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(12) See also I. Wahlberg, S.-O. Almqvist, T. Nishida, and C. R. Enzell, *Acta Chem. Scand., Ser. B*, **29**, 1047 (1976).
(13) That the signal of H-19 is a singlet requires an explanation. Although it is impossible to construct satisfactory models for **11** and **12**, use of somewhat more flexible models indicates that the dihedral angle between H-16 and H-19 is such that $J_{16,19}$ should be close to zero.
(14) Although ketenes readily react with methanol which is used as a solvent, thermally allowed intramolecular reaction of the strained double bond with properly aligned ketene might well take precedence over intermolecular solvent addition.
(15) V. Baburao, Ph.D. Dissertation, Florida State University, 1972.
(16) W. C. Agosta and A. B. Smith, *J. Am. Chem. Soc.*, **93**, 5513 (1971).
(17) The emission spectra were determined by Mr. Al Marinari in the manner described in ref 5.
(18) R. L. Cargill, W. A. Bundy, D. M. Pond, A. B. Sears, J. Saltiel, and J. Winterle, *Mol. Photochem.*, **3**, 000 (1971), and references cited therein. In the rigid 2-alkyl cyclopentenones discussed in this reference the lowest triplet is π-π^*, but it is apparently very close in energy to n-π^* with the result that vibronic mixing is favored. In such situations, caution is required in relating low temperature spectroscopic observations in rigid systems to room temperature solution photochemistry; moreover, in systems with closely lying lowest excited states the reactive state need not be the one possessing the lowest energy.[19-21]
(19) P. J. Wagner, A. E. Kemppainen, and H. N. Schott, *J. Am. Chem. Soc.*, **92**, 5280 (1970); **95**, 5604 (1973).
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(22) Melting points are uncorrected. Analyses were carried out by Dr. F. Pascher, Bonn, Germany. NMR spectra were run on Varian HA-60 or Bruker HX-270 MHZ instruments in $CDCl_3$ and Me_4Si as internal standard, unless otherwise noted. Values for line positions are expressed in parts per million, coupling constants are expressed in hertz. Signals are characterized as d, doublet; t, triplet, q, quartet; br, broad singlet; m, multiplet; c, complex signal whose center is given. Unmarked signals are singlets. Infrared spectra were determined on a Perkin-Elmer Model 257 grating spectrometer in KBr pellets or as Nujol mulls. Ultraviolet spectra were recorded on a Carey Model 14 recording spectrophotometer in 95% ethanol, ORD or CD spectra on a Jasco Model ORD/UV-5 recording spectrophotometer. Silica gel $PF_{254+366}$ (Merck) was used for preparative TLC.

Asymmetric Reduction with Chiral Reagents from Lithium Aluminum Hydride and (*S*)-(−)-*N*-(*o*-Substituted benzyl)-α-phenylethylamines

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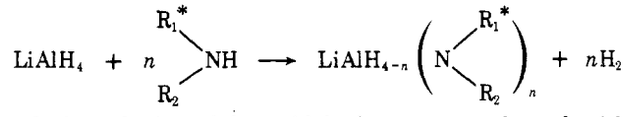
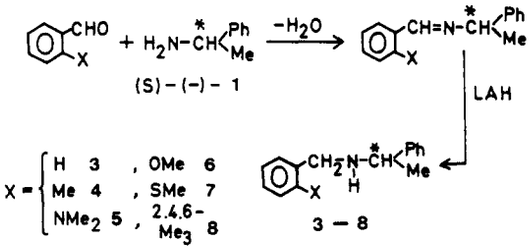
Asymmetric reduction of carbonyl compounds with chiral hydride reagents modified by (*S*)-(−)-*N*-(*o*-substituted benzyl)-α-phenylethylamines (**3**–**8**) in toluene was investigated in order to clarify the role of the functional group in the amine ligands on the stereoselectivity. Of all the functional groups in the chiral secondary amines tested, the NMe_2 group exerted a remarkable effect on the asymmetric reduction of ketones (toluene solvent) affording fairly good optical yields [PhCH(OH)CH_3, 43% ee; PhCH(OH)Et, 52% ee; and PhCH(OH)Bu-*t*, 47% ee]. The presence of additives such as 1,2-dimethoxyethane or *N,N,N′,N′*-tetramethylethylenediamine in the reaction mixture caused a dramatic decrease in the stereoselectivity, while that of 1,2-dimethylmercaptoethane did not. These observations strongly suggest that chelate ring formation in the chiral hydride reagent is one of the essential factors for the high observed stereoselectivities.

Reduction of an achiral carbonyl compound by a chiral reducing agent to give unequal amounts of the enantiomeric secondary carbinol has been the subject of much study. Most of such studies have been carried out by use of $LiAlH_4$ derivatives modified by the various chiral ligands.[1] One of the prerequisites for a useful chiral ligand is that it be readily available in optically pure form and that it can be easily recovered from the reaction mixture without any loss of optical purity. So far, various naturally occurring chiral carbinols and their derivatives, such as alkaloids,[2] monosaccharides,[3] terpene alcohols,[4] and tartaric acid derivatives,[5] have been so employed. Recently, synthetic chiral ligands such as (+)-(2*S*,3*R*)-4-dimethylamino-3-methyl-1,2-diphenyl-2-butanol,[6,7] oxazoline derivatives[8] and amino carbinols[9] have been used for the formation of $LiAlH_4$ complexes which provided substantial stereoselectivity.

These hydride reagents employed so far mostly have been limited to the chiral carbinol or amino carbinol complexes and little is known[10] concerning the stereoselectivity of carbonyl reductions with chiral amine–$LiAlH_4$ complexes. A systematic study of the effect of functional group substituents on the chiral amine ligands should afford a better understanding of the mechanism of these asymmetric reductions as well as the necessary information for the design of a more effective chiral amine–$LiAlH_4$ reagent. We have begun such a study using various chiral secondary amines (**3**–**8**) for the reaction with $LiAlH_4$ in various molar ratios. The effect of three achiral complexing additives also has been studied. The chiral reducing agent can be represented by the following scheme.



Ortho-substituted benzaldehydes were condensed with (*S*)-(−)-α-phenylethylamine (**1**) to give the corresponding Schiff bases which were in turn reduced with excess $LiAlH_4$ in boiling ether. The (*S*)-(−)-*N*-(*o*-substituted benzyl)-α-phenylethylamines (**3**–**8**) thus obtained were purified by



fractional distillation under reduced pressure. These chiral amines are tabulated in Table I.

It was shown conclusively that there was no racemization during the synthesis of amine **3**. The NMR spectrum of *dl* amine **2** in the presence of the chiral shift reagent Eu(hfc)$_3$, tris[3-(heptafluoropropylhydroxymethylene-*d*-campho-

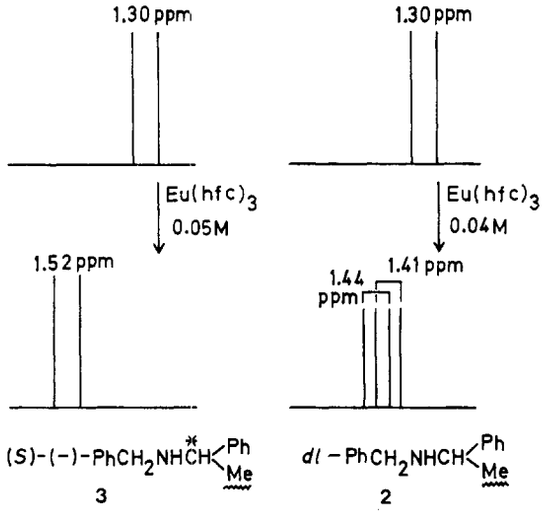


Figure 1. 90-MHz ^1H NMR spectra of Me group of racemic and (*S*)-(−)-*N*-benzyl-α-phenylethylamine (**3**) in the presence of Eu(hfc)$_3$, tris[3-(heptafluoropropylhydroxymethylene-*d*-camphorato]europium(III).

Table I. (*S*)-(−)-*N*-(*o*-Substituted benzyl)-α-phenylethylamines

Chiral amines[a]				
No.	Ortho substituent (X)	$[\alpha]^{25}_D$	Bp, °C (Torr)	Yield, %
3	H	−49.2° (*c* 6.04)[b]	102 (0.03)	83
4	Me	−40.7° (*c*, 4.85)[b]	104–105 (0.002)	86
5	NMe_2	−53.5° (*c* 6.59)[b]	128–130 (0.001)	72
6	OMe	−73.7° (*c* 4.82)[b]	128–130 (0.01)	82
7	SMe	−58.7° (*c* 6.20)[b]	135–137 (0.005)	73
8	2,4,6-Me_3	−21.9° (*c* 4.57)[b]	126 (0.01)	80

[a] All compounds gave satisfactory N analysis. [b] Solvent: cyclopentane.

rato]europium(III), reveals the methyl signal as a pair of doublets, one set for each diastereomeric complex. Product **3** prepared from (*S*)-(−)-**1** showed only one set of doublets as seen in Figure 1. Therefore, **3** is enantiomerically pure within the limits of this NMR determination. Based on this it is assumed that **4**–**8** are also enantiomerically pure.

The asymmetric reductions of carbonyl compounds with chiral $LiAlH_4$ complexes have been generally conducted in ether solvents. In the present study, however, the reductions were carried out in toluene solvent in order to eliminate any influence due to coordination of the solvent. $LiAlH_4$ reacts with the excess chiral amines in toluene to give a complex evolving 1 mol of hydrogen at room temperature. At elevated temperature, however, successive reaction takes place evolving 2–3 mol of hydrogen according to the molar ratio of chiral amine employed. The complexes thus formed are soluble in toluene and do not separate even at −78 °C. The reduction of acetophenone with these complexes was carried out under various experimental conditions designed to explore the effect on the extent of asymmetric reduction exerted by (a) ortho substituents in the chiral amine ligands, (b) different molar ratios of the amines to $LiAlH_4$, (c) reaction temperature, and (d) the presence of added achiral complexing agents. The results are summarized in Table II.

Pertinent observations are as follows: (1) In some cases, the degree of asymmetric induction increased with increasing molar ratio of chiral amines to $LiAlH_4$. (2) All of the asymmetric reductions of acetophenone with these complexes (amine/$LiAlH_4$ 3/1) at 0 °C afforded corresponding (*R*)-(+)-carbinol except for the case in which the chiral amine carried the OMe group. (3) In many cases, the extent of preferential attack on the si face of acetophenone with various chiral hydride reagents decreased with decreasing reaction temperature. (4) The highest stereoselectivity was attained with reagent **5** (X = NMe_2, the ratio amine **5**/$LiAlH_4$ 3/1), at 0 °C. Contrary to the expectation, however, the stereoselectivity did not increase with decreasing temperature in this case. (5) As shown in Table III, fairly good optical yields were also obtained for the reduction of PhCOEt and PhCOBu-*t* with this reagent.

As to the roles of NMe_2 group in the chiral amine ligand for stereoselectivity, three possible functions—steric, electronic, and coordinating effects—can be expected. It has been suggested that the presence of coordinating groups such as NMe_2[2] or OMe[9] in the chiral ligand may be necessary for high stereoselectivity, but crucial experimental data about this suggestion have not been reported yet. In order to elucidate this problem, the asymmetric reduction of PhCOEt with $LiAlH_4$–amine **5** complex was carried out in the presence of additives. As shown in Table IV, addition of a two-molar ratio of *N,N,N′,N′*-tetramethylethylenediamine or 1,2-dime-

Table II. Asymmetric Reduction of Acetophenone with Chiral Reagents from $LiAlH_4$ and (*S*)-(−)-*N*-(*o*-Substituted benzyl)-α-phenylethylamines [$HN(R_1{*})R_2$]

$$PhCOCH_3 + LiAlH_{4-n}\left(N\begin{matrix}R_1{*}\\R_2\end{matrix}\right)_n \longrightarrow \begin{matrix}Ph\\CH_3\end{matrix}\!>\!CHOH$$

	Chiral amines			Carbinol stereoselectivity	
Registry no.	No.	Ortho substituent	Amine/$LiAlH_4$ mol ratio	0 °C % ee	−78 °C % ee
61491-37-0	**3**	H	2.0	(*R*) 6.8	
			3.0	(*R*) 10.7	(*S*) 5.4
61491-38-1	**4**	Me	2.0	(*R*) 14.0	
			3.0	(*R*) 8.4	(*R*) 6.1
61491-39-2	**5**	NMe_2	1.0	(*S*) 5.0	(*S*) 7.2
			2.0	(*R*) 27.0	(*R*) 18.4
			3.0	(*R*) 43.0	(*R*) 30.8
61506-24-9	**6**	OMe	2.0	(*R*) 5.0	
			3.0	(*S*) 1.2	(*S*) 15.3
61491-40-5	**7**	SMe	2.0	(*R*) 4.7	
			3.0	(*R*) 4.4	(*S*) 18.0
61522-03-0	**8**	2,4,6-Me_3	2.0	(*R*) 9.0	
			3.0	(*R*) 10.8	(*R*) 18.0

Table III. Asymmetric Reduction of Ketones with $LiAlH_4$–(Amine 5)$_3$ Complex

			Carbinol	
Registry no.	Ketone	Extent of redn, %	(Stereoselectivity) % ee	$[\alpha]^{20}_D$
93-55-0	PhCOEt	90	(*R*) 52[a]	
938-16-9	PhCOBu-*t*	90	(*R*) 47	+11.3° (*c* 6.40, benzene)[b]
712-50-5	PhCO-C_6H_{11}	95	(*R*) 14	+ 2.8° (*c* 7.07, EtOH)[c]
1667-01-2	MeCO-mesityl	28	(*R*) 20	+10.3° (*c* 1.55, EtOH)[d]

[a] % ee was determined through its (*R*)-(+)-MTPA ester. [b] R. McLeod, F. J. Welch, and H. S. Mosher, *J. Am. Chem. Soc.*, **82**, 876 (1960). [c] M. P. Balfe, G. H. Beaven, and J. Kenyon, *J. Chem. Soc.*, 376 (1951). [d] V. Prelog, E. Philbin, E. Watanabe, and M. Wilhelm, *Helv. Chim. Acta*, **39**, 1086 (1956).

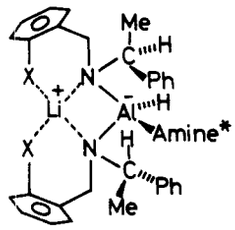
Table IV. Asymmetric Reduction of Propiophenone with $LiAlH_4$-(Amine 5)$_3$ in the Presence of Additives

Additives (XCH_2CH_2X) group X	Carbinol: Extent of redn, %	$[\alpha]^{20}_D$	(c in MeOH)	(Stereoselectivity) % ee
NMe_2	72	+1.1	(2.3)	(R)[a] 3.2
OMe	97.5	−0.5	(4.0)	(S) 1.4
SMe	99	+18.7	(4.2)	(R) 54
No additive added	98	+17.5	(4.3)	(R) 51

[a] R. H. Pickard and J. Kenyon, *J. Chem. Soc.*, **99**, 45 (1911).

thoxyethane to the reaction mixture caused a dramatic decrease in stereoselectivity, with or without inversion of the sign of induction, whereas the addition of 1,2-dimethylmercaptoethane did not. These results indicate that coordination of the ortho NMe_2 group of the reagent with Li cation undoubtedly plays an important role in the stereoselectivity.

The structure of these chiral amine–$LiAlH_4$ complexes in toluene is still obscure. However, it is reasonable to assume that the structures of these complexes resemble that proposed for sodium dihydrobis(2-ethoxymethoxy)aluminate.[11] It is



9 X = NMe_2, OMe, SMe

known[12] that the stabilities of crown ligand–alkaline metal complexes (cation K^+) decrease in the order of electronegativities of the heteroatoms (O > NR > S) in the macrocyclic ligand. The order of chelate ring stabilities of these $LiAlH_4$–amine complexes might be also the same as that of the crown ligand–alkaline metal complexes.

If the stability constant of the chelate ring formation were the sole controlling factor for the stereoselectivity, one might expect that the extent of asymmetric induction would decrease as X in the chiral ligand was changed from OMe to NMe_2 to SMe. This is contrary to observation (Table II). These results suggest that the ortho X substituent functions in more than one capacity, probably both as a coordinating substituent and as a substituent which exerts steric effects as well. In the case of $LiAlH_4$–amine **5** complex represented by formula **9**, two axially oriented N–Me groups are present in the chelate ring when X = NMe_2. These two axial N–Me groups could restrict the conformation of the chiral moiety around the C–N bond thus leading to higher asymmetric induction than observed when X = OMe or SMe. In these latter complexes the methyl groups can assume a nonhindering equatorial orientation.

It is worthwhile to note that the formation of the chelate ring is an important factor to enhance the stereoselectivity even though the chiral center of the ligand is not included in the chelate ring.

Further investigation to explore the more effective chiral amine hydride complex is now in progress.

Experimental Section

Instruments. NMR spectra were taken on a Hitachi R-22, 90-MHz spectrometer. Optical rotations were taken on a Perkin-Elmer 241 electronic polarimeter using 1-dm thermostated microcell. VPC analyses were made on a Shimazu GC-5A using PEG 20M or polydiethylene glycol succinate, 1.5 m × 3 mm column. Preparative VPC was carried out on a Varian Aerograph (Model 700) using the same stationary phase, 2–3 m × 4 mm column.

Solvent and Reagent. Toluene was distilled over NaH and stored over Linde molecular sieve 3A. A stock $LiAlH_4$ solution in ether was passed through a glass filter under nitrogen and stored in a flask closed with a rubber septum. It was analyzed by iodometry[13] immediately prior to use. Aliquots were removed by syringe as needed.

(*S*)-(−)-*N*-Benzyl-α-phenylethylamine (3). A solution of benzaldehyde (15 g) and (*S*)-(−)-phenylethylamine (1) [15 g, $[\alpha]^{20}_D$ −39° (neat)], in 60 mL of benzene was refluxed for 2 h with a Dean-Stark water separator. After the benzene had been removed by distillation, the remaining Schiff base was dissolved in 45 mL of ether, which was then added to a stirred ether solution (75 mL) containing excess $LiAlH_4$ during 30 min. Reflux was continued further for 4 h, after which excess $LiAlH_4$ was decomposed by dropwise addition of ethyl acetate. The reaction mixture was dissolved (dilute HCl) and extracted with ether; the water layer was made alkaline (NaOH) and the separated oil was extracted with ether. The ether extract was washed (H_2O, three times), dried ($MgSO_4$), and concentrated. Fractional distillation under reduced pressure afforded colorless oil, bp 102 °C (0.03 Torr), 21.6 g (83% from the starting 1). VPC analysis indicated that the amine 3 was almost pure (PEG 20M, 1.5 m × 3 mm, 180 °C, N_2 70 mL, retention time 10.9 min), $[\alpha]^{20}_D$ −49.2° (*c* 6.04, cyclopentane).

Anal. Calcd for $C_{15}H_{17}N$: N, 6.38. Found: N, 6.63.

By a similar procedure, the amines (*S*)-(−)-*N*-(*o*-methylbenzyl)- (**4**), (*S*)-(−)-*N*-(*o*-dimethylaminobenzyl)- (**5**), (*S*)-(−)-*N*-(*o*-methoxybenzyl)- (**6**), (*S*)-(−)-*N*-(*o*-methylmercaptobenzyl)- (**7**), (*S*)-(−)-*N*-(2,4,6-trimethylbenzyl)- (**8**) phenylethylamines were also prepared. Satisfactory analytical data (±0.3% for N) were reported for all of these new compounds. These amines were stored in a refrigerator under argon atmosphere.

Asymmetric Reduction of Ketone with $LiAlH_4$–Chiral Amine 5 Complex (Representative Example). Under nitrogen, 1.2 mmol of $LiAlH_4$ in ether was transferred to a 30-mL flask. The ether was removed under high vaccum around 60 °C and the remaining $LiAlH_4$ was allowed to react with 907 mg (3.6 mmol) of amine **5** in 4 mL of toluene. After hydrogen evolution had ceased, the flask was immersed in an oil bath (135 °C) for 10 min, then refluxed for 5 min in order to complete the complex formation. At this point, the solution turned to deep red and most of the $LiAlH_4$ went into solution leaving a small amount of solid that did not dissolve. When cooled, the solution faded to a pale yellow color. To the stirred, cooled toluene solution was added dropwise 120 mg (1.0 mmol) of $PhCOCH_3$ at 0 °C. After the reaction mixture was left for 12 h at 0 °C, excess hydride was decomposed by adding 1 drop of water (evolution of gas) and then excess dilute HCl to remove amine **5**. The ether extract was washed (H_2O, three times), dried ($MgSO_4$), and concentrated. The remaining crude carbinol was purified by preparative VPC to remove the unreacted $PhCOCH_3$ (ca. 10%). (*R*)-(+)-$PhCH(OH)CH_3$ thus obtained had a rotation of $[\alpha]^{20}_D$ +18.1° (*c* 7.3, cyclopentane). The enantiomeric purity of the carbinol was estimated to be 43% ee by reference to the calibration curve[14] developed by Mosher and Reich.

Asymmetric Reduction of Propiophenone with $LiAlH_4$–(Amine 5)$_3$ in the Presence of Additives. A chiral hydride complex solution made of 4.8 mmol of $LiAlH_4$ and 3.63 g (14.4 mmol) of amine **5** in 16 mL of toluene was divided into four portions (flask no. 1–4). To the above three flasks (no. 1–3) containing the hydride solution (1.2 mmol) were added 2.4 mmol of additives, 1,2-dimethoxyethane (216 mg, no. 1), *N,N,N′,N′*-tetramethylethylenediamine (278 mg, no. 2), and 1,2-dimethylmercaptoethane (293 mg, no. 3). After these flasks were immersed in ice bath, 100 mg (0.75 mmol) of PhCOEt was added dropwise to each hydride solution. Processing as in the case of $PhCOCH_3$, to remove the unreacted ketone and additives, gave partially active PhCH(OH)Et. The enantiomeric purity of the carbinol, $[\alpha]^{20}_D$ +17.5° (*c* 4.3, MeOH), obtained in the control reaction, which had no additive, was confirmed to be 51% ee (*R*)-(+) by NMR method[7] through its (*R*)-(+)-α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) ester. These data are summarized in Table IV.

Acknowledgment. The authors wish to express their deep gratitude to Professor Harry S. Mosher, Stanford University, for his helpful suggestions throughout this work.

Registry No.—**1**, 2627-86-3; **3**, 17480-69-2; **4**, 61491-04-1; **5**, 61491-05-2; **6**, 61491-06-3; **7**, 61491-07-4; **8**, 61491-08-5; benzaldehyde, 100-2-7; acetophenone, 98-86-2.

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Preparation and Reactions of Diorganocuprate Reagents Derived from 2-Lithio-3,3-diethoxypropene. Functionalized Reagents for the Transfer of an α Acrolein Carbanion Equivalent

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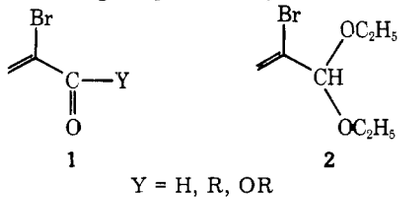
The preparation of several cuprate reagents from 2-lithio-3,3-diethoxypropene is described. The reactivity of these reagents is described with a variety of α,β unsaturated ketones to afford 1,4 adducts in moderate to excellent yields depending upon steric hindrance in the enone. Allylic halides couple but epoxides and saturated vinyl halides are unreactive. Enolate oxygenation experiments are described which allow introduction of an α oxygen via epoxidation of the derived enol trimethylsilyl ether. An interesting solvent effect is observed for this process. The use of ether affords α-benzoyloxy ketones and methylene chloride the α-trimethylsilyloxy ketone. Some model compound experiments suggest that this solvent effect might be general.

The application of organocopper chemistry to synthesis has seen an enormous amount of activity in the recent past. These organometallic reagents have found wide use for selective coupling and alkylation reactions,[2] conjugate addition to various α,β unsaturated carbonyl derivatives,[3,4] as well as acylation.[5] However, the majority of the activity has been directed toward the utilization of simple, readily available lithium reagents. Relatively little is known about the potential for successful formation and use of cuprate reagents containing highly functionalized ligands. Among the examples already documented is the work of the Syntex group on the transfer of the prostaglandin β side chain,[6] as well as the work of Eaton[7] and Heathcock,[8] and that from our laboratories.[9,10]

One class of carbanions which would be particularly valuable would be those derived from α-bromo acrylate derivatives (**1**). A number of potential applications including the synthesis of derivatives of the much sought after α-methylene-γ-butyrolactones[11] were apparent. Marino's elegant use of α-bromoacrylic ester[12] provides a valuable reagent in certain cases; however, this organometallic reagent seems to be of much lowered reactivity, and does not appear to undergo conjugate addition cleanly. Ficini[13] and later Depazay[14] prepared what appeared to be a more promising carbanion for complex formation by metalation of α-bromoacrolein diethyl acetal (**2**). This reagent presumably would satisfy the requirements of complex formation in a more straightforward way and is presumably convertible to all the required oxidation states. After our studies of the complexes derived from this carbanion were nearly completed, two preliminary reports[15,16] of the formation of cuprate reagents derived from **2** appeared. We now report the results of our studies of the utility of these reagents.



1 **2**

Y = H, R, OR

We found initially that the homogeneous diorganocuprate reagent derived from **2** and cuprous iodide in the usual fashion proved to be relatively difficult to handle, providing solutions which were not completely homogeneous. The reagent was indeed present as was demonstrated by its addition in moderate yield to 2-cyclohexen-1-one. We turned to the use of mixed reagents without further study in hopes of achieving the preparation of reagents soluble in the usual reaction media, ether and tetrahydrofuran (THF). Mixed diorganocuprate reagents were prepared utilizing *n*-pentynylcopper (**4**),[17] phenylthiocopper (**6**),[18] and *tert*-butylethynylcopper (**5**).[19] Only the latter reagent provided, reproducibly, a nicely soluble reagent. A similar conclusion was reached by Marino.[15]

All the reagents react with 2-cyclohexen-1-one to afford adduct **3** as shown in Table I. Ether appears to be a superior solvent to THF where applicable.

We then set out to determine the reactivity of the cuprate reagent (**5**) [R = $(CH_3)_3CC{\equiv}C-$] with various unsaturated ketones, halides, and epoxides. From the results in Table II, for enones, the reactivity seems comparable to most cuprate reagents. The branched ligand is sterically somewhat more demanding as can be seen by the reduction in yield as the substitution at the β carbon increases. This effect is generally observed, but it is significant that moderate yields are obtained from quite hindered enones such as **7** and **8**. Other