Asymmetric Induction in the Conjugate Addition Reactions of Chiral Organo(hetero)cuprates

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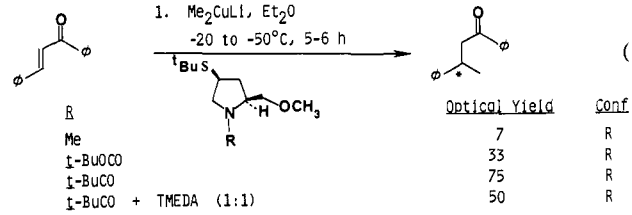
Abstract: The reactions of cyclohexenone, cyclopentenone, (*E*)-3-penten-2-one, and (*E*)-3-octen-2-one with chiral organo(hetero)cuprates containing Me, *n*-Bu, or *tert*-butyl transferable ligands afforded the adducts in optical yields as high as 41-83%. Variation in the chiral nontransferable ligands derived from (*S*)-proline involves, formally, replacement of the hydroxy group of (*S*)-prolinol with a methoxy, pyrrolidyl, phenylthio, or methylthio substituent. The extent of asymmetric induction was a function of all the experimental variables while the absolute stereochemistry was dependent upon substrate structure, cuprate composition, and solvent.

We have, over the past few years, examined the chemo- and stereoselective reactions of organocuprates with α-oxoketene dithioacetals[1] and vinylogous thiol esters.[2] These studies provided considerable insight into the complexities of organocopper conjugate addition reactions since the observed selectivities were influenced by all of the experimental variables. Our experience in unravelling and exploiting the complex influence of substrate structure, cuprate reagent, cuprate composition, transferable ligand, temperature, and solvent in these substitution reactions (conjugate addition-elimination) coupled with recent advances in the development of second generation organocopper reagents (e.g., amido,[3] phosphido,[3] and "higher order"[4] cuprates) encouraged us to search for procedures for effecting the conjugate addition process with asymmetric induction. We now report on the reactions of four enones with chiral organo(hetero)cuprates and the influence of various experimental parameters upon the extent and absolute stereochemistry of the asymmetric induction. The role of substrate structure, cuprate reagent, chiral ligand, cuprate composition, transferable ligand, solvent, temperature, and added salts have been examined. A simple model has been proposed to account for the results which display good internal consistency over a wide range of experimental variation.

Background. Organocopper conjugate addition reactions occupy a central niche in synthetic organic chemistry.[5] They provide one of the few generally reliable methods for constructing new carbon-carbon bonds β to a carbonyl functional group and the type and variety of ligands that can be transferred to an α,β-unsaturated carbonyl compound complement the stabilized carbanions employed in the Michael reaction. The importance of this reaction has prompted numerous searches for procedures and methods to effect the conjugate addition process with asymmetric induction. These efforts have focused on four strategies utilizing either: (1) a chiral medium generally in the form of chiral coordinating ligands, (2) cuprates containing a chiral nontransferable ligand (RL*CuM), (3) cuprates containing a chiral transferable ligand (R*LCuM), or (4) chiral substrates. The methods involving chiral substrates or cuprates containing chiral transferable ligands generate, initially at least, diastereomeric products, and procedures have been developed that afford high diastereomeric excesses (de). The use of a chiral medium or of cuprates containing a chiral nontransferable ligand lead to the selective formation of one enantiomer, and no general or efficient method involving these approaches has been developed.

Kretchmer[6a] reported the first attempt to effect organocopper conjugate addition reactions with asymmetric induction in 1972. He employed magnesium dialkylcuprates (R_2CuMgX) in the presence of (-)-sparteine and obtained optical yields of 3-6%. More recently Seebach and co-workers[7] have obtained higher optical yields for lithium dialkylcuprates (12-15%), organozinc compounds (23.5%), and organolithium compounds (28-58% with 1-nitropropene) employing amino ethers derived from tartaric acids. A very recent study[8] employed 4-(alkylthio)hydroxyproline derivatives as tridentate coordinating ligands and achieved enantiomeric excesses (ee) as high as 75% (eq 1). The amides



(1)

R	Optical Yield	Conf
Me	7	R
t-BuOCO	33	R
t-BuCO	75	R
t-BuCO + TMEDA (1:1)	50	R

proved superior to the amines indicating the importance of chiral ligand-lithium complexation which was confirmed by the decrease in the ee upon addition of TMEDA. Despite this impressive achievement a limited study of one substrate and one transferable ligand, R(t), does not establish the potential generality or efficiency of methods based upon external chiral ligands in the reaction medium.

The optical yields reported for conjugate addition reactions employing cuprates with chiral nontransferable ligands have also been generally disappointing. An early study[9] of heterocuprates [(R*OCuR)Li] generated from nine amino alcohols [cinchonidine, cinchonine, *R*-(-)-2-aminobutyl alcohol, *S* (+)-valinol, *R*-(-)-α-

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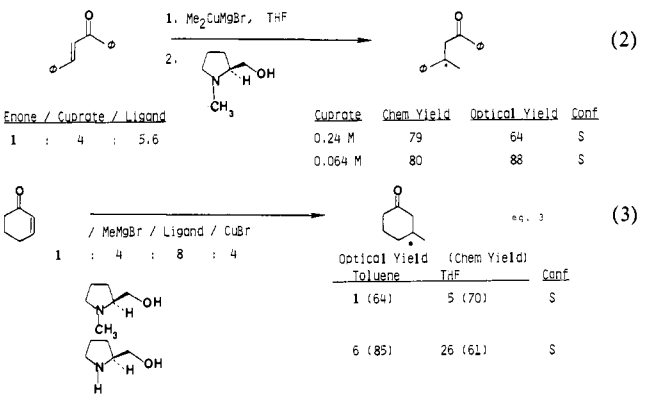
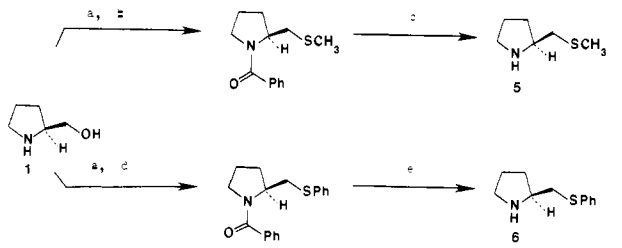
phenylglycinol, plus four aromatic imines] afforded optical yields of 0–31%. Similarly, heterocuprates derived from simple chiral alcohols[10] and amines[10] and from (−)-*N*-methylepherine[6b] or 1,2:5,6-di-*O*-isopropylidine-α-D-glycofuranose[6b] afforded equally low optical yields. Modest optical yields (12–68%) were first reported by Mukaiyama[11] employing chalcone, (*S*)-*N*-methylprolinol, and magnesium dimethylcuprate in THF. The highest optical yield of 68% was achieved by using a large excess of Grignard reagent, copper(I) halide, and chiral ligand to the enone (8.8:4:5.6:1, respectively) (eq 2). This work was extended by Leyendecker[12] (eq 3) who examined the reactions of cyclo-



hexenone, 4-phenyl-3-buten-2-one, and chalcone substrates with chiral magnesium heterocuprates derived from (*S*)-prolinol and (*S*)-*N*-methylprolinol. The optical yields ranged from 1–41% and increased on going from toluene to THF for the (*S*)-*N*-methylprolinol derived cuprate and decreased for the (*S*)-prolinol bound cuprate. Asymmetric induction was viewed as arising from magnesium–arene π-coordination in the *N*-methyl system and hydrogen–carbonyl chelation in the prolinol system. Although higher optical yields were generally obtained with prolinol than with *N*-methylprolinol, chalcone proved an exception. These observations served as the basis for postulating two different chelation mechanisms and established a substrate dependence of optical yields. A subsequent study[13] compared the prolinol ligands to the higher homologues (methoxyethyl side chain) which proved less effective (2–0% ee). Higher optical yields were achieved upon dilution suggesting the importance of an internally chelated species, and these conditions afforded the highest optical yield observed to date (88% for reaction of a magnesium cuprate with chalcone, eq 2) for a cuprate containing a chiral nontransferable ligand. Although these studies were severely limited in their examination of substrates, transferable ligands, and cuprate compositions, they did indicate that moderate optical yields appeared to uniquely arise from prolinol derived chiral ligands. From this vantage point, it is interesting and noteworthy that the derived 1-amino-2-(methoxymethyl)pyrrolidinehydrazone methodology of Enders has yielded excellent optical yields in Michael type conjugate addition reactions to α,β-unsaturated esters.[14]

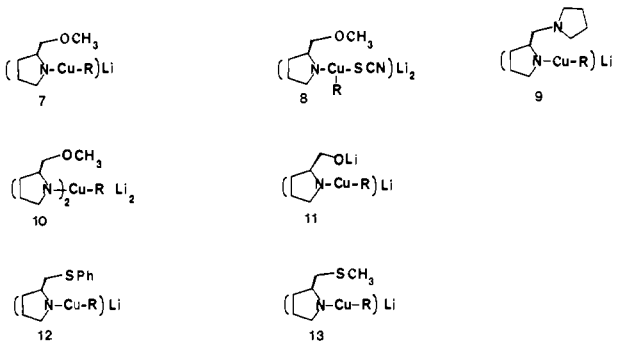
Methodologies based upon diastereoselective carbon–carbon bond formation have, in general, been more successful. Incorporation of the chiral center in the transferable ligand has yielded several reactions which exhibit high diastereomeric excesses.[15–17]

Scheme I[a]



[a] (a) Benzoyl chloride, $CHCl_3$, 91%; (b) *n*-Bu_3P, Me_2S_2, pyridine, 79%; (c) 2 N HCl, 76%; (d) *n*-Bu_3P, Ph_2S_2, pyridine, 84%; (e) 2 N HCl 89%.

Chart I.[a] Cuprate Compositions Examined



[a] These representations are employed to indicate stochiometry and are not intended to imply actual structures.

Poor to good optical (16.5–75.4%) yields have been obtained with cuprates derived from chiral azaenolates.[15] Similarly high diastereoselectivites have resulted from the elegant work of Posner[18] on chiral enones and Oppolzer[19] on chiral enoates. Although these approaches do represent elegant general solutions to the problem of asymmetric induction in organocopper conjugate addition reactions they are limited in terms of ease, stepwise efficiency, or carbonyl functionality.

Preparation Experiments. The chiral ligands **1–3** and **5–6** were readily prepared from L-proline. Reduction of L-proline [$LiAlH_4$, THF, 87%][20] afforded L-(+)-2-pyrrolidinemethanol (**1**) which was

converted [(i) HCO_2Et, 95%; (ii) NaH, MeI, THF, 89%; (iii) 10% KOH, 80%] into L-(+)-2-(methoxymethyl)pyrrolidine (**2**) according to the procedure of Seebach.[21] Protection of L-proline as the *tert*-butylcarbonate [di-*tert*-butyldicarbonate, NaOH, THF, 85%][22] followed by treatment of the carboxylic acid with pyrrolidine [Et_3N, $ClCO_2Et$, THF, 73%][23] afforded amide **4**. The

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sequence of Otani and Yamada[23] involving deprotection of the amine [CF_3COOH, 99%] and reduction of the amide [$LiAlH_4$, THF, 67%] afforded L-(+)-2-(1-pyrrolidinylmethyl)pyrrolidine (**3**).

The previously unknown chiral ligands **5–6** with sulfur heteroatom containing side chains were prepared from L-prolinol as outlined in Scheme I. Protection of the amine as the benzyl amide[24] followed by treatment of the alcohol with tri-*n*-butylphosphine and dimethyl disulfide or diphenyl disulfide in pyridine[25] afforded upon deprotection the methylthio and phenylthio analogues **5** and **6**, respectively.

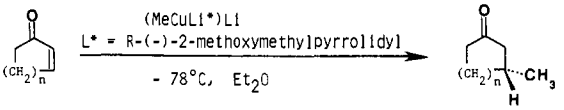
Results

Reaction of cyclohexenone, in the initial experiment, with lithium methyl[(*S*)-2-(methoxymethyl)pyrrolidino]cuprate at −25 °C in Et_2O afforded (*S*)-3-methylcyclohexanone in 77% yield and with an optical purity of 82% (Table I, entry 1). Although this first experiment provided a very good optical yield, it soon became evident that the optical yields would be system dependent with considerable variation. Subsequent examination of systems arising from the various combinations of four enones, three transferable ligands, five prolinol derived chiral ligands (**1–3, 5–6**), seven cuprate compositions (**7–13**, Chart I), and three solvents generated a set of data that is tabulated in Table I. Although considerable variation in optical yields was observed from run to run in the early experiments (13%, entries 1 and 2), this variation decreased to more modest proportions in latter experiments (entries 4 and 6, 9 and 10, 17 and 18, 20 and 21, 25 and 26, 29 and 30, 36 and 37; 1–7%).

Examination of all the results tabulated in Table I reveals several important trends and interesting patterns. First, although the optical yields increase at lower reaction temperatures (compare entries 1–2 and 4, 22 and 23, 25–27, 29–31, and 41 and 42), the change, i.e., is relatively small for methylcuprates in comparison with *n*-butyl- and *tert*-butylcuprates. Second, the optical yields were solvent dependent and generally increased along the solvent series THF < Et_2O < $PhCH_3$ (compare entries 4, 7 and 8 where a lower optical yield was obtained in $PhCH_3$ than in Et_2O, 9–11, 14–18, 31 and 32, 33 and 34, 42 and 43, and 45 and 46). In a similar fashion, lower optical yield was obtained when methyllithium containing excess lithium bromide was used to generate the cuprate reagents (compare entries 1–3). Preparation of halide free cuprate reagents,[28] however, did not always lead to improved optical yields (compare entries 4–6, 15 and 16). Third, the optical yields were substrate dependent and generally increased along the series cyclopentenone < acyclic enones ≤ cyclohexenone where comparable reaction conditions permit comparison. The most striking observation, here, was the consistently low optical yields obtained with cyclopentenone. Fourth, the optical yields were also dependent upon the transferable ligand R_t. The highest optical yields were observed for R_t = Me (83% for cyclohexenone and 3-octen-2-one, entries 1, 4, 11, and 51) and generally declined for R_t = *n*-Bu and *t*-Bu (compare entries 1, 2, and 4 with 22–28 and 41–47 with 48–51), although R_t = *t*-Bu gave the highest optical yield for cyclopentenone (50%, entry 40). Fifth, the nature of the side chain of the prolinol derived chiral ligands was found, in one instance, to have a severe effect upon the asymmetric induction process. Although the cuprates derived from the chiral ligands containing methoxy-, (phenylthio)-, or (methylthio)methyl side chains afforded similar optical yields under similar reaction conditions, the cuprate derived from the chiral ligand containing a pyrrolidinomethyl side chain ($-CH_2-NC_4H_8$) gave very poor optical yields (0.5–8%, entries 13 and 35). In general, slightly higher optical yields (~8%) were obtained for the cuprate containing the methylthio group than for the one containing the phenylthio group (entries 15 and 19, 50 and 51). Interestingly, the cuprate derived from the dianion of (*S*)-prolinol (Chart I, **11**) afforded lower optical yields than the lower order **7** (14–21%) or thiocyanate higher order **8** (4–13%) cuprates generated from (*S*)-(−)-2-(methoxymethyl)pyrrolidine (compare entries 4, 6, 9 and 10, and 20 and 21).

The most striking patterns to emerge from these data involved the absolute stereochemistry of the conjugate addition product. The *S*-(−)-prolinol derived chiral ligands (L* in RL*CuLi, etc.) induced predominant formation of either the R or S enantiomer depending upon solvent, cuprate composition, and substrate structure. An interesting set of patterns involving absolute stereochemistry emerged which are not artifacts of priority sequence rules. First, the lower order cuprates (RL*CuLi) selectively afforded the S enantiomer in ether (entries 1–6, 13, 15, 16, 19, 22–28, 29–31, 35, 38–42, 46 and 47) and the R enantiomers in THF (entries 7, 14, 43, 45). Second, the cuprate solutions of stoichiometry $(RL_2^*Cu)Li_2$, $RL^*{=}CuLi_2$ (from the prolinol N, *O*-dianion) and the higher order cuprate $(RL^*CuSCN)Li_2$ selectively afforded the R enantiomers in ether (entries 9 and 10, 12, 20 and 21, 33, 44, 49). Reaction of *trans*-3-penten-2-one and *trans*-3-octen-2-one with *n*-butyl- and methylcuprates, respectively, afforded enantiomeric products with lower order cuprates as expected (entries 41, 42, 46, 47 vs. 48, 50, and 51) and only the R enantiomer with higher order cuprates (entries 44, 49). Fourth, the lower order cuprates in toluene selectively afforded the R enantiomers (entries 8, 17 and 18, 32, 36 and 37). The higher order cuprate $(RL^*CuSCN)Li_2$ in toluene, however, afforded the R enantiomer with cyclohexenone and the S enantiomer with cyclopentenone (entries 11, 34). This was confirmed in a separate set of experiments (for cyclohexenone: 68% yield, 79% ee, R configuration; for cyclopentenone: 70% yield, 43% ee, S configuration).

Two experiments were run with cuprate **7** (R = Me) derived from *R*-(−)-2-(methoxymethyl)pyrrolidine (eq 4). Cyclohexenone and cyclopentenone afforded the (*R*)-3-methyl derivatives in Et_2O in optical yields comparable to those obtained with the *S*-(+)-2-(methoxymethyl)pyrrolidine derived cuprate.



(4)

n	% Yield	Optical Yield
1	45	24
2	66	77

Although the optical yields are sensitive to all of the reaction parameters and in some instances vary significantly from run to run, they display a remarkable internal consistency over a wide range of structural variation in substrate, transferable ligand, and cuprate composition. Over the range of structural variation the highest optical yields obtained for cyclohexenone and acyclic enones range from 56 to 83% while lower optical yields are obtained from cyclopentenone (41–50%). *S*-Prolinol derived ligands consistently afford the S enantiomer with lower order cuprates in diethyl ether and the R enantiomer whenever an additional ligand is present [THF, higher order cuprates $(RL^*CuSCN)Li_2$, and cuprate solutions with stoichiometry of $R_2L^*CuLi_2$ or $RL^* = CuLi_2$].

Discussion

The sensitivity of the optical yields to substrate structure, chiral ligand, cuprate composition, solvent, temperature, and external ligands makes it difficult to access the importance of individual changes. This is compounded by the complexity of organocopper conjugate addition reactions and lack of a thorough understanding of the reaction mechanism.[5,29] Nevertheless, the trends obtained

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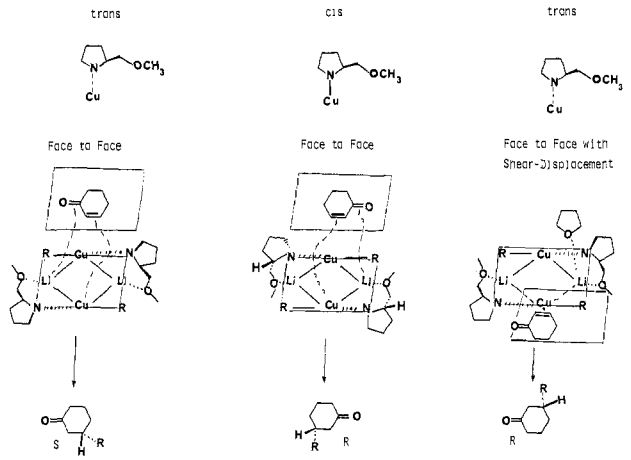
Scheme II



from the collective results provide clues about the more important factors influencing the asymmetric induction process. The fluctuation in chemical yields is attributed, in part, to the volatility of the products since the reactions were run until starting enone was consumed as determined by TLC analysis. Little polymeric material was evident at the origins of these TLC chromatograms.

Although the optical yields increase at lower reaction temperatures, this increase is very small for the methylcuprates. The greater increase in optical yields at lower reaction temperatures for the *n*-butyl- and *tert*-butylcuprates may reflect reagent thermal stability[3b,30] toward decomposition or ligand exchange[28] leading to multiple cuprate reagents. Similar rationalizations could be employed to account for the general decrease in optical yields as the transferable ligand is changed along the series Me, *n*-Bu, and *t*-Bu. The increase in optical yield, however, on going from a methylcuprate to a *tert*-butylcuprate in reactions with cyclopentenone, a planar molecule, suggests that the important factor involves topological constraints in the substrate–cuprate interaction.

The decrease in optical yields when THF is employed as the solvent or when excess LiBr is present suggests an incorporation of these external ligands in the cuprate structure.[29c,30b] Indeed the general increase in optical yields along the solvent series THF, Et_2O, $PhCH_3$ parallels solvent basicity in an inverse fashion, although these solvent changes will undoubtedly affect the extent of cuprate aggregation and may promote structural changes in the cuprate cluster unrelated to external ligands. Nevertheless, higher order cuprates with an additional ligand in the metal cluster and lower order cuprates in THF afforded the opposite enantiomer than that obtained with lower order cuprates in Et_2O.

The influence of substrate structure, cuprate composition, and solvent upon the induced absolute stereochemistry is more difficult to understand but can be rationalized by a simple model which requires several basic assumptions and postulates (Scheme II). One, the cuprate reagent is assumed to be a dimer with a planar array of metal atoms.[5d,29b,c,31] The chiral ligands are assumed to be located at the diagonal corners of the planar array of metal atoms to minimize unfavorable electronic and steric interactions. An unspecified cubane structure has been suggested for $[(LiCuPh_2 \cdot Et_2O)_4]$ which could present planar faces to an attacking reagent.[32] Two, bidentate coordination of the chiral ligand to the metal cluster through the heteroatom of the side chain is assumed to be necessary for high asymmetric induction as suggested by previous studies.[8,11-13,16] Three, note that inversion of configuration about the N-atom can afford two diastereomeric chiral ligands. Dreiding models indicate that they best coordinate to the planar cuprate cluster in a different chiral sense and appear to lead to enantiomeric products. The stereoisomer with the N–Cu bond trans to the side chain is assumed to be favored and comparison can be made with hydrindane (a [4.3.0] carbocyclic system where the trans isomer is ~0.58 (liquid phase) −1.04 (heats of combustion) kcal/mol more stable than the cis isomer).[33] These structures possess a C_2 axis of symmetry perpendicular to the planar array of metal atoms making the two alkyl ligands equivalent. The presence of C_2 symmetry often proves to be particularly effective in asymmetric induction.[34]

Four, preequilibrium complexation has been consistently invoked in organocopper conjugate addition reactions, and there is some experimental evidence for this preequilibrium.[29b,c,30b] Although this preequilibrium is generally thought to involve Li···enone–oxygen complexation, the geometry of the oxygen orbitals[35a] involved and the possibility of intermolecular complexation (e.g., in an aggregate) appear not to have been carefully considered. Alternative possibilities include copper–olefin π-complexation,[29a,e,f] and a two point contact involving olefin–copper and carbonyl–lithium[35b] π-complexes can be readily accommodated in molecular models. Assume that maximum reactivity is favored by face-to-face approach of the enone and cuprate cluster, although a less effective arrangement involving shear displacement of the two reactants can also lead to products, albeit in the opposite chiral sense.

Five, the alkyl group transfer from the face-to-face arrangement is postulated to afford the S enantiomer for the cuprate with the N–Cu bond trans to the side chain ($-CH_2OCH_3$) and to the R enantiomer for the cis relationship. These relationships (in the cyclic enones at least) are not artifacts of the sequence rule since the *tert*-butyl group has the highest priority and the methyl and *n*-butyl groups have the next to lowest priority and consequently give rise to the same R or S notation when delivered to the same face of the enone. The approach involving face-to-face orientation with shear displacement will afford opposite results (i.e., trans → R and cis → S).

Six, the reversal of chiral induction observed with lower order cuprates in THF and the higher order cuprates can be explained by the presence of additional ligands in the cuprate cluster which favor the arrangement involving face-to-face approach with shear displacement. However, the lower order cuprate **12** (R = Me) afforded the R enantiomer upon reaction with cyclohexenone in toluene even when halide free solutions of the cuprate were em-

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(35) (a) 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 hybrid 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 and references cited therein. (b) 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.

Table I. Asymmetric Induction in Organocopper Conjugate Addition Reactions Employing (*S*)-Prolinol Derived Chiral Heterocuprates

entry	substrate	R_t	side chain (CH_2X) of L* X	cuprate	temp, °C	solvent	yield,[a] %	product	optical purity[b,c]	config	ref
	2-cyclohexenone							3-methylcyclohexanone			6b, 27a, b
1		Me	OCH_3	**7** (RL*Cu)Li	−25	Et_2O	77		82	*S*	
2							44		69	*S*	
3				**7** (RL*Cu)Li/LiBr			35		63	*S*	
4				**7** (RL*Cu)Li	−78		41		83	*S*	
5							73		75[d]	*S*	
6					−110		69		79	*S*	
7					−78	THF	59.7		53	*R*	
8						$PhCH_3$	62.5		70	*R*	
9				**8** (RL*CuSCN)Li_2		Et_2O	57.0		75[c]	*R*	
10							38.4		73	*R*	
11						$PhCH_3$	67.7		83	*R*	
12				**9** (RL_2*Cu)Li_2		Et_2O	23.8		20	*R*	
13			*c*-NC_4H_8	**10** (RL*Cu)Li		Et_2O	38.7		8	*S*	
14			SPh	**12**		THF	70.0		52	*R*	
15						Et_2O	77.5		71[c]	*S*	
16							68.2		73[d]	*S*	
17						$PhCH_3$	64.9		75	*R*	
18							71		80	*R*	
19			SCH_3	**13**		Et_2O	68		80	*S*	
20			OH	**11** (RL*=Cu)Li		Et_2O	53.4		62	*R*	
21							53.8		69	*R*	
								3-*n*-butylcyclohexanone			27b
22		*n*-Bu	OCH_3	**7** (RL*Cu)Li	−25	Et_2O	41.6		28	*S*	
23					−78		37.9		56	*S*	
24			SCH_3	**13**			46		58	*S*	
								3-*tert*-butylcyclohexanone			6b, 27a
25		*t*-Bu	OCH_3	**7** (RL*Cu)Li	−25	Et_2O	82.8		52	*S*	
26							28.0		53	*S*	
27					−78		24.8		67	*S*	
28			SCH_3	**13**			51		69	*S*	
	2-cyclopentenone							3-methylcyclopentanone			27b
29		Me	OCH_3	**7** (RL*Cu)Li	−25	Et_2O	50.3		20	*S*	
30							34.1		16	*S*	
31					−78		35.8		23	*S*	
32						$PhCH_3$	70.2		37	*R*	
33				**8** (RL*CuSCN)Li_2		Et_2O	50.9		33[c]	*R*	
34						$PhCH_3$	77.1		41	*S*	
35			*c*-NC_4H_8	**9** (RL*Cu)Li		Et_2O	34.9		0.5	*S*	
36			SPh	**12** (RL*Cu)Li		$PhCH_3$	58.2		32	*R*	
37							60		35	*R*	
38			SCH_3	**13**		Et_2O	60		33	*S*	
								3-*tert*-butylcyclopentanone			27d
39		*t*-Bu	OCH_3	**7**			56		35	*S*	
40			SPh	**12** (RL*Cu)Li	−78	Et_2O	50.4		50	*S*	
	trans-3-penten-2-one							4-methyl-2-octanone			27f
41		*n*-Bu	OCH_3	**7** (RL*Cu)Li	−25	Et_2O	32.1		49	*S*	
42					−78		35.8		64	*S*	
43						THF	62.2		38	*R*	
44				**8** (RL*CuSCN)Li_2		Et_2O	37.3		68	*R*	
45			SPh	**12** (RL*Cu)Li		THF	48.2		46	*R*	
46						Et_2O	50.9		61	*S*	
47			SCH_3	**13**			52		64	*S*	
	trans-3-octen-2-one										
48		Me	OCH_3	**7** (RL*Cu)Li	−78	Et_2O	45.8		58	*R*	
49				**8** (RL*CuSCN)Li_2			56.0		75	*R*	
50			SPh	**12** (RL*Cu)Li			42.0		74	*R*	
51			SCH_3	**13**			77.8		83	*R*	

[a] Yields are based upon isolated products purified by chromatography on silica gel. [b] Optical yields were determined from measurements of the optical rotation. [c] Optical yields were also determined by ^{13}C NMR spectroscopy on the chiral ketals prepared from the ketone and (2*R*,3*R*)-(−)-2,3-butanediol. See ref 26; entry, de (9, 80%), (15, 68%), (33, 39%). [d] Halide free cuprate reagents were employed.

ployed (56% yield, 75% optical yield, compare with entries 17 and 18). This result indicates a possible change in cuprate structure with a change in solvent since the additional ligand in the form of halide ion was removed.

Although several of these assumptions find ample literature precedent, it must be reiterated that the structure and aggregation of the cuprate reagents are unknown. This is particularly true for the higher order cuprates. *The reversal in the chiral sense of induction in systems containing additional ligands may reflect significant geometrical and structural changes in the cuprate cluster rather than a subtle change in the orientation of the reacting components.* The complexity of cuprate structures has recently been demonstrated,[28] although the most informative situation (Me_2CuLi in the absence of LiI) does not correspond to any of the examples of our preliminary study. Nevertheless, despite the tenuous and speculative nature of these assumptions and postulates, the model successfully rationalizes a body of data that exhibits a remarkable internal consistency over a wide range of structural variation and experimental conditions.

This analysis reveals two potential sources of inefficiency in these ligands. First, conformational mobility of the side chain can reduce the effectiveness of the Li-heteroatom coordination.

The generally superior performance of the amidocuprates of our study relative to the alkoxycuprates of previous studies may be due, in part, to the relative conformational mobilities of the ligands at the point of attachment to the copper center. In the amidocuprates of the present study, optical yields decrease as the steric bulk of the group attached to the heteroatom side chain increases ($-SCH_3$ > SPh ~8%) and almost goes to zero for the ligand containing the pyrrolidenomethyl side chain. Second, configurational inversion about nitrogen apparently leads to diastereomeric cuprate clusters which afford enantiomeric products. A mixture of the two reagents, or an interconversion of the two, will lead to lower optical yields.

In summary, the magnitude of the optical yields obtained in the reactions of organo(hetero)cuprates containing (*S*)-prolinol derived chiral ligands is a function of all of the experimental variables. Consequently, the reaction conditions can be manipulated to afford optical yields as high as 41–83% in the present study. The variation in absolute stereochemistry as a function of substrate structure, cuprate composition, and solvent can be rationalized by a simple model which suggests sources of inefficiency in the asymmetric induction process. The present study provides a greater insight into the factors affecting enantioselective asymmetric induction in organocopper conjugate addition reactions than the limited studies of the past decade. Efforts are currently underway to develop potentially more effective chiral ligands.

Experimental Section

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded as deuteriochloroform solutions on a JEOL-FX90Q Fourier transform spectrometer. Chemical shifts are reported in parts per million relative to tetramethylsilane as internal standard. Carbon nuclear magnetic resonance (^{13}C NMR) chemical shifts are reported in parts per million relative to deuteriochloroform (δ 77.0). Infrared spectra (IR) were recorded on a Perkin-Elmer 710B grating spectrophotometer as chloroform solutions, unless otherwise noted. Peak intensities were recorded as strong (s), medium (m), or weak (w). The 1601-cm^{-1} signal of polystyrene was used for calibration. Optical rotations were measured at 25 °C with a Rudolph Autopol III or Perkin-Elmer Model 241 polarimeter.

Diethyl ether (ether) and tetrahydrofuran (THF) were distilled from sodium/benzophenone ketyl immediately before use. Toluene was dried over sodium and then fractionally distilled. Pyridine was refluxed with solid KOH and then fractionally distilled. Copper(I) bromide was purchased from Alfa and purified according to a slightly amended literature procedure.[36] After being dissolved in 48% HBr, the CuBr was precipitated by adding water and then collected by filtration. The precipitate was subsequently washed with water, ethanol, and ether and then dried under vacuum at 60 °C. Copper thiocyanate was prepared according to a literature procedure.[37] Methyl disulfide, phenyl disulfide, (2*R*,3*R*)-(−)-2,3-butanediol, di-*tert*-butyl dicarbonate, 3-penten-2-one, tri-*n*-butylphosphine, D-proline, and L-proline were obtained from Aldrich and used without further purification. All alkyllithium reagents were purchased from Alfa and titrated with diphenylacetic acid according to the method of Kofron and Baclawski.[38] Experiments using excess lithium bromide employed a methyllithium complex with lithium bromide available from Aldrich.

2-Cyclohexenone,[39] 2-cyclopentenone,[40] and 3-octen-2-one[41] were synthesized according to established literature procedures. All three α,β-unsaturated ketones as well as 3-penten-2-one were distilled and stored over 4Å molecular sieves.

The following specific rotations have been reported for the saturated ketones: 3-methylcyclohexanone, *R*-(+) $[\alpha]_D$ +14.2 (*c* 4.13, $CHCl_3$);[27b] 3-*n*-butylcyclohexanone, $[\alpha]_D$ +19.3;[27c] 3-*tert*-butylcyclohexanone, *S*-(−) $[\alpha]_D^{22}$ −25.2 (*c* 3.1, $CHCl_3$),[27a] *R*-(+) $[\alpha]_D$ +27.5 (*c* 0.5 $CHCl_3$);[6b,27a] 3-methylcyclopentanone, *R*-(+)[42a] $[\alpha]_D^{25}$ +154.8 (*c* 0.73, $CHCl_3$),[27b] $[\alpha]_D$ +154.8 (*c* 0.6, MeOH);[42b] 3-*tert*-butylcyclopentanone, *S*-(−) $[\alpha]_D$ = −161.9 (*c* 0.86, MeOH).[27d] 4-Methyl-2-octanone [calculated *R*-(+) $[\alpha]_D^{25}$ +8.3] was correlated with 3-methylheptanoic acid [*S*-(−) $[\alpha]_D$ −4.2 (neat),[43a] *R*-(+) $[\alpha]_D$ +6.3 (*c* 1, heptane)[43b] via the haloform reaction.[44]

L-(+)-2-Pyrrolidinemethanol. L-Proline was reduced with lithium aluminum hydride to L-(+)-2-pyrrolidinemethanol according to an established procedure in 87% yield.[20] The oily sample showed the following: bp 70–72 °C (2 mmHg) and $[\alpha]_D^{20}$ +41.0 (*c* 1.0, benzene); lit.[21] bp 58 °C (0.9 mmHg) and $[\alpha]_D^{20}$ +40 (*c* 1.0, benzene).

L-(+)-2-(Methoxymethyl)pyrrolidine. An oily sample was prepared from L-(+)-2-pyrrolidinemethanol according to the reported method[21] in 80% yield: bp 65–68 °C (35 mmHg) and $[\alpha]_D^{20}$ +3.08 (*c* 0.35, benzene); lit.[21] bp 36–38 °C (10 mmHg) and $[\alpha]^{20}$ +3 (*c* 2, benzene).

L-(+)-2-(1-Pyrrolidinylmethyl)pyrrolidine. This compound was prepared from L-(+)-proline according to the procedure of Otani and Yamada[23] except that the protecting group utilized was a *tert*-butylcarbamate.[22] Cleavage of the carbamate was performed by using trifluoroacetic acid, 20 °C, 1 h. The overall yield from L-proline was 50%: bp 106–108 °C (20 mmHg) and $[\alpha]_D^{20}$ +8.75 (*c* 1.0, EtOH); lit.[23b] bp 99–101 °C (12 mmHg) and $[\alpha]_D^{20}$ +8.5 (*c* 2.4, EtOH).

***N*-Benzoyl-L-(+)-2-pyrrolidinemethanol.** Preparation was carried out according to a literature procedure[24] from L-(+)-2-pyrrolidinemethanol in 91% yield based on the amount of benzoyl chloride. Purification was carried out by using column chromatography with 40% ethyl acetate/60% petroleum ether, v/v.

L-(+)-2-[(Phenylthio)methyl]pyrrolidine. *N*-Benzoyl-L-(+)-2-pyrrolidinemethanol (2.55 g, 12.4 mmol) was treated with phenyl disulfide (4.06 g, 18.6 mmol) in the presence of tri-*n*-butylphosphine (4.63 mL, 18.6 mmol) in 10 mL of dry pyridine at room temperature for 48 h under N_2. The dark red solution was poured into a 50-mL mixture of ethyl acetate/water (1:1). The organic layer was separated off and washed 6 times with 20 mL of water. After drying over sodium sulfate, the organic layer was concentrated in vacuo. MPLC with 2–25% ethyl acetate/petroleum ether v/v yielded 88% of the N-protected ligand: MS, *m/e* 297.1176 (M^+) (calcd for $C_{18}H_{19}NOS$, 297.1187).

N-Benzoyl-L-(+)-2-[(Phenylthio)methyl]pyrrolidine (3.26 g, 11.0 mmol) was refluxed with 10 mL of 6 N HCl for 24 h. After having been cooled to room temperature, the solution was made basic with 2 N NaOH and then extracted 6 times with 25 mL of ether. The combined organic layers were dried over sodium sulfate and concentrated in vacuo. The ligand was purified by Kugelrohr distillation to give an 88% yield: bp 89–91 °C (0.1 mmHg); $[\alpha]_D^{20}$ +16.8 (*c* 0.56, $CHCl_3$); IR (neat) 3340 (w), 3060 (m), 2960 (s), 2880 (m), 1580 (m), 1480 (m), 1440 (m), 1400 (m), 1090 (m), 1030 (m), 940 (s), 700 (s) cm^{-1}; NMR ($CDCl_3$) δ 1.43–2.08 (m, 4 H), 2.91 (m, 4 H), 3.03 (s, 1 H), 3.28 (m, 1 H), 7.27 (m, 5 H); ^{13}C NMR δ 24.7, 30.6, 39.0, 45.7, 57.4, 125.7, 128.6 (2C), 129.1 (2C), 135.9.

L-(+)-2-[(Methylthio)methyl]pyrrolidine. *N*-Benzoyl-L-(+)-2-pyrrolidinemethanol (2.17 g, 10.6 mmol), tri-*n*-butylphosphine (3.96 mL, 15.9 mmol), methyl disulfide (1.43 mL, 15.9 mmol), and pyridine (10 mL) were stirred under N_2 at room temperature for 48 h. The solution was diluted with 50 mL of a 1:1 mixture of ethyl acetate/water. The organic layer was washed 6 times with 20 mL of water, dried over sodium sulfate, and concentrated in vacuo. Purification by MPLC (20% ethyl acetate/petroleum ether, v/v) affords the N-protected ligand in 63% yield.

The N-benzoyl protecting group was removed as described above and after Kugelrohr distillation afforded the ligand in 86% yield: bp 60–63 °C (30 mmHg); IR (neat) 3400 (br s), 2980 (s), 2930 (w), 2880 (w), 1650 (s), 1590 (m), 1440 (s), 1100 (m), 1050 (s), 890 (m) cm^{-1}; NMR ($CDCl_3$) δ 1.35 (m, 2 H), 1.84 (m, 2 H), 2.13 (s, 3 H), 2.70 (br s, 1 H), 2.85 (m, 2 H), 3.00 (m, 2 H), 3.28 (t, J = 6.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$) 15.9, 25.1, 30.9, 40.4, 46.1, 57.6.

Conjugate Addition of Chiral Organocuprates to α,β-Enones. Methyllithium (0.68 mL, 1.14 mmol) was added dropwise to a 0 °C solution of the chiral amine (1.14 mmol) and 2 mL of solvent in a septum-sealed, 25-mL round-bottomed flask under N_2. After 15 min, the yellow solution was transferred under N_2 by using a double tipped needle to a two-necked flask which contained copper(I) bromide (0.1627 g, 1.13 mmol) and 5 mL of solvent at −40 °C. The appropriate alkyllithium was added via syringe, and the mixture was slowly warmed to 0 °C over 30 min. The cuprate (Me, light brown; *n*-Bu, black; *t*-Bu, orange-brown) was then cooled to −78 °C, and the enone (1.00 mmol) was added in 2.0 mL of solvent via syringe. After 60–90 min, the reaction was quenched with 5 mL of saturated aqueous ammonium chloride. The reaction mixture was allowed to warm to room temperature and filtered through Celite

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to remove the copper salts, and the residue was washed with 10 mL of ether (Et_2O). The filtrate was extracted 3 times with 10 mL of Et_2O. The combined organic layers were washed 2 times with 10 mL of 2 N HCl and once with brine. After drying over $MgSO_4$, the organic layer was concentrated in vacuo to afford the conjugate addition product which was purified by medium-pressure liquid chromatography (MPLC) (pentane/5-25% ether, v/v).

Conjugate Addition of Higher Order Organocuprates to α,β-Unsaturated Enones. The formation and subsequent reaction of the higher order organocuprates was identical with the above procedure except that copper(I) thiocyanate (0.1273 g, 1.14 mmol) was used instead of copper(I) bromide.

Conjugate Addition of Chiral Organocuprate 11 to α,β-Enones. Prolinol (0.1173 g, 1.16 mmol) was dissolved in 5 mL of ether (Et_2O) in a septum sealed 50-mL, two-necked, round-bottomed flask under N_2. The solution was cooled to -25 °C. Methyllithium (2 equiv, 1.66 mL, 2.32 mmol) was added dropwise. After 30 min, copper(I) bromide (1.663 g, 1.16 mmol) was added via a solid addition funnel followed immediately by the addition of 1 more equiv of methyllithium (0.83 mL, 1.16 mmol). The tan mixture was stirred at -25 °C for 30 min. Upon warming to 0 °C over 15 min the mixture turned dark brown. The cuprate was cooled to -78 °C, and 2-cyclohexen-1-one (0.0993 g, 1.00 mmol) was added in 2 mL of ether. After 3 h, the reaction was warmed to -50 °C where stirring was continued for 1 more h. Saturated aqueous ammonium chloride (5 mL) was added to quench the reaction. The reaction mixture was warmed to room temperature and filtered through Celite. The filtrate was extracted 3 times with 15 mL of Et_2O. The combined organic layers were washed 2 times with 10 mL of 2 N HCl and once with 5 mL of brine, dried over $MgSO_4$, and concentrated in vacuo to yield 3-methylcyclohexan-1-one. The product was purified by MPLC.

Conjugate Addition of Halide Free Organocuprates to α,β-Enones. Methyl copper free of LiBr was prepared according to Lipshultz's[28] procedure. A 10-mL centrifuge tube containing copper(I) bromide (0.0998 g, 0.69 mmol) and 2 mL of THF under N_2 was cooled to -78 °C. Methyllithium (0.46 mL, 0.69 mmol) was added dropwise. A yellow precipitate formed as the mixture was warmed to 0 °C. The tube was spun in a centrifuge, and the clear yellow supernant liquid was removed via a syringe. The methyl copper was washed 3 more times with 2 mL of THF, respectively. After the final washing, 1 mL of Et_2O was added, and the slurry was cooled to -78 °C. The lithium anion of L-(+)-2-[(phenylthio)methyl]pyrrolidine which was formed by the addition of methyllithium (0.46 mL, 0.69 mmol) to the (phenylthio)amine (0.1357 g, 0.70 mmol) at 0 °C was added by cannula. The yellow solution was warmed to 0 °C and then recooled to -78 °C. 2-Cyclohexen-1-one (0.0605 g, 0.63 mmol) in 1 mL of Et_2O was added, the stirring was continued for 90 min. Saturated aqueous ammonium chloride (5 mL) was added to quench the reaction. After filtering through Celite, the filtrate was extracted 3 times with 10 mL of Et_2O. The combined organic layers were washed twice with 5 mL of 2 N HCl and once with 5 mL of brine. Drying over $MgSO_4$ and concentration in vacuo afforded 3-methylcyclohexanone which was purified by MPLC.

Recovery of Chiral Ligands. The procedure[45] of Mukaiyama was employed. The acidic solution from the organocuprate conjugate addition workup was neutralized with solid $NaHCO_3$ and concentrated in vacuo. The residue was diluted with 5 mL of 10% NaOH and then extracted 4 times with 10 mL of ether. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo to yield the chiral amines in 75% yield with no detectable racemization occurring.

General Procedure for the Preparation of Diastereomeric Ketals.[26] The 3-substituted cycloalkanones were dissolved in benzene and treated with 2 equiv of (*R,R*)-(-)-2,3-butanediol and a catalytic amount of *p*-toluenesulfonic acid in a one-necked, 25-mL, round-bottomed flask equipped with a Dean-Stark trap, condenser, and N_2 inlet. The solution was refluxed for 24 h, cooled, and concentrated in vacuo. The residue, dissolved in 10 mL of pentane, was washed with 5 mL of saturated $NaHCO_3$ and then 5 mL of 5% $NaHSO_3$. The two aqueous layers were each back-extracted with 5 mL of pentane. The combined organic layers were dried over K_2CO_3, concentrated in vacuo, and purified by MPLC. The optical purity of the ketals was determined by ^{13}C NMR.

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Registry No. **1**, 23356-96-9; **2**, 63126-47-6; **3**, 51207-66-0; **5**, 106865-55-8; **6**, 106865-52-5; *N*-benzoyl-L-(+)-2-pyrrolidinemethanol, 65950-13-2; *N*-benzoyl-L-(+)-2-[(phenylthio)methyl]pyrrolidine, 106865-53-6; phenyl disulfide, 882-33-7; *N*-benzoyl-L-2-[(methylthio)-methyl]pyrrolidine, 106865-54-7; *trans*-3-penten-2-one, 3102-33-8; copper(I) bromide, 7887-70-4; (*S*)-3-methylcyclopentanone, 6672-24-8; (*R*)-3-methylcyclopentanone, 6672-30-6; (*S*)-3-*tert*-butylcyclopentanone, 66007-65-6; (*S*)-4-methyl-2-octanone, 106865-56-9; (*R*)-4-methyl-2-octanone, 106865-57-0; tributylphosphine, 998-40-3; methyl disulfide, 624-92-0; 2-cyclohexen-1-one, 930-68-7; 2-cyclopentenone, 930-30-3; *trans*-3-octen-2-one, 18402-82-9; methyllithium, 917-54-4; butyllithium, 109-72-8; *tert*-butyllithium, 594-19-4; copper(I) thiocyanate, 1111-67-7; (*S*)-3-methylcyclohexanone, 24965-87-5; (*R*)-3-methylcyclohexanone, 13368-65-5; (*S*)-3-butylcyclohexanone, 72746-41-9; (*S*)-3-*tert*-butylcyclohexanone, 57287-85-1; (2*R*,3*R*)-(-)-2,3-butanediol, 24347-58-8.

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An ab Initio Study on $(C_5H_5V)_2C_8H_8$

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Abstract: The bonding in the organometallic compound μ-(η^5:η^5-cyclooctatetraene)bis[(η^2-cyclopentadienyl)vanadium] involves a complex mixture of metal-metal and metal-ligand contributions. Although there is a direct V-V 3d interaction, it is not as strong as a double bond with some triple bond character as has been suggested based upon experiment. The balance between metal-metal and metal-ligand bonding results in the appearance of a low-lying triplet state which retains the V-V 3d bonding. A small singlet-triplet separation is consistent with the change in magnetic properties with temperature.

I. Introduction

The organometallic compound $(C_5H_5V)_2C_8H_8$ has been synthesized and its structure determined,[1] see Figure 1. The two V atoms are bonded to a common C_8H_8, group, and this constrains the V-V distance to be relatively short. The measured V-V bond length of 2.44 Å (compared to 2.62 Å in bulk V[2]) is sufficiently

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