flask was heated under nitrogen for 2 h at 160–170 °C (oil bath temperature), allowed to cool, and refrigerated overnight. The product was collected by filtration, washed successively with DMF, ethanol, and ether, and dried in vacuo to give 0.14 g (47%) of a yellow powder, mp > 300 °C. The analytical sample was prepared by recrystallization from DMF: IR (KBr) 3440, 3385, 3340, 2220, 1700 (br), 1665, 1635, 1600 cm^{-1}. The compound was too insoluble in Me_2SO or TFA for determination of its NMR spectrum.

Anal. Calcd for $C_{14}H_9N_5O_3$: C, 56.95; H, 3.17; N, 23.72. Found: C, 56.76; H, 3.38; N, 23.42.

2,4-Diamino-6,8-dihydro-7-[4-(carbomethoxy)phenyl]-8-oxopyrrolo[3,4-*g*]pteridine (3a). A slurry of 0.31 g (1 mmol) of **13a** and 0.48 g (4 mmol) of guanidine acetate in 20 mL of dry DMF was heated under nitrogen at 140–145 °C (oil bath temperature) for 2 h. The solution was then allowed to cool, and the precipitate was collected by filtration, washed thoroughly with DMF, and dried in vacuo to give 0.32 g (91%) of a light orange solid, mp > 330 °C, which analyzed correctly without further purification: NMR (TFA, external Me_4Si) δ 4.15 (s, 3 H), 5.38 (s, 2 H), 7.58 (br s, 2 H), 8.05, 8.35 (A_2B_2 q, J = 9 Hz, 4 H), 8.58 (br s, 2 H); ^{13}C NMR (TFA-*d*) δ 171.7, 166.0, 164.8, 158.0, 155.0, 150.9, 149.1, 143.2, 133.4, 130.5, 127.0, 123.2, 55.0, 53.1; IR (KBr) 3430, 3300, 3130, 1715, 1695, 1660, 1620, 1600 cm^{-1}.

Anal. Calcd for $C_{16}H_{13}N_7O_3$: C, 54.73; H, 3.73; N, 27.91. Found: C, 54.45; H, 3.77; N, 28.18.

2,4-Diamino-6,8-dihydro-7-(4-carboxyphenyl)-8-oxopyrrolo[3,4-*g*]pteridine (3b). Method A. A solution of 0.61 g (1.8 mmol) of **12b** in 30 mL of dry DMF contained in a 100-mL round-bottom flask was slowly heated under nitrogen to 150 °C (oil bath temperature) for 1.5 h. The resulting mixture was allowed to cool to room temperature and 1.07 g (9.0 mmol) of guanidine acetate was added along with 30 mL of DMF. The mixture was then heated slowly to 155 °C, kept at 155–165 °C for 2 h, and allowed to cool, and the product was collected by filtration, washed successively with DMF, ethanol, and ether, and dried in vacuo to give 0.58 g (77%) of the guanidinium salt of **3b**: mp > 330 °C; ^{13}C NMR (TFA-*d*) δ 173.7, 166.0, 164.9, 158.0, 155.0, 151.0, 149.1, 143.1, 134.1, 129.5, 127.0, 123.2, 53.0. A slurry of 0.29 g of this material in 5 mL of TFA was warmed to a gentle boil, allowed to cool, and then placed in the freezer overnight. The product was collected by filtration, washed with a small amount of TFA, rinsed with ether, and dried in vacuo to give 0.24 g (58%, based on **12b**) of **3b** as its trifluoroacetate monohydrate: mp > 330 °C; NMR (TFA, external Me_4Si) δ 5.38 (s, 2 H), 7.60 (br, 2 H), 8.09, 8.40 (A_2B_2 q, J = 9 Hz, 4 H), 8.55 (br, 2 H); IR (KBr) 3340 (br), 3100 (br), 1635 with shoulders at 1650, 1675, 1690, 1710, and 1720, 1605, 1510 cm^{-1}.

Anal. Calcd for $C_{17}H_{12}N_7O_5F_3 \cdot H_2O$: C, 43.50; H, 3.01; N, 20.89; F, 12.14. Found: C, 43.68; H, 2.80; N, 20.82; F, 12.01.

Method B. A slurry of 0.12 g (0.4 mmol) of **13b**, 0.24 g (2.0 mmol) of guanidine acetate, and 12 mL of dry DMF was heated at reflux under nitrogen for 2 h. The mixture was cooled to room temperature, and the product was collected by filtration, washed successively with DMF, ethanol, and ether, and dried in vacuo to yield 0.11 g (66%) of a yellow powder, mp > 330 °C, which was converted to its trifluoroacetate monohydrate as described in method A.

Registry No. 3a, 79722-41-1; **3b** quanidinium salt, 79722-43-3; **3b** trifluoroacetate salt, 79722-44-4; **6**, 73198-30-8; **7**, 73198-25-1; **8**, 79722-45-5; **9**, 79722-46-6; **10**, 79722-47-7; **11**, 79722-48-8; **12a**, 79722-49-9; **12b**, 79722-50-2; **13a**, 79722-51-3; **13b**, 79722-52-4; **14**, 50382-11-1; **15**, 638-07-3; **16**, 79722-53-5; ethyl *p*-aminobenzoate, 94-09-7; aminomalononitrile tosylate, 5098-14-6; methyl *p*-aminobenzoate, 619-45-4; *p*-aminobenzoic acid, 150-13-0; quanidine acetate, 34771-62-5.

Lewis Acid Mediated Reactions of Organocopper Reagents. Entrainment in the Conjugate Addition to α,β-Unsaturated Ketones, Esters, and Acids via the $RCu \cdot BF_3$ System[1]

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Lewis acid mediated reactions of organocopper reagents with various kinds of α,β-unsaturated carbonyl derivatives are described. $RCu \cdot BF_3$, as well as RCu–other Lewis acid systems, is useful for the conjugate addition to the α,β-unsaturated ketones and esters, whose double bonds are sterically crowded. Certain α,β-unsaturated carboxylic acids also undergo a 1,4-addition through this reagent. Methyl sorbate undergoes a 1,4-addition via $BuCu \cdot BF_3$, while undergoing a 1,6-α,δ-addition via Bu_2CuLi. $BuCu \cdot BF_3$ reacts more readily with an aldehyde than with a ketone; the degree of chemoselectivity is greater than that of Bu_2CuLi, BuLi, or BuMgBr. The R_2CuLi–BF_3 system is useful for the double alkylation of α,β-unsaturated esters at the β-position and the carbonyl center. Stereochemical aspects of these new copper reagents are also reported.

The conjugate addition of organometallic reagents (R–M) to α,β-unsaturated carbonyl compounds is a highly useful reaction as a basic strategy for organic synthesis. Although organometallic compounds such as M = Li,[2] B,[3] Al,[4] Al–Ni,[5] Si–Ti,[6] Zr–Ni,[7] or Zn[8] have provided convenient methods to the conjugate addition, organocopper derivatives are definitely the most widely used reagents and possess the most universal applicability.[9] Unfortunately, however, the introduction of alkyl substituents at

(1) For a preliminary report on some aspects of the present study, see: Yamamoto, Y.; Maruyama, K. *J. Am. Chem. Soc.* **1978**, *100*, 3240.

(2) Binns, M. R.; Haynes, R. K.; Houton, T. L.; Jackson, W. R. *Tetrahedron Lett.* **1980**, 573. E-Bouz, M.; Wartski, L. *Ibid.* **1980**, 2877 and references cited therein.

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(4) Hooz, A. J.; Layton, R. B. *J. Am. Chem. Soc.* **1971**, *93*, 7320.

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(6) Hosomi, A.; Sakurai, H. *J. Am. Chem. Soc.* **1977**, *99*, 1673.

(7) Schwartz, J.; Loots, M. J.; Kosugi, H. *J. Am. Chem. Soc.* **1980**, *102*, 1333.

(8) Daviand, G.; Massy, M.; Miginiac, P. *Tetrahedron Lett.* **1970**, 5169. For other organometallic compounds, see also ref 9b.

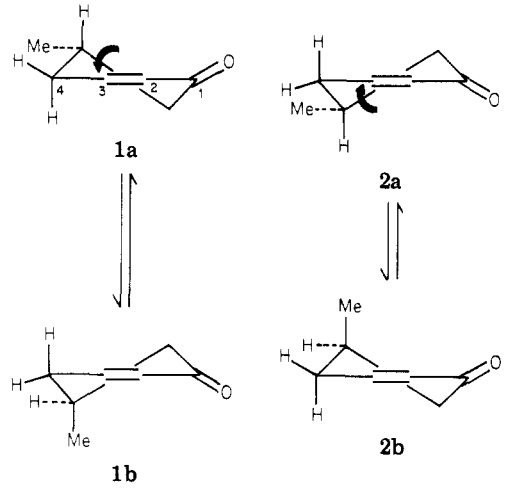
(9) (a) Posner, G. H. "An Introduction to Synthesis Using Organocopper Reagents"; Wiley: New York, 1980. (b) Posner, G. H. *Org. React.* **1972**, *19*, 1. (c) House, H. O. *Acc. Chem. Res.* **1976**, *9*, 59.

0022-3263/82/1947-0119$01.25/0

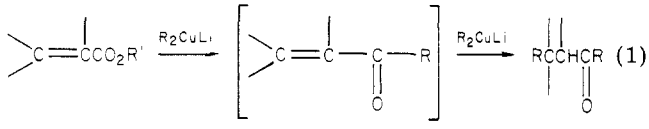
the double bond of enones, enoate esters, or related compounds prevents or frequently halts the conjugate addition. Furthermore, the conjugate addition to α,β-unsaturated carboxylic acids has scarcely been achieved by using the previously known organometallic reagents. In 1978, we communicated that some of these problems were solved by using the $RCu{\cdot}BF_3$ system.[1] It was rather curious that no such approach was available at the outset of our work, since the activation of a carbonyl group with Lewis acids was a widely used method in organic synthesis. Recently, it was reported that $RCu{\cdot}AlCl_3$[10] and $Me_2CuLi{\cdot}BF_3$[11] are very useful for the conjugate addition to certain α,β-unsaturated ketones. We now report a fully detailed report of the previous work together with the 1,2-addition reaction of RCu–Lewis acids, the stereochemical aspect, and the reaction via the Bu_2CuLi–BF_3 system.

α,β-Unsaturated Carbonyl Derivatives. The reactions of α,β-unsaturated ketones, esters, carboxylic acids, and nitriles with organocopper reagents are summarized in the Table I. Acyclic β-mono-, and α,β-disubstituted unsaturated ketones undergo a facile 1,4-addition via $RCu{\cdot}BF_3$ (entries 1–4 and 10–12). On the other hand, the reaction of the β,β-disubstituted ketone is accompanied with almost equal amounts of the 1,2-addition (entries 5 and 6). Quite interestingly, $BuCu{\cdot}BF_3$ adds to the β,β,α-trisubstituted ketone selectively in a 1,4 manner, while Bu_2CuLi adds in a 1,2 manner. These results suggest that the β-substituent retards the 1,4-addition and forward the 1,2-addition, while the α-substituent prevents the 1,2-addition. Consequently, the regioselectivity must depend upon the size of substituents at the β, α, and α' positions and upon the nature of reagents. The usefulness of $RCu{\cdot}BF_3$ is clearly demonstrated by the conjugate addition to this type of trisubstituted ketone (entries 7–9). Such an "entrainment" also works with an alkylcopper substituted with a functional group, as recently reported by Schostarez and Paquette,[12a] and with $MeCu{\cdot}BF_3$ as reported by Karpf and Dreiding.[12b]

The stereochemical aspect of $BuCu{\cdot}BF_3$ is investigated with the cyclic α,β-unsaturated ketone (entries 13 and 14). As is expected from the earlier work with MeCu derivatives,[13] the trans isomer is obtained predominantly through both $BuCu{\cdot}BF_3$ and Bu_2CuLi. The conformation of a six-membered enone and the stereochemistry of the addition of nucleophiles such as thiophenoxides or alkoxides to the double bond are studied in detail.[14] Both enantiomers of 5-methyl-2-cyclohexen-1-one exist in two conformations (**1a,b** and **2a,b**). It is well recognized that the incoming nucleophile attacks from the antiparallel direction to the axial hydrogen on the C-4. Since such an antiparallel attack is shielded by the axial methyl group of **1b** and **2b**, the nucleophile reacts with **1a** and **2a**; the antiparallel attack is indicated by arrows. Consequently, the trans isomer is predominantly produced. The conjugate addition to the transoid enone is more effective with Bu_2CuLi than with $BuCu{\cdot}BF_3$ (entries 13) and 14), while that to the cisoid enone proceeds more smoothly with $BuCu{\cdot}BF_3$ than with Bu_2CuLi (entries 10 and 11). This marked contrast is presumably due to the cyclic transition state of $RCu{\cdot}BF_3$, as previously proposed.[1] Such a high reactivity toward cisoid enones is also observed for organoboron[15] and aluminum compounds.[16]



β-Mono, α,β-di-, and β,β-disubstituted unsaturated esters undergo a 1,4-addition with the aid of $RCu{\cdot}BF_3$ (entries 15–18, 21–23, and 25–27). The corresponding cuprate reagent cannot effectively add to most of these esters in a 1,4 manner and instead gives the dialkylation product (entries 19, 28, and 29). The reaction proceeds through a 1,2-addition–conjugate addition sequence (eq 1).[17] Interestingly, the cuprate–BF_3 system selectively affords the dialkylation product (entries 20 and 24).



(1)

α,β-Unsaturated carboxylic acids also undergo a 1,4-addition (entries 30, 31, 33, and 34) though the yield is not so good in the disubstituted acids. β,β-Disubstitution almost completely prevents the conjugate addition (entry 32). The reaction of α,β-unsaturated nitriles with $BuCu{\cdot}BF_3$ is not satisfactory; the conjugate addition product is obtained in low yield (entries 35–37) together with the dialkylated ketone as a major byproduct. The α,β-disubstituted nitrile does not give an appreciable amount of the desired 1,4-adduct (entries 38–42). Conjugate addition to α,β-unsaturated amides is not realized so far even by using a RCu–Lewis acid system.

$\alpha,\beta,\gamma,\delta$-Unsaturated Carbonyl Compounds. Methyl sorbate underwent a 1,4-addition with $BuCu{\cdot}BF_3$, while undergoing a 1,6-α,δ-addition with Bu_2CuLi (eq 2).[18] Sorbic acid reacted with 3 equiv of $BuCu{\cdot}BF_3$ to give a 1,6-α,δ-adduct as a major product along with the 1,4-adduct (eq 3). It is clear that the regiochemistry via $BuCu{\cdot}BF_3$ is a marked contrast to that via Bu_2CuLi and $BuCu{\cdot}MgX_2$[19] and rather similar to that of BuMgX.[19] This regiochemical characteristic is explained by the cyclic transition state as previously proposed.[1] However, the reason for the predominant 1,6-addition to the acid is not clear.

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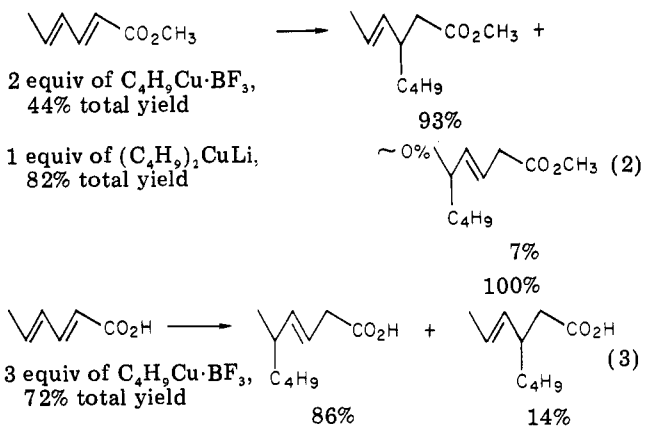
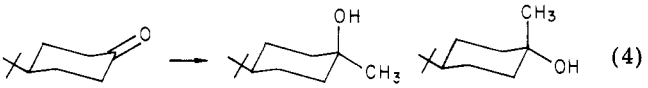
(11) Smith, A. B., III; Jerris, P. J. *J. Am. Chem. Soc.* **1981**, *103*, 194.
(12) (a) Schostarez, H.; Paquette, L. A. *J. Am. Chem. Soc.* **1981**, *103*, 722. (b) Karpf, M.; Dreiding, A. S. *Helv. Chim. Acta* **1981**, *64*, 1123.
(13) House, H. O.; Fischer, W. F., Jr. *J. Org. Chem.* **1968**, *33*, 949.
(14) Hiemstra, H.; Wynberg, H. *J. Am. Chem. Soc.* **1981**, *103*, 417.
(15) Bruhn, M.; Brown, C. H.; Collins, P. W.; Palmer, J. R.; Dajani, E. Z.; Pappo, R. *Tetrahedron Lett.* **1976**, 235. Sinclair, J. A.; Molander, G. A.; Brown, H. C. *J. Am. Chem. Soc.* **1977**, *99*, 954.
(16) Pappo, R.; Collins, P. W. *Tetrahedron Lett.* **1972**, 2627. Collins, P. W.; Dajani, E. Z.; Bruhn, M. S.; Brown, C. H.; Palmer, J. R.; Pappo, R. *Tetrahedron Lett.* **1975**, 4217. See also ref 4.
(17) Kindt-Larsen, T.; Bitsch, V.; Andersen, I. G. K.; Jart, A.; Munch-Petersen, J. *Acta Chem. Scand.* **1963**, *17*, 1426.
(18) See also: Bretting, C.; Munch-Petersen, J.; Jorgensen, P. M.; Refn, S. *Acta Chem. Scand.* **1960**, *14*, 151.
(19) Munch-Petersen, J.; Bretting, C.; Jorgensen, P. M.; Refn, S.; Andersen, V. K. *Acta Chem. Scand.* **1961**, *15*, 277.



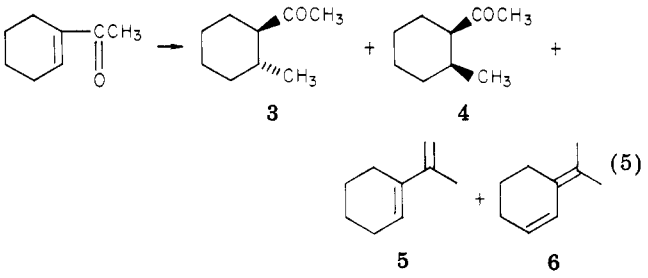
Simple Ketones and Aldehydes. Although the reaction of RCu with aldehydes or ketones such as propanal, benzaldehyde, cyclohexanone, and acetophenone was sluggish, the alkylation product was obtained in high yield via $RCu{\cdot}BF_3$; normally, use of 2 equiv of $BuCu{\cdot}BF_3$ was required to obtain the desired product in >90% yield. Chemoselectively of typical butyl–organometallic compounds is summarized in the Table II. It is noteworthy that $BuCu{\cdot}BF_3$ exhibits a high chemoselectivity, and the selectivity disappears with butyllithium. The reaction of α-bromoacetophenone with $MeCu{\cdot}BF_3$ gave acetophenone, and the alkylation product was not obtained.

Stereochemical Aspects. The stereochemistry of a 1,2-addition via $MeCu{\cdot}BF_3$ was investigated for *tert*-butylcyclohexanone (eq 4).[20] The ratio of the axial/equatrial



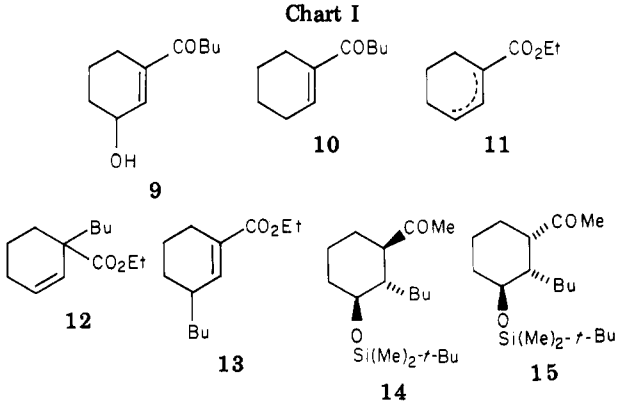
$CH_3Cu{\cdot}BF_3$ (3 equiv)	68%	32%
CH_3Li (1 equiv)	84% (79%)[21]	16% (21%)[21]
$CH_3Li{\cdot}Al(C_2H_5)_3$ (1 equiv)	87%	13%

alcohol was 68/32; small amounts of the dehydrated olefins were detected as a byproduct. The stereoselectivity was not so high in comparison with MeLi[21] or $MeLi{\cdot}Et_3Al$. A detailed investigation of the stereochemistry of the conjugate addition was carried out on 1-acetylcyclohexene (Table III, eq 5). In all cases, the cis product **4** is obtained

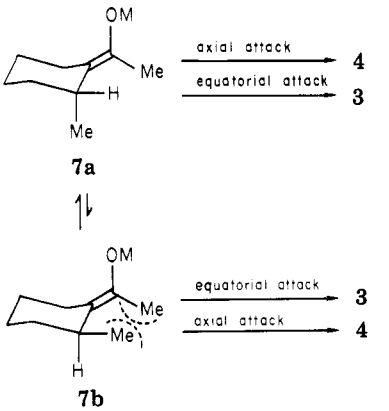


predominantly (**4**/**3** ratio of 1.8–6) along with small amounts of the dehydrated olefins **5** and **6** derived from the 1,2-adduct. When the reaction mixture was stirred at room temperature for a prolonged period after being quenched, **4** underwent epimerization to **3**. The isomer ratio also depends upon the temperature of quenching (entries 1 and 2): **4**/**3** ratio of 6 at −75 °C and 3 at 0 °C. The cis preference is easily understood by the stereochemical behavior of the enolate intermediate. The antiparallel attack to the ketone leads to the enolate **7**.[22]

Chart I



While the equatrial attack on **7b** is more favorable than the axial attack,[23] the axial attack on **7a** occurs more



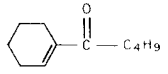
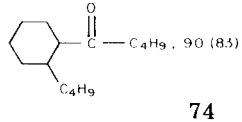
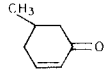
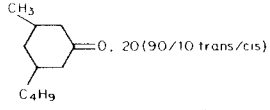
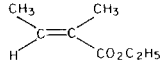
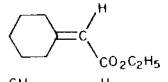
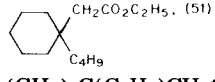
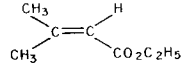
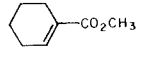
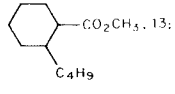
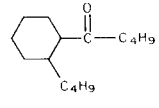
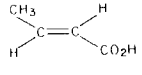
readily than the equatorial attack owing to the steric bulkiness of methyl group. As mentioned later, **7b** may be less stable than **7a** owing to the steric repulsion between the methyl group and the substituent of the double bond. Consequently, the cis isomer is formed predominantly regardless of the reagent systems.

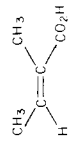
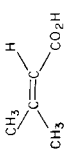
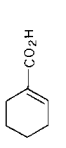
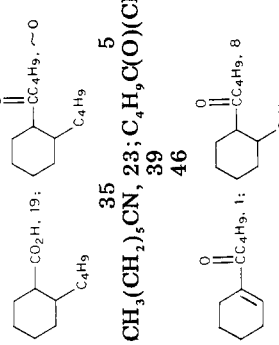
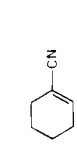
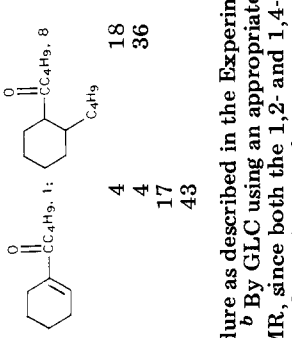
It is an interesting observation that the cis preference is greater with $MeCu{\cdot}BF_3$ than with the cuprate or the phosphine complex[24] (entries 6 and 8). This may be a reflection of the change of the equilibrium between **7a** and **7b** or of the change of the intermediate, that is, the enolate vs. α-matalla ketone.[25] Unfortunately, it is not possible at the present time to provide a clear explanation. Finally, it should be mentioned briefly that a new organocopper species, $MeCu{\cdot}BF_3{\cdot}P(Bu)_3$, is soluble in ether though $MeCu{\cdot}BF_3$ is insoluble in ether or THF. The ether solution is colorless and stable at 0 °C. The detailed chemistry of this species will be published in due course.

Competition between Conjugate Addition and Substitution. The conjugate addition and the substitution reactions[26] are the two major types of organocopper reactions. It is theoretically interesting to know the regiochemical behavior of organocopper reagents toward a

(20) For the detailed investigation on this system, see: Ashbey, E. C.; Noding, S. A. *J. Org. Chem.* **1979**, *44*, 4371.
(21) Macdonald, T. L.; Still, W. C. *J. Am. Chem. Soc.* **1975**, *97*, 5280.
(22) Although two geometrically isomeric enolates are possible in such an intermediate, it does not exert a significant influence upon the conclusion.
(23) Zimmerman, H. E.; Mariano, P. S. *J. Am. Chem. Soc.* **1968**, *90*, 609.
(24) Suzuki, M.; Suzuki, T.; Kawagishi, T.; Noyori, R. *Tetrahedron Lett.* **1980** 1247.
(25) Such a possibility is also conceivable for the stereoselective addition of $RCu{\cdot}BR_3'$ to certain triple bonds: Yamamoto, Y.; Yatagai, H.; Maruyama, K. *J. Org. Chem.* **1979**, *44*, 1744.
(26) For the substitution reaction via $RCu{\cdot}BF_3$ and the related Lewis acid system, see: Yamamoto, Y.; Yamamoto, S.; Yatagai, H.; Maruyama, K. *J. Am. Chem. Soc.* **1980**, *102*, 2318.

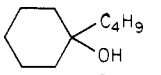
Table I. Reaction of α,β-Unsaturated Carbonyl Derivatives[a]

entry	carbonyl compd	reagent (amt, equiv)	product, % yield[b]	% starting matl recovd[b]
1	$C_6H_5CH{=}CHC(O)CH_3$	$C_4H_9Cu{\cdot}BF_3$ (1)	$C_6H_5CH(C_4H_9)CH_2C(O)CH_3$, 86	6
2		$C_4H_9Cu{\cdot}BF_3$ (2)	(90)	
3		$CH_3Cu{\cdot}BF_3$ (1)	$C_6H_5CH(CH_3)CH_2C(O)CH_3$, 40	52
4		$CH_3Cu{\cdot}BF_3$ (2)	82 (72)	8
5	$(CH_3)_2C{=}CHC(O)CH_3$	$C_4H_9Cu{\cdot}BF_3$ (1)[c]	$(CH_3)_2C(C_4H_9)CH_2C(O)CH_3$, 58 (53); $(CH_3)_2C{=}CHC(CH_3)(C_4H_9)OH$, 42	
6		$C_4H_9Cu{\cdot}BF_3$ (2)[c]	55 45	
7	$(CH_3)_2C{=}C(CH_3)C(O)CH_3$	$C_4H_9Cu{\cdot}BF_3$ (2)	$(CH_3)_2C(C_4H_9)CH(CH_3)C(O)CH_3$, 74 (66); $(CH_3)_2C{=}C(CH_3)C(CH_3)(C_4H_9)OH$, 7	
8		$(C_4H_9)_2CuLi$ (1)	16 64	17
9		$(C_4H_9)_2CuLi$ (2)	19 77	
10		$C_4H_9Cu{\cdot}BF_3$ (1)	 90 (85)	3
11		$(C_4H_9)_2CuLi$ (1)	74	20
12		C_4H_9Cu (1)	6	59
13		$C_4H_9Cu{\cdot}BF_3$ (1)	 20 (90/10 trans/cis)	75
14		$(C_4H_9)_2CuLi$ (1)	72 (91/9 trans/cis)	25
15	$CH_3CH{=}CHCO_2CH_3$	$C_4H_9Cu{\cdot}BF_3$ (2)	$CH_3CH(C_4H_9)CH_2CO_2CH_3$, 95 (88)	
16		$C_4H_9Cu{\cdot}BF_3$ (2)	$CH_3C(C_4H_9)HCH(CH_3)CO_2C_2H_5$, 92 (85); $CH_3C(C_4H_9)HCH(CH_3)C(O)C_4H_9$, trace	3
17		$C_4H_9Cu{\cdot}BF_3$ (3)	96 1	
18		BF_3 (2)-C_4H_9Cu (2)[d]	85 1	13
19		$(C_4H_9)_2CuLi$ (2)	16 57	26
20		BF_3 (1)-$(C_4H_9)_2CuLi$ (2)[d]	8 85	2
21		$C_4H_9Cu{\cdot}BF_3$ (2)	 51)	e
22		$C_4H_9Cu{\cdot}BF_3$ (2)[e]	$(CH_3)_2C(C_4H_9)CH_2CO_2C_2H_5$, 80 (70); $(CH_3)_2C(C_4H_9)CH_2C(O)C_4H_9$, 1	14
23		$C_4H_9Cu{\cdot}BF_3$ (3)	94 2	
24		BF_3 (1)-$(C_4H_9)_2CuLi$ (2)[d]	16 50	29
25		$C_4H_9Cu{\cdot}BF_3$ (1)	 13;	87
26		$C_4H_9Cu{\cdot}BF_3$ (2)	20 	75
27		$C_4H_9Cu{\cdot}BF_3$ (3)	30	66
28		$(C_4H_9)_2CuLi$ (1)	30	12
29		$(C_4H_9)_2CuLi$ (2)	6 81	
30		$C_4H_9Cu{\cdot}BF_3$ (3)	$CH_3CH(C_4H_9)CH_2CO_2H$, (86)	e

31		$C_4H_9Cu\cdot BF_3$ (3)	$CH_3C(C_4H_9)HCH(CH_3)CO_2H$, (51); $CH_3C(C_4H_9)HCH(CH_3)C(O)C_4H_9$, *e* (small amounts)	30
32		$C_4H_9Cu\cdot BF_3$ (4)	$(CH_3)_2C(C_4H_9)CH_2CO_2H$, trace	90
33		$C_4H_9Cu\cdot BF_3$ (2)		66
34		$C_4H_9Cu\cdot BF_3$ (3)	5	43
35	CH_2=CHCN	$C_4H_9Cu\cdot BF_3$ (1)	$CH_3(CH_2)_5CN$, 23; $C_4H_9C(O)(CH_2)_5CH_3$, trace	*e*
36		$C_4H_9Cu\cdot BF_3$ (2)	39	5
37		$C_4H_9Cu\cdot BF_3$ (3)	46	10
38		$C_4H_9Cu\cdot BF_3$ (1)		59
39		$C_4H_9Cu\cdot BF_3$ (2)	4	40
40		$C_4H_9Cu\cdot BF_3$ (3)	4	7
41		$(C_4H_9)_2CuLi$ (3)	17	4
42		$(C_4H_9)_2CuLi$ (3)	43	5

[a] All reactions were carried out on a 1-mmol scale in ether with the same procedure as described in the Experimental Section, except where otherwise indicated. Isolation was performed on a 10-mmol scale. We omit hereafter the *n* designation for n-C_4H_9. [b] By GLC using an appropriate internal standard, except where otherwise indicated (isolated yield given in parentheses). [c] The product distribution was determined by ^1H NMR, since both the 1,2- and 1,4-adducts exhibited the same retention time on GLC (DC-550 column). [d] An ether solution of the substrate–BF_3·OEt_2 mixture was added to an ether solution of copper reagent. [e] Not determined.

Table II. Chemoselectivity[a]

butyl-organometal (mmol)	$C_2H_5CH(OH)C_4H_9$, mmol[b]	 mmol[b]
$C_4H_9Cu\cdot BF_3$ (1)	0.69	0.01
$C_4H_9Cu\cdot BF_3$ (2)	0.90	0.05
$(C_4H_9)_2CuLi$ (1)	0.70	0.22
C_4H_9Cu (1)	0.17	
C_4H_9MgBr (1)	0.80	0.11
C_4H_9Li (1)	0.40	0.48

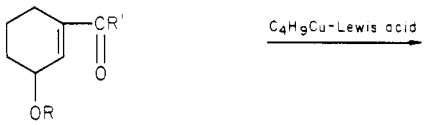
[a] A premixed ether solution of propanal (1 mmol) and cyclohexanone (1 mmol) was added to an ether solution of butyl-organometal at −70 °C. [b] By GLC (CW 20M).

Table III. Reaction of Methyl Organometallic Compounds with 1-Acetylcyclohexene[a]

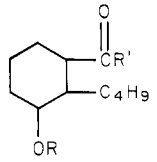
entry	methyl-organometal (equiv)	% product[b] 3	4	5	6	starting ketone recovd,[b] %
1	$CH_3Cu\cdot BF_3$ (1)	9	54	5	trace	33
2	$CH_3Cu\cdot BF_3$ (1)[c]	17	51	2	trace	25
3	$CH_3Cu\cdot BF_3$ (2)	15	61	trace	8	8
4	$CH_3Cu\cdot BF_3$ (3)	19	54	1	5	trace
5	CH_3Cu (1)[d]			1	trace	90
6	$(CH_3)_2CuLi$ (1)[d]	29	64	trace	1	3
7	$CH_3Cu\cdot TiCl_4$ (1)	1	8	4	4	50
8	$CH_3Cu\cdot P(C_4H_9)_3$ (1)[d]	20	35	trace	1	36
9	$CH_3Cu\cdot BF_3\cdot P(C_4H_9)_3$ (1)	7	32	5	trace	35

[a] All reactions were carried out on a 1-mmol scale. The reaction was quenched at −75 °C, except where otherwise indicated. [b] By GLC. [c] Quenched at 0 °C. [d] Quenched at −30 to −40 °C.

molecule which possesses two or more potential attacking positions. Especially, to our knowledge, there is no information so far on the competition between the two major reaction types in a single molecule. From this point of view, **8** is a well-designed compound. Furthermore, the conversion shown in eq 6 is an important key step for the



8a, R = $SiMe_2(t\text{-Bu})$; R′ = OC_2H_5
b, R = H; R′ = OC_2H_5
c, R = $SiMe_2(t\text{-Bu})$; R′ = Me

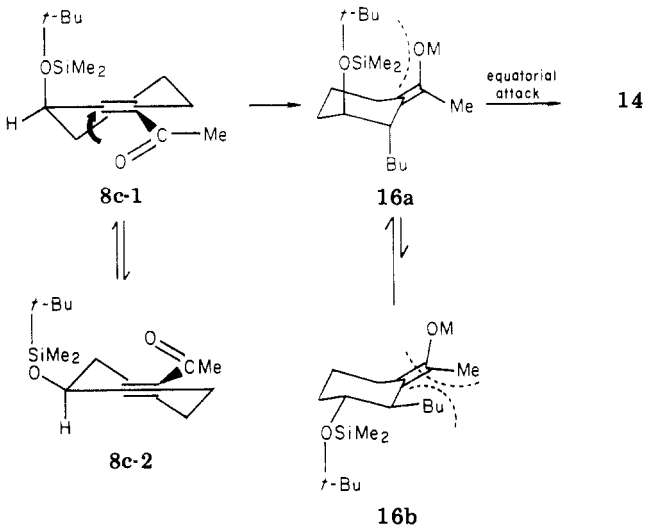


(6)

synthesis of certain alkaloids, studied by Ibuka's group.[27] The reaction of **8a** with 3 equiv of $BuCu\cdot BF_3$ gave small amounts of the alkylation products at the carbonyl center (**9** and **10**, Chart I); the major product was recovered **8a**. Although the reaction with Bu_2CuLi in the presence of $AlCl_3$, $EtAlCl_2$, and Et_2AlCl was examined, **8a** was recovered again as a major product. The reaction of **8b** with 4 equiv of $BuCu\cdot BF_3$ afforded the substitution products

(27) Ibuka, T.; Minakata, H.; Mitsui, Y.; Taga, T.; Inubushi, Y. Abstracts of 23rd symposium on the Chemistry of Natural Products, J. Sakakibara: Nagoya City University, Nagoya, Japan, 1980, p 351.

Scheme I



at the γ- and α-positions (**12**, 20%; **13**, 55%) along with the small amounts of the reduced product **11**, while that with 2 equiv of BF_3–4 equiv of Bu_2CuLi gave **11** as a major product along with trace amounts of **12** and **13**. Here also, other Lewis acid systems such as $AlCl_3$, Et_2AlCl, and $TiCl_4$–Bu_2CuLi were examined. Again, **11** was obtained as a major product. Such a tendency of a cuprate reagent has been reported in other systems.[28]

Finally, conjugate addition was realized with **8c** by using 2 equiv of BuCu·BF_3; **14** was obtained in 75% yield. The other isomer (**15**) was not detected by ^1H NMR analysis of the reaction mixture. The stereochemistry of **14** seems to be inconsistent with the observation in the case of 1-acetylcyclohexene, since the incoming butyl group and the carbonyl group exhibit the trans relation. This can be understood as follows. The butyl group attacks from the antiparallel direction of **8c-1**, leading to **16**[22] (Scheme I). Although **16b** possesses two equatorial substituents, the butyl group and the substituent of the double bond must occupy nearly the same plane,[29] and hence the steric repulsion forces the enolate to take the conformation **16a**. Since the attack from the axial side is completely halted by the large *tert*-butyldimethylsilyl group, the protonation occurs from the equatorial side to produce **14**. In any event, the conjugate addition occurs in ketone **8c**, while the substitution reactions at the α, γ, and C=O positions take place in the esters **8a,b**.

In conclusion, RCu·BF_3, as well as other Lewis acid–RCu systems, is useful for the conjugate addition to the sterically crowded α,β-unsaturated ketones and esters and to certain unsaturated carboxylic acids. R_2CuLi–BF_3 is also useful for the double alkylation of α,β-unsaturated esters at the β-position and the carbonyl center.

Experimental Section

NMR spectra were recorded on JEOL PS-100 spectrometers; chemical shifts are expressed in parts per million relative to Me_4Si. IR spectra were recorded on a Hitachi 215 spectrophotometer, and GLC analyses were performed on a JEOL JGC-20K instrument using a 2-m column packed with SE-30, silicon DC-550, or CW-6000 on Celite 545 AW and a Golay column coated with squalene. GC/MS was measured on a Hitachi-MR-1 instrument (22 eV). Elemental analyses were performed by the Kyoto University Microanalytical Laboratories, and the results were within the accepted limits (±0.3%). All temperatures are uncorrected.

Materials. Reagent grade solvents were purified by standard techniques and kept over a drying agent. Organometallic compounds were prepared or purchased as previously described.[26] 3,4-Dimethylpent-3-en-2-one was prepared by the method of House:[30] bp 150 °C; IR (CCl_4) 1684, 1615 cm^{-1}; NMR (CCl_4) δ 1.74 (s, 3 H), 1.83 (s, 6 H), 2.13 (s, 3 H); mass spectrum, *m/e* 112 (M^+). 1-Cyclohexenenitrile was prepared by the known method:[31] bp 70 °C (15 mmHg); IR (CCl_4) 2220, 1635 cm^{-1}; NMR (CCl_4) δ 1.68–1.80 (m, 4 H), 2.22 (br s, 4 H), 6.50–6.60 (m, 1 H); mass spectrum, *m/e* 107 (M^+). 1-Cyclohexenecarboxylic acid was prepared by the hydrolysis of the corresponding nitrile with KOH–ethylene glycol:[32] bp 105–107 °C (4 mmHg); IR (CCl_4) 3400–2800, 2800–2400, 1690, 1640 cm^{-1}; NMR (CCl_4) δ 1.56–1.72 (m, 4 H), 2.22 (br s, 4 H), 7.04–7.14 (m, 1 H), 11.20 (br s, 1 H); mass spectrum, *m/e* 126 (M^+). Methyl 1-cyclohexenecarboxylate was prepared from the corresponding acid with MeOH–HCl: bp 60 °C (1 mmHg); IR (CCl_4) 1710, 1640 cm^{-1}; NMR (CCl_4) δ 1.68 (br s, 4 H), 2.24 (br s, 4 H), 3.74 (s, 3 H), 6.96–7.06 (m, 1 H); mass spectrum, *m/e* 140 (M^+). 1-(1-Cyclohexenyl)pentan-1-one was prepared from the reaction of 1-cyclohexenecarboxylic acid (1.26 g, 10 mmol) with butyllithium (20 mmol) in ether as reported in the literature:[33] bp 90 °C (1 mmHg); IR (CCl_4) 1670, 1640 cm^{-1}; NMR (CCl_4) δ 1.0 (t, J = 6 Hz, 3 H), 1.20–1.56 (m, 4 H), 1.56–1.80 (m, 4 H), 2.00–2.40 (m, 4 H), 2.60 (t, J = 7 Hz, 2 H), 6.70–6.90 (m, 1 H); mass spectrum *m/e* 166 (M^+). 1-Acetylcyclohexene was prepared by a similar method with MeLi:[33] bp 60 °C (20 mmHg); IR (CCl_4) 1660, 1640 cm^{-1}; NMR ($CDCl_3$) δ 1.45–1.75 (m 4 H), 2.10–2.50 (m, containing s at 2.24, 7 H), 6.85 (m, 1 H); mass spectrum, *m/e* 124 (M^+). 5-Methyl-2-cyclohexenone was prepared as described previously.[26] Ethyl cyclohexylideneacetate was prepared by the method of Wolinsky and Erickson:[34] bp 76–77 °C (4 mmHg); IR (CCl_4) 1730, 1645 cm^{-1}; NMR (CCl_4) δ 1.22 (t, J = 7 Hz, 3 H), 1.6 (br s, 6 H), 2.16 (br s, 2 H), 2.78 (br s, 2 H), 4.00 (q, J = 7 Hz, 2 H), 5.44 (br s, 1 H); mass spectrum, *m/e* 168 (M^+). **8a–c** were given to us by Professor Ibuka. Other chemicals were purchased and used as such.

General Procedure for the Lewis Acid Mediated Conjugate Addition. In a 200-mL flask, equipped with a magnetic stirrer and maintained under N_2, were placed 1.9 g (10 mmol) of CuI and 20 mL of dry ether. BuLi in hexane (1.3 M, 10 mmol) was added at −30 °C, and the resulting mixture was stirred at this temperature for 20 min. The mixture was then cooled to −70 to −75 °C and Lewis acids such as BF_3-OEt_2 (47%, 1.3 mL, 10 mmol), $AlCl_3$–ether solution (10 mmol), or Et_2AlCl–ether solution (10 mmol) were added. After the mixture was stirred for a while, α,β-unsaturated carbonyl compounds (10 mmol) were added. The mixture was allowed to slowly warm to room temperature with stirring and then cooled to 0 °C with an ice bath. The reaction was quenched with saturated aqueous NH_4Cl solution. The reaction mixture was directly analyzed by GLC with an appropriate internal standard. For isolation, the reaction mixture was extracted twice with ether, and the combined organic layer was dried over anhydrous Na_2SO_4. When the reaction proceeded smoothly and the desired product was obtained in high yield, simple distillation via a Kugelrohr apparatus gave the corresponding 1,4-adduct in a substantially pure form. An analytically pure sample was obtained by further purification of this distillate through preparative GLC. When a mixture of 1,4-adduct, 1,2-adduct, and the substitution products was obtained, the separation was performed by preparative GLC or with column chromatography on silica gel. Slightly different conditions were used in the reaction of MeCu·BF_3; MeCu was prepared at 0 °C and then cooled to −70 to −75 °C. When BF_3-OEt_2 was added to this yellow

(28) Claesson, A.; Sahlberg, C. *J. Organomet. Chem.* **1979**, *170*, 355. Logusch, E. W. *Tetrahedron Lett.* **1979**, 3365.

(29) It has been suggested that the enolates of 2-alkyl-substituted cyclohexanones undergo distortion due to the steric repulsion between the alkyl group and the OM group: Caine, D. "Carbon–Carbon Bond Formation"; Augustine, R. L., Ed.; Marcel Dekker: New York, 1979; Vol. 1, p 223. See also: Narula, A. S. *Tetrahedron Lett.* **1981**, 2017.

(30) House, H. O.; Chu, C.; Wilkins, J. M.; Umen, M. J. *J. Org. Chem.* **1975**, *40*, 1460.

(31) Abramovitch, R. A.; Struble, D. L. *Tetrahedron* **1968**, *24*, 357.

(32) House, H. O.; Umen, M. J. *J. Org. Chem.* **1973**, *38*, 3893. See also: "Organic Syntheses"; Wiley: New York, 1963; Collect. Vol. IV, p 93.

(33) Jorgenson, M. J. *Org. React.* **1970** *18*, 1.

(34) Wolinsky, J.; Erickson, K. L. *J. Org. Chem.* **1965**, *30*, 2208.

suspension, the color did not change. Lithium dibutylcuprate in ether was prepared by the addition of 2 equiv of butyllithium in hexane to an ether suspension of CuI at −30 °C, and then the substrate was added at this temperature. Lewis acid mediated reaction of Bu_2CuLi was carried out by the addition of an ether solution of the substrate–Lewis acid mixture to the cuprate solution at −30 °C.

4-Phenyl-2-octanone:[35] bp 100 °C (0.1 mmHg); IR (CCl_4) 1720 cm^{-1}; NMR (CCl_4) δ 0.83 (t, J = 6 Hz, 3 H), 1.00–1.70 (m, 6 H), 1.90 (s, 3 H), 2.57 (d, J = 6 Hz, 2 H), 2.88–3.20 (m, 1 H), 7.07 (br s, 5 H); mass spectrum, m/e 204 (M^+).

4-Phenyl-2-pentanone:[36] bp 70 °C (0.1 mmHg); IR (CCl_4) 1725 cm^{-1}; NMR (CCl_4) δ 1.21 (d, J = 7 Hz, 3 H), 1.92 (s, 3 H), 2.48–2.64 (m, 2 H), 3.04–3.32 (m, 1 H), 7.08 (br s, 5 H); mass spectrum, m/e 162 (M^+).

4,4-Dimethyl-2-octanone:[37] bp 83–85 °C (20 mmHg); IR (CCl_4) 1725 cm^{-1}; NMR (CCl_4) δ 0.96 (br s, 9 H), 1.24 (br s, 6 H), 2.04 (s, 3 H), 2.23 (s, 2 H); mass spectrum, m/e 156 (M^+).

2,4-Dimethyl-2-octen-4-ol: bp 83–85 °C (20 mmHg); IR (CCl_4) 3600, 1640 cm^{-1}; NMR (CCl_4) δ 0.89 (br t, J value was not obvious, 3 H), 0.96 (br s, 3 H), 1.20 (br s, 6 H), 1.66 (s, 3 H), 1.80 (s, 3 H), 5.06–5.12 (m, 1 H); mass spectrum, m/e 156 (M^+). Anal. ($C_{10}H_{20}O$) C, H. An authentic sample was prepared by the reaction of 4-methyl-2-pentanone with BuLi in ether at −78 °C.

3,4,4-Trimethyl-2-octanone: bp 100 °C (10 mmHg); IR (CCl_4) 1710 cm^{-1}; NMR (CCl_4) δ 0.88 (t, J = 6 Hz, 3 H), 0.90 (s, 6 H), 0.98 (d, J = 7 Hz, 3 H), 1.23 (br s, 6 H), 2.06 (s, 3 H), 2.40 (q, J = 7 Hz, 1 H); mass spectrum, m/e 170 (M^+). Anal. ($C_{11}H_{22}O$) C, H.

2,3,4-Trimethyl-2-octen-4-ol: bp 100 °C (10 mmHg); IR (CCl_4) 3610, 1680 cm^{-1}; NMR (CCl_4) δ 0.89 (t, J = 6 Hz, 3 H), 1.25 (br s, 9 H), 1.55 (s, 3 H), 1.63 (s, 3 H), 1.88 (s, 3 H); mass spectrum, m/e 170 (M^+). Anal. ($C_{11}H_{22}O$) C, H. An authentic sample was prepared from the reaction of the trisubstituted enone with BuLi at −78 °C.

1-(2-Butylcyclohexyl)pentan-1-one: bp 100 °C (1 mmHg); IR (CCl_4) 1700 cm^{-1}; NMR (CCl_4) δ 0.8–1.0 (m, 6 H), 1.0–1.4 (m, 10 H), 1.4–1.7 (m, 6 H), 1.7–2.0 (m, 3 H), 2.36 (t, J = 6 Hz, 2 H), 2.45–2.64 (m, 1 H); mass spectrum, m/e 224 (M^+). Anal. ($C_{15}H_{28}O$) C, H. The stereochemistry between the butyl and pentanoyl group on the six-membered ring was not determined.

3-Butyl-5-methylcyclohexanone: bp 100 °C (20 mmHg); IR (CCl_4) 1703 cm^{-1}; NMR (CCl_4) δ 1.0 (br t, J = 6 Hz, 6 H), 1.40–1.55 (m, 6 H), 1.55–2.04 (m, 4 H), 2.04–2.56 (m, 4 H); mass spectrum, m/e 168 (M^+). This ketone was converted to 1-butyl-3-methylcyclohexane through the Wolff–Kishner reduction: $NH_2NH_2{\cdot}H_2O$ (0.2 mL), KOH (0.2 g), $HOCH_2CH_2OCH_2CH_2OH$ (2 mL), ketone (0.17 g, 1 mmol), 100–180 °C, 5 h. The resulting hydrocarbon was analyzed by GLC using a capillary column (squalene, 0.25 mm i.d. × 45 m), as reported previously.[26]

Methyl 3-methylheptanoate:[38] bp 100 °C (18 mmHg); IR (NaCl) 1745 cm^{-1}; NMR (CCl_4) δ 0.90 (br t including d, J = 6 Hz, 6 H), 1.28 (br s, 6 H), 1.80–2.00 (m, 1 H), 2.00–2.40 (m, 2 H), 3.58 (s, 3 H); mass spectrum, m/e 158 (M^+).

Ethyl 2,3-dimethylheptanoate: bp 95 °C (25 mmHg); IR (NaCl) 1740 cm^{-1}; NMR (CCl_4) δ 0.80–1.30 (m, 18 H), 1.60–1.80 (m, 1 H), 2.10–2.40 (quintet, J = 7 Hz, 1 H). The ratio of diastereomers was not obvious; although the GLC analyses (DC-550 and SE-30) showed a sharp single peak, it was highly probable that the diastereomers could not be separated under these conditions. Authentic material was prepared from the corresponding acid obtained below.

6,7-Dimethyl-5-undecanone:[17] bp 65 °C (1 mmHg); IR (NaCl) 1710 cm^{-1}; NMR (CCl_4) δ 0.80–1.00 (m, 12 H), 1.10–1.60 (m, 11 H), 2.10–2.40 (m, 3 H); mass spectrum, m/e 198 (M^+). The ratio of diastereomers was not determined.

Ethyl (1-butylcyclohexyl)acetate: bp 80 °C (4 mmHg); IR (NaCl) 1720 cm^{-1}; NMR (CCl_4) δ 0.92 (t, J = 6 Hz, 3 H), 1.20–1.50 (m, 16 H), 2.18 (s, 2 H), 4.04 (q, J = 7 Hz, 2 H); mass spectrum m/e 226 (M^+). Anal. ($C_{14}H_{26}O_2$) C, H.

Ethyl 3,3-dimethylheptanoate: bp 90–93 °C (25 mmHg); IR (NaCl) 1740 cm^{-1}; NMR (CCl_4) δ 0.96 (br s, 9 H), 1.16–1.32 (m, 9 H), 2.10 (s, 2 H), 4.05 (q, J = 7 Hz, 2 H); mass spectrum, m/e 186 (M^+). Anal. ($C_{11}H_{22}O_2$) C, H. See also ref 39. The ester was converted into the corresponding acid as mentioned below.

7,7-Dimethyl-5-undecanone: bp 65 °C (1 mmHg); IR (CCl_4) 1710 cm^{-1}; NMR (CCl_4) δ 0.88 (br t, J = 6 Hz, 6 H), 0.90 (s, 6 H), 1.25 (br s, 10 H), 2.06–2.35 (m, 4 H); mass spectrum, m/e 198 (M^+). Anal. ($C_{13}H_{26}O$) C, H. See also ref 39.

Methyl 2-butylcyclohexanecarboxylate: bp 60 °C (1 mmHg); IR (CCl_4) 1725 cm^{-1}; NMR (CCl_4) δ 0.90 (t, J = 6 Hz, 3 H), 1.04–1.36 (m, 6 H), 1.36–1.67 (m, 6 H), 1.67–2.40 (m, 3 H), 2.46–2.68 (m, 1 H), 3.66 (s, 3 H). The stereochemistry between the butyl and methoxycarbonyl group was not determined. An authentic material was prepared from the corresponding acid obtained below.

3-Methylheptanoic acid:[38] bp 75 °C (1 mmHg); IR (NaCl) 3500–2800, 2800–2400, 1715 cm^{-1}; NMR (CCl_4) δ 0.89 (t, J = 6 Hz, 3 H), 0.97 (d, J = 6 Hz, 3 H), 1.28 (br s, 6 H), 1.80–2.00 (m, 1 H), 2.08–2.35 (m, 2 H), 10.30 (br, 1 H); mass spectrum, m/e 144 (M^+).

2,3-Dimethylheptanoic acid:[17] bp 105–108 °C (8 mmHg); IR (NaCl) 3500–2800, 2800–2400, 1710 cm^{-1}; NMR (CCl_4) δ 0.94 (br t including d, J = 6 Hz, 6 H), 1.14 (d, J = 6, 6 Hz, 3 H), 1.30 (br s, 6 H), 1.70–1.90 (m, 1 H), 2.20–2.50 (m, 2 H), 10.80 (br, 1 H); mass spectrum, m/e 158 (M^+).

3,3-Dimethylheptanoic Acid. Although this acid was not isolated from the $BuCu{\cdot}BF_3$ reaction, its retention time on GLC (DC-550 and CW 20 M) was easily found by analysis of the hydrolysis solution of ethyl 3,3-dimethylheptanoate obtained above. Thus, it was revealed that only trace amounts of the acid were produced from the $BuCu{\cdot}BF_3$ reaction.

2-Butylcyclohexanecarboxylic acid: bp 115 °C (4 mmHg); IR (CCl_4) 3500–2800, 2800–2400, 1700 cm^{-1}; NMR (CCl_4) δ 0.90 (br t, J = 6 Hz, 3 H), 1.28 (br s, 6 H), 1.68 (br s, 9 H), 2.40–2.60 (m, 1 H), 10.80 (br, 1 H); mass spectrum, m/e 184 (M^+). Anal. ($C_{11}H_{20}O_2$) C, H. The stereochemistry was not obvious, though a sharp single peak was observed on GLC (DC-550).

Heptanenitrile:[40] bp 85 °C (20 mmHg); IR (CCl_4) 2270 cm^{-1}; NMR (CCl_4) δ 0.93 (t, J = 6 Hz, 3 H), 1.20–1.80 (br m, 8 H), 2.30 (t, J = 6 Hz, 2 H).

Undecan-5-one:[41] bp 80 °C (2 mmHg); IR (CCl_4) 1710 cm^{-1}; NMR (CCl_4) δ 0.90 (br, t, J = 6 Hz, 6 H), 1.10–1.70 (m, 12 H), 2.32 (t, J = 6 Hz, 4 H); mass spectrum, m/e 170 (M^+).

Methyl 3-(1-propenyl)heptanoate: bp 70 °C (1 mmHg); IR (NaCl) 1740, 965 cm^{-1}; NMR (CCl_4) δ 0.90 (t, J = 6 Hz, 3 H), 2.27 (br s, 6 H), 1.66 (d, J = 6 Hz, 3 H), 2.18 (d, J = 6 Hz, 2 H), 2.20–2.30 (m, 1 H), 3.60 (s, 3 H), 5.20–5.50 (m, 2 H); mass spectrum, m/e 184 (M^+). Anal. ($C_{11}H_{20}O_2$) C, H. The irradiation at the olefinic protons converted the doublet at δ 1.66 ($CH_3C{=}$) into a sharp singlet. The strong absorption at 965 cm^{-1} and a sharp single peak on GLC (DC-550 and CW 6000) indicated the trans configuration.

Methyl 5-methyl-3-nonenoate: bp 70 °C (1 mmHg); IR (NaCl) 1740, 965 cm^{-1}; NMR (CCl_4) δ 0.88–1.02 (m, 6 H), 2.24 (br s, 6 H), 1.98–2.20 (m, 0.5 H), 2.20–2.42 (m, 0.5 H), 2.94 (t, J = 6 Hz, 2 H), 3.58 (s, 3 H), 5.10–5.50 (m, 2 H); mass spectrum, m/e 184 (M^+). This 1,6-α,δ-adduct was isolated from the cuprate reaction. The irradiation at the olefinic protons converted the triplet at δ 2.94 ($=CCH_2CO$) into a doublet (the ratio of peak height 1:1). This experiment, together with the characteristic peaks between δ 1.98 and 2.42 suggested that the 1,6-α,δ-adduct consisted of a mixture of the cis and trans isomers (1:1). Actually, the GLC examination (DC 550) showed two near peaks in the region of 1,6-adduct, whose cis/trans ratio was 1:1. If one of these peaks was the 1,6-γ,δ-adduct as observed in the reaction of *sec*-butyl sorbate with $BuCu{\cdot}MgX_2$,[19] each chemical shift of two olefinic protons should be separated significantly, and the carbonyl

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absorption should appear at 1730–1710 cm^{-1}. Further, the irradiation between δ 1.98 and 2.42 changed the peak in the olefinic region. Therefore, we excluded the possibility of the 1,6-γ,δ-adduct. Interestingly, the GLC examination of the minor component obtained from the $BuCu·BF_3$ reaction showed a single peak in the region of the 1,6-adduct.

5-Methyl-3-nonenoic acid:[19] 85 °C (0.5 mmHg); IR (NaCl) 3500–2800, 2800–2400, 1720, 965 cm^{-1}; NMR (CCl_4) δ 0.90 (t, J = 6 Hz, 3 H), 0.98 (d, J = 7 Hz, 3 H), 2.26 (br s, 6 H), 2.0–2.24 (m, 1 H), 3.0 (d, J = 6 Hz, 2 H), 5.32–5.44 (m, 2 H), 10.80 (br s, 1 H); mass spectrum, m/e 170 (M^+). Irradiation at the olefinic protons converted the doublet at δ 3.0 (=CCH_2CO) into a sharp singlet. A sharp single peak on GLC (CW 6000), strong IR absorption at 965 cm^{-1}, and the irradiation experiment indicated the trans 1,6-α,δ structure. Finally, the acid was converted into the methyl ester with MeOH–HCl, which showed the same retention time as one of the two peaks of an authentic sample obtained above.

3-(1-Propenyl)heptanoic Acid. This 1,4-adduct was not isolated in pure form but was contaminated with significant amounts of the 1,6-α,δ-adduct (the 1,6-adduct was isolated in pure form by chromatography through a short column of silica gel with benzene as the eluant followed by distillation): mass spectrum, m/e 170 (M^+); NMR (CCl_4; deduced from the mixture) δ 0.90 (t, J = 6 Hz, 3 H), 2.26 (br s, 6 H), 1.65 (d, J = 6 Hz, 3 H), 2.00–2.24 (m, 1 H), 2.25 (d, J= 6 Hz, 2 H), 5.32–5.44 (m, 2 H). The irradiation of the olefinic protons converted the doublet (CH_3C=) at δ 1.65 into a sharp singlet. Further, the methyl ester derived from the acid exhibited the same retention time on GLC (CW 6000) as the 1,4-adduct obtained above.

Stereochemical Aspects. An ether solution of *tert*-butylcyclohexanone (1 mmol) was added to an ether solution of organometallic compounds at −70 °C, and the mixture was allowed to warm to 0 °C. The reaction was quenched by saturated aqueous NH_4Cl solution, and the organic layer was analyzed by GLC (CW 6000, 10%, 2 m). $MeLi·Et_3Al$ was prepared by the addition of an equivalent amount of Et_3Al in hexane to an ether solution of MeLi at −70 °C. The reaction of 1-acetylcyclohexene with methylcopper derivatives was carried out as described in the general procedure; the reaction temperature and quenching temperature are indicated in the Table III. The reaction mixture was analyzed by GLC with SE-30 (10%, 2 m) and with *n*-tridecane as an internal standard. *trans*-1-Acetyl-2-methylcyclohexane (**3**):[5b] IR (CCl_4) 1710 cm^{-1}; NMR (CCl_4) δ 0.81 (d, J = 7 Hz, 3 H), 1.0–2.1 (br m, maxima at 1.28 and 1.75, 10 H), 2.04 (s, 3 H). *cis*-1-Acetyl-2-methylcyclohexane (**4**):[5b] IR (CCl_4) 1710 cm^{-1}; NMR (CCl_4) δ 0.82 (d, J = 7 Hz, 3 H), 1.0–1.9 (br m, 9 H), 2.02 (s, 3 H), 2.0–2.6 (br m, 1 H). The chemical shifts of **3** and **4** were identical with the reported data.[5b] Furthermore, epimerization from **4** to **3** was observed upon treatment with NaOEt. 1-Isopropenylcyclohexene (**5**) was isolated by preparative GLC (SE-30): IR (CCl_4) 880 cm^{-1}; NMR (CCl_4) δ 1.40–1.75 (br m, maximum at 1.63, 4 H), 1.84 (s, 3 H), 1.95–2.35 (br m, maximum at 2.15, 4 H), 4.74 (br s, 1 H), 4.85 (br s, 1 H), 5.80 (br t, 1 H); mass spectrum, m/e 122 (M^+). The chemical shifts were identical with the reported data.[42] Isopropylidenecyclohexene (**6**) was also isolated similarly: NMR (CCl_4) δ 1.67 (s, 6 H), 2.35–1.76 (m, 6 H), 5.54 (m, 1 H), 6.27 (d, J = 10 Hz, 1 H); mass spectrum, m/e 122 (M^+). The chemical shifts were identical with the reported data.[43]

Reaction of 8. A procedure similar to that used above was employed. The analysis of the reaction mixture by GLC (DC 550, 5%, 2 m) revealed that large amounts of **8a** were recovered. Because of this disappointing result, we did not determine the exact yields of **9** and **10** but had an interest in their structures. **9** and **10** were isolated by column chromatography through silica gel with ether–hexane (1:9) as the eluant. **9**: IR (CCl_4) 3600, 1670 cm^{-1}; NMR (CCl_4) δ 0.94 (t, J = 7 Hz, 3 H), 1.18–2.00 (m, 8 H), 2.20 (br s, 2 H), 2.44 (br s, 1 H), 2.62 (t, J = 7 Hz, 2 H), 4.30 (br s, 1 H), 6.70 (br s, 1 H); mass spectrum, m/e 182 (M^+). Anal. ($C_{11}H_{18}O_2$) C, H. **10** was identified by comparison with authentic material (Table I). In the reaction of **8b**, the products **11**–**13** were identified by the comparison of their GC/MS with those of the products obtained via $BuCu–AlCl_3$.[10a] The reaction of **8c** with 2 equiv of $BuCu·BF_3$ was carried out similarly. **14** was isolated by chromatography through a short column of silica gel with ether–hexane (1:9), followed by Kugelrohr distillation: bp 100 °C (1 mmHg) [lit.[10b] bp 110 °C (3 mmHg)]; IR (CCl_4) 1700 cm^{-1}; NMR ($CDCl_3$) δ 0.04 (s, 6 H), 0.88 (br s, 12 H), 1.20–1.80 (m, maximum at 1.27, 13 H), 2.14 (s, 3 H), 2.30 (m, 1 H), 3.41 (m, 1 H). The NMR spectra ($CDCl_3$) of the reaction mixture did not exhibit a signal at δ 2.08 which corresponded to the $COCH_3$ protons of **15**.[10b]

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Registry No. **3**, 5222-61-7; **4**, 5222-62-8; **5**, 6252-18-2; **6**, 6248-81-3; **8a**, 73934-59-5; **8b**, 79663-63-1; **8c**, 76711-47-2; **9**, 79663-64-2; **10**, 30857-54-6; **11**, 79663-99-3; **12**, 73934-60-8; **13**, 73934-61-9; **14**, 76711-55-2; methyl sorbate, 1515-80-6; sorbic acid, 110-44-1; 4-*tert*-butylcyclohexanone, 98-53-3; *cis*-4-*tert*-butyl-1-methyl-1-cyclohexanol, 16980-56-6; *trans*-4-*tert*-butyl-1-methyl-1-cyclohexanol, 16980-55-5; 4-phenyl-2-octanone, 35583-33-6; 4-phenyl-2-pentanone, 17913-10-9; 4,4-dimethyl-2-octanone, 49585-97-9; 2,4-dimethyl-2-octen-4-ol, 76008-28-1; 3,4,4-trimethyl-2-octanone, 58105-39-8; 2,3,4-trimethyl-2-octen-4-ol, 79663-65-3; 1-(2-butylcyclohexyl)pentan-1-one, 79663-66-4; *cis*-3-butyl-5-methylcyclohexanone, 79663-67-5; *trans*-3-butyl-5-methylcyclohexanone, 79663-68-6; methyl 3-methylheptanoate, 67061-26-1; ethyl 2,3-dimethylheptanoate, 67061-27-2; 6,7-dimethyl-5-undecanone, 79663-69-7; ethyl (1-butylcyclohexyl)acetate, 67061-28-3; ethyl 3,3-dimethylheptanoate, 51756-26-4; 7,7-dimethyl-5-undecanone, 51756-27-5; methyl 2-butylcyclohexanecarboxylate, 79663-70-0; 3-methylheptanoic acid, 53663-30-2; 2,3-dimethylheptanoic acid, 67061-25-0; 3,3-dimethylheptanoic acid, 67061-30-7; 2-butylcyclohexanecarboxylic acid, 67061-29-4; heptanenitrile, 629-08-3; undecan-5-one, 33083-83-9; methyl (*E*)-3-(1-propenyl)heptanoate, 67061-31-8; methyl (*E*)-5-methyl-3-nonenoate, 67061-32-9; methyl (*Z*)-5-methyl-3-nonenoate, 79663-71-1; (*E*)-5-methyl-3-nonenoic acid, 67061-34-1; (*E*)-3-(1-propenyl)heptanoic acid, 67061-33-0; 1-acetylcyclohexene, 932-66-1; 4-phenyl-3-buten-2-one, 122-57-6; 4-methyl-3-penten-2-one, 141-79-7; 3,4-dimethylpent-3-en-2-one, 684-94-6; 1-(1-cyclohexenyl)pentan-1-one, 30857-54-6; 5-methyl-2-cyclohexenone, 7214-50-8; methyl 2-butenoate, 18707-60-3; ethyl 2-methyl-2-butenoate, 55514-48-2; ethyl cyclohexylideneacetate, 1552-92-7; ethyl 3-methyl-2-butenoate, 638-10-8; methyl 1-cyclohexenecarboxylate, 18448-47-0; 2-butenoic acid, 3724-65-0; 2-methyl-2-butenoic acid, 13201-46-2; 3-methyl-2-butenoic acid, 541-47-9; 1-cyclohexenecarboxylic acid, 636-82-8; 2-propenenitrile, 107-13-1; 1-cyclohexenenitrile, 1855-63-6; 3-heptanol, 589-82-2; 1-butylcyclohexanol, 5445-30-7; propanal, 123-38-6; cyclohexanone, 108-94-1; $C_4H_9Cu·BF_3$, 68079-35-6; $CH_3Cu·BF_3$, 68079-36-7; $(C_4H_9)_2CuLi$, 24406-16-4; C_4H_9Cu, 34948-25-9; C_4H_9Br, 109-65-9; C_4H_9Li, 109-72-8; CH_3Cu, 1184-53-8; $(CH_3)_2CuLi$, 15681-48-8; $TiCl_4$, 16028-76-5; $CH_3Cu·P(C_4H_9)_3$, 24743-95-1.

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