplet quencher. Quantitatively, the amount of **12** found in the tubes with heptene was 53% that formed in the controls.

The acetone sensitization experiment was done by using 0.013 M *endo*-BBOC plus 1.6 M acetone in methanol (the solution was degassed with argon prior to addition of the acetone). Photolysis was carried to 40% loss of starting material using the Rayonet reactor and 300-nm lamps. Analysis was on column C at 150 °C.

For the determination of ϕ_{dis}, the Rayonet reactor was equipped with five 254-nm lamps and a turntable. A solution of 1-phenyl-2-butene (1.72×10^{-2} M) in hexane was used for actinometry[13] and duplicate tubes, photolyzed for 15 min, provided a light intensity measurement of $(5.53 \pm .02) \times 10^{16}$ photons/s into the 4-mL solutions. Simultaneously, solutions of *endo*-BBOC in cyclohexane (1.19×10^{-2} M) and in methanol (1.04×10^{-2} M), and *exo*-BBOC in cyclohexane (1.30×10^{-2} M) and methanol (1.10×10^{-2} M), were charged with hexedecane, degassed, and irradiated in duplicate for 15 and 150 min, respectively. All analyses were by column C at 150 °C. Losses of starting material ranged from 5.4 to 22%, and ϕ_{dis} values were 0.081 (*endo*-BBOC/MeOH), 0.065 (endo-BBOC/cyclohexane), 0.0076 (*exo*-BBOC/MeOH), and 0.0034 (*exo*-BBOC/cyclohexane).

Ground-State Solvolyses. A 0.028 M solution of *endo*-BBOC in 10:1 methanol–water containing 0.027 M silver nitrate was stirred at room temperature for 2 h. After addition of several mg of NaCl, the solution was filtered and analyzed on column C at 150 °C. The products were **21** and **23** in a ratio of 56:44. In a comparable experiment with *exo*-BBOC, but for 48 h, **21** and **22** were observed, along with alcohol (**18**). Relative amounts were 18%:45%:37%, respectively. The rate study employed 22 mg of *endo*-BBOC (0.021 M) and 19 mg of *exo*-BBOC (0.020 M) in 5.5 mL of 10:1 methanol–water. An aliquot (0.5 mL) was removed for analysis, 8 mg of silver nitrate (0.021 M) was added, and the solution was stirred at 27 °C for 1.5 h. Several mg of NaCl was added, the solution filtered, and the filtrate analyzed on column C at 150 °C. Losses observed were 47.4% for *endo*-BBOC and 3.7% for *exo*-BBOC.

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Registry No. **12**, 24309-44-2; **14**, 84799-79-1; **16**, 105087-92-1; **17**, 13351-26-3; **18**, 105087-88-5; **19**, 105087-89-6; **20**, 15391-62-5; **21**, 24309-43-1; **22**, 105087-91-0; **23**, 105018-91-5; **24**, 84758-42-9; *exo*-BBOC, 105018-90-4; *endo*-BBOC, 105087-90-9; 3-chlorobenzo[6,7]bicyclo[3.2.1]octa-2,6-diene, 13351-27-4.

(33) Tanida, H.; Miyazaki, S. *J. Org. Chem.* **1971**, *36*, 425–435.

(34) These peaks did not match those for *endo*-benzobicyclo[2.2.2]-oct-5-en-2-yl methyl ether (retention time 18.7 min) or *endo*-benzo-[6,7]bicyclo[3.2.1]oct-6-en-2-yl methyl ether (retention time 15.8 min).

A Stereoselective Synthesis of α,β-Unsaturated Ketones Involving the Reactions of Organocuprates with β-Alkylthio α,β-Enones

R. Karl Dieter* and Louis A. Silks, III

Department of Chemistry, Clemson University, Clemson, South Carolina 29634-1905, and Department of Chemistry, Boston University, Boston, Massachusetts 02215

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The substitution reactions of *E* and *Z* vinylogous thiol esters with organocuprates has been examined as a potential stereoselective synthetic route to α,β-enones. The stereoselectivities of the reactions were dependent upon substrate structure, cuprate reagent, cuprate transferable ligand, solvent, and temperature. The *E* vinylogous thiol esters all underwent reaction in THF with net retention of configuration except **26** which afforded net inversion with Me_2CuLi. In diethyl ether, the *E* vinylogous thiol esters generally afforded net inversion of configuration and only gave retention for enone **9** and for sterically hindered enone/cuprate pairs. The *Z* vinylogous thiol esters uniformly afforded reaction with net retention in either THF or diethyl ether with the exception of enone **34** which gave inversion with [*sec*-$Bu_2CuSCN]Li_2$. These results can be explained in terms of an addition–elimination pathway and several possible mechanisms are discussed.

We have, over the past few years, been exploring the chemistry of α-oxo ketene dithioacetals for use in the regio-, chemo-, and stereoselective construction of carbon–carbon bonds.[1] A full account of the chemo- and

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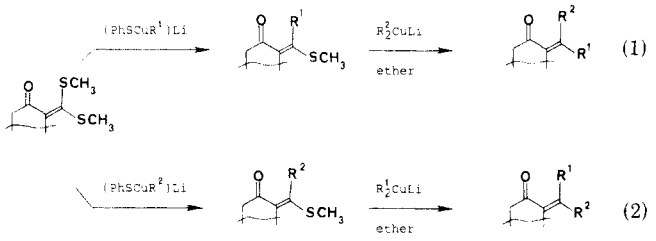
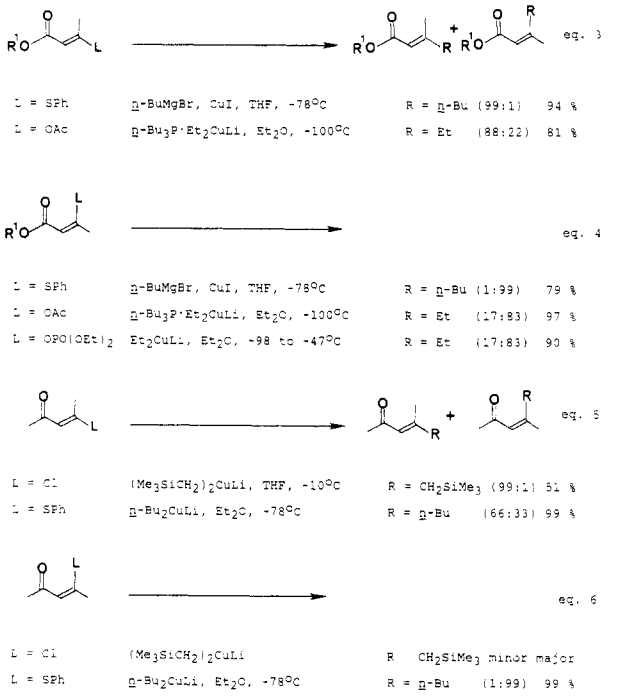
stereoselective reactions of organocuprates with α-oxo ketone dithioacetals to afford β-alkylthio α,β-enones (vinylogous thiol esters) has been reported.[2] The good to excellent stereoselectivity exhibited by this reaction prompted the pursuit of a stereoselective synthesis of tri- and tetrasubstituted α,β-enones[3] via sequential organocopper substitution reactions with α-oxo ketene dithioacetals and the intermediate vinylogous thiol esters. In principle, either the *E* or *Z* olefin could be prepared by simply choosing the appropriate sequence of operations (eq 1 and 2). The reactions of *E* β-alkylthio α,β-enones



with organocuprates containing primary alkyl ligands was shown, in a preliminary report,[4] to proceed stereoselectively with predominant inversion of configuration in diethyl ether and with predominant retention of configuration in THF. A *Z* β-alkylthio and a *Z* β-arylthio α,β-enone, however, underwent the organocopper substitution reaction with net retention of configuration in diethyl ether and in THF. These observations were of synthetic significance since they indicated that reaction of a mixture of *E* and *Z* β-alkylthio α,β-enones with organocuprates would afford, in diethyl ether, the same stereoisomer in a highly stereoselective process and would provide an efficient stereoselective synthesis of α,β-enones.

We now report, in this full account, the influence of secondary and tertiary alkyl substituents at the β-carbon atom of the enone and the effect of organocuprates containing transferable secondary and tertiary alkyl ligands on the degree and direction of stereoselectivity in the substitution reactions. The reaction has also been examined for 6-(1-(methylthio)alkylidene)-2-cyclohexenone derivatives. A β-chloro enone and an *E* and *Z* β-alkylthio α,β-enoate have also been examined in order to provide a link between these previously studied substrates and the β-alkylthio α,β-enones of the present study. The results of this investigation indicate that the direction and degree of stereoselectivity in the reactions of the enones with organocuprates depends in a complicated way upon substrate structure, transferable cuprate ligand, cuprate reagent, solvent, and reaction temperature. The reaction is believed to proceed by an addition–elimination mechanism and the results appear to indicate the possibility of a plurality of reaction pathways.

Chart I



Background

The substitution reactions of organocuprates with α,β-unsaturated carbonyl compounds containing a good leaving group at the β-carbon atom has received considerable attention as a versatile procedure for the synthesis of β-alkyl-substituted α,β-enones and enoates. Substrates containing halide,[5] acetate,[6] phosphate,[7] alkoxy,[8] alkylthio,[9] and tosyloxy[5a,10] substituents as the leaving group have been examined. The extensively studied ester derivatives containing halide,[5a-b,h] phenylthio,[9e-g] acetoxy,[6] phosphate,[7] or tosyloxy[5a,10] leaving groups undergo the reaction with predominant retention of configuration (Chart I, eq 3 and 4) to afford a stereoselective route to α,β-enoates. The major interest, in this reaction, has been the stereoselective synthesis of trisubstituted olefins typically found in the insect juvenile hormones and acyclic terpene precur-

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(2) Dieter, R. K.; Silks, L. A., III; Fishpaugh, J. R.; Kastner, M. E. *J. Am. Chem. Soc.* **1985**, *107*, 4679.

(3) For alternative routes to acyclic or exocyclic tri- and tetrasubstituted α,β-unsaturated ketones, see: (a) Fleming, I.; Newton, T. W.; Roessler, F. *J. Chem. Soc., Perkins. Trans. 1* **1981**, 2527. (b) Fleming, I.; Perry, D. A. *Tetrahedron Lett.* **1981**, *22*, 5095. (c) Hoye, T. R.; Bottorff, K. J.; Caruso, A. J.; Dellaria, J. F. *J. Org. Chem.* **1980**, *45*, 4287. (d) van den Goorbergh, J. A. M.; van der Gen, A. *Tetrahedron Lett.* **1980**, *21*, 3621. (e) Bodalski, R.; Pietrusiewicz, K. M.; Monkiewicz, J.; Koszuk, J. *Ibid.* **1980**, *21*, 2287. (f) Marfat, A.; McGuirk, P. R.; Helquist, P. *Tetrahedron Lett.* **1978**, 1363. (g) Dauben, W. G.; Michno, D. M. *J. Org. Chem.* **1977**, *42*, 682. (h) Trost, B. M.; Stanton, J. L. *J. Am. Chem. Soc.* **1975**, *97*, 4018. (i) Reich, H. J.; Rengo, J. M.; Reich, I. L. *Ibid.* **1975**, *97*, 5434. (j) Malone, G. R.; Meyers, A. I. *J. Org. Chem.* **1974**, *39*, 623. (k) Portnoy, N. A.; Morrow, C. J.; Chattha, M. S.; Williams, J. C., Jr.; Aguiar, A. M. *Tetrahedron Lett.* **1971**, 1401. Chattha, M. S.; Aguiar, A. M. *Ibid.* **1971**, 1419. (l) Faulk, D. D.; Fry, A. *J. Org. Chem.* **1970**, *35*, 364.

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(9) (a) Dieter, R. K.; Fishpaugh, J. R.; Silks, L. A. *Tetrahedron Lett.* **1982**, *23*, 3751. (b) Johansen, O. H.; Undheim, K. *Acta Chem. Scand., Ser. B* **1979**, 33B, 460. (c) Martin, S. F.; Moore, D. R. *Tetrahedron Lett.* **1976**, 4459. (d) Coates, R. M.; Sandefur, L. D. *J. Org. Chem.* **1974**, *39*, 275. (e) Kobayashi, S.; Meguro-ku, O.; Mukaiyama, T. *Chem. Lett.* **1974**, 705. (f) Kobayashi, S.; Mukaiyama, T. *Ibid.* **1974**, 1425. (g) Kobayashi, S.; Takei, H.; Mukaiyama, T.; Meguro-ku, O. *Ibid.* **1973**, 1097. (h) Posner, G. H.; Brunelle, D. J. *J. Chem. Soc., Chem. Commun.* **1973**, 907. (i) Corey, E. J.; Chen, R. H. K. *Tetrahedron Lett.* **1973**, 3817.

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sors.[5d,6,7,9e-g] The nature of the leaving group, the cuprate reagent, solvent, and configuration of the starting enone appear to have little influence upon the degree or direction of stereoselectivity in these reactions.

Significantly, only three isolated examples appeared, prior to our preliminary report, which described stereoselective organocuprate substitutions for the more reactive ketone substrates. investigations by Posner and Brunelle[9h,11] and Casey[5b] (Chart I, eq 5 and 6) indicated that the *E* and *Z* stereoisomers of a β-phenylthio and β-chloro α,β-enone, respectively, underwent the substitution reaction with net retention of configuration. Taken together, these results were similar to those reported for the ester analogues in that the stereoselectivity of the reaction appeared to be relatively insensitive to various reaction parameters. The substitution reaction of a β-halo α,β-enone with a cyclopropylcuprate, however, was reported by Piers to be completely nonstereoselective.[5d] These limited studies did not foreshadow the complexity of the substitution process that we were to uncover upon examination of solvent effects and the influence on the reaction of primary, secondary, and tertiary alkyl substituents and ligands, respectively, present in the enones and organocuprates.

Results

The stereoselectivity in the substitution reactions of organocuprates with vinylogous thiol esters displayed considerable sensitivity toward several reaction parameters. This was sometimes manifested in a wide variation in isomer ratios from experiment to experiment. In general, it appeared that high stereoselectivities required careful control of the reaction temperature during the enone addition process. Although cannula transfer of a precooled enone solution to a cold organocuprate solution is a viable technique, we often employed a different procedure that consistently afforded high and reproducible stereoselectivities. A 10–15-mL solution of an organocuprate in a 250-mL three necked, round-bottomed flask was cooled to −78 °C with a dry ice–acetone bath. The flask was submerged to the neck joints so that the entire bulb of the flask was cold. The enone (1.0 mmol scale) in 5.0 mL of solvent was added over a period of 1 min via syringe with the syringe needle touching the side of the glass neck. This technique insured that the emerging stream of liquid broadened to cover a wide surface area before entering the cuprate solution. This process appeared to be superior to dropwise addition, indicating a possible effect of high local concentrations, although this factor was not examined in a systematic way.

The reactions of organocuprates with vinylogous thiol esters can be described as proceeding with net retention or inversion of configuration if the newly introduced alkyl group is on the same or opposite side, respectively, of the carbon–carbon double bond than the alkylthio substituent which it replaces. The combination of primary, secondary, and tertiary β-alkyl substituted substrates and organocuprates containing primary, secondary, and tertiary alkyl transferable ligands affords a confusing number of permutations. For ease of presentation, the reactions of substrates containing a primary, and a secondary or tertiary β-alkyl substituent will be described separately. The effect of utilizing cuprates containing primary, secondary, or tertiary alkyl transferable ligands will, where examined, be presented within each substrate group.

The degree and direction of stereoselectivity in the reactions of cuprates with vinylogous thiol esters containing a primary β-alkyl substituent exhibited a complex dependence on several experimental variables and are recorded in Table I. The cyclopentanone derivatives **1** and **2** and acyclic *E* vinylogous thiol esters **3–7** underwent the substitution reaction with net inversion of configuration in diethyl ether and with net retention in THF (Table I, entries 1–3, 5, 6–8, 18–24, 26–29). The methyl ketones **3** and **4** (entries 6–8 and 18–20) and the isopropyl ketones **6** and **7** (entries 23, 24, and 26–29) gave products of the same configuration and in similar ratios under comparable experimental conditions. The α′-substitution patterns in these acyclic substrates did not affect the stereochemical outcome in reactions with primary alkyl cuprates. The stereoselectivities of these reactions were high in Et_2O (88–96%) but generally decreased for the acyclic substrates when less reactive cuprates (e.g., Me_2CuLi) were employed in THF (entries 19, 20, and 27). In fact, replacement of the diethyl ether of a commercial methyllithium solution with THF resulted in essentially no stereoselectivity (entry 20). The methylcuprate did give good selectivity (90%) in THF with **5** which contained a phenylthio leaving group (entry 22). Enone **5** (X = Ph), however, afforded lower selectivity (86 vs. 96%) than enone **4** (X = CH_3) in Et_2O under conditions leading to net inversion of configuration (entries 18 and 21). Although the selectivities were temperature-dependent (entries 2, 3, 7, 8 24, and 27), the results are obscured since Me_2S was often used as an additive to facilitate the reaction at lower temperatures. It is important to note that in one experiment, 1.4 g of **4** underwent reaction with Me_2CuLi in ether to afford enone **15a** in 92% yield as a 92:8 mixture of *E* and *Z* stereoisomers.

The cyclohexenone *E* vinylogous thiol ester **8** reacted with primary alkylcuprates with net inversion of configuration in ether (entry 30) while the 3-isopropoxy analogue **9** reacted with retention of configuration in either ether or THF (entries 31–34). The cyclohexanone derivatives **10–11** afforded a more complicated pattern. Reaction of **10** with *n*-butylcuprates gave extremely variable results with various cuprate compositions. *n*-Bu_2CuLi gave retention in both ether and THF while [*n*-$Bu_2CuSCN]Li_2$ gave inversion in ether and no selectivity in THF (entries 35–38). Similarly, $(Me_2CuSCN)Li_2$ gave inversion of configuration in ether with modest selectivity (entries 42 and 43). In general, the reactions of primary alkylcuprates with the six-membered ring analogues **8–11** consistently afforded lower stereoselectivities (68–80% for R_2CuLi) than the corresponding five-membered ring or acyclic substrates. Interestingly, the highest stereoselectivities (83–92%) were obtained with the higher order cuprates $[R_2CuSCN]Li_2$ in reactions with cyclohexenones **8–9** (entries 30, 32, and 34).

Vinylogous thiol esters **12–13** containing an α-methyl substituent also underwent reaction with primary alkylcuprates with net inversion of configuration in ether (entries 44–46). In this instance, the more reactive and thermally unstable *n*-Bu_2CuLi gave no selectivity with **12** while Me_2CuLi gave excellent selectivity (94%) with **13** even though the solution was allowed to warm from −78 to 0 °C. Reaction of **12** with [*n*-$Bu_2CuSCN]Li_2$ did afford excellent selectivity (90%).

Treatment of vinylogous thiol esters containing a primary β-alkyl substituent with secondary and tertiary al-

(11) Brunelle, D. J. Ph.D Dissteration, The John Hopkins University, Baltimore, MD, 1974. The assignment of *E* and *Z* configurations for the starting β-alkylthio α,β-enones and products presented in eq 5 and 6 are reversed from those given in the Dissertation. The value of δ 2.10 given for the β-methyl substituent of (*Z*)-4-methyl-3-octen-2-one (p 147) is more consistent with the *E* isomer. See ref 12.

Table I. Substitution Reactions of *E* β-Alkylthio α,β-Enones Containing a β-Primary Alkyl Substituent with Organocuprates

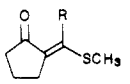
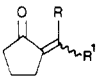
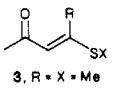
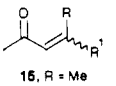
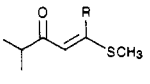
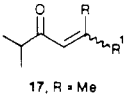
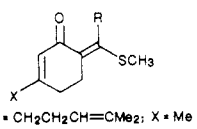
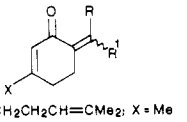
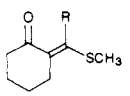
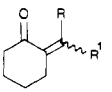
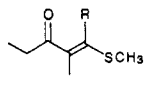
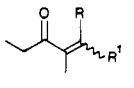
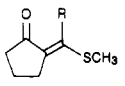
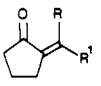
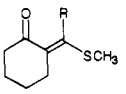
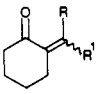
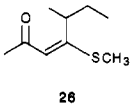
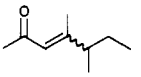
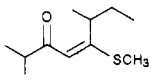
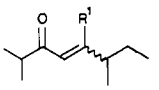
entry	substrate	cuprate ligand R^1	cuprate[d]	solvent[e]	temp, °C	product, (*E*:*Z*)[a-c]	% yield[f]	config[g]
	 1, R = Me					 14, R = Me		
1		**a**, *n*-Bu	A	Et_2O	−78	(12:88)[a]	84	I
2			A	THF	−60	(88:12)[a]	90	R
3			A	THF, Me_2S	−78	(90.2:9.8)[a]	78	R
4		**b**, R = *t*-Bu	A	Et_2O, Me_2S	−60	(25:75)[a]	80	I
	2, R = *n*-Bu					**14**, R = *n*-Bu		
5		**a**, Me	A	Et_2O, Me_2S	−78	(93:7)[a]	83	I
	 3, R = X = Me					 15, R = Me		
6		**a**, *n*-Bu	A	Et_2O	−65	(4.9:95.1)[a]	97	I
7			A	THF	−65	(70:30)[a]	87	R
8			A	THF, Me_2S	−78	(97.4:2.6)[a]	93	R
9		**b**, *sec*-Bu	B	Et_2O	−55	(92:8)[a,b]	60	R
10			A	Et_2O, Me_2S	−55	(80:20)[b]	60	R
11			B	Et_2O	−40	(46:54)[a]	98	I
12			B	Et_2O	−60	(61:39)[a]	45	R
13			B	THF	−60	(78:22)[a]	51	R
14			A	THF, Me_2S	−40	(94:6)[b]	58	R
		c, *t*-Bu						
15			B	Et_2O	−60	(59:41)[a]	68	R
16			A	THF	−60	(78:22)[a]	36	R
17			A	THF	−50	(>95:5)[b]	52	R
	4, R = *n*-Bu; X = Me					**15**, R = *n*-Bu		
18		**a**, Me	A	Et_2O	−65	(96.3:3.7)[a]	95	I
19			A	THF	−35	(30:70)[a,b]	77	R
20			A	THF[h]	−65	(46:54)[a]	76	R
	5, R = *n*-Pr; X = Ph					**16**, R = *n*-Pr		
21		Me	A	Et_2O, Me_2S	−60	(86:14)[a]	93	I
22			A	THF, Me_2S	−35	(10:90)[a]	81	R
	 6, R = Me					 17, R = Me		
23		**a**, *n*-Bu	A	Et_2O	−78	(4:96)[a]	98	I
24			A	THF, Me_2S	−18	(60:40)[a]	79	R
25		**b**, *sec*-Bu	B	Et_2O	−58	(11:89)[a]	85	I
	7, R = *n*-Bu					**17**, R = *n*-Bu		
26		**a**, Me	A	Et_2O	−78	(91:9)[a]	99	I
27			A	THF	−18	(33:67)[a]	89	R
28			C	Et_2O	−78	(84:16)[a]	86	I
29			B	Et_2O	−78	(93:7)[a]	90	I
	 8, R = $CH_2CH_2CH{=}CMe_2$; X = Me					 18, R = $CH_2CH_2CH{=}CMe_2$; X = Me		
30		Me	B	Et_2O	−60	(83:17)[c]	100	I
	9, R = Me; X = O-*i*-Pr					**19**, R = Me; X = O-*i*-Pr		
31		*n*-Bu	A	Et_2O, Me_2S	−63	(76:24)[b,c]	95	R
32			B	Et_2O	−60	(92:8)[b,c]	100	R
33			A	THF, Me_2S	−30	(77:23)[b,c]	98	R
34			B	THF	−55	(85:16)[b,c]	90	R
	 10, R = Me					 20, R = Me		
35		**a**, *n*-Bu	A	Et_2O, Me_2S	−60	(68:32)[c]	69	R
36			B	Et_2O	−60	(20:80)[c]	32	I
37			B	THF	−60	(50:50)[a]	55	
38			A	THF, Me_2S	−60	(80:20)	78	R
39		**b**, *sec*-Bu	A	Et_2O, Me_2S	−78	(30:70)[a,c]	99	I
40		**c**, *t*-Bu	A	Et_2O, Me_2S	−58	(54:46)[c]	70	R
41			B	Et_2O	−78	(>95:5)[b]	47	R
	11, R = *n*-Bu					**20**, R = *n*-Bu		
42		**a**, Me	B	Et_2O	−57	(70:30)[a]	75	I
43			B	Et_2O	−45	(77:23)[a]	96	I

Table I (Continued)

entry	substrate	cuprate ligand R^1	cuprate[d]	solvent[e]	temp, °C	product, (E:Z)[a-c]	% yield[f]	config[g]
	 12, R = Me					 21, R = Me		
44		*n*-Bu	A	Et_2O	−78	(50:50)[a]	79	
45			B	Et_2O	−78	(10:90)[a]	99	I
	13, R = *n*-Bu					21, R = *n*-Bu		
46		Me	A	Et_2O	0	(94:6)[a]	95	I

[a] Isomer ratios determined by VPC. [b] Isomer ratios determined by NMR integrations. [c] Isomer ratios determined from isolated products. [d] Cuprates: A = R_2CuLi. B = $(R_2CuSCN)Li_2$. C = $(Me_2CuCN)Li_2$. [e] The solvent indicated is diluted with the solvent of the commercial or prepared alkyllithium reagents in ratios between 5:1 and 13:1. These solvents are diethyl ether for methyllithium and (4-methyl-3-pentenyl)lithium, hexane for *n*-butyllithium, cyclohexane for *sec*-butyllithium, and pentane for *tert*-butyllithium. [f] Yields are based upon isolated products existing as mixtures of diastereomers. [g] Net stereoselectivity of the reaction: I = inversion of configuration. R = retention of configuration. [h] Et_2O from the methyllithium solution was removed and replaced with THF prior to cuprate preparation.

Table II. Substitution Reactions of *E* β-Alkylthio α,β-Enones Containing Secondary and Tertiary β-Alkyl Substituents with Organocuprates

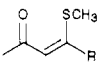
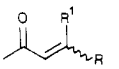
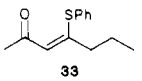
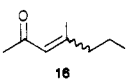
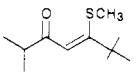
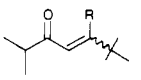
entry	substrate	cuprate ligand R^1	cuprate[d]	solvent[e]	temp, °C	product, (E:Z)[a-c]	% yield[f]	config[g]
	 22, R = c-C_3H_5[h]					 28, R = c-C_3H_5		
1		Me	C	Et_2O	−78	(95:5)[a]	97	I
	23, R = *t*-Bu					14b, R = *t*-Bu		
2		Me	A	Et_2O, Me_2S	−55	(>95:5)[b]	85	I
						29, R = *t*-Bu		
3		*sec*-Bu	B	Et_2O	−50	(10:90)[a]	73	R
	 24, R = *sec*-Bu					 20b, R = *sec*-Bu		
4		Me	B	Et_2O	−60	(>78:22)[c]	87	I
	25, R = *t*-Bu					20c, R = *t*-Bu		
5		Me	A	Et_2O	−55	(>5:95)[b]	88	R
6			B	Et_2O	−62	(>5:95)[b]	88	R
	 26					 15b		
7		Me	A	Et_2O	−50	(96:4)[a,b]	80	I
8				THF, Me_2S	−68	(65:35)[a]	94	I
9				THF	−50	(55:45)[a]	51	I
	 27					 17b		
10		Me	A	Et_2O, Me_2S	−65	(96:4)[a]	78	I

[a] Isomer ratios were determined by VPC. [b] Isomer ratios were determined by NMR integration. [c] Isomer ratios were determined from isolated products. [d] Cuprates: A = R_2CuLi. B = $(R_2CuSCN)Li_2$. C = $(Me_2CuCN)Li_2$. [e] The solvent indicated is diluted with the solvent of the commercial alkyllithium reagents in ratios between 5:1 and 13:1. These solvents are diethyl ether for methyllithium and cyclohexane for *sec*-butyllithium. [f] Yields are based upon isolated products existing as a mixture of diastereomers. [g] Net stereoselectivity of the reaction: I = inversion of configuration. R = retention of configuration. [h] A 70:30 mixture of *E*:*Z* isomers.

kylcuprates afforded mixed results (Table I). Reaction of cyclohexanone **10** (entry 39) and isopropyl enone **6** (entry 25) with *sec*-Bu_2CuLi and [*sec*-$Bu_2SCN]Li_2$, respectively, occurred with net inversion of configuration in ether while reaction of methyl enone **3** with *sec*-Bu_2CuLi yielded net retention in either ether or THF (entries 10, 14). The higher order cuprate [*sec*-$Bu_2CuSCN]Li_2$ afforded variable selectivity in ether (92–46% retention) with **3** but generally gave retention in both ether and THF (entries 9 and 11–13). Thus, the methyl (**3**) and isopropyl (**6**) ketones afforded products of opposite configuration upon reaction with secondary alkylcuprates in contrast to the insensitivity of the reactions to the α′-substitution pattern when primary alkylcuprates were employed. Reaction of vinylogous thiol esters containing a primary β-alkyl substituent with tertiary alkylcuprates in ether resulted in inversion of configuration for cyclopentanone **1** (entry 4) and retention for cyclohexanone **10** (entries 40 and 41). Methyl ketone **3** afforded net retention in either ether or THF (entries 15–17). The selectivity was modest for **1** and poor to excellent for **3** and **10**, varying with reaction conditions and individual runs.

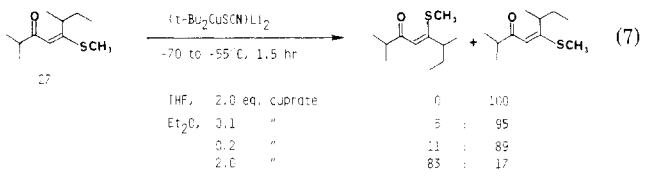
The *E* vinylogous thiol esters **22**, **24**, **26**, and **27** containing a β-secondary alkyl substituent all underwent reaction with lithium dimethylcuprate in diethyl ether with net inversion of configuration (Table II, entries 1, 4, 7, and 10). The stereoselectivity was excellent for the five-membered ring and acyclic substrates (≥95:5) and moderate (78:22) for the six-membered ring substrate, consistent with earlier observations. It is synthetically noteworthy that

Table III. Substitution Reactions of *Z* β-Alkylthio α,β-Enones with Organocuprates

entry	substrate	cuprate ligand R^1	cuprate[c]	solvent[d]	temp, °C	products (*E*:*Z*)[a,b]	% yield[e]	config[f]
	 30, R = Me					 15a, R = Me		
1		*n*-Bu	A	Et_2O	−78	(4:96)[a]	61	R
2			A	THF	−78	(8:92)[a]	64	R
	31, R = *sec*-Bu					**15b**, R = *sec*-Bu		
3		Me	B	Et_2O	−78	(95:5)[a]	93	R
	32, R = *t*-Bu					**15c**, R = *t*-Bu		
4		Me	B	Et_2O	−60	(>95:5)[b]	88	R
	 33					 16		
5		Me	A	Et_2O	−78	(97:3)[a]	91	R
6			A	Et_2O, THF	−78	(93:7)[a]	69	R
	 34					 35		
7		**a**, Me	A	Et_2O, Me_2S	−60	>(95:5)[b]	76	R
8		**b**, *sec*-Bu	B	Et_2O	−78	(11:89)[b]	44	I

[a] Isomer ratios were determined by VPC. [b] Isomer ratios were determined by NMR integration. [c] Cuprates: A = R_2CuLi. B = $(R_2CuSCN)Li_2$. C = $(Me_2CuCN)Li_2$. [d] The solvent indicated is diluted with the solvent of the commercial alkyllithium reagents in ratios between 5:1 and 13:1. These solvents are diethyl ether for methyllithium, hexane for *n*-butyllithium, and cyclohexane for *sec*-butyllithium. [e] Yields are based upon isolated products existing as a mixture of diastereomers. [f] Net stereoselectivity of the reaction: I = inversion of configuration. R = retention of configuration.

2-(1-(methylthio)-1-cyclopropylmethylene)cyclopentanone existing as a 70:30 *E*/*Z* mixture underwent reaction with $(Me_2CuCN)Li_2$ to afford 2-(1-cyclopropylethylidene)-cyclopentanone as a 95:5 *E*/*Z* mixture (entry 1). The methyl ketone **26** afforded very little selectivity in THF with overall net inversion (entries 8 and 9). Reaction of isopropyl enone **27** containing a β-*sec*-butyl substituent with a tertiary alkyl cuprate afforded a very low yield of substitution product and gave predominantly isomerization of the *E* vinylogous thiol ester to the *Z* isomer in 64% yield. This isomerization process was dependent upon the amount of organocopper reagent present and occurred only in ether (eq 7). Treatment of the *Z* isomer of enone **27**



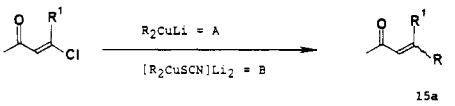
(7)

with 2 equiv of $(t\text{-}Bu_2CuCN)Li_2$ in ether afforded isomerization to give a 19:81 *E*/*Z* isomer mixture.

The *E* vinylogous thiol esters **23** and **25** containing a β-*tert*-butyl substituent afforded products with either retention or inversion of configuration depending on substrate structure and branching of the cuprate transferable ligand (Table II). Cyclopentanone **23** afforded inversion of configuration with Me_2CuLi and retention with [*sec*-$Bu_2CuSCN]Li_2$ (entries 2 and 3) while cyclohexanone **25** afforded retention with methyl cuprates (entries 5 and 6). In the latter reaction, dialkyl and higher order thiocyanate cuprates afforded identical yields and stereoselectivities.

The *Z* vinylogous thiol esters **30–34** containing either a primary, secondary, or tertiary β-alkyl substituent all underwent reaction with primary alkylcuprates with net retention of configuration in either ether or THF (Table III, entries 1–7). The stereoselectivity in all instances was very high (≥92:8). Reaction of isopropyl enone **34** containing a β-*tert*-butyl substituent with a *sec*-butylcuprate proceeded in a highly stereoselective manner with inversion of configuration (entry 8).

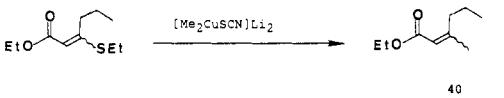
The reactions of β-chloro enones **36–37** with *n*-Bu_2Li and $[Me_2CuSCN]Li_2$, respectively, exhibited very poor stereoselectivity with net inversion of configuration in either ether or THF (eq 8). The *E* and *Z* β-alkylthio α,β-enoates



eq. 8

	R^1	R	Reaction Conditions	(E:Z)	% Yield	Confg
36	Me	n-Bu	A Et_2O, Me_2S, −65°C	(40:60)	89	I
			A THF, Me_2S, −78°C	(35:65)	68	I
37	n-Bu	Me	B Et_2O, −60°C	(70:30)	68	I
			B THF, −60°C	(58:42)	68	I

38–39 reacted with primary alkylcuprates to afford substitution products with net retention of configuration in either ether or THF (eq 9). Interestingly, the *E* isomer



eq. 9

Isomer	Reaction conditions	(E:Z)	% Yield	Config
38 E	Et_2O, 25°C, 12 h	(50:50)	53	
	THF, 25°C, 12 h	(10:90)	72	R
39 Z	Et_2O, −78°C	(99:1)	99	R
	THF, 0°C	(90:10)	82	R

was less reactive than the *Z* isomer and the selectivity appeared to be rather insensitive to the quenching temperatures. The *E* isomer gave no selectivity in ether.

Discussion

The investigation of stereoselectivity in these substitution reactions required a method for assigning olefin configuration in the starting vinylogous thiol esters and

product α,β-enones. Fortunately, it is well-documented that a β-methyl substituent syn to a ketone or ester carbonyl in α,β-unsaturated carbonyl compounds resonates downfield relative to the anti methyl substituent in the NMR spectrum.[2,12] Consequently, the NMR chemical shifts of the β-methyl, β-methylene, or γ-methine protons of β-secondary alkyl substituents provide a reliable guide for the assignment of olefin configuration. In many instances, the *E* and *Z* α,β-enones were independently obtained as the major products in separate experiments by utilization of complimentary substrate–cuprate pairs. This facilitated purification of the individual *E* and *Z* isomers and permitted lower limits on the stereoselectivity to be readily established from the NMR spectrum of the crude product mixture. Isomer ratios determined by VPC analysis or by weight of purified products were generally consistent with those established from the NMR spectrum of the crude product mixture. α,β-Enones **14b**, **28**, and **35a**, however, underwent partial isomerization on the VPC column or during chromatographic purification, distorting the isomer ratios originally obtained from the substitution reaction as determined by NMR analysis of the crude reaction mixture. The assignment of olefin stereochemistry to (*E*)- and (*Z*)-**21** was made on the basis of the chemical shifts (δ 1.80, *E* isomer; δ 1.67 *Z* isomer) of the β-methyl absorptions. This trend is consistent with the assignment of the methyl absorptions in 4,5-dimethyl-4-hexen-3-one (C2-Me, δ 1.79; β-syn Me, 1.79; β-anti Me, 1.77), although 4,5-dimethyl-3-penten-2-one exhibits the same chemical shift (δ 1.81) for the β-syn and β-anti methyl groups.[13]

Vinylogous thiol esters **25**, **32**, and **34** containing a β-*tert*-butyl substituent initially posed some difficulty in the assignment of olefin configuration. The assignment of (*E*)-**25** was made by analogy with (*E*)-**23** which was determined by X-ray analysis[2] while (*Z*)-**32** and (*Z*)-**34** were assigned on the basis of difference NOE experiments. The assignment of the *Z* configuration to **32** and **34** was consistent with the NMR chemical shifts of the α-olefinic protons in these substrates.[2]

Despite a decade of intensive investigation, the mechanism of organocopper conjugate addition reactions is not well-understood. Mechanistic investigations are hampered by the lack of information on the actual structures of the cuprate reagents, their state of aggregation in various solvents, and the nature of intermediates involved in these very fast reactions. The picture is further clouded by the myraid cuprate compositions that can be prepared[14] which afford the same basic transformation but give rise to subtle differences in yields, stereoselectivity, and chemoselectivity.[2] Recently, it has been shown that the method of preparation can lead to four different reagents with the composition Me_2CuLi.[15]

The original proposal of House[16] involving a single electron transfer explains the correlation between enone reduction potential and the facility of an enone for conjugate addition. Nevertheless, recent studies have increasingly suggested that the reaction proceeds by direct nucleophilic addition of the cuprate to the β-carbon atom of the enone.[17,18] Spectroscopic[16c,17d,19] studies and the influence of coordinating solvents[16b,20] on the reaction rate have indicated the importance of a cuprate–enone complex in the initial stages of the reaction. Early suggestions[16c,17d] centered on an enone oxygen–cuprate lithium interaction, although it is not clear that the oxygen orbitals containing the lone pairs have the correct geometry[21] to interact, in a face to face approach, with a lithium atom in a planar cuprate cluster. This approach geometry would more likely involve interaction of the lithium atom with the π-bond of the carbonyl.[22] In addition, it seems unlikely that a planar cuprate cluster could span with equal facility the oxygen and β-carbon atoms of a trans and cis enone[23] which undergo conjugate addition reactions with equal facility.[17d] These difficulties could undoubtedly be circumvented by interaction of the enone with several cuprate units in an aggregate.

More recently, several workers have suggested that the initial complex involves the carbon–carbon double bond[17e,18,19,24,25] and the cuprate reagent and the principal interaction has been pictured as involving filled d orbitals on copper with the π-antibonding orbital of the enone. Low temperature ^{13}C NMR studies of enoate/cuprate mixtures exhibit upfield shifts for the olefinic carbons consistent with an electron-rich olefin–copper π-complex.[19] Although two intermediate complexes were detected in the proton NMR spectrum, those resonances attributed to a lithium–oxygen complex are absent when LiI is removed from the reaction mixture. This study could not, however, rule out the potential existence or importance of a Li–O coordination within the observable olefin–copper π-complex. The role of lithium within the complex is clearly important[26] since the rate of organocopper conjugate ad-

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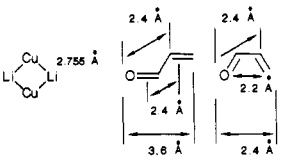
(21) A recent study of the geometry of europium–ketone complexes provides evidence for a linear (180°) rather than bent (120°) C–O–Eu bond angle. In this view, the lone pairs on oxygen are located in nonequivalent p and sp orbitals. Although experimental evidence indicates a bent geometry for protonated carbonyl groups (H–O–C, 115°), molecular orbital calculations (STO-3G and STO-3/21G) indicate a linear geometry for Li^+. A linear geometry appears to be preferred when the cation can function as "both a σ and π acceptor". See: Raber, D. J.; Janks, C. M.; Johnston, M. D., Jr.; Raber, N. K. *J. Am. Chem. Soc.* **1980**, *102*, 6591.
(22) An X-ray study of ketone enolate anions has indicated the possibility of "electron donation from the C=C π-bonds" to the Li atoms in an aggregate. See: Williard, P. G.; Carpenter, G. B. *J. Am. Chem. Soc.* **1986**, *108*, 462.
(23) The Cu···Li distances in the planar cuprate species $[Cu_2Li_2(C_6H_4CH_2NMe_2\text{-}2)_4]$ were found to be 2.730 and 2.775 for a mean value of 2.755 Å. See: van Koten, G.; Jastrzebski, J. T. B. H.; Muller, F.; Stam, C. H. *J. Am. Chem. Soc.* **1985**, *107*, 697. The linear distances C_α—O, C_β—O, and $C{=}O_{midpoint}{-}C{=}C_{midpoint}$ as measured from Dreiding molecular models are indicated below:



(24) (a) Berlan, J.; Battioni, J.-P.; Koosha, K. *Bull. Soc. Chim. Fr.* **1979**, 183; (b) *J. Organomet. Chem.* **1978**, *152*, 359; (c) *Tetrahedron Lett.* **1976**, 3351.
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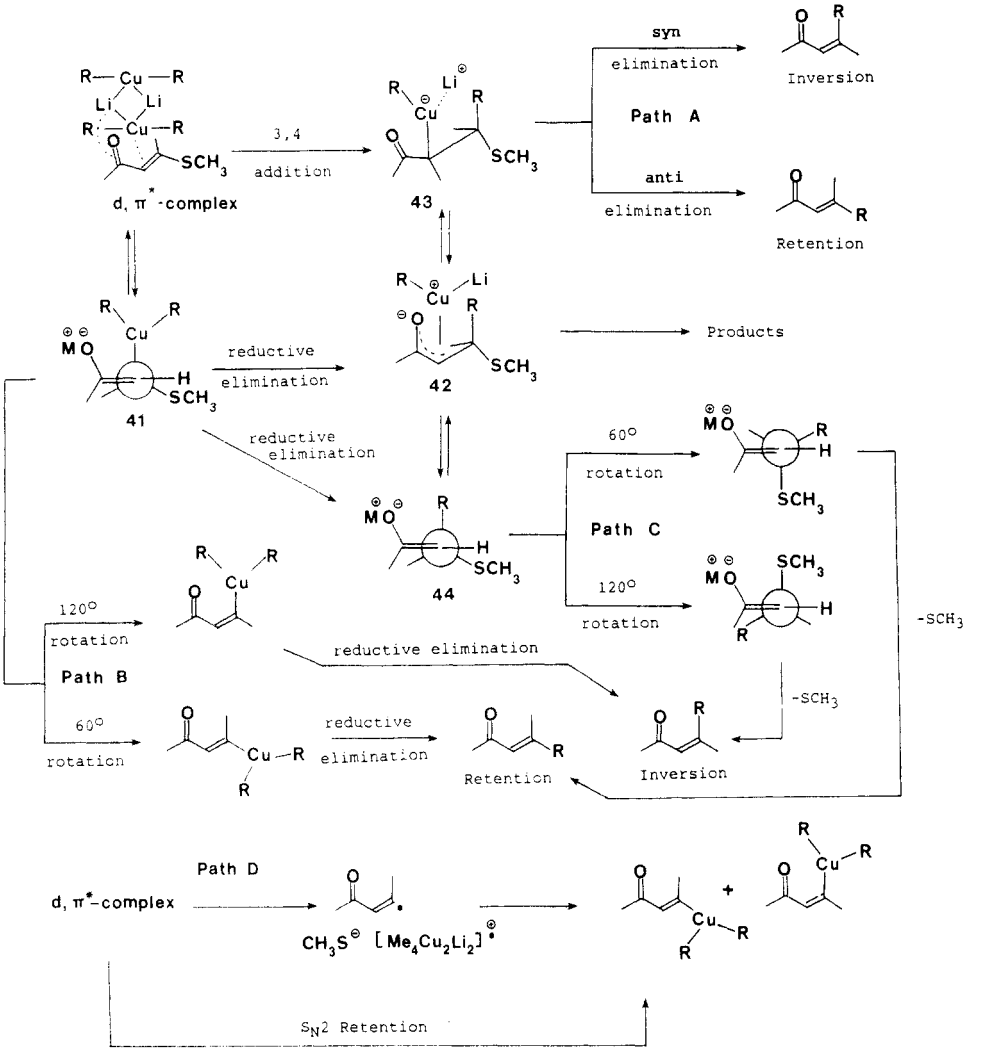
Scheme I



dition reactions is slowed in the presence of external ligands such as THF and halide ions.[16b,20] Consideration of bond lengths in α,β-enones and in a neutral diarylcuprate obtained from an X-ray structure[23] reveal several interesting relationships. The Li and Cu atoms in a planar metal cluster can easily span the O and β-C atoms in a cisoid enone but not in a transoid enone. Alternatively, arbitrary positioning of the Cu atom at the midpoint of the C=C places the C=O over the Li atom in both the transoid and cisoid enones. The overlap is not quite as good for the cisoid enone because of the shorter distance between the midpoints of the C=O and C=C bonds (2.2 Å vs. 2.4 Å). This favorable geometry allows consideration of a two-point contact involving olefin–copper and carbonyl–lithium π-complexes.

At this point the various mechanistic schemes converge with collapse of the complex or combination of the radical ions to form a Cu(III) species (Scheme I, **41**) which has never been detected spectroscopically and is invoked by analogy with Au(I) chemistry.[18b,20,27] It has been suggested that the Cu(III) intermediate can be avoided by invoking participation of both copper atoms in the cuprate dimer.[28] Reductive elimination from the Cu(III) intermediate leads to a species which has been formulated as an enolate–copper π-complex (**42**),[17e] an α-cuprio ketone (**43**),[24,25] or as copper[29] or lithium (**44**)[16a,b,30] enolates. Investigations by House have provided evidence for the formation of intermediate lithium enolate anions at 0 °C although it could not be determined whether the conjugate adduct which was insoluble at low temperatures (−44 to −78 °C) was a lithium or copper enolate.[16a,b,30] The nature of the enolate anion generated by organocopper conjugate addition remains a point of controversy.[31]

Several workers have suggested an alternative mechanism involving direct addition of the Cu–R bond across the C=C to afford an α-cuprio ketone (Scheme I, d,π* complex → **43**).[24,25] In this context, it is interesting to note that the Cu–Li bond distance is quite similar to the enone O–C_α distance[23] and molecular orbital calculations indicate an empty p-orbital on Cu perpendicular to the plane of the metal atoms.[32] There are, however, conceptional difficulties with this view. First, the olefin π-orbitals are orthogonal to the Cu–R bond, although the addition could be represented in a manner similar to that depicted for

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hydroboration (e.g., $[\pi^2s + \sigma^2a + \omega^0s]$).[33] Second, the coefficient at C_α in the enone LUMO is relatively small[34] and would give rise to a small bonding interaction.[35] Third, several investigators[18b,36] have observed olefin isomerization prior to conjugate addition which is more plausibly explained by either the SET mechanism[36] or reversible formation of the β-Cu(III) σ-complex.[17e,18b]

Although the substitution reactions of vinylogous thiol esters with organocuprates could proceed by a concerted S_N2[37] or oxidative addition[38] process similar to those proposed for the substitution reactions of vinyl halides with cuprates,[39] the addition–elimination pathway originally proposed by Casey[6c] seems more plausible. This is particularly so since the vinyl halide reactions proceed with retention of configuration and the vinylogous thiol ester substitutions display variable configurational selectivity. The addition–elimination pathway, however, can accommodate all of the proposed mechanistic schemes (Scheme I), assuming that radical recombination is faster than bond rotations. An investigation of vinylogous thiol ester stabilities indicated that product distributions were kinetically controlled in the substitution reactions of α-oxo ketene dithioacetals with organocuprates.[2] The high stereoselectivities in reactions leading to enones with similar substituents at the β-carbon atom (e.g., *n*-Bu and Me) of the present study also suggest a kinetically controlled process. The complex results ranging from highly selective inversion, thru nonstereoselective, to highly selective retention can best be explained by an addition–elimination sequence in which the stereochemistry of the process is determined in the elimination step (i.e., $k_{el} > k_{rot.}$). The elimination event can, in principle, occur from the Cu(III) (path B), α-cuprio ketone (path A), or enolate (path C) intermediate. Elimination of the leaving group prior to reductive elimination (path B) could occur and would be dependent upon the relative rates of the two processes. If reductive elimination and leaving group expulsion occur at rates roughly of the same magnitude, then the relative rates of the two processes could be inverted by subtle changes in cuprate reagent, substrate structure, or reaction conditions. A vinyl copper species has been postulated as an intermediate in the reductions of β-acetoxy analogues and was implicated by deuterium trapping experiments.[6c] Although vinylcuprate intermediates could also arise via a SET mechanism involving configurationally unstable vinyl radical intermediates[40] (path D), this model appears unlikely since it would need to accommodate the observed high stereoselectivities with the rapid rate of vinyl radical inversion [$k_{inversion}$ (−180°) ≥ 3×10^7 s^{-1} for the 1-propenyl radical]. In addition, this pathway would be expected to afford substantial quantities of reduction products arising from H-abstractions as steric interactions become more substantial in the cuprate reagent/substrate interaction. Although these reduction products were occasionally seen, they were present as very minor components of the product mixtures even for the sterically hindered reactant pairs. Consequently, reduction of the C–S bond by SET from the cuprate appears to be a minor noncompetitive reaction pathway. Naso and co-workers[41] have recently concluded that this pathway is not involved in the analogous substitution reactions of 1-halogeno-2-phenylethylenes and 1-halogeno-2-(phenylsulfonyl)ethylenes. α-Cuprio ketone intermediates can, in principle, also afford products with net retention or inversion of configuration via an anti or syn elimination, respectively, of "Cu–SCH_3" and need not arise by a direct addition process (**42** → **43**, path A). In these addition–elimination mechanisms the stereochemical outcome results from a competitive play between the relative rates of elimination (k_{el}) and bond rotations ($k_{rot.}$) which will be influenced by solvent, substituents, substrate structure (cyclic, acyclic, etc.), and nature of the intermediate enolate.

In organocopper conjugate addition mechanisms involving either SET or nucleophilic addition of copper to the β-carbon of the enone, addition of a cuprate reagent to a vinylogous thiol ester should lead to an intermediate enolate anion or α-cuprio ketone containing a good leaving group at the γ-carbon atom (paths B and C). In order for this leaving group to be expelled by the enolate anion, there must be rotation about the γ-carbon atom so that the C–S bond of the leaving group and the enolate π-cloud can achieve an antiperiplanar arrangement necessary for facile elimination. This can be achieved by a 60% rotation leading to retention of configuration or a 120° rotation leading to inversion of configuration.[42] The concept of minimum motion in the transition state should favor a 60° motion leading to retention of configuration and this should be exaggerated by any structural feature or medium effect that would tend to accelerate the elimination process. A theoretical rationale for preferential 60° rotation involves hyperconjugation between the π orbital and the σ*(C–L) orbital of the leaving group. A 60% motion allows continuous overlap of the orbitals involved while a 120° rotation must pass thru an orthogonal arrangement.[42b,43] This picture is, indeed, very much in accord with the experimental results. In the very effective coordinating solvent THF the reaction proceeds with predominant retention of configuration in all instances but two. Here, the coordinating solvent (which coordinates to Li^+) affords an unencumbered more basic enolate anion[44] favoring rapid elimination leading to retention of configuration. In Et_2O, a less effective coordinating solvent, the reaction generally affords inversion of configuration. The cyclohexenone **9** containing a 3-isopropoxy substituent, however, affords net retention in ether in contrast to the 3-methylcyclohexenone **8**. In the former case the resonance participation of the 3-isopropoxy substituent favors rapid elimination overriding the solvent influence. In a similar manner, the tendency of the ester analogues to afford high selectivity with net retention of configuration in THF or no selectivity (eq 9, for the *E* isomer) in ether is consistent with the more basic ester enolate anion favoring rapid elimination of the leaving group. This is also consistent with the general observation that k_{el} becomes smaller as charge dispersal becomes greater in the intermediate carbanion[42b] involved in the addition–elimination pathways. This rationale does not explain, however, why poorer selectivity was obtained

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with Me_2CuLi in pure THF which was not diluted with Et_2O from the methyllithium solution (Table I, entries 19 and 20). Here, prior isomerization of the starting material is a possibility (vide infra). The nonstereoselective reaction of ester **38** with Me_2CuLi in Et_2O (eq 9) results from a competition between the more basic enolate favoring rapid elimination with retention and those factors favoring elimination with inversion in Et_2O. This is also seen for ketones **4** and **5** where the substrate with the better leaving group[9g] affords poorer selectivity in Et_2O (Table I, entries 18 and 21). The two reactions yielding inversion in THF involve enone **26** (Table II, entries 8 and 9) containing a β-*sec*-butyl substituent and the observed poor selectivity with net inversion can be understood either in terms of pre- and/or postisomerization events or rotomer distributions in the intermediate enolate anion prior to elimination. In the latter scenerio, motion of the *sec*-butyl group past the enolate oxygen atom and its attendent solvent shell should be sterically disfavored.

It is interesting that the less reactive Me_2CuLi[16b] affords much poorer selectivity in THF than in ether. THF is known to slow down the rate of organocopper conjugate addition reactions by coordinating with the cuprate cluster.[16b,20] However, if the elimination step is crucial in determining the stereochemical outcome of the reaction, then the initial addition process might be expected to have relatively little influence. The possibility exists, however, that if the rate of conjugate addition is slow with Me_2CuLi in THF, then competitive isomerization of the substrate can occur, affording poor stereoselectivity since both the *E* and *Z* vinylogous thiol esters undergo substitution in THF with net retention of configuration. Nevertheless, the stereoselectivity obtained with Me_2CuLi can be increased by changing the leaving group[9g] from SMe to SPh (compare entries 19, 20, and 22, Table I) although this conclusion must be tempered by the fact that Me_2S was used as an additive in the latter experiment. The effect of added Me_2S, if any, is unclear since it makes a large difference in some cases (entries 7 and 8, Table I) and little or none in others (entries 2, 3, and 24, Table I). The coupling of cuprate reactivity with leaving group ability, if real, raises the possibility that if reductive elimination is slow and elimination of the leaving group is fast then formation of a vinylcuprate may occur (path B). This type of an intermediate has been invoked[6c] to account for the formation of reduction products in these substitution reactions, although whether it is formed by direct substitution, SET, or addition–elimination is open to question. Alternatively, the coupling of cuprate reactivity with leaving group ability can be accommodated by the variable transition state postulated for nucleophilic vinylic substitution.[42b]

The tendency of the substitution reaction with *E* vinylogous thiol esters (α,β-enones) to afford products with predominant inversion of configuration in ether is in marked contrast to the general tendenacy of the ester analogues to give retention of configuration. Again, if the events leading to conjugate addition are fast, then the stereochemistry of the substitution should be determined in the elimination step. Inversion of configuration, however, requires a 120° rotation about the β–γ C–C bond prior to elimination of the methylthio substituent in opposition to the general preference for 60° rotation.[42b,43] This can be rationalized by invoking S–Cu complexation in the less coordinating solvent, Et_2O, which would of necessity require 120° rotation of the sulfur substituent to the same face of the enone as the approaching or complexed cuprate reagent.[45] Evidence for this sulfur–copper complexation involves the isomerization of (*E*)-**26** to (*Z*)-**26** when treated with (t-$Bu_2CuSCN)Li_2$ in ether (eq 7). Pure (*E*)-**26** and (*Z*)-**26** afforded the same *E*/*Z* isomer ratio, suggesting an equilibrium process, although these isomer ratios could not be obtained with catalytic amounts of the cuprate reagent. Equilibration in the presence of the cuprate favors the *Z* isomer while equilibration with HCl in $CDCl_3$ favors the *E* isomer (81:19, *E*/*Z*). This isomerization process did not occur in THF in contrast to a recent report that 4-phenyl-3-buten-2-one underwent isomerization in ether or THF with Me_2CuLi at temperatures below that required for conjugate addition.[18b] This isomerization process was viewed as involving equilibration between a cuprate–olefin π-complex and β-Cu(III) σ-complex.

Alternatively, inversion of configuration in ether could result from initial isomerization of the *E* vinylogous thiol ester to the *Z* isomer which undergoes reaction with retention of configuration in either ether or THF. Qualitatively, the *Z* isomers have appeared to be more reactive than the *E* isomers, consistent with an earlier report on α,β-unsaturated sulfones.[41] In this view, retention of configuration is the normal process and is subverted in ether by intervention of an isomerization pathway. Reaction of the *Z* isomers with retention of configuration in ether is also consistent with the Cu–S complexation postulate since the spatially proximate enolate oxygen atom should interfere with this complexation.

Examination of Tables I–III, however, reveals that those reactions of *E* vinylogous thiol esters which give retention of configuration in ether involve either sterically hindered substrates (Table I, entries 44–46, and Table II, entries 5 and 6) or sterically hindered transferable cuprate ligands (Table I, entries 9, 10, 12, 15, 35, 40, and 41, and Table II, entries 3 and 12). These steric interactions could either significantly slow down conjugate addition relative to isomerization, alter the rotomer distribution in the enolate anion **44** prior to elimination, or retard reductive elimination relative to leaving group expulsion (path B). The observation that retention of configuration in ether is obtained when steric hinderance is present in the substrate or cuprate reagent favors the view that rotomer distributions in the enolates **41** or **44** are responsible for the observed isomer ratios since these are the very systems that should favor isomerization prior to conjugated addition which would lead to inversion of configuration. Consequently, it appears that inversion of configuration in ether occurs only with moderately reactive and unhindered reactant pairs. If substrate structural features or substrate–cuprate reactivity profiles favor rapid elimination of the leaving group, retention of configuration results from minimum motion and continuous orbital overlap in the transition state. The sterically hindered reactant pairs appear to be subject to kinetically controlled rotomer distributions, suggesting a similar process for systems affording inversion of configuration, although prior isomerization followed by substitution with retention can not be ruled out.

From this perspective, the apparently contradictory results in eq 3 (L = SPh) and entry 21, Table I, can be reconciled. The *E* vinylogous thiol ester in eq 3 underwent the reaction with n-Bu_2CuLi in ether with net retention (66:33) while the analogous substrate **5** affords net inversion with Me_2CuLi. The reaction in eq 3 involves a better

(45) An astute referee has suggested that the isomerization depicted in eq 7 may result from Li^+ (from the cuprate or LiX) present in the reaction mixture. It is suggested that the effect of Li^+ should be greater in Et_2O than in THF consistent with the observed results. This is entirely plausible and was not ruled out.

leaving group[9g] than we generally employed (SPh > SCH_3), an accelerating solvent, and a very reactive cuprate which should combine to favor rapid elimination leading to retention. Utilization of the better leaving group (i.e., **5**) in conjunction with a less reactive cuprate moderates the rate of reaction and inversion of configuration is observed. This is in accord with either prior isomerization or a variable transition state for nucleophilic vinylic substitution where the stereoselectivity reflects the relative values of $k_{rot.}$ and k_{el}. The poor stereoselectivities observed for the six-membered ring analogues **9–11** and acyclic enone **3** with *sec*-butylcuprates can be rationalized in a similar manner. Here steric interactions arising from conformations of the six-membered ring or the cuprate will favor prior isomerization or an increase of $k_{rot.}$ relative to k_{el}.

Reaction of β-chloro enones **36–37** (eq 8) affords poor selectivity with net inversion of configuration in either ether or THF. Similar reactions of 1-halogeno-2-(phenylsulfonyl)ethylenes with Me_2CuLi afforded increasingly poorer stereoselectivities along the series Br < Cl < F for the cis isomers and complete retention for the trans isomers.[41] Substrate **36** has also been reported to undergo the substitution reaction with $(Me_3SiCH_2)_2CuLi$ with net retention of configuration (eq 5).[6e] In our experiments, the chloro enones afforded far poorer stereoselectivities than the methylthio enones and gave net inversion in contrast to the above observations. Discussion of leaving group ability (nucleofugality) provides little insight because of the difficulty of acessing its importance and establishing a relative ranking.[46] Elimination, according to a perturbation treatment, involves electron transfer from the 2p orbital of the carbanion (i.e., the enolate) to the σ* orbital of the carbon-leaving group bond (C–L). Stabilization of the transition state for elimination is determined by both polarity and strength (D) of the C–L bond. Bond polarity plays a greater role in the nucleofugality of Cl^- while bond strength (D) plays a greater role for second row nucleofuges. Alternatively, the greater polarity of the C–Cl bond may inductively stabilize the intermediate enolate anion which, with a longer lifetime, leads to poorer stereoselectivity via enone isomerization or rotational events ($k_{rot.} > k_{el}$). The tendency toward inversion may be suggestive of enone isomerization. The net retention observed with **36** and $(Me_3SiCH_2)CuLi$ raises an interesting question as to the role of silicon.

In summary, the stereoselectivity in the reactions of organocuprates with β-alkylthio α,β-enones is in accord with an addition–elimination pathway for nucleophilic vinylic substitution.[42b,47] The strongly activating (pK_a = 10–20) ketone group with a smaller value for k_{el} provides a more sensitive probe than moderately activating (pK_a = 20–31) ester analogues with larger k_{el} values. In this view, the range of selectivities reflect the relative values of $k_{rot.}$ and k_{el} which will be influenced by substrate structure, solvent effects, transferable ligand, and temperature. Further refinement to include a variable transition state allows consideration of cuprate reactivity in contributing to the observed stereoselectivites. The general preference for 60° rotation is borne out in the present study and the high selectivity with inversion observed for moderately reactive and unhindered *E* vinylogous thiol esters and cuprates appears to be the exception with narrow structural requirements. Inversion of configuration can arise from copper–sulfur complexation leading to 120° rotation or via prior isomerization followed by substitution with retention. Although the results obtained with sterically hindered reactant pairs is suggestive of a 120° rotation process, both pathways may be operating as substrate, cuprate, and reaction conditions are varied. It is also not clear when the elimination event occurs. The timing of this process and the actual intermediate involved (e.g., enolate, α-cuprio ketone, etc.) should have some influence upon the stereoselectivity of the elimination. The wide range of stereoselectivities observed in these reactions indicates a complex sequence of steps with comparable rate constants whose relative magnitudes may be altered by structural and medium effects to provide several mechanistic pathways. Nevertheless, the present study indicates that the factors affecting this sensitivity can be manipulated and exploited in a stereoselective synthesis of α,β-enones that can be carried out on a synthetically useful scale.

Experimental Section

Proton NMR spectra were recorded as $CDCl_3$ solutions, unless otherwise noted, on either a Varion EM-360L or JEOL-FX90Q instrument. Chemical shifts are reported as values in parts per million relative to tetramethylsilane as internal standard. Unless otherwise noted, the carbon NMR (^{13}C NMR) chemical shifts are in parts per million downfield from tetramethylsilane and are referenced with respect to internal $CDCl_3$ (δ 77.0). Infrared spectra were recorded on a Perkin-Elmer 710B grating spectrophotometer as CCl_4 solutions unless otherwise noted. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were determined by Atlantic Microlab Inc., Atlanta, GA.

CuI was freshly purified by dissolving an appropriate quantity of CuI in boiling saturated NaI(aq) over a period of 30 min. Pure CuI was produced by cooling and diluting the solution with H_2O, followed by filtration and washing sequentially with H_2O, EtOH, EtOAc, ether, and pentane and drying in vacuo for 24 h.[48] CuBr was purified according to a procedure employed for CuCl that was slightly modified.[49] Commercial CuBr (Alfa) was dissolved in 48% HBr, precipitated by the addition of water, and filtered. The precipitate was washed sequentially with H_2O, EtOH, and Et_2O and then dried in vacuo. CuSCN was prepared according to an established procedure.[50] CuCN was obtained from Matheson Coleman and Bell and used without further purification. The concentration of alkyllithium reagents in commercial solutions was determined by titration of diphenylacetic acid to the yellow end point.[51] Thiophenol was distilled and stored over 3-Å molecular sieves. Tetrahydrofuran and Et_2O were distilled from sodium/benzophenone prior to use.

General Procedure A. Conjugate Addition Using Dialkylcuprates (R_2CuLi). The copper(I) salt (1 mmol) and 20 mL of diethyl ether were placed in a three-necked 250-mL flask fitted with a N_2 inlet, septum, and stopper. The mixture was chilled with a dry ice–acetone bath and the alkyllithium reagent (2 mmol of RLi) was added (R = Me, 0 °C; cyclopropyl, *n*-Bu, *sec*-Bu, *t*-Bu, −30 °C). After 0.5 h, the resulting solutions were clear and colorless (R = Me) or brown and opaque. The solutions were then chilled to −78 °C and the substrates were added as 2.5-mL solutions via syringe with the syringe needle touching the side of the glass neck so that the emerging stream of liquid broadened to cover a wide surface area before entering the cuprate solution. The reactions were monitored by TLC until starting material was consumed. The reactions were quenched at −78 °C with saturated aqueous NH_4Cl, warmed to room temperature, and then poured into a mixture consisting of 50 mL of ether (Et_2O) and saturated aqueous NH_4Cl and stirred for 15 min. The copper salts were filtered off with the aid of Celite. The filtrate was

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extracted with 3 × 25 mL of Et_2O, washed with brine, dried over $MgSO_4$, and concentrated in vacuo to afford the crude product, which was purified by medium pressure liquid chromatography (MPLC).

2-(1-Methylpentylidene)cyclopentanone (14a). In 20 mL of ether was placed 0.7844 g of $(Me)_2SCuBr$[52] (3.8 mmol), and the mixture was chilled to −40 °C followed by addition of 3.8 mL of *n*-butyllithium (2.0 M, 7.64 mmol). The solution was stirred for 0.5 h and then cooled to −78 °C whereupon **1** (1.116 g, 7.16 mmol) was added as a solution in ether (5 mL). The solution was stirred at −78 °C for 15 min, warmed to −60 °C over 45 min, quenched with MeOH, and then poured into 25 mL of saturated aqueous NH_4Cl. The aqueous phase was extracted with ether (3 × 30 mL) and the combined organic phase was dried ($MgSO_4$), filtered, and concentrated in vacuo to give 0.1950 g. VPC analysis of the crude material revealed an 88:12 ratio of *E*/*Z* isomers. Purification by preparative TLC (1000 μm, SiO_2; eluted 4× with petroleum ether/2% ethyl acetate, v/v) gave two fractions. The major fraction (0.829 g, R_f2 0.31) afforded the *Z* isomer and the minor one (0.0232 g, R_f1 0.25) gave the *E* isomer for an 84% overall yield.

Z isomer: IR 2920 (s), 2860 (s), 1700 (s), 1615 (s), 1450 (s), 1440 (s), 1410 (s), 1320 (s), 1255 (s), 1205 (s), 1170 (s), 1000 (m), 820 (m) cm^{-1}; ^1H NMR δ 0.83 (t, *J* = 7 Hz, 3 H), 1.20–1.65 (m, 4 H), 1.80 (t, *J* = 1.4 Hz, 3 H), 1.84 (t, *J* = 8 Hz, 2 H), 2.21 (t, *J* = 8 Hz, 2 H), 2.45–2.65 (m, 4 H); ^{13}C NMR δ 206.6, 151.5, 130.4, 40.3, 32.7, 30.3, 29.3, 22.5, 22.0, 19.1, 13.7.

E isomer: IR 2960 (s), 2940 (s), 2860 (m), 1706 (s), 1620 (s), 1460 (w), 1260 (m), 1180 (s), 910 (s) cm^{-1}; ^1H NMR δ 0.92 (t, *J* = 6.3 Hz, 3 H), 1.07–1.60 (m, 4 H), 1.88 (quint, *J* = 8 Hz, 2 H), 1.92–2.40 (m, 4 H), 2.19 (t, *J* = 2 Hz, 3 H), 2.64 (t, *J* = 8 Hz, 2 H); ^{13}C NMR δ 207.6, 150.8, 130.4, 40.2, 37.7, 29.0, 28.8, 22.6, 19.4, 18.1, 13.7.

Anal. Calcd for $C_{11}H_{18}O$: C, 79.47; H, 10.91. Found: C, 79.45; H, 10.96.

(*Z*)-2-(1,2,2-Trimethylpropylidene)cyclopentanone (14b). To CuBr (0.6620 g, 4.61 mmol) was added enough Me_2S to form a homogeneous solution which was diluted with 20 mL of ether. The mixture was chilled to −35 to −40 °C and 4.9 mL (9.31 mmol) of *tert*-butyllithium was added dropwise. After 0.5 h, the resulting light brown solution was cooled to −78 °C and a prechilled solution of **1** (0.180 g, 1.15 mmol) was added slowly. After 1.0 h, the reaction was warmed to −60 °C and quenched with saturated aqueous NH_4Cl, and the mixture was filtered through Celite. Standard workup and purification by MPLC (R_f 0.16, petroleum ether/2% ethyl acetate, v/v) afforded 0.1534 g of (*E*)- and (*Z*)-**14b** (80%) from which the *Z* isomer could be isolated; IR 2960 (s), 1700 (s), 1580 (s), 1360 (m), 1190 (s), 1130 (s), 980 (m) cm^{-1}; ^1H NMR δ 1.23 (s, 9 H), 1.67–2.03 (m, 2 H), 1.88 (t, *J* = 1.5 Hz, 3 H), 2.32 (t, *J* = 7 Hz, 2 H), 2.63 (t, *J* = 7 Hz, 2 H); ^{13}C NMR δ 205.1, 159.4, 131.9, 41.5, 36.8, 32.8, 28.6 (3C), 21.0, 19.2.

(*E*) 2-(1,2,2-Trimethylpropylidene)cyclopentanone (14b). To CuBr (0.4035 g, 2.81 mmol) was added enough Me_2S to dissolve the CuBr. The solution was diluted with 20 mL of ether and chilled to −35 °C to −40 °C, and 4.0 mL (5.6 mmol) of methyllithium was added dropwise. After 0.5 h, the resulting light brown solution was cooled to −78 °C, and a prechilled solution of **23** (0.2785 g, 1.41 mmol) was added slowly. After 1.0 h, the reaction was warmed to −60 °C and subsequently quenched with saturated aqueous NH_4Cl. Standard workup and purification by preparative TLC (1000 μm, SiO_2) gave 0.1980 g (85%) of *E* (>95:5) **14b**. The *E* isomer (R_f 0.20, petroleum ether/2% ethyl acetate, v/v) was isolated: IR ($CHCl_3$) 2900 (s), 1690 (s), 1590 (s), 1440 (m), 1370 (m), 1220 (s), 1190 (s), 1000 (s), 830 (s) cm^{-1}; ^1H NMR δ 1.18 (s, 9 H), 1.83 (quint, *J* = 7 Hz, 2 H), 2.10–2.37 (m, 2 H), 2.23 (t, *J* = 1 Hz, 3 H), 2.18 (t, *J* = 7 Hz, 2 H); ^{13}C NMR δ 209.6, 168.5, 131.3, 39.0, 37.9, 31.2, 28.3 (3 C), 19.5, 15.9.

4-Methyl-3-octen-2-one (15a). In 10 mL of ether was placed 0.2500 g of CuI (1.30 mmol), and the mixture was chilled to 0 °C, whereupon 1.73 mL of methyllithium (1.5 M, 2.6 mmol) was added via syringe; stirring was continued for 0.5 h. This solution was then chilled to −78 °C, and 4 (0.1907 g, 1.1 mmol) was added in 6 mL of ether. After 45 min the reaction was quenched with methanol; the temperature had risen to −65 °C over that period. Standard workup gave 0.2496 g of crude material. VPC analysis (OV 101, 10%) indicated an *E*/*Z* ratio of 96.3:3.7. Purification by MPLC afforded 0.1478 g (95%).

In a separate experiment, a mixture of 0.2500 g of CuI (1.31 mmol) in 10 mL of ether was cooled to −50 °C to −40 °C before the addition of 1.33 mL of *n*-BuLi (1.97 M, 2.62 mmol). This solution was stirred for 45 min and was subsequently chilled to −76 °C. **3** (0.153 g, 1.2 mmol) was added (6 mL ether) as a prechilled solution. After 45 min, the reaction was quenched with methanol at −65 °C. The reaction mixture was diluted with saturated aqueous NH_4Cl, extracted with ether (3 × 25 mL), dried with $MgSO_4$, and concentrated in vacuo to give 0.1931 g of crude material. VPC analysis (OV 101, 10%) indicated an *E*/*Z* ratio of 4.9:95.1. Purification by MPLC (SiO_2; 10% ether/petroleum ether, v/v) gave 0.1595 g (97%) of pure material consisting of both isomers (*E* isomer, R_f 0.27; *Z* isomer, R_f 0.36).

E isomer: IR 2960 (s), 2920 (s), 2860 (m), 1682 (s), 1610 (s), 1350 (m), 1210 (m), 962 (w), 905 (s) cm^{-1}; ^1H NMR δ 0.91 (t, *J* = 6 Hz, 3 H), 1.12–1.43 (m, 4 H), 2.02–2.23 (m, 2 H), 2.12 (d, *J* = 1 Hz, 3 H), 2.17 (s, 3 H), 6.08 (s, 1 H); ^{13}C NMR δ 197.9, 159.3, 123.7, 33.0, 32.2, 29.9, 25.0, 22.3, 13.4.

Z isomer: IR 2960 (s), 2920 (s), 2850 (m), 1680 (s), 1620 (s), 1370 (m), 1350 (m), 1180 (m), 1160 (m), 1155 (m), 955 (m), 905 (m) cm^{-1}; ^1H NMR δ 0.94 (t, *J* = 6 Hz, 3 H), 1.12–1.56 (m, 4 H), 1.88 (d, *J* = 1.2 Hz, 3 H), 2.14 (s, 3 H), 2.59 (t, *J* = 7 Hz, 2 H), 6.08 (s, 1 H); ^{13}C NMR δ 198.4, 158.4, 123.7, 40.5, 31.2, 25.0, 21.9, 18.8, 13.4.

Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 77.19; H, 11.55.

4,5-Dimethyl-3-hepten-2-one (15b). To 0.4260 g of CuSCN (3.5 mmol) in diethyl ether (20 mL), cooled to −20 °C to −30 °C, was added via syringe 5.3 mL (7.0 mmol) of *sec*-butyllithium. The clear tan solution was stirred for 0.5 h and then chilled to −78 °C whereupon a prechilled solution of **3** (0.2277 g, 1.75 mmol) in 10 mL of ether was added via syringe. Stirring was continued for 1.5 h; the temperature had risen to −40 °C. Standard workup and purification by MPLC (petroleum ether/5% ethyl acetate, v/v) gave the *E* (R_f1 0.58) and *Z* (R_f2 0.63) isomers in 98% yield.

E isomer: IR 2940 (s), 2900 (s), 2840 (s), 1670 (s), 1600 (s), 1440 (s), 1370 (s), 1340 (s), 1250 (s), 1105 (s), 900 (s), 830 (m) cm^{-1}; ^1H NMR δ 0.80 (t, *J* = 7 Hz, 3 H), 1.02 (d, *J* = 7 Hz, 3 H), 1.10–1.65 (m, 2 H), 2.05 (d, *J* = 1 Hz, 3 H), 2.17 (s, 3 H), 1.94–2.28 (m, 1 H), 6.03 (s, 1 H); ^{13}C NMR δ 198.8, 162.7, 122.9, 45.8, 31.7, 27.5, 18.8, 15.7, 11.9.

Z isomer: IR 2960 (s), 2879 (s), 1680 (s), 1610 (s), 1460 (s), 1380 (s), 1120 (m), 1060 (s), 850 (s) cm^{-1}; ^1H NMR δ 0.83 (t, *J* = 7 Hz, 3 H), 0.98 (d, *J* = 7 Hz, 3 H), 1.37 (quint, *J* = 7 Hz, 2 H), 1.75 (d, *J* = 1 Hz, 3 H), 2.15 (s, 3 H), 3.71 (sextet, *J* = 7 Hz, 1 H), 6.05 (s, 1 H); ^{13}C NMR δ 198.1, 162.4, 124.7, 35.7, 31.7, 27.6, 18.9, 18.3, 11.8.

Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 77.10; H, 11.54.

4,5,5-Trimethyl-3-hexen-2-one (15c). In a flame-dried, 250-mL, round-bottomed flask charged with 0.2448 g of CuSCN (2.0 mmol) in 20 mL of diethyl ether, cooled to 0 °C (under N_2), was added 2.9 mL of methyllithium (1.4 M, 4.0 mmol). After being stirred for 30 minutes, the resulting clear colorless solution was chilled to −78 °C. Substrate **32** (0.0868 g, 0.5 mmol) was then added as an ethereal solution (5 mL) via syringe. The solution was stirred until starting material was consumed by TLC (−55 °C quench temperature). Standard workup gave 0.0920 g of a light yellow oil. Purification by MPLC (R_f 0.41, petroleum ether/2% ethyl acetate, v/v) afforded an 88% yield of material (0.0625 g, *E*/*Z* >95:5): IR 2950 (s), 2880 (m), 1680 (s), 1600 (s), 1460 (m), 1350 (m), 1250 (m), 1180 (m), 905 (s) cm^{-1}; ^1H NMR δ 1.10 (s, 9 H), 2.11 (d, *J* = 0.8 Hz, 3 H), 2.19 (s, 3 H), 6.14 (s, 1 H); ^{13}C NMR δ 199.2, 165.5, 120.6, 37.7, 31.7, 28.1 (3 C), 15.5.

In a different experiment, the *Z* isomer was observed (^1H NMR δ 1.85, $=CCH_3$) and could not be separated by normal chromatographic techniques.

4-Methyl-3-hepten-2-one (16).[53] In a flame-dried round-bottomed flask under N_2 were placed 0.2280 g of CuI (1.19 mmol) and 5 mL of diethyl ether. This suspension was chilled to 0 °C

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using an ice bath, and 1.47 mL of methyllithium was added. After 0.5 h, the clear, colorless solution was chilled to −78 °C and **33** (0.2036 g, 0.92 mmol) was added as a prechilled (−78 °C) ethereal solution (5 mL) via a double-tipped needle. The reaction was quenched after 1 h with methanol (−78 °C). After warming to ambient temperature, saturated aqueous NH_4Cl was added. Standard workup gave 0.1667 g of a yellow oil. VPC (10% OV 101, 10-ft column) indicated a 97:3 E/Z mixture. Purification by bulb-to-bulb distillation (1 mmHg, 30 °C) afforded 0.1057 g (91.3%) of pure material.

In a separate experiment, 0.150 g (0.68 mmol) of **33**, 0.1935 g of CuI (1.0 mmol), and 1.25 mL of methyllithium (2.0 mmol) were used. The solvent was changed to THF. The reaction was identically run as above and gave a 69.2% yield of **16** consisting of a 93:7 E/Z mixture. Purification by MPLC (E isomer, R_f 0.25; Z isomer, R_f 0.31 petroleum ether/6% ethyl acetate, v/v) afforded the pure isomer. E isomer: ^{1}H NMR δ 0.91 (t, J = 7 Hz, 3 H), 1.20–1.79 (m, 2 H), 2.21 (s, 3 H), 2.16 (s, 3 H), 6.12 (s, 1 H).

Z isomer: ^{1}H NMR δ 0.93 (t, J = 7 Hz, 3 H), 1.12–1.65 (m, 2 H), 1.85 (s, 3 H), 2.14 (s, 3 H), 2.57 (t, J = 8 Hz, 2 H), 6.07 (s, 1 H).

2,5-Dimethyl-4-nonen-3-one (17a). To 20 mL of ether were added 0.2 mL of dimethyl sulfide and 0.2507 g of CuI (1.31 mmol). This mixture was chilled to 0 °C and 1.74 mL of methyllithium was added (2.67 mmol). Stirring was continued for 0.5 h, and then the mixture was chilled to −78 °C whereupon **7** (0.2022 g, 1.01 mmol) was added in 5 mL of ether. After 1 h, the reaction was quenched with methanol. Saturated aqueous NH_4Cl was added and standard workup gave 0.2106 g. VPC analysis (OV 101, 10%) showed a 91:9 E/Z mixture. Purification by MPLC (10% ether/petroleum ether, v/v) gave 0.1690 g of **17a** (99%).

In a separate experiment, substrate **6** was used. To 0.2439 g (1.27 mmol) of CuI, in 20 mL ether, was added at −40 °C 1.13 mL of n-butyllithium (2.55 mmol). The mixture was stirred for 0.5 h and cooled to −78 °C, and **6** (0.1826 g, 1.16 mmol) was then added dropwise. After 1 h, the reaction was quenched (−76 °C) with methanol. Saturated aqueous NH_4Cl was added and standard workup gave a light yellow oil. VPC analysis indicated a 4:96 E/Z mixture. Purification by MPLC (2% ethyl acetate/petroleum ether, v/v) gave 0.1907 g (98%) of both isomers.

E isomer (R_f 0.49): IR 2960 (s), 2920 (s), 2865 (s), 1690 (s), 1615 (s), 1460 (s), 1380 (s), 1130 (s), 1060 (s), 960 (m) cm^{-1}; ^{1}H NMR δ 0.92 (t, J = 7 Hz, 3 H), 1.08 (d, J = 7 Hz, 6 H), 1.23–1.68 (m, 4 H), 2.01–2.27 (m, 2 H), 2.13 (s, 3 H), 2.61 (hept, J = 7 Hz, 1 H), 6.10 (s, 1 H); ^{13}C NMR δ 203.9, 158.4, 121.5, 41.0, 40.6, 29.3, 21.9, 18.7, 17.9 (2C), 13.3; mass spectrum, m/e 168.15134 (M^+) (calcd for $C_{11}H_{20}O$, 168.15142.

Z isomer (R_f 0.58): IR (CH_2Cl_2) 2950 (s), 2920 (s), 2850 (s), 1680 (s), 1605 (s), 1460 (s), 1380 (s), 1200 (s), 850 (s) cm^{-1}; ^{1}H NMR δ 0.92 (t, J = 7 Hz, 3 H), 1.05 (d, J = 7 Hz, 6 H), 1.12–1.56 (m, 4 H), 1.88 (s, 3 H), 2.37–2.77 (m, 3 H), 6.10 (s, 1 H); ^{13}C NMR δ 205.1, 160.6, 123.2, 41.4, 33.4, 29.9, 26.3, 22.8, 18.3(2C), 13.9.

2,5,6-Trimethyl-4-octen-3-one (17b). To a mixture of CuSCN (0.3287 g, 2.7 mmol) in ether (20 mL) cooled to −10 °C to −20 °C was added dropwise 4.1 mL of sec-butyllithium (1.33 M, 5.45 mmol). After 0.5 h, the light tan solution was chilled to −78 °C, and **6** (0.2108 g, 1.35 mmol) was added via syringe. After 1.5 h, the temperature had risen to −58 °C, and TLC indicated the reaction was complete. The reaction was quenched with saturated aqueous NH_4Cl and standard workup gave 0.2357 g of a yellow oil. Purification by TLC using a preparative plate (1000 μm SiO_2, 1% ethyl acetate/petroleum ether, v/v) afforded the pure Z isomer (R_f 0.28, 0.1492 g, 66%) and a minor fraction [which was a mixture of the E and Z isomers (0.0421 g), for an overall yield of 85%]. VPC analysis of the crude mixture indicated an E/Z ratio of 11:89.

In a separate experiment, substrate **27** (Table II) was utilized. To 0.1764 g of CuBr (1.23 mmol) was added 1 mL of dimethyl sulfide. After 5 min of stirring, 5 mL of ether was added and the solution chilled to 0 °C. Addition of 1.64 mL of methyllithium (1.5 M, 2.46 mmol), after stirring for 0.5 h, generated the cuprate. The reaction was cooled to −78 °C, and **27** (0.0610 g, 0.31 mmol) was added as a precooled solution (5 mL of ether). Stirring was continued for 1 h, and then the solution was warmed to −65 °C at which time the reaction was quenched with methanol. Standard workup gave 0.0615 g of crude material. The residue was purified by preparative TLC chromatography (1000 μm SiO_2, 2% ethyl acetate/petroleum ether, v/v) to give 0.0398 g (78%) which consisted of a 95:5 E/Z (R_f Z 0.49; R_f E 0.58) isomeric ratio by VPC (OV 101, 10%).

E isomer: IR 2960 (s), 2920 (s), 2860 (s), 1670 (s), 1620 (s), 1460 (s), 1380 (s), 1120 (s), 1060 (s) cm^{-1}; ^{1}H NMR δ 0.83 (t, J = 7 Hz, 3 H), 1.05 (d, J = 7 Hz, 3 H), 1.09 (d, J = 7 Hz, 6 H), 1.37 (quint, J = 7 Hz, 2 H), 1.89–2.28 (m, 1 H), 2.05 (d, J = 1 Hz, 3 H), 2.61 (hept, J = 7 Hz, 1 H), 6.09 (s, 1 H); ^{13}C NMR δ 205.0, 162.9, 121.5, 46.0, 41.5, 27.5, 18.8, 18.3 (2C), 15.9, 14.9.

Z isomer: IR 2960 (s), 2870 (m), 1687 (s), 1610 (s), 1440 (m), 1380 (m), 1350 (m), 1210 (m), 1170 (s), 950 (m) cm^{-1}; ^{1}H NMR δ 0.69–1.14 (m, 6 H), 1.08 (d, J = 7 Hz, 6 H), 1.20–1.54 (m, 2 H), 1.77 (d, J = 1 Hz, 3 H), 2.50 (hept, J = 7 Hz, 1 H), 3.73 (sep, J = 7, Hz, 1 H), 6.10 (s, 1 H); ^{13}C NMR δ 203.6, 161.6, 123.2, 40.9, 35.4, 27.2, 18.4 (2C), 17.9, 17.7, 11.3.

3-Methyl-6-(1,5-dimethyl-4-hexenylidene)-2-cyclohexen-1-one (18). To 0.1072 g of CuSCN (0.88 mmol) in 15 mL of ether, cooled to −10 °C to 0 °C, was added 1.26 mL of methyllithium (1.4 M, 1.76 mmol). After 0.5 h, the solution was chilled to −78 °C, and **8** (0.1837 g, 0.74 mmol) was added via syringe (10 mL ether). Stirring was continued for 1 h at −78 °C and then for 0.5 h at −60 °C. The reaction was quenched at −60 °C with saturated aqueous NH_4Cl and standard workup gave 0.1686 g of a light yellow oil. Purification by preparative TLC (1000 μm SiO_2, petroleum ether/10% ethyl acetate, v/v) gave two fractions: the E isomer, 0.1332 g (83% yield, R_f1 0.51), and the Z isomer, 0.0280 g (17% yield, R_f2 0.54), were obtained in quantitative yield.

E isomer: IR 2963 (s), 2930 (s), 2850 (s), 1658 (s), 1610 (s), 1420 (s), 1380 (s), 1300 (s), 1210 (s), 1130 (s), 862 (m) cm^{-1}; ^{1}H NMR δ 1.60 (s, 3 H), 1.68 (s, 3 H), 1.93 (s, 3 H), 2.08 (s, 3 H), 1.85–2.28 (br m, 6 H), 2.65 (t, J = 6 Hz, 2 H), 5.13 (br s, 1 H), 5.87 (s, 1 H); ^{13}C NMR δ 191.4, 159.0, 145.4, 131.9, 128.8, 124.1, 123.2, 36.0, 32.0, 27.6, 26.6, 25.4, 23.4, 20.8, 17.3.

Z isomer: IR 2950 (s), 2900 (s), 2735 (s), 1650 (s), 1610 (s), 1440 (s), 1380 (s), 1300 (s), 1220 (s), 880 (s) cm^{-1}; ^{1}H NMR δ 1.65 (s, 6 H), 1.85 (s, 3 H), 1.92 (s, 3 H), 2.01–2.90 (m, 8 H), 5.16 (t, J = 7 Hz, 1 H), 5.87 (s, 1 H); ^{13}C NMR δ 190.7, 158.2, 145.5, 131.0, 128.7 (2C), 124.0, 35.6, 31.6, 27.8, 27.0, 25.3, 23.3, 20.2, 17.2; mass spectrum, m/e 218.1666 (M^+) (calcd for $C_{15}H_{22}O$, 218.1670).

3-(1-Methylethoxy)-6-(1-methylpentylidene)-2-cyclohexen-1-one (19). To a solution of 2 mL of $(Me)_2S$, 0.4116 g of CuBr (2.9 mmol), and 30 mL of THF, cooled to −30 °C, was added 2.6 mL of n-butyllithium (2.20 M, 5.7 mmol). After 0.5 h, the resulting black solution was chilled to −78 °C, and **9** (0.1607 g, 0.72 mmol) in 10 mL of THF was added directly to the cuprate solution and stirred for 1 h, at which time the temperature had risen to −30 °C. The reaction was quenched with saturated aqueous NH_4Cl and extracted with ether (3 × 25 mL). The ethereal extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo to give 0.1485 g of crude material. Purification by preparative TLC (1000 μm SiO_2, petroleum ether/10% ethyl acetate, v/v) gave two fractions: the E isomer, 0.1205 g (R_f1 0.58), and the Z isomer, 0.0473 g (R_f2 0.74), were obtained in 98% overall yield. The E/Z ratio was 77:23 by VPC and 72:28 by weight of isolated materials.

E isomer: IR 2960 (s), 2920 (s), 2880 (m), 1640 (m), 1605 (s), 1375 (m), 1320 (m), 1300 (m), 1190 (s), 1105 (m) cm^{-1}; ^{1}H NMR δ 0.92 (t, J = 6 Hz, 3 H), 1.07 (d, J = 6 Hz, 6 H), 1.07–1.30 (m, 4 H), 1.90 (s, 3 H), 2.10–2.50 (m, 6 H), 4.20 (hept, J = 6 Hz, 1 H), 5.34 (s, 1 H); ^{13}C NMR δ 191.7, 174.0, 128.4, 104.6, 70.3, 35.7, 35.1, 30.4, 30.2, 26.2, 22.3, 21.2 (2C), 20.6, 13.6; mass spectrum, m/e 236.17556 (M^+) (calcd for $C_{15}H_{24}O_2$, 236.17763).

Z isomer: IR 2920 (m), 2860 (m), 1640 (m), 1605 (s), 1370 (m), 1320 (w), 1300 (m), 1190 (s), 1120 (m), 920 (w) cm^{-1}; ^{1}H NMR δ 0.91 (t, J = 7 Hz, 3 H), 1.29 (d, J = 6 Hz, 6 H), 1.20–1.40 (m, 4 H), 1.63 (s, 3 H), 2.30–2.70 (m, 6 H), 4.43 (hept, J = 6 Hz, 1 H), 5.34 (s, 1 H); ^{13}C NMR δ 191.7, 174.2, 145.6, 128.5, 105.0, 70.7, 35.5, 30.8, 30.4, 26.9, 22.9, 21.5 (2C), 20.5, 13.9.

2-(1-Methylpentylidene)cyclohexanone (20a). Procedure A was followed using 0.1301 g (0.77 mmol) of **10**, 0.4391 g (3.06 mmol) of CuBr, and 2.38 mL (2.57 M) of n-butyllithium. Purification by MPLC (R_f 0.16, E isomer; R_f 0.23, Z isomer; petroleum ether/2% ethyl acetate, v/v) afforded a 69% yield consisting of a 68:32 E/Z mixture as determined by isolated yields.

E isomer (0.065 g, 47%): IR 2915 (s), 2860 (s), 1610 (s), 1450 (m), 1290 (s), 1130 (s), 1070 (m), 1040 (m), 1010 (m) cm^{-1}; ^{1}H NMR

δ 0.90 (t, J = 7 Hz, 3 H), 1.12–1.56 (m, 4 H), 1.63–1.96 (m, 4 H), 1.93 (t, J = 1 Hz, 3 H), 2.10 (br t, J = 8 Hz, 2 H), 2.24–2.50 (m, 4 H) cm^{-1}; ^{13}C NMR δ 204.5, 144.6, 132.4, 42.6, 34.9, 29.6, 29.3, 24.6 (2 C), 22.6, 20.7, 13.7; mass spectrum, m/e 180.1513 (M^+) (calcd for $C_{12}H_{20}O$, 180.1514).

Z isomer (0.0300 g, 22%): IR 2940 (s), 2860 (s), 1570 (s), 1450 (m), 1250 (m), 1120 (m), 1005 (m), 970 (m), 910 (w) cm^{-1}; ^1H NMR δ 0.90 (t, J = 7 Hz, 3 H), 1.10–1.50 (m, 4 H), 1.50–1.96 (m, 4 H), 1.75 (s, 3 H), 2.13–2.81 (m, 6 H); ^{13}C NMR δ 204.5, 145.6, 132.8, 42.8, 35.8, 30.8, 30.1, 24.7 (2C), 22.8, 19.7, 13.9.

A different experiment conducted in diethyl ether involving substrate **11** was run as follows: to a mixture of 0.1960 g of CuSCN (1.6 mmol) and 20 mL of ether cooled to 0 °C was added 2.15 mL of methyllithium (3.2 mmol). After 0.5 h, the solution was chilled to −78 °C and a prechilled solution of **11** (85.4 mg, 0.4 mmol) was added (10 mL of ether). Stirring was continued for 1 h at which time the temperature had risen to −45 °C. The reaction was quenched with saturated aqueous NH_4Cl and standard workup gave 0.1090 g of crude material. VPC analysis of the crude mixture (OV 101, 10%) indicated a 77:23 E/Z ratio. TLC purification (1000 μm SiO_2, petroleum ether/2% ethyl acetate) gave two fractions. The first fraction gave (0.0350 g) mainly the E isomer. The second fraction (0.0346 g) existed as a mixture of both the E and Z isomers. The total yield was 96%.

2-(1,2-Dimethylbutylidene)cyclohexanone (20b). To a mixture of CuSCN (0.2398 g, 1.97 mmol) in ether (10 mL) cooled to 0 °C was added 2.6 mL of methyllithium (1.5 M, 3.9 mmol). After 0.5 h, the solution was chilled to −78 °C and a prechilled solution of **24** (Table II) (0.1045 g, 0.94 mmol) was added via syringe (2.0 mL of ether). After 1 h, the temperature was allowed to rise to −60 °C, and the reaction was quenched with saturated aqueous NH_4Cl. Standard workup gave 0.1389 g of crude material. Purification by preparative TLC (1000 μm SiO_2, petroleum ether/2% ethyl acetate, v/v) gave two fractions (0.0769 g, 87% total yield).

The E isomer (0.060 g, 68%) was isolated as a clear, colorless oil (R_f 0.25): IR 2980 (s), 2935 (s), 2870 (s), 1675 (s), 1595 (m), 1450 (m), 1285 (m), 1220 (m), 1130 (m), 1070 (m) cm^{-1}; ^1H NMR δ 0.74 (t, J = 6.5 Hz, 3 H), 0.90 (d, J = 7 Hz, 3 H), 1.24 (q, J = 6 Hz, 2 H), 1.58 (t, J = 1.2 Hz, 3 H), 1.40–1.90 (m, 4 H), 2.04–2.50 (m, 5 H); ^{13}C NMR δ 205.8, 147.0, 133.1, 43.1, 37.2, 29.3, 27.3, 25.2, 24.9, 18.2, 14.2, 12.2.

The Z isomer (0.0169 g) was isolated as a clear oil (R_f 0.20) in 19% yield; IR 2970 (s), 2935 (s), 2860 (s), 1670 (m), 1600 (m), 1440 (m), 1265 (s), 1135 (m), 1070 (m) cm^{-1}; ^1H NMR δ 0.77 (t, J = 6.0 Hz, 3 H), 0.98 (d, J = 7 Hz, 3 H), 1.20 (q, J = 6 Hz, 2 H), 1.60 (s, 3 H), 1.50–1.80 (m, 4 H), 2.00–2.30 (m, 4 H), 2.99 (m, 1 H); ^{13}C NMR δ 206.0, 146.4, 134.4, 43.6, 38.0, 30.6, 27.7, 25.6, 25.3, 19.0, 12.7, 12.3.

2-(1,2,2-Trimethylpropylidene)cyclohexanone (20c). To a flame-dried, three-necked, 250-mL flask were added 0.0494 g (0.406 mmol) of CuSCN and 10–15 mL of ether; this was chilled to −30 °C to −20 °C, and 0.416 mL of *tert*-butyllithium (0.811 mmol) was added dropwise. After 0.5 h, the dark blue cuprate solution was chilled to −78 °C, and 0.0628 g of **10** (0.37 mmol) was added as a prechilled ethereal solution via syringe. The reaction was monitored by TLC. After 0.25 h, the reaction was complete and quenched with saturated aqueous NH_4Cl. Standard workup afforded 0.0885 g of crude material. Purification by preparative TLC (1000 μm, SiO_2) gave 31 mg (47% yield) of the E isomer (>95:5 by NMR, R_f 0.40, petroleum ether/5% ethyl acetate, v/v): IR (CH_2Cl_2) 2960 (s), 2950 (s), 2870 (s), 1695 (s), 1600 (w), 1495 (w), 1480 (m), 1455 (m), 1360 (m), 1320 (m), 1220 (m), 1140 (m), 1120 (m), 1070 (m), 980 (w) cm^{-1}; ^1H NMR δ 1.18 (s, 9 H), 1.65–2.14 (m, 4 H), 2.16 (s, 3 H), 2.59 (t, J = 7 Hz, 2 H), 3.33 (t, J = 7 Hz, 2 H); ^{13}C NMR δ 211.3, 148.1, 144.6, 45.2, 40.5, 38.9, 30.1 (3 C), 28.7, 26.9, 20.5.

In a separate experiment, enone **25** was used. To a mixture of 4.333 g of CuBr (30.2 mmol) and 80 mL of ether, cooled to −15 °C to 0 °C, was added dropwise 40.3 mL of methyllithium (1.5 M, 60.5 mmol) via syringe. After stirring 0.5 h, the colorless liquid was chilled to −78 °C using a dry ice–acetone bath, and **25** (1.6010 g, 7.55 mmol) was added as a precooled (−78 °C, 20 mL of ether) solution. After 1 h, the temperature was allowed to rise to −60 °C to −55 °C, at which time the reaction was quenched with saturated aqueous NH_4Cl. Standard workup and purification by MPLC (5% ethyl acetate/petroleum ether, v/v) gave 1.2318 g, 88% yield existing as a >5:95 $E:Z$ mixture. For the Z isomer: ^1H NMR δ 1.21 (s, 9 H), 1.76 (t, J = 1 Hz, 3 H), 1.61–2.06 (m, 4 H), 2.45 (t, J = 7 Hz, 2 H), 2.68 (t, J = 7 Hz, 2 H).

4,5-Dimethyl-4-nonen-3-one (21). To 0.3633 g of CuBr (2.5 mmol) dissolved in dimethyl sulfide was added 20 mL of ether. This was cooled to 0 °C, and 3.61 mL of methyllithium was added (1.4 M, 5.05 mmol). After 0.5 h, **13** (0.100 g, 0.51 mmol) was added in 10 mL of ether. The reaction was monitored by TLC; starting material was consumed when the temperature rose to 0 °C. The reaction was quenched with saturated aqueous NH_4Cl. Standard workup gave 0.1203 g of crude material. Preparative TLC purification (SiO_2, 1000 μm) gave 0.0924 g (95%) of material existing as a 6:94 E/Z mixture by VPC (OV 101, 10%).

In a separate experiment, substrate **12** was used. A flame-dried, 250-mL, round-bottomed flask, under N_2, was charged with 0.5895 g of CuSCN (4.85 mmol). To this was added 20 mL of diethyl ether, and the temperature was lowered to −20 °C and 6.64 mL (1.46 M, 9.69 mmol) of n-butyllithium was added. After stirring for 0.5 h, the temperature was lowered to −78 °C, and 0.5817 g of **12** (0.37 mmol) was added. After 15 min TLC analysis of the reaction indicated consumption of starting material. The reaction was quenched at −78 °C with saturated aqueous NH_4Cl, and standard workup gave 0.7820 g of crude material. Purification by MPLC (E isomer, R_f1 0.34; Z isomer, R_f2 0.39; petroleum ether/2% ethyl acetate, v/v) afforded a 99% yield in a 10:90 $E:Z$ ratio by VPC.

E isomer: IR 2940 (s), 2880 (m), 1680 (s), 1435 (m), 1370 (m), 1345 (m), 1090 (w), 1025 (w) cm^{-1}; ^1H NMR δ 0.84 (t, J = 7 Hz, 3 H), 0.96 (t, J = 8 Hz, 3 H), 1.00–1.40 (m, 4 H), 1.78–1.83 (br s, 6 H), 1.50–1.72 (m, 2 H), 2.28 (q, J = 8 Hz, 2 H); ^{13}C NMR δ 209.1, 139.2, 131.2, 34.8, 34.5, 29.6, 22.7, 20.1, 14.9, 13.9, 8.0; mass spectrum, m/e 168.15092 (M^+) (calcd for $C_{11}H_{20}O$, 168:15142).

Z isomer: IR 2970 (s), 2940 (s), 2880 (s), 1685 (s), 1475 (m), 1395 (m), 1030 (w) cm^{-1}; ^1H NMR δ 0.85 (t, J = 7 Hz, 3 H), 1.02 (t, J = 8 Hz, 3 H), 1.12–1.56 (m, 4 H), 1.67 (s, 3 H), 1.83 (br s, 3 H), 2.05 (t, J = 8 Hz, 2 H), 2.48 (q, J = 8 Hz, 2 H); ^{13}C NMR δ 209.5, 139.2, 132.1, 35.2, 34.8, 30.8, 22.8, 18.3, 15.2, 13.9, 7.6.

2-(1-Cyclopropylethylidene)cyclopentanone (28). To CuSCN (0.0814 g, 0.67 mmol) and 10 mL of ether, cooled to 0 °C, was added 0.84 mL of methyllithium (1.59 M, 1.34 mmol). After 0.5 h, the solution was chilled to −78 °C, and 0.1012 g (0.52 mmol) of prechilled **22** was added. After 1 h, the reaction was quenched with saturated aqueous NH_4Cl and standard workup gave 0.167 g of crude material.

Purification by preparative TLC (1000 μm SiO_2, R_f 0.45, petroleum ether/5% ethyl acetate) gave 0.1067 g (97%): IR 2910 (s), 2850 (s), 1695 (s), 1600 (s), 1440 (s), 1410 (s), 1375 (s), 1280 (s), 1200 (s), 1180 (m), 1170 (m), 960 (m) cm^{-1}; ^1H NMR δ 0.67–0.89 (m, 4 H), 1.34–2.10 (m, 3 H), 1.83 (t, J = 1.9 Hz, 3 H), 2.32 (t, J = 7 Hz, 2 H), 2.81 (t, J = 7 Hz, 2 H); ^{13}C NMR δ 206.8, 151.7, 137.0, 40.5, 29.0, 19.2, 16.5, 11.2, 5.5 (2 C); mass spectrum, m/e 150.10736 (M^+) (calcd for $C_{10}H_{14}O$, 150.10447.

The Z isomer was not isolated due to similar R_f values; however, its ^1H NMR β-methyl absorption occurred at δ 1.40 and the cyclopropyl methine absorption at δ 3.66.

2-[1-(1,1-Dimethylethyl)-2-methylbutylidene]cyclopentanone (29). In a flame-dried, round-bottomed flask under N_2 were placed 0.6983 g of CuSCN (5.74 mmol) and 15 mL of diethyl ether. This was cooled to −35 °C to −40 °C, and 8.6 mL of *sec*-butyllithium (1.33 M, 11.4 mmol) was added. After being stirred for 0.5 h, the solution was chilled to −78 °C and substrate **23** (0.2871 g, 1.44 mmol) was added as a solution (5 mL of ether) via syringe. The reaction was monitored by TLC and the reaction was quenched at −50 °C with saturated aqueous NH_4Cl. Standard workup afforded 0.3109 g of crude material.

Purification by MPLC (R_f 0.15, petroleum ether/1% ethyl acetate, v/v) afforded a 73% yield of the E isomer: IR 2960 (s), 2860 (s), 1700 (s), 1565 (m), 1460 (m), 1380 (m), 1170 (m), 1120 (s) cm^{-1}; ^1H NMR δ 0.67–1.03 (m, 6 H), 1.03–1.30 (m, 2 H), 1.25 (s, 9 H), 1.30–2.01 (m, 3 H), 2.05–2.38 (m, 2 H), 2.41–2.90 (m, 2 H).

2,5,6,6-Tetramethyl-4-hepten-3-one (35a). To 0.2427 g of CuBr (1.7 mmol) was added dimethyl sulfide until a clear solution resulted. Ether (20 mL) was added and the mixture was cooled to 0 °C. Methyllithium (2.27 mL, 3.4 mmol) was added dropwise

via syringe. After 0.5 h, the liquid was chilled to −78 °C, and prechilled **34** (Table III) (0.0846 g, 0.42 mmol) was added as an etheral solution via syringe. After 1.0 h, the temperature was allowed to rise to −60 °C at which time the reaction was quenched with saturated aqueous NH_4Cl. Standard workup gave 0.0742 g of clear yellow oil. TLC purification (1000 μm SiO_2 plate, 2% ethyl acetate/petroleum ether, v/v) with two elutions gave two fractions. Fraction 1 afforded starting material (0.020 g). Fraction 2 (R_f 0.16) afforded the *E* isomer in 76% yield (0.0542 g): IR 2960 (s), 2860 (m), 1680 (m), 1600 (m), 1460 (m), 1378 (m), 1365 (m), 1255 (m) 1067 (m), 1020 (m) 904 (m) cm^{-1}; ^1H NMR δ 1.12 (d, *J* = 7.1 Hz, 6 H), 1.09 (s, 9 H), 2.12 (s, 3 H), 2.63 (hept, *J* = 7 Hz, 1 H), 6.18 (s, 1 H); ^{13}C NMR δ 205.7, 165.7, 118.9, 41.8, 37.8, 28.6 (3C), 18.3 (2C), 15.6.

2,6-Dimethyl-5-(1,1-dimethylethyl)-4-octen-3-one (35b). To 0.1628 g of CuSCN was added 10 mL of diethyl ether and the mixture was chilled to −20 to −10 °C. *sec*-Butyllithium, 1.4 mL (1.75 M, 2.45 mmol), was added; the solution was stirred for 0.5 h, cooled to −78 °C, and then treated with an ethereal solution of **34**. Standard workup and TLC purification (1000 μm, SiO_2, petroleum ether/2% ethyl acetate, v/v) afforded 0.0750 g of **35b**: ^1H NMR δ 0.86 (t, *J* = 7 Hz, 3 H), 1.07 (d, *J* = 7 Hz, 6 H), 1.13 (s, 9 H), 1.19 (d, *J* = 6.5 Hz, 3 H), 1.26–2.42 (br m, 3 H), 2.65 (hept, *J* = 7 Hz, 1 H), 6.08 (s, 1 H); *Z* isomer, 5.82 (s, 1 H, 11%).

Ethyl 3-Methyl-2-hexenoate (40).[54] Procedure A was followed employing ester **39** except CuSCN was used. The reaction was quenched at −78 °C. Purification by MPLC (*E* isomer, R_f 0.16; *Z* isomer, R_f 0.27; petroleum ether/2% ethyl acetate, v/v) afforded a 99% yield.

E isomer: IR 2980 (s), 2920 (s), 1708 (s), 1590 (m), 1450 (m), 1370 (m), 1180 (s) cm^{-1}; ^1H NMR δ 0.92 (t, *J* = 7 Hz, 3 H), 1.05 (t, *J* = 8 Hz, 3 H), 1.05–1.79 (m, 2 H), 2.01–2.28 (m, 2 H), 2.14 (s, 3 H), 4.17 (q, *J* = 8 Hz, 2 H), 5.70 (s, 1 H); ^{13}C NMR δ 166.6, 159.6, 115.5, 59.1, 42.8, 20.4, 18.3, 14.1, 13.4.

In a separate experiment, (*E*)-ethyl 3-(ethylthio)-2-hexenoate (**38**) was employed in THF and the *Z* isomer was obtained by MPLC in which the crude product consisted of a 10:90 *E*/*Z* mixture in 72% yield.

Z isomer: IR 2980 (s), 2920 (s), 2880 (s), 1710 (s), 1450 (m), 1380 (m), 1260 (s), 1115 (s), 1020 (m) cm^{-1}; ^1H NMR δ 0.94 (t, *J* = 7 Hz, 3 H), 1.25 (t, *J* = 7 Hz, 3 H), 1.25–1.47 (m, 2 H), 1.87 (d, *J* = 1 Hz, 3 H), 2.41 (t, *J* = 8 Hz, 2 H), 4.15 (q, *J* = 7 Hz, 2 H), 5.67 (s, 1 H); ^{13}C NMR δ 166.8, 159.7, 116.6, 59.7, 35.2, 22.0, 21.4, 14.3, 14.0.

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Registry No. **1**, 84308-03-2; **2**, 84308-04-3; **3**, 86310-01-2; **4**, 86310-02-3; **5**, 96899-05-7; **6**, 86310-03-4; **7**, 86310-04-5; **8**, 96899-20-6; **9**, 84308-09-8; **10**, 84308-07-6; **11**, 96899-12-6; **12**, 87615-89-2; **13**, 96899-34-2; (*E*)-**14a**, 86310-07-8; (*Z*)-**14a**, 86310-06-7; (*E*)-**14b**, 104664-45-1; (*Z*)-**14b**, 104664-55-3; (*E*)-**15a**, 23732-25-4; (*Z*)-**15a**, 36219-17-7; (*E*)-**15b**, 104664-46-2; (*Z*)-**15b**, 104664-56-4; (*E*)-**15c**, 23732-21-0; (*Z*)-**15c**, 83810-24-6; (*E*)-**16**, 23732-22-1; (*Z*)-**16**, 23732-23-2; (*E*)-**17a**, 86310-09-0; (*Z*)-**17a**, 86310-08-9; (*E*)-**17b**, 104664-54-2; (*Z*)-**17b**, 104664-57-5; (*E*)-**18**, 56001-51-5; (*Z*)-**18**, 56001-48-0; (*E*)-**19**, 104664-47-3; (*Z*)-**19**, 104664-58-6; (*E*)-**20a**, 104664-48-4; (*Z*)-**20a**, 104664-59-7; (*E*)-**20b**, 104664-49-5; (*Z*)-**20b**, 104664-60-0; (*E*)-**20c**, 104664-50-8; (*Z*)-**20c**, 104664-61-1; (*E*)-**21**, 104664-51-9; (*Z*)-**21**, 104664-62-2; (*E*)-**22**, 96899-09-1; (*Z*)-**22**, 96899-10-4; **23**, 84308-05-4; **24**, 96899-14-8; **25**, 96899-16-0; **26**, 96899-23-9; **27**, 96899-29-5; (*E*)-**28**, 104664-52-0; (*Z*)-**28**, 104664-63-3; (*E*)-**29**, 104664-53-1; (*Z*)-**29**, 104664-64-4; **30**, 62453-10-5; **31**, 96899-24-0; **32**, 96899-26-2; **33**, 86310-05-6; **34**, 96899-32-0; (*E*)-**35a**, 104664-65-5; (*Z*)-**35b**, 104664-66-6; (*E*)-**35b**, 104664-67-7; (*E*)-**36**, 49784-51-2; (*E*)-**37**, 91667-33-3; (*E*)-**38**, 104664-69-9; (*Z*)-**39**, 104664-68-8; (*E*)-**40**, 22210-21-5; (*Z*)-**40**, 22210-22-6; BuLi, 109-72-8; *t*-BuLi, 594-19-4; MeLi, 917-54-4; *sec*-BuLi, 598-30-1.

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Notes

Total Synthesis of (±)-Isocyclocelabenzine

Hideo Iida, Kiyoshi Fukuhara, Yoshiaki Murayama, Mitsuo Machiba, and Toyohiko Kikuchi*

Tokyo College of Pharmacy, 1432-1, Horinouchi Hachioji, Tokyo 192-03, Japan

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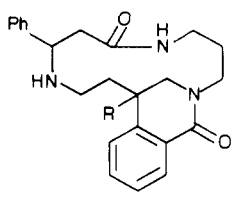
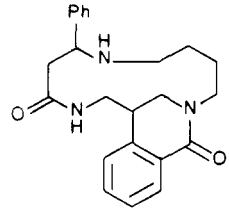
A new family of spermidine alkaloids typified by isocyclocelabenzine (**1**), 13-hydroxyisocyclocelabenzine (**2**), and cyclocelabenzine (**3**) were isolated from *Maytenus mossmbicensis* by Wagner and his co-workers.[1] All three



1; R=H
2; R=OH



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of these alkaloids each show the 13-membered lactam ring of celabenzine being linked to the benzoyl residue within the spermidine unit. These compounds have yet to be synthesized. We recently synthesized (±)-celabenzine and (−)-dihydrocelacinnine by the intramolecular reductive amination of an aldehyde to bring about the closure of the macrocyclic ring.[2] The present paper describes a total synthesis of isocyclocelabenzine in which the macrocyclic ring is formed by the successive intramolecular reductive amination of aldehyde.

The first step in the synthesis was the construction of lactam **9**, which was synthesized from homophthalimide derivative **4** as a key fragment.

Treatment of 2-benzylhomophthalimide with sodium *tert*-butoxide followed by ethyl bromoacetate in *tert*-butyl alcohol at room temperature gave **4**. The reduction of **4** with $LiAlH_4$ in isopropyl ether under reflux for 24 h yielded the isoquinoline derivative **5**. Debenzylation of **5** with

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