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Enantioselective Conjugate Addition to Cyclic Enones with Scalemic Lithium Organo(amido)cuprates, Part IV.[1] Relationship Between Ligand Structure and Enantioselectivity[2]

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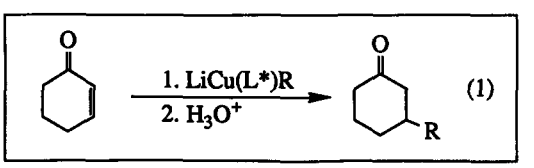
ABSTRACT

Scalemic lithium amides derived from primary and secondary amines react with organocopper compounds in ether or dimethyl sulfide to form lithium organo(amido)cuprates capable of enantioselective conjugate addition to 2-cycloalkenones. The most successful heterocuprate, in which the chiral ligand is *(S)*-*N*-methyl-1-phenyl-2-(1-piperidinyl)ethanamine, *(S)*-MAPP, **13**, reacts with cyclic enones to form products with up to 97% ee. Non-linear asymmetric induction was observed with the cuprate formed from ligand **13**.

Introduction

Enantioselective conjugate addition to enones is a reaction of considerable synthetic potential whose realization has been sought for over 25 years.[3,4] A common approach to solving this problem has been to modify cuprate reagents in order to render them enantioselective. One method of rendering cuprates enantioselective is to employ a scalemic[5] anionic substrate, L*, as a covalently bound non-transferable ligand (eq 1). In principle, this conserves precious transferable ligands R while rendering the reagent enantioselective.



(1)

This approach has been used with considerable success by a number of research groups. Scalemic alkoxides[6,7] mono and dialkylamides[8,9,10] and arenethiolates[11] have been used as non-transferable cuprate ligands with enantioselectivities as high as 95% being achieved. While these and many other efforts represent a significant advance in this field, there is yet no general solution to the problem of achieving efficient enantioselective conjugate addition. Ideally, one would like to find a scalemic reagent which is easily obtained, catalytic and which reacts with a broad range of substrates in high yield and enantioselectivity. The reagents developed to date fail in one or more of these areas.[12]

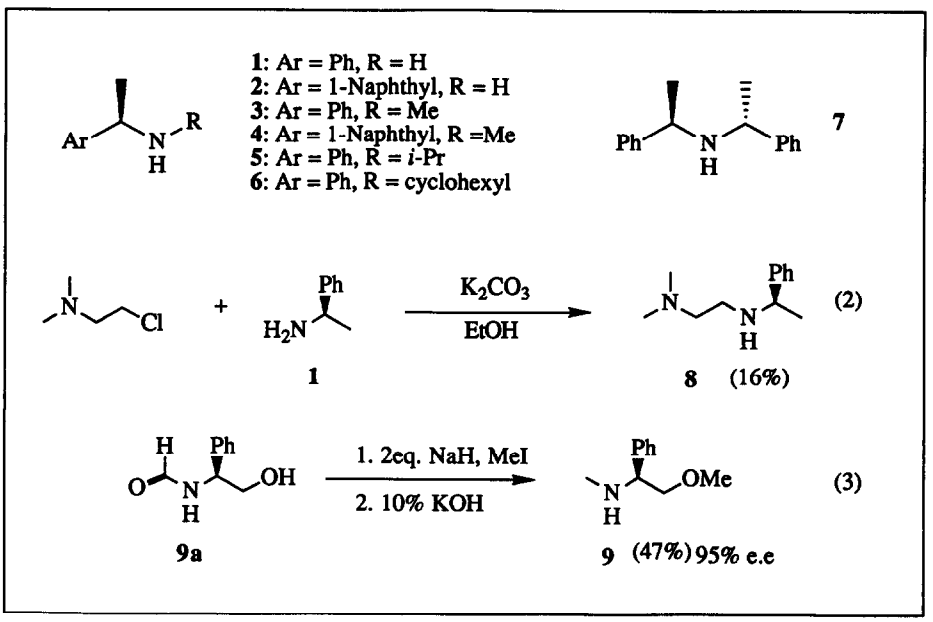
Several years ago we began a program to find a cuprate reagent capable of satisfying the above criteria for the ideal enantioselective conjugate addition reagent. We decided to explore the use of lithium organo(amido)cuprates in which copper(I) possesses a non-transferable scalemic amido ligand and a transferable organo ligand. This choice was prompted largely by the reports of Bertz, Dabbagh and Villacorta who

demonstrated that achiral lithium organo(amido)cuprates are efficient reagents for conjugate addition.[13] At the time, few details existed on the structure and state of aggregation of heterocuprates, a situation which persists. Furthermore, many aspects of cuprate chemistry were unknown or poorly defined such as the effect of solvent[14] and various salts[15] on cuprate structure and reactivity. We recognized that our search for an enantioselective cuprate reagent would initially be somewhat Edisonian in nature. We began with the premise that a heterocuprate with a chiral non-transferable ligand offered us the greatest possibility of success. We did not, however, want to screen scalemic ligands purely at random. Our initial approach, therefore, was to screen a number of ligands in order to find a cuprate capable of some degree of enantioselection. Upon finding a "lead" compound, we then systematically modified its structure to optimize the reactivity of the cuprate and to discern the relationship between ligand structure and cuprate enantioselectivity. Our efforts are reported herein.

Results and Discussion

Synthesis of the Chiral Ligands

In order to pursue this study, we accumulated 31 scalemic amines to be screened as cuprate ligands. Amines **1-7** were either obtained commercially or synthesized using published procedures. Alkylation of **1** with dimethylaminoethyl chloride gave ligand **8** (eq 2). (*S*)-*N*-Methyl-1-phenyl-2-methoxyethanamine, **9**, was made by dialkylating (*S*)-N-formyl phenylglycinol and removing the formyl group (eq 3).



Most of the amines used in this study were prepared by a three-step procedure consisting of protecting the amine group of an amino acid or chiral amine, coupling the protected substrate with an achiral amine to form the corresponding carbamate-amide or diamide[16] and reducing the functional groups with $LiAlH_4$ to give the

corresponding di-, tri- or tetraamines (Table 1). Two coupling reagents were used: isobutyl chloroformate (IBCF) or 1,3-dicyclohexylcarbodiimide (DCC). The enantiomeric purity of the products was determined by chiral HPLC using a Chiralcel OD (10% *iso*-propanol-hexane). We generally experienced fewer racemization problems with IBCF and therefore used this reagent more often. We used four protecting groups: the carbobenzoxy (Cbz), formyl (For), acetyl (Ac) and benzoyl (Bz) groups. In some cases, we experienced problems with racemization during the coupling procedure. The enantiomeric purity of formyl protected substrates degraded ca. 25% during the IBCF coupling reaction in the synthesis of ligand precursors **10a** and **12a**. In contrast, the Cbz protected substrates showed only 1-6% racemization under the same conditions and became the method of choice in these reactions. Coupling (*R*)-N-Cbz-phenylglycine with diethyl amine occurred with a high degree of racemization. Running this reaction strictly at -15°C and using a slight deficiency of the amine helped minimize but not altogether eliminate racemization. Amide **21a** did not form using the IBCF procedure and was, therefore, formed by transforming the protected acid to the acid chloride using PCl_5 and coupling it with piperidine. This reaction occurred with 14% racemization. Buono *et al.* have reported an azide coupling method which minimizes racemization during the formation of chiral amides.[17]

We have since modified a procedure developed by Dieter et al.[18] for making ligand **13**. Reaction of (*R*)-1-phenyl-2-(1-piperidinyl)ethanol, **33**, obtained by the reaction of piperidine with commercially available (*R*)-styrene oxide, with methanesulfonyl chloride and triethylamine followed by reaction with aqueous methylamine yields (*R*)-**13** (eq 4).[19] As noted by Dieter et al., this reaction occurs with retention of configuration presumably via an intermediate aziridinium species.

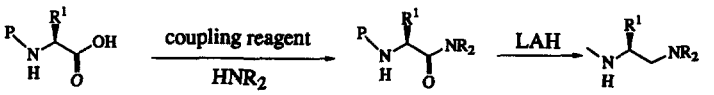
Removal of the Cbz group from amides **13a**, **23a** and **29a** by catalytic hydrogenation followed by $LiAlH_4$ reduction provided compounds **18**, **27b** and **28**, which were used as ligands or as intermediates (Table 2). Ligands **21**, **27** and **30** were obtained by reductive amination of **18**, **27b**, and **28** respectively with the appropriate ketone or aldehyde.

Conjugate Addition of Chiral Cuprates to 2-Cyclohexenone

Our study consisted of forming the lithium organo(amido)cuprates from the corresponding lithium amides of amines **1-31** and Me, *n*-Bu or phenylcopper and reacting these reagents with cyclic enones ranging in ring size from 5 to 8 (Table 3). To monitor the enantioselectivity in these reactions, we needed a reliable analytical procedure. The ee's of chiral cyclic ketones have been determined by converting them to their corresponding diastereomeric ketals with 2,3-butanediol and examining their ^{13}C NMR spectra or by taking the optical rotation of the product.[6-11] We found in most cases that we could more accurately and conveniently determine ee's of 3-*n*-butylcyclohexanone by forming the diastereomeric ketals with (+)-diethyl tartrate followed by GC analysis or by chiral GC using 30 m Chiraldex APH™or BPH™ columns.

The results of these reactions are shown in Table III. These cuprates can be put roughly into 3 groups; those in which R^3=H (ligands **1-8**), R_3=OMe or NR_2 (ligands **9-27**) and R^3=$N(Me)CH_2CH_2N(Me)_2$ (ligands **25-31**). Ligands **1-8** as a group performed poorly (entries 1-23). Several interesting trends, however, manifest themselves in this as well as the other two groups. First, the reactions give significantly better results in DMS than in ether or THF. The superior properties of DMS as a solvent in cuprate reactions was recently

Table 1. Synthesis of Chiral Amines.



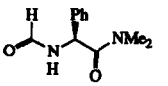
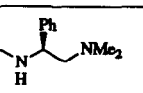
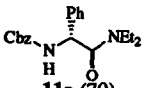
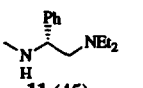
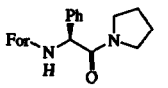
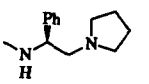
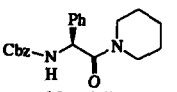
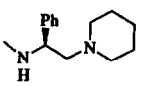
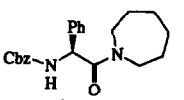
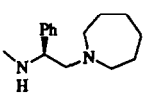
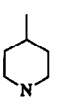
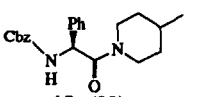
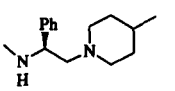
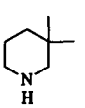
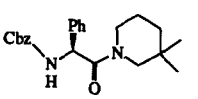
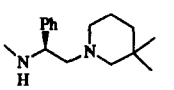
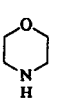
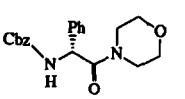
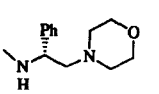
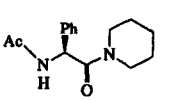
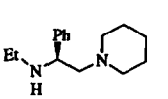
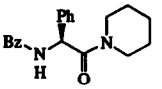
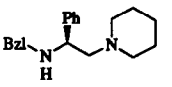
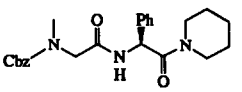
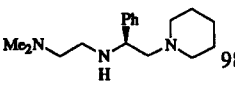
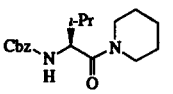
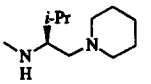
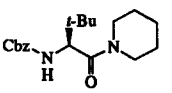
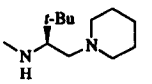
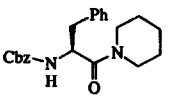
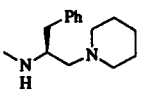
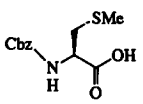
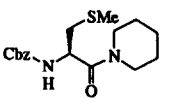
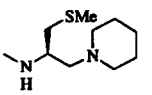
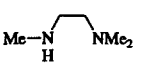
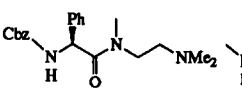
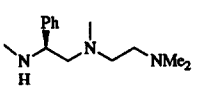
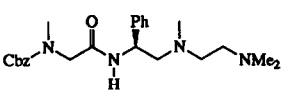
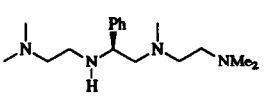
N-Protected Amino Acid	Amine	Reagent	Amide (% yield)	Amine (% yield)	% e.c.
(*S*)-For-phenyl-Gly	$HNMe_2$	IBCF	 **10a** (56)	 **10** (81)	74
(*R*)-Z-phenyl-Gly	$HNEt_2$		 **11a** (70)	 **11** (45)	95
(*S*)-For-phenyl-Gly			 **12a** (40)	 **12** (68)	75
(*S*)-Z-phenyl-Gly			 **13a** (94)	 **13** (68)	98
			 **14a** (62)	 **14** (68)	94
			 **15a** (98)	 **15** (65)	98
			 **16a** (90)	 **16** (71)	97
(*R*)-Z-phenyl-Gly			 **17a** (80)	 **17** (52)	95
(S)-Ac-phenyl-Gly			 **19a** (36)	 **19** (51)	98

Table I. (cont.)

N-Protected Amino Acid	Amine	Reagent	Amide (% yield)	Amine (% yield)	% e.e.
(*S*)-Bzl-phenyl-Gly		IBCF	 **20a** (33)	 **20** (61)	98
Cbz-Sar	**18**		 **22a** (73)	 **22** (49)	98
(*S*)-Cbz-Leu			 **23a** (62)	 **23** (69)	99
(*S*)-Cbz-t-butyl-Leu		PCl_5	 **24a** (67)	 **24** (76)	86
(*S*)-Cbz-Phe		DCC	 **25a** (99)	 **25** (72)	ND
			 **26a** (78)	 **26** (60)	ND
(*S*)-Cbz-phenyl-Gly			 **29a** (86)	 **29** (63)	91
Z-Sar	**28**		 **31a** (88)	 **31** (52)	91

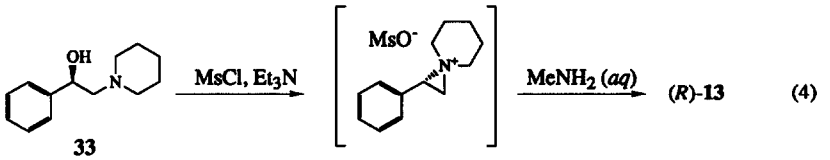
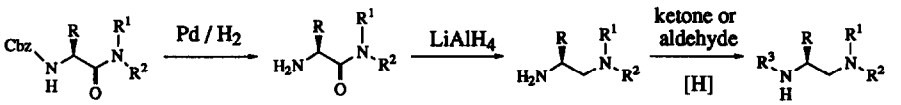
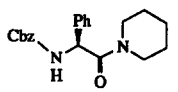
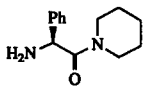
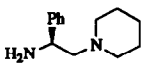
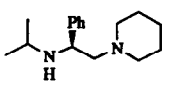
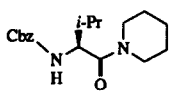
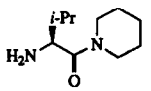
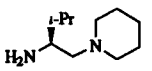
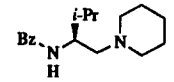
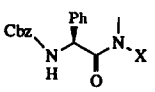
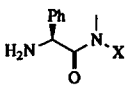
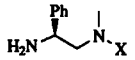
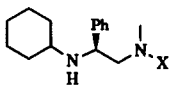


Table 2. The Synthesis of Chiral Amines.



Protected Amide	Amide (% yield)	Amine (% yield)	Amine (% yield)	% e.e.
 **13a**	 **18a** (96)	 **18** (46)	 **21** (45)	98
 **23a**	 **27a** (96)	 **27b** (90)	 **27** (34)	99
 **29a**	 **28a** (92)	 **28** (70)	 **30** (83)	91

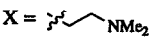
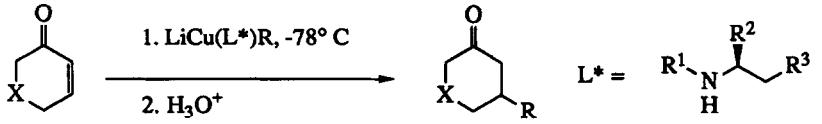
X = 

Table 3. Enantioselective Conjugate Addition to Enones with Scalemic Lithium Organo(amido)cuprates



X = $(CH_2)_n$, n = 0-3

Entry	Ligand L*	Enone	R	Solvent	% Yield	% ee	R/S
1	(*R*)-**1**	2-cyclohexenone	*n*-Bu	DMS	88	4	R
2				ether	66	15	R
3		2-cycloheptenone			91	7	R
4	(*R*)-**2**	2-cyclohexenone		DMS	88	9	R
5				ether	62	13	R
6	(*R*)-**3**			DMS	84	50	S
7				ether/DMS	53	24	R
8				ether	46	21	R
9			Ph	ether/DMS	44	10	R
10		2-cycloheptenone	*n*-Bu	ether	42	19	S
11	(*R*)-**4**	2-cyclohexenone		DMS	74	51	S
12				ether/DMS	45	18	R
13				ether	51	6	R
14	(*R*)-**5**			DMS	64	29	R
15				ether/DMS	28	8	S
16		2-cycloheptenone	Me	ether	30	4	S
17			*n*-Bu		72	1	R
18	(*R*)-**6**	2-cyclohexenone		DMS	59	29	R
19				ether/DMS	11	7	R
20	(*R,R*)-**7**			DMS	43	43	R
21				ether/DMS	25	3	S
22		2-cycloheptenone		ether	45	2	S
23	(*R*)-**8**	2-cyclohexenone		DMS	58	32	R
24	(*S*)-**9**				92	68	S
25				ether/DMS	79	16	S
26		2-cycloheptenone		ether	40	35	S
27	(*S*)-**10**			DMS	89	19	S
28				ether	61	15	S
29			Me		26	10	S
30	(*R*)-**11**		*n*-Bu		68	37	R
31	(*S*)-**12**	2-cyclohexenone			75	37	S
32	(*R*)-**12**	2-cycloheptenone			46	94	R
33			Me		25	76	R
34	(*S*)-**13**	2-cyclopentenone			40	32	R
35			*n*-Bu		51	45	S
36		2-cyclohexenone	Me		57	58	S
37			*n*-Bu		92	83	S
38			Ph		30	97	S
39		2-cycloheptenone	Me		60	97	S
40			*n*-Bu		63	97	S

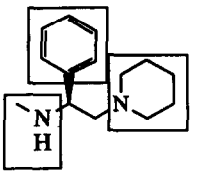
41		2-cyclooctenone	Me		48	67	ND
42			*n*-Bu		50	86	ND
43		4,4-dimethyl-2-cyclohexenone			45	59	ND
44		5,5-dimethyl-2-cyclohexenone			47	53	ND
45		6,6-dimethyl-2-cyclohexenone			43	66	ND
46		3-methyl-2-cyclohexenone			0	0	-
47		4-phenyl-3-buten-2-one			34	2	ND
48	(*S*)-**14**	2-cyclohexenone			42	33	S
49		2-cycloheptenone			65	86	S
50	(*S*)-**15**	2-cyclohexenone			69	84	S
51		2-cycloheptenone			57	85	S
52			Me		4	95	S
53			*n*-Bu		57	85	S
54	(*S*)-**16**	2-cyclohexenone			71	55	S
55		2-cyclopentenone	Me		43	4	R
56	(*R*)-**17**	2-cyclopentenone			54	0	-
57		2-cycloheptenone			67	37	R
58			*n*-Bu		35	83	R
59	(*R*)-**18**		Me		7	73	R
60			*n*-Bu		35	12	R
61	(*S*)-**18**	2-cyclohexenone			43	0	-
62	(*S*)-**19**	2-cycloheptenone			19	50	S
63	(*S*)-**20**				41	6	R
64		2-cyclopentenone			46	11	R
65		2-cycloheptenone	*n*-Bu		33	11	S
66	(*S*)-**21**				76	4	S
67		2-cyclohexenone			52	19	S
68				DMS	49	10	S
69	(*S*)-**22**				25	11	R
70	(*S*)-**23**				79	25	S
71		2-cycloheptenone		ether	35	68	S
72	(*S*)-**24**	2-cyclohexenone			28	28	S
73	(*S*)-**25**				63	10	S
74		2-cyclopentenone	Me		43	3	S
75	(*S*)-**26**	2-cyclohexenone	*n*-Bu		45	38	R
76				DMS	77	9	S
77	(*S*)-**27**				63	19	R
78	(*S*)-**28**				61	4	S
79	(*S*)-**29**				100	71	S
80				ether	75	55	S
81				THF	4	6	R
82		2-cycloheptenone		ether	89	9	S
83	(*S*)-**30**			DMS	6	8	R
84	(S)-**31**				2	1	S

Reactions were typically run on a 1 mmol scale at -78° C.

reported by Bertz.[20] Second, ligands in which R^1 = Me perform better than those in which R^1 = H or alkyl groups other than Me. Interestingly, ligand **7** performed only about as well as **3** and **4** even though it is a ligand with C_2 symmetry. Third, changing R^2 from phenyl to 1-naphthyl does not improve the enantioselectivity of this reagent.

In the second group, we examined the effect of adding a second site of chelation to the chiral amine. Ligand **9**, with its methyl ether gave respectable results in DMS but not in ether (entries 24-26). Ligand **10**, R^3=NMe_2 gave poor but similar results in both DMS and ether (entries 27-29). Ligands **12-15** in which R^3=pyrrolidinyl, piperidinyl, hexahydroazepinyl, and 4-methylpiperidinyl respectively, gave in many cases extremely good results with several transferable ligands (entries 31-53). Ligand **13**, N-methyl-1-phenyl-2-(1-piperidinyl)ethanamine, in fact, is our best ligand discovered to date for which we have given the acronym MAPP. Surprisingly, **17**, with a morpholinyl substituent, is a poor ligand in these reactions. Ligands **18-22** with something other than an N-methyl group, gives poor results relative to **13**. Ligands **23-27** exemplify the debilitating effect of substituting the phenyl group with non-aromatic groups. Ligands **28-31** manifest the effect some of the above substitution patterns and the effect of using an ethylene diamine derivative as an auxilliary chelating group. As shown, these ligands are inferior to the best ligand **13**.

These results, taken together, suggest that the most successful ligand for this system has three major characteristics, i.e. an N-methyl group on the secondary amine, a phenyl substituent at the stereogenic center and a piperidinyl substituent as epitomized by ligand **13** (Figure I). Significant deviations from this ligand structure result in poorer enantioselectivities.



(*S*)-**13**

Figure I. Optimum features of scalemic diamines for use as a non-transferable lithium cuprate ligand

Several factors adversely affect enantioselectivity in these reactions. When these reactions are run in THF, regardless of the amidocuprate, the enantioselectivity drops to ca. 0%. The reactions perform best when run in DMS especially with monodentate ligands. Use of CuCN rather than CuI as the starting copper salt also results in ca. 0% enantioselection. Similar to observations made by Corey et al.,[6] we have found that the quality of alkyllithium is also important in the overall success of these reagents especially when using *n*-butyllithium. *n*-Butyllithium, which has not been properly cared for, tends to reduce enantioselectivities in these reactions.

We have observed non-linear asymmetric induction in the reactions involving our best ligand, **13**. When **13**, with varying degrees of enantiomeric purity, is used in the conjugate addition of *n*-Bu to 2-cycloheptenone, the product is obtained with a higher degree of enantiomeric purity than the ligand used in the reaction (Table 4).[21] The phenomenon of asymmetric amplification is characteristic of chemical reagents which employ more than one chiral auxiliary at some point in the reaction manifold.[22] The working model for these reagents we currently use is that of a dimer whose stoichiometric formula is $[LiCu(MAPP)(n\text{-}Bu)]_2$ (see below). Our results can be rationalized if one assumes that the reagent reacts in its dimeric form, that the (*S,S*), (*R,R*) and (*S, R*) complexes are formed with roughly equal facility, and that the meso dimer formed from an *R* and *S* ligand is unreactive relative to (*S,S*) or (*R,R*) dimeric cuprates. One can compute the relative amounts of (*S,S*), (*R,R*) and (*S, R*) complexes present in the reaction mixture using the formulas:

% SS dimer = 100(S x S); % RR dimer = 100(R x R); % SR(meso) dimer = 2 x 100(S x R)
By assuming the meso complex is unreactive and by factoring in the inherent enantioselectivity of the reaction, one can compute an expected enantiomeric purity for products synthesized using a cuprate derived from ligand of a certain enantiomeric purity. For example, 56% ee (*S*)-MAPP (78% S and 22% R) would form dimers consisting of (0.78 x 0.78) x 100 or 60.8 % SS, 2(0.78 x 0.22) x 100 or 34.3 % SR, and (0.22 x 0.22) x 100 or 4.8 % RR enantiomers. Ignoring the meso complex and recomputing the ee of the SS/RR dimers gives [(60.8 - 4.8) + (60.8 + 0.48)] x 100 = 85.3 % ee. Factoring in the inherent enantioselectivity of 96 % gives (85.3 % x 0.96) = 81.9 %. This assumes that there is little or no ligand exchange during the reaction which would allow the minor enantiomer, present primarily in the unreactive meso dimer, to leak back into the reaction manifold. When we quench these reactions at -78° C, we obtain the results shown in entries 1-4. When we allow our reaction to warm to -20° C before quenching, we obtain the result in entry 5. This observation may result because of slow ligand exchange at -78° C which increases on warming. Gilman reagents are known to undergo rapid ligand exchange even at fairly low temperatures.[23] The bidentate nature of the scalemic ligands may slow ligand exchange relative to normal cuprates.

Table 4. Non-Linear Enantioselective Conjugate Addition of Scalemic LiCu(MAPP)(*n*-Bu) to 2-Cycloheptenone.

Entry	% ee of MAPP	Observed % ee of Product	Expected % ee of Product
1	>99	97	97
2	84	94	94.6
3	78	88	93.6
4	56	81	81.9
5	56	47	81.9

Cuprate Structure

A major goal of this study was to begin to understand the effect of ligand structure on cuprate enantioselectivity. We also sought to use this information to help discern the structure of these reagents and the mechanistic pathway by which they operate. The biggest impediment to understanding this reaction is the lack of structural and aggregational information relative to cuprates in general and amidocuprates in particular. Several homocuprate structures have been solved by X-ray crystallography. In ether[24] and DMS[25] these compounds crystallize as dimers similar to the structures first proposed by Pearson and Gregory.[26] Although they are generally portrayed as being flat, their crystal structures reveal them to be puckered. Interestingly, when these cuprates are formed in THF or in the presence of chelators such as 14-crown-4, they form monomeric structures.[27]

To date, the structures of amidocuprates have not been elucidated. The structure of $[Cu(NEt)_2]_4$ has been

solved[28] and found to be tetrameric, reminiscent of homocuprates. Dieter and Tokles have presented a detailed model of similar amidocuprates in which the nitrogen and carbon ligands alternate.[8a] Dieter and coworkers have also recently reported NMR studies of achiral lithium organo(amido)cuprates in THF which show a single predominant species consistent with a dimeric structure.[29] We believe, based on evidence in the literature and our own synthetic results, that in relatively non-polar solvents, our amidocuprates are dimeric and similar in nature to the model proposed by Dieter and Tokles (Figure 2). In this model, the amido group serves as a bridging ligand between copper and lithium.[30] The tertiary amine is bound to the lithium and acts as an internal site of solvation.[31] The N-methyl groups of this structure can either point up or down relative to the plane of the complex. The N-methyl and phenyl groups should prefer to be anti to one another rather than eclipsed in order to avoid undesirable steric interactions. To assume a conformation in which the N-methyl groups point up and are not eclipsed relative to the phenyl groups, the (*S*)-amido ligands must be positioned in the lower right or upper left hand corners as shown. Conversely, to be pointing down, they must be in the upper right or lower left hand corners. Such a complex, in its idealized form, is C_2 symmetric with a chiral plane passing through the four metal atoms. The N-methyl groups serve to position significant steric hindrance at two of the four corners of the complex leaving two corners with relatively little steric bulk. The phenyl groups act to block reaction of the substrates from the underside of the complex. These structural speculations are consistent with the observation of asymmetric amplification.

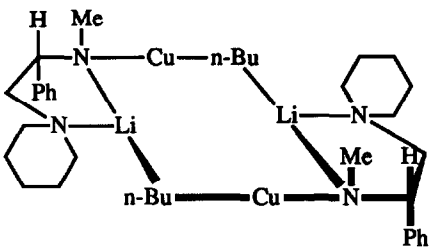
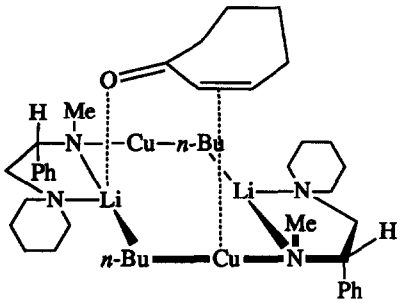


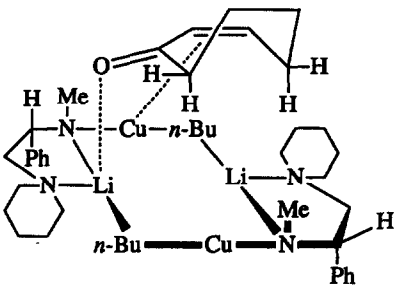
Figure 2. Proposed Structure of [LiCu(*S*-MAPP)(*n*-Bu)]$_2$

Our working model for the origin of enantioselection is as follows. First, the enone complexes with one of the lithium ions through the carbonyl oxygen.[32] This serves two purposes: 1. to activate the enone and 2. to tether the enone to the complex making for a more intimate and stereochemically well-defined interaction. Second, one of the copper atoms interacts with the enone system with the ultimate result of transferring an R group to the β-position. Our reactions do not shed light on the particular mechanistic pathway in which this transfer may take place. Very likely, however, the process begins with the formation of diastereomeric copper (I)-enone complexes such as those described in the literature.[33] In complex, A, the enone-copper complex is situated such that there is little steric interaction with the lower right N-methyl group. In the diastereomeric complex B, the pseudoaxial hydrogens interact with the N-methyl group. This we believe will be the higher energy complex and will therefore be disfavored. This predicts, for most substrates, the R vs S selectivity. It also suggests that the highly puckered 2-cycloheptenone is more likely to have a large energy difference between its two diastereomeric complexes than the smaller and relatively flat 2-cyclopentenone. 2-Cyclooctenone, though, puckered, may be too big for the cuprate pocket to react with as high of enantioselectivity compared to 2-cycloheptenone. When the *S*-MAPP ligand is used, for most cases where absolute configuration was determined, the *S*-enantiomer of the product was obtained. One exception to this is the reaction of 2-cyclopentenone with LiCu((*S*)-MAPP)Me which gives (*R*)-3-methylcyclopentanone as the predominant

enantiomer. The model, though useful for helping orient our thinking on this subject, needs verification and further refining.



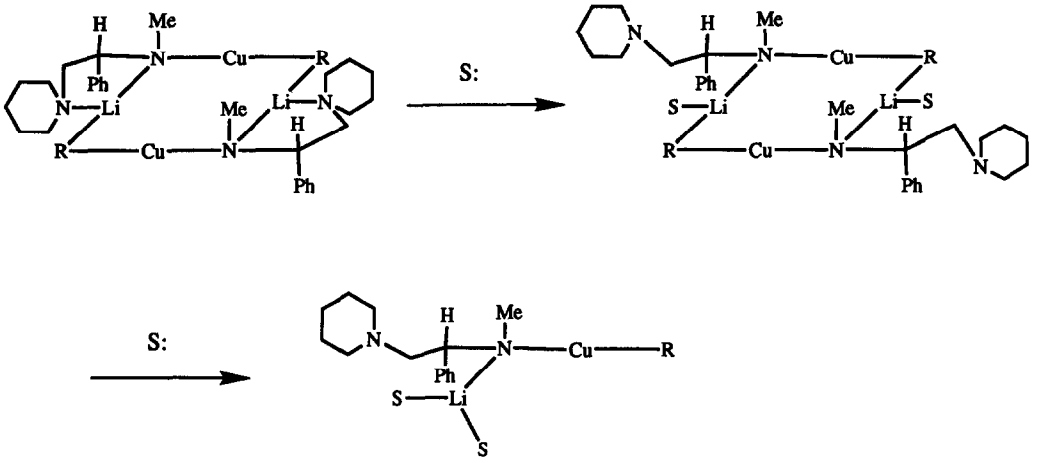
A



B

As mentioned, we observed that when these reactions are run in THF, the enantioselectivity drops to 0%. Van Koten and Noltes[34] have shown that THF competes effectively with tertiary amines for coordination sites on lithium in cuprates. It is likely that in THF, the auxilliary piperidinyl chelating group is displaced which breaks the stereochemical definition of the complex rendering it non-enantioselective (Scheme 1). The complex may further break into monomers by additional THF solvation of the lithium ion.

Scheme 1.



This model constitutes a starting point in our investigation of the structural and reactivity features of this cuprate. We still have much to learn particularly about aggrgegation states and detailed structure of such cuprates in order to develop a model with greater predictive power. Suffice it to say, this type of reagent manifests at times impressive enantioselectivities depending on the substrate, ligand, solvent and counterions present in the reaction mixture. We are continuing to examine the synthetic properties of this and other similar chiral amidocuprate reagents and the structure and mode of operation of this reagent.

Experimental

General. GC analyses were performed using a Hewlett-Packard Model 5890 gas chromatograph with FID detector and H_2 or He as a carrier. THF, ether and DMS were freshly distilled from Na/benzophenone before use in cuprate conjugate addition reactions. All cuprate reactions were performed in oven-dried glassware under Ar. The enantiomeric purity of amines **10, 12-16, 18, 22-24, 27-31** were determined by the ^{1}H NMR analysis of the corresponding amides of (*R*)- and (*S*)-α-methoxy-α-trifluoromethylphenylacetyl chloride (MTPA-Cl, both >98% ee).[35] The enantiomeric purity of ligands **11-13, 17, 19** and **20** were also determined by HPLC using a Daicel Chiralcel OD™ column (2.5% 2-propanol/hexane). The enantiomeric purity of the intermediate amide products also was determined by chiral HPLC using a Chiralcel OD™ column (10%*iso*-propanol-hexane).(*R*)-1-phenylethanamine and (*R*)-1-(1-naphthyl)ethanamine were obtained from Aldrich. (*R*)-N-Methyl-1-phenylethanamine ($[\alpha]^{25}_D$ +74.9° (c 1.02, $CHCl_3$)), **3**, and (*R*)-N-methyl-1-(1-naphthyl)-ethanamine ($[\alpha]^{25}_D$ +90.4° (c 1.35, $CHCl_3$)), **4**, were prepared using the procedure of Paquette and Freeman.[36] (*R,R*)-Di-(1-phenylethyl)amine, **7**, was prepared using the procedure of Overberger *et al.*[37] The enantiomeric purity of 3-*n*-butylcyclohexanone, 3-methylcyclopentanone, and 3-methylcyclooctanone were determined by GC using a 10 or 30 m x 0.25 mm Chiraldex APH capillary column (Astec Inc., Whippany, NJ). 3-Methylcyclohexanone, 3-methylcyclopentanone and 3-*n*-butylcycloheptanone were determined by GC using a 30 m x 0.25 mm Chiraldex BPH capillary column (Astec Inc., Whippany, NJ). The R/S designation of the predominant enantiomers of 3-methylcyclopentanone and 3-methylcyclohexanone were determined by comparing the chiral GC retention times of these products with those of authentic material obtained commercially (Aldrich) whereas those of 3-n-butylcyclopentanone, 3-n-butylcyclohexanone, 3-phenylcyclohexanone[38] and 3-methylcycloheptanone were determined by comparing the optical rotation of the products with literature values.[39] The absolute configurations of 3-n-butylcycloheptanone, 3-methylcyclooctanone, and 3-n-butylcyclooctanone have not been determined. We have tentatively assigned an absolute configuration to 3-n-butylcycloheptanone by comparing its optical rotation with the literature value of (*R*)-3-methylcycloheptanone.

(*R*)-N-Isopropyl-1-phenylethanamine, 5. A suspension of PtO_2[40] (20 mg), in 5 mL of abs EtOH, was shaken under H_2 (15-30 psi) for 30 min. (*R*)-1-Phenylethanamine (3.0 g, 25 mmol), acetone (1.9 mL, 26 mmol), and abs EtOH (5 mL) were added and the mixture was shaken under H_2 (30 psi) for 6 h. The reaction mixture was filtered and concentrated to afford an oily residue, which was chromatographed (silica gel, 5:1 hexanes-EtOH) followed by Kugelrohr distillation (148°C, 7 mmHg) to afford 2.5 g (62%) of a colorless oil: $[\alpha]^{25}_D$ +59.9° (c 2.05, $CHCl_3$); IR (neat) 3321 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.99 (dd, 6), 1.32 (d, 3), 2.60 (m, 1), 3.86 (m, 1), 7.26 (m, 5); MS *m/z* 164 (M^+ +1).

(*R*)-N-Cyclohexyl-1-phenylethanamine, 6. (*R*)-1-Phenylethanamine (3.0 g, 25 mmol) and cyclohexanone (2.7 g, 28 mmol) were dissolved in 20 mL of benzene and refluxed for 1 h with removal of water using a Dean-Stark trap. The reaction solution was concentrated to give the crude imine which was then added to a suspension of $LiAlH_4$ (1.6 g, 42 mmol) in 20 mL of THF at 0°C under Ar. The reaction mixture was warmed to 23°C, refluxed for 2 h and quenched with 5 mL of water in 150 mL of THF followed by 5 mL of 15% NaOH. The suspension was filtered and concentrated to afford an oily residue. The residue was dissolved in 100 mL of ethyl acetate, dried (anhyd Na_2SO_4), concentrated and chromatographed (silica gel, 3:1 ethyl acetate-hexanes) followed by Kugelrohr distillation (120°C, 0.02 mmHg) to afford 3.8 g (75%) of a colorless oil: $[\alpha]^{25}_D$ +67.7° (c 1.53, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.91-1.28 (m, 6), 1.32 (d, 3), 1.46-1.80 (m, 4), 2.00 (d, 1), 2.25 (m, 1), 3.95 (q, 1), 7.27 (m, 5); MS *m/z* 203 (M^+). Anal. Calcd for $C_{14}H_{21}N$: C, 82.70; H, 10.41; N, 6.89. Found: C, 82.80; H, 10.54; N, 7.00.

(*R*)-N-(N,N-Dimethyl-2-aminoethyl)-1-phenylethanamine, 8. (*R*)-1-Phenylethanamine (3.6 g, 30 mmol) was dissolved in abs EtOH (50 mL). A solution of 2-dimethylaminoethyl chloride hydrochloride (4.3 g, 30 mmol) in abs EtOH (50 mL) was added, and the reaction mixture was stirred for 15 min at 80°C. Powdered K_2CO_3 (8.3 g, 60 mmol) was added, and the mixture was refluxed with stirring for 4 h, cooled and allowed to stand for a week. A white precipitate was removed by filtration, and the filtrate was concentrated to afford a crude oily product. This oil was purified by column chromatography (silica gel, 10:1 ethyl acetate-Et_3N) and Kugelrohr distillation (110°C, 0.1 mmHg) to afford 0.9 g (16%) of a colorless oil: $[\alpha]^{26}_D$ +46.7° (c 1.79, $CHCl_3$); IR (neat) 3299 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.37 (d, 3), 1.80 (s, 1), 2.17 (s, 6), 2.26-2.61 (m, 4), 3.75 (q, 1), 7.35 (m, 5); MS *m/z* 192 (M+). Anal. Calcd for $C_{12}H_{20}N_2$: C, 74.95; H, 10.48; N,

14.57. Found: C, 74.83; H, 10.38; N, 14.49.

(*S*)-N-Methyl-1-phenyl-2-methoxyethanamine, 9. Methyl iodide (3.8 g, 27 mmol) and NaH (0.60 g, 25 mmol) were added to a solution of N-formyl-2-amino-2-phenylethanol[41] (1.5 g, 9.0 mmol) in 20 mL of THF at 23°C. The mixture was refluxed 3 h and treated with saturated Na_2CO_3 and extracted with ethyl acetate (2 X 100 mL). The organic layer was dried (anhyd Na_2SO_4), concentrated and chromatographed (silica gel, 1:3 hexanes-ethyl acetate) to afford 1.5 g (85%) of a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.74 (d, 3), 3.42 (s, 3), 3.85 (d, 2), 4.76 (t, 1), 7.20-7.45 (m, 6), 8.25 (d, 1).

Amide **9a** (1.5 g, 7.8 mmol) and 10% KOH (20 mL) were refluxed with stirring for 2 h. Upon cooling, the reaction mixture was extracted with ether (3 X 100 mL). The ether layer was dried (anhyd Na_2SO_4) and concentrated to afford the crude product, which was purified by Kugelrohr distillation (90°C, 0.05 mmHg) to afford 0.7 g (55%, 96% ee) of a colorless oil: $[\alpha]^{27}_D$ +98.4° (c 1.01, $CHCl_3$); IR (neat) 3346 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.88 (s, 1), 2.30 (s, 3), 3.37 (s, 3), 3.45 (d, 2), 3.78 (dd, 1), 7.35 (m, 5); CIMS (isobutane) *m/z* 166 (M$^+$+1). Anal. Calcd for $C_{10}H_{15}NO$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.68; H, 9.13; N, 8.47.

General Procedures for the Synthesis of N-Methyl-1-phenyl-1,2-diamines. Di- and triamines **10-17, 19, 20 and 22-24** were synthesized according to the following two-step procedure for **13** using isobutyl chloroformate (IBCF) as the coupling reagent. Di-, tri- and tetraamines **25, 26** and **31** were synthesized according to the procedure for **29** using DCC as the coupling reagent. In all cases involving reduction with $LiAlH_4$, the procedure used to make **13** was employed.

(*S*)-N-Methyl-1-phenyl-2-(1-piperidinyl)ethanamine, 13. 4-Methylmorpholine (14.4 g, 142 mmol) and isobutyl chloroformate (19.4 g, 142 mmol) were added to a solution of (*S*)-N-carbobenzoxyphenylglycine[42] (40.6 g, 142 mmol) in 350 mL of THF at -15°C with stirring for 5 minutes. A THF solution of piperidine (12.1 g, 142 mmol) was added with stirring to the reaction mixture at -15°C resulting in the formation of a white precipitate. The reaction was stirred for 1 h at -15°C and then for 4 h at 23° C. The reaction mixture was concentrated and dissolved in 650 mL of ethyl acetate and 100 mL of water. The two-phase mixture was partitioned, and the ethyl acetate layer was washed with 1 N HCl (2 X 250 mL), water (100 mL), 5% $NaHCO_3$ (2 X 250 mL), and water (250 mL) followed by saturated NaCl (200 mL). The ethyl acetate layer was dried (anhyd Na_2SO_4) and concentrated to afford crude **13a** as an oil (47.2 g, 134 mmol, 94%). The product sometimes crystallizes on standing and can be purified by preparative HPLC (silica gel, 3:1 hexanes-ethyl acetate) giving white crystals: mp 76.5-77.5°C; IR (neat) 3306, 1724, 1650 cm^{-1}; ^{1}H NMR (200 MH_z, $CDCl_3$) 1.52 (m, 6), 3.50 (m, 4), 5.04 (dd, 1), 5.59 (d, 1), 6.46 (d, 1), 7.40 (m, 10).

Crude carbobenzoxyamide, **13a**, (47.2 g, 134 mmol) was dissolved in dry THF (250 mL) and added dropwise to a suspension of $LiAlH_4$ (40.8 g, 1.08 mol) in 350 mL of THF at 0°C under Ar. The suspension was refluxed for 12 h, cooled to 0°C and treated with 300 mL of THF and 50 mL of water followed sequentially by 50 mL of 15% NaOH and 30 mL of water. After filtration of the resulting suspension, the solid residue was washed with 200 mL of THF. The THF washing and filtrate were combined and concentrated to afford an oily residue. This oily residue was dissolved in 1N HCl (280 mL), and the acidic solution was washed with ether (2 X 400 mL). The water layer was treated with 5N KOH followed by extraction with ether (2 X 400 mL). This ether layer was dried (anhyd $MgSO_4$) and concentrated to afford 25.0 g of crude amine. The amine was purified by vacuum distillation (98-100°C, 0.05 mmHg) to afford 19.9 g (91.3 mmol, 68% yield, 98% ee) of a colorless oil: $[\alpha]^{26}_D$ +109.1° (c 1.88, $CHCl_3$); IR (neat) 3329 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.40 (m, 2), 1.58 (m, 4), 2.37 (s, 3), 2.20-2.65 (m, 7), 3.60 (dd, 1), 7.35 (m, 5); MS *m/z* 219 (M$^+$ +1). Anal. Calcd for $C_{14}H_{22}N_2$: C, 77.01; H, 10.16; N, 12.83. Found: C, 77.24; H, 10.23; N, 12.94.

(*S*)-N^1,N^2,N^2-Trimethyl-1-phenyl-1,2-ethanediamine, 10. Using the procedure for **13**, (*S*)-N-formylphenylglycine[43] (5.0 g, 28 mmol) and dimethylamine (1.2 g, 27 mmol) were converted to the corresponding amide, which was purified by preparative HPLC (silica gel, ethyl acetate) to give 3.1 g (56%) of **10a**: IR (KBr) 3320, 1670, 1634 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.98 (d, 6), 5.93 (d, 1), 7.38 (m, 6), 8.18 (s, 1).

Reduction of amide **10a** (2.0 g, 9.7 mmol) with $LiAlH_4$ (3.1 g, 80 mmol) gave crude **10**, which was purified by Kugelrohr distillation (73°C, 0.06 mmHg) to give 1.4 g (81%, 74% ee) of a colorless oil: $[\alpha]^{25}_D$ +93.8° (c 2.02, $CHCl_3$); IR (neat) 3326 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.16 (dd, 1), 2.29 (s, 6), 2.31 (s, 3), 2.54 (dd, 1), 3.59 (dd, 1), 7.31 (m, 5); MS *m/z* 178 (M$^+$).

(*R*)-N¹-Methyl-N²,N²-diethyl-1-phenyl-1,2-ethanediamine, 11. Using the procedure for **13**, (*R*)-N-carbobenzoxyphenylglycine, (4.3 g, 15 mmol) and diethylamine (1.1 g, 15 mmol) were converted to the corresponding amide, which was purified by preparative HPLC (silica gel, ethyl acetate) to give (3.6 g, 11 mmol, 70%) of a colorless oil: IR (KBr) 3292, 1712, 1635, cm⁻¹; ¹H NMR (200 MHz, $CDCl_3$) δ 0.9 (t, 3), 1.1 (t, 3), 3.0-3.4 (m, 3), 3.53 (m, 1), 5.05 (dd, 2), 5.5 (d, 1), 6.35 (d, 1) 7.2-7.4 (m, 10); MS *m/z* 341 (M+ +1).

Amide **11a** (4.5 g, 13 mmol) was reduced with Red-Al (63 mL) and the crude product was purified by Kugelrohr distillation (140-160°C, 0.2 mmHg) to give 1.2 g (45%, 95% ee) of pure **11**: $[\alpha]^{25}_D$ -135.4° (c 1.92, $CHCl_3$); IR (neat) 3319, cm⁻¹; ¹H NMR (200 MHz, $CDCl_3$) δ 1.0 (t, 6), 2.3 (s, 3), 2.5 (m, 7), 3.5 (dd, 1), 7.3 (m, 5); MS *m/z* (relative intensity) 207. Anal. Calcd for $C_{13}H_{22}N_2$: C, 75.47; H, 10.72. Found: C, 75.81; H, 10.57.

(*S*)-N-Methyl-1-phenyl-2-(1-pyrrolidinyl)ethanamine, 12. Using the procedure for **13**, (*S*)-N-formylphenylglycine, (5.0 g, 28 mmol) and pyrrolidine (2.0 g, 28 mmol) were converted to the corresponding amide, which was purified by preparative HPLC (silica gel, ethyl acetate) to give (2.6 g, 11 mmol, 40%) of a colorless oil: IR (KBr) 3327, 1679, 1630, cm⁻¹; ¹H NMR (200 MHz, $CDCl_3$) δ 1.84 (m, 4), 3.08 (m, 1), 3.53 (m, 3), 5.73 (d, 1), 7.36 (m, 6), 8.19 (s, 1).

Amide **12a** (2.5 g, 11 mmol) was reduced with $LiAlH_4$ (3.4 g, 88 mmol) and the crude product was purified by Kugelrohr distillation (103°C, 0.02 mmHg) to give 1.5 g (68%, 74% ee) of pure **12**: $[\alpha]^{25}_D$ +67.2° (c 2.39, $CHCl_3$); IR (neat) 3325, cm⁻¹; ¹H NMR (200 MHz, $CDCl_3$) δ 1.70-1.93 (m, 4), 2.16-2.89 (m, 6), 2.30 (s, 3), 3.58 (dd, 1), 7.31 (m, 5); MS *m/z* 205 (M+). Anal. Calcd for $C_{13}H_{20}N_2$: C, 76.42; H, 9.87; N, 13.71. Found: C, 76.23; H, 9.69; N, 13.58.

(*R*)-**12** (90% ee) was also synthesized from (*R*)-N-carbobenzoxyphenylglycine using the procedure for making (*S*)-**13** as outlined above.

(*S*)-N-Methyl-1-phenyl-2-(1-hexahydroazepinyl)ethanamine, 14. Using the procedure for **13**, hexahydroazepine (1.0 g, 10 mmol) and (*S*)-N-carbobenzoxyphenylglycine (2.9 g, 10 mmol) were converted to the corresponding amide, which was purified by preparative HPLC (silica gel, 1:2 ethyl acetate-hexanes) to give 2.3 g (62%) of a white crystalline solid. IR (neat) 3298, 1751, 1644, cm⁻¹; ¹H NMR (200 MHz, $CDCl_3$) δ 1.20-1.80 (m, 8), 3.12-3.70 (m, 4), 5.07 (q, 2), 5.57 (d, 1), 6.38 (br d, 1), 7.31 (m, 10).

Amide **14a** (2.2 g, 6.0 mmol) was reduced with $LiAlH_4$ (2.3 g, 60 mmol) yielding an oily residue, which was purified by Kugelrohr distillation (120°C, 0.02 mmHg) to give 1.0 g (68%, 94% ee) of a colorless oil $[\alpha]^{25}_D$ +101.5° (c 2.11, $CHCl_3$); IR (neat) 3316 cm⁻¹; ¹H NMR (200 MHz, $CDCl_3$) δ 1.45-1.79 (m, 9), 2.30 (s, 3), 2.37-2.82 (m, 6), 3.51 (dd, 1), 7.32 (m, 5); MS *m/z* 233 (M+ +1). Anal. Calcd for $C_{15}H_{24}N_2$: C, 77.53; H, 10.41; N, 12.06. Found: C, 77.31; H, 10.25; N, 11.97.

(*S*)-N-Methyl-1-phenyl-2-(4-methyl-1-piperidinyl)ethanamine, 15. Using the procedure for **13**, (*S*)-N-carbobenzoxyphenylglycine (5.0 g, 18 mmol) and 4-methylpiperidine (1.7 g, 17 mmol) were converted to **15a** (6.2 g, 98%): IR (neat) 3305, 1644 cm⁻¹; ¹H NMR (200 MHz, $CDCl_3$) δ 0.94 (d, 3), 1.27 (t, 1), 1.38-1.73 (m, 4), 2.51-3.02 (m, 2), 3.73 (br d, 1), 4.57 (br t, 1), 5.03 (q, 2), 5.58 (t, 1), 6.43 (m, 1), 7.36 (m, 10).

Amine **15a** (6.1 g, 17 mmol) was reduced with $LiAlH_4$ (6 g, 163 mmol) to **15**, which was purified by Kugelrohr distillation (110°C, 0.01 mmHg) to give 2.5 g (65%, 97% ee) of a colorless oil: $[\alpha]^{25}_D$ +96.5° (c 1.56, $CHCl_3$); IR (neat) 3322 cm⁻¹; ¹H NMR (200 MHz, $CDCl_3$) δ 0.92 (d, 3), 1.10-1.45 (m, 4), 1.50-1.71 (m, 2), 1.76-3.13 (m, 6), 2.30 (s, 3), 3.61 (dd, 1), 7.34 (m, 5); CIMS (isobutane) *m/z* 233 (M+ +1). Anal. Calcd for $C_{15}H_{24}N_2$: C, 77.53; H, 10.41; N, 12.06. Found: C, 77.35; H, 10.54; N, 12.01.

(*S*)-N-Methyl-1-phenyl-2-(3,3-dimethyl-1-piperidinyl)ethanamine, 16. Using the procedure for **13**, (*S*)-N-carbobenzoxy phenylglycine, (5.0 g, 18 mmol) and 3,3-dimethylpiperidine (2.0 g, 28 mmol) were converted to the corresponding amide, which was purified by preparative HPLC (silica gel, ethyl acetate) to give (6.0 g, 16.2 mmol, 90%) of **16a**: IR (neat) 3306, 1646 cm⁻¹; ¹H NMR (200 MHz, $CDCl_3$) δ 0.74 (s, 2), 0.98 (s, 4), 1.21-1.67 (m, 4), 2.80-3.88 (m, 4), 5.04 (m, 2), 5.58 (dd, 1), 6.43 (dd, 1), 7.36 (m, 10).

Amide **16a** (5.0 g, 13 mmol) was reduced with $LiAlH_4$ (4.0 g, 110 mmol) and the crude product was purified by Kugelrohr distillation (120°C, 0.01 mmHg) to give 2.3 g (71%, 97% ee) of a colorless oil: $[\alpha]^{25}_D$ +103.3° (c 2.05, $CHCl_3$); IR (neat) 3323, cm⁻¹; ¹H NMR (200 MHz, $CDCl_3$) δ 0.94 (d, 6), 1.21 (t, 2), 1.59

(m, 2), 1.91 (d, 1), 2.15-2.50 (m, 6), 2.31 (s, 3), 3.60 (dd, 1), 7.30 (m, 5); CIMS (methane) *m/z* 247 (M+ +1), 246 (M+, 9%), 245 (M-1, 42%). Anal. Calcd for $C_{16}H_{26}N_2$: C, 78.00; H, 10.64; N, 11.37.

(*R*)-N-Methyl-1-phenyl-2-(4-morpholinyl)ethanamine, 17. Using the procedure for **13**, (*R*)-N-carbobenzoxyphenylglycine (47.1 g, 139 mmol) and morpholine (14.4 g, 165 mmol) were converted to the crude amide **17a**, which was purified by preparative HPLC (silica gel, 3:1 hexanes-ethyl acetate) (45 g, 80%).

Amide **17a** (27.6 g, 78 mmol) was reduced with $LiAlH_4$ (24.2 g, 636 mmol) in THF and the crude amine was purified by Kugelrohr distillation (138°C, 1.0 mmHg) to afford 8.9 g (52%, >95 % ee) of a colorless oil: $[\alpha]^{25}_D$ -96.0° (c 2.06, $CHCl_3$); IR (neat) 3324 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.25 (s, 3), 2.3-2.7 (m, 7), 3.6 (dd, 1), 3.7 (m, 4), 7.3 (m, 5); MS *m/z* 221 (M+ +1), 219 (M+ -1). Anal. Calcd for $C_{13}H_{20}N_2O$: C, 70.69; H, 9.13;. Found: C, 70.73; H, 9.00.

(*S*)-1-Phenyl-2-(1-piperidinyl)ethanamine, 18. Pd-C (10%, 0.6 g) was added to a solution of **13a** (9.6 g, 27 mmol) in MeOH under Ar. The suspension was stirred under H_2 (30 psi) for 2 hrs. The reaction mixture was filtered and concentrated to afford **18a** (5.7 g, 96%): IR (neat) 3366, 1642, cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.50 (m, 6), 2.07 (s, 2), 3.49 (m, 4), 4.72 (s, 1), 7.32 (m, 5).

Amino amide **18a** (1.4 g, 6.4 mmol) was reduced with $LiAlH_4$ (1.1 g, 29 mmol) according to the procedure for **13** to afford an oily residue, which was purified by column chromatography (silica gel, 15:1:0.2 ethyl acetate-MeOH-NH_4OH) followed by Kugelrohr distillation (155°C, 0.1 mmHg) to give 0.6 g (46%) of a colorless oil: $[\alpha]^{26}_D$ +51.4° (c 1.31, $CHCl_3$); IR (neat) 3366 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.45 (m, 2), 1.58 (m, 4), 1.76 (s, 2), 2.20-2.65 (m, 6), 4.12 (dd, 1), 7.35 (m, 5); MS*m/z* 204 (M+). Anal. Calcd for $C_{13}H_{20}N_2$: C, 76.42; H, 9.87; N, 13.71. Found: C, 76.23; H, 9.79; N, 13.63.

(*S*)-N-Ethyl-1-phenyl-2-(1-piperidinyl)ethanamine, 19. Using the procedure for **13**, N-acetyl-(*S*)-phenylglycine[44] (4.8 g, 25 mmols) piperidine (2.13 g, 25 mmols) **19a** (2.3 g, 36%: mp 128-135°C; $[\alpha]^{25}_D$ +121.3° (c = 1.86, $CHCl_3$); IR 1672, 1622 cm^{-1}; ^{1} H NMR; 200 MHz ($CDCl_3$) δ 0.8-1.1 (m, 1), 1.3-1.6 (m, 5), 1.95 (s, 3), 3.2-3.3 (m, 2), 3.4-3.5 (m, 1), 3.7-3.8 (m, 1), 5.83 (d, 1), 7.05-7.10 (d, 1), 7.2-7.4 (m, 5). ^{13}C NMR 200 MHz ($CDCl_3$) 23.84, 24.72, 25.86, 25.98, 43.93, 46.90, 54.17, 69.62. MS *m/z* 260 (M+).

Amide **19a** (1.3 g, 5.1 mmol) was reduced with $LiAlH_4$ (2.0 g, 52 mmol) and the crude product was purified by Kugelrohr distillation (138°C, 0.7 mmHg) to give 0.6 g (51%) of pure **19**: $[\alpha]^{25}_D$ +95.3° (c = 2.17, $CHCl_3$); IR (neat) 3304, cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.1 (t, 3), 1.4-1.7 (m, 6), 2.1 (s, 1), 2.2-2.6 (m, 8), 3.78 (dd, 1H), 7.2-7.4 (m, 5H); ^{13}C NMR ($CDCl_3$) 15.88, 25.00, 26.64, 42.49, 55.19, 60.54, 66.99, 127.46, 127.88, 128.76, 143.71.

(*S*)-N-Benzyl-1-phenyl-2-(1-piperidinyl)ethanamine, 20. Using the procedure for **13**, N-benzoyl-(*S*)-phenylglycine[44] (6.4 g, 25 mmols) and piperidine (2.1 g, 25 mmols) were converted to **20a**: (2.6 g, 33%); $[\alpha]^{25}_D$ +121.3° (c = 1.86, $CHCl_3$); IR (KBr) 3384 1654, 1624 cm^{-1}; ^{1} H NMR; 0.9-1.1 (m, 1), 1.4-1.7 (m, 5H), 3.3-3.6 (m, 3), 3.7-3.8 (m, 1), 6.05 (d, 1), 7.2-7.6 (m, 8), 7.85 (dd, 2), 7.95 (d, 1). ^{13}C NMR 200 NMHz ($CDCl_3$) δ 24.74, 25.87, 25.98, 44.03, 46.93, 54.70, 127.62, 128.46, 128.66, 128.92, 129.49, 132.02, 256.06; MS *m/z* 322 (M+).

Amide **20a** (2.3 g, 8 mmols) was reduced with $LiAlH_4$ (3.0 g, 80 mmol) and the crude product was purified by Kugelrohr distillation (245°C, 0.25 mmHg) to give 1.4 g (61%) of a crystalline solid: mp 57-61°C; $[\alpha]^{25}_D$ +107° (c = 1.98, $CHCl_3$); IR (KBr) 3297, cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.4-1.7 (m, 6), 2.2-2.5 (m, 6), 3.4-3.8 (m, 3), 7.2-7.5 (m, 10); MS *m/z* 295 (M+).

(*S*)-N-Isopropyl-1-phenyl-2-(1-piperidinyl)ethanamine, 21. Platinum(IV) oxide (30 mg) was suspended in abs EtOH (8 mL) and shaken for 30 min under H_2 (30 psi). A mixture of 2.2 g (11 mmol) of mine **(*S*)-18**, 0.75 g (13 mmol) of acetone, and 8 mL of abs EtOH were added to the reaction mixture. The suspension was shaken for 24 hrs under H_2 (40 psi). The catalyst was removed by filtration and the solvent was evaporated to afford crude product, which was purified by chromatography (silica gel, 1:6 ethyl acetate-hexanes) and by Kugelrohr distillation (155°C, 0.05 mm Hg) to afford 1.2 g of a colorless oil (45%): $[\alpha]^{27}_D$ +81.2° (c 1.03, $CHCl_3$); IR (neat) 3298 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.00 (dd, 6), 1.40 (m, 2), 1.58 (m, 4), 2.01 (s, 1), 2.20-2.65 (m, 7), 3.85 (dd, 1), 7.35 (m, 5); CIMS (isobutane) *m/z* 247 (M+ +1).

(*S*)-N-(2-(N,N-Dimethylamino)ethyl)-1-phenyl-2-(1-piperidinyl)ethanamine, 22. N-carbobenzoxysarcosine (3.4 g, 15 mmol) and amine amide **18a** (2.9 g, 13 mmol) were converted to the corresponding N-carbobenzoxy diamide using the procedure for **28a**. The product was purified by column chromatography (silica gel, ethyl acetate : hexanes = 3 : 1) to give (4.1 g, 9.7 mmol, 73%) of **22a**; IR (neat) 3316, 1682, 1651 cm^{-1}; ^{1}H NMR (200MHz, $CDCl_3$) δ 1.52 (m, 6), 2.98 (s, 3), 3.55 (m, 4), 3.92 (m, 2), 5.12 (d, 2), 5.83 (d, 1), 7.25 (m, 10), 7.48 (br s, 1).

Amide **22a** (3.8 g, 8.9 mmol) was reduced with $LiAlH_4$ (4.9 g, 125 mmol) in refluxing THF to the corresponding amine, which was purified by column chromatography (silica gel, ethyl acetate : methanol : NH_4OH = 5 : 1 : 0.2) followed by Kugelrohr distillation (170°, 0.02 mm Hg) to give 1.2 g (49%) of a colorless oil: $[\alpha]^{25}_D$ + 80.0° (c 2.00, $CHCl_3$); IR (neat) 3304 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.49 (m, 6), 1.67 (br s, 1), 2.16 (s, 6), 2.21-2.59 (m, 10), 3.71 (dd, 1), 7.30 (m, 5). Anal. Calcd for $C_{17}H_{29}N_3$: C, 74.13; H, 10.61; N, 15.26. Found: C, 73.93; H, 10.65; N, 15.34.

(*S*)-N-Methyl-1-isopropyl-2-(1-piperidinyl)ethanamine, 23. Using the procedure for **13**, (*S*)-N-carbobenzoxyvaline (5.0 g, 20 mmol) and piperidine (1.7 g, 20 mmol) were converted to the corresponding amide, which was purified by preparative HPLC (silica gel, 1:2 ethyl acetate-hexanes) to give 4.1 g (62%) of a white crystalline solid. IR (neat) 3284, 1719, 1636 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.91 (dd, 6), 1.43-1.74 (m, 6), 1.93 (m, 1), 3.41-3.61 (m, 4), 4.56 (dd, 1), 5.09 (s, 2), 5.66 (br d, 1), 7.35 (m, 5).

Amide **20a** (3.8 g, 12 mmol) was reduced with $LiAlH_4$ (3.7 g, 96 mmol) yielding an oily residue, which was purified by Kugelrohr distillation (125°C, 2.5 mmHg) yielding 1.58 g (69%, 99% ee) of a colorless oil: $[\alpha]^{25}_D$ +85.6° (c 2.10, $CHCl_3$); IR (neat) 3322 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.88 (dd, 6), 1.32-172 (m, 6), 1.90 (m, 1), 2.05-2.62 (m, 7), 2.40 (s, 3); MS *m/z* 185 (M^+ +1). Anal. Calcd for $C_{11}H_{24}N_2$: C, 71.68; H, 13.12; N, 15.20. Found: C, 71.84; H, 12.98; N, 15.35.

(*S*)-N-Methyl-1-*tert*-butyl-2-(1-piperidinyl)ethanamine, 24.(*S*)-N-Carbobenzoxy-*tert*-butylleucine[45] (4.3 g, 16 mmol) was dissolved in 45 mL of ether under Ar. PCl_5 (3.7 g, 18 mmol) was added at -15°C to the solution. The reaction mixture was stirred at -15°C until all PCl_5 was dissolved (ca. 15 min). A solution of piperidine (7.4 g, 87 mmol) in ether (50 mL) was slowly added to the solution at -15°C. The reaction mixture was stirred at -15°C for 15 min, then warmed to RT over a period of 1 h followed by stirring for an additional h. Ethyl acetate (250 mL) was added to the reaction mixture. The mixture was washed with 1 N HCl (4 x 150 mL), saturated Na_2CO_3 (2 x 150 mL), water (150 mL) and saturated NaCl (100 mL). The ethyl acetate layer was dried (Na_2SO_4) and concentrated to afford crude amide which was purified by preparative HPLC (silica gel, 3:1 hexanes-ethyl acetate) to afford 3.6 g (67%) of a colorless oil: IR (neat) 3287, 1713, 1633 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.97 (s, 9), 1.47-1.69 (m, 6), 3.38-3.72 (m, 4), 4.61 (d, 1), 5.09 (dd, 2), 5.63 (d, 1), 7.37 (m, 5).

Amide **24a** (2.2 g, 6.6 mmol) was reduced with $LiAlH_4$ (1.9 g, 50 mmol) to afford 1.2 g of crude **24**, which was purified by Kugelrohr distillation (73°C, 0.01 mmHg) to afford 1.0 g (76%, 85% ee) of a colorless oil: $[\alpha]^{26}_D$ +93.0° (c 1.54, $CHCl_3$); IR (neat) 3322 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.85 (s, 9), 1.36 (m, 2), 1.50 (m, 4), 1.72 (s, 1), 2.02-2.25 (m, 6), 2.45 (s and m, 5); CIMS (isobutane) *m/z* 199 (M^+ +1). Anal. Calcd for $C_{12}H_{26}N_2$: C, 72.67; H, 13.21; N, 14.12. Found: C, 72.81; H, 13.41; N, 14.31.

(*S*)-N-Methyl-1-phenyl-3-(1-piperidinyl)-2-propanamine, 25. Using the procedure for **13**, (*S*)-carbobenzoxyphenylalanine (20 g, 67 mmol) and piperidine (4.3 g, 51 mmol) were converted to **25a**, which was purified by column chromatography (silica gel, 2:3 ethyl acetate-hexanes, 18.3 g, 99%): IR (neat) 3272, 1714, 1644, 1634 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.20-1.63 (m, 6), 2.93-3.29 (m, 4), 3.48 (dd, 2), 4.88 (dd, 1), 5.07 (s, 2), 5.82 (d, 1), 7.30 (m, 10).

Amide **25a** (18.3 g, 50.0 mmol) was reduced with $LiAlH_4$ (15.6 g, 400 mmol) to give crude oil. This oil was purified by column chromatography (silica gel, ether followed by 8:1:0.2 ether-MeOH-NH_4OH) and by vacuum distillation (123-5°C, 0.07 mmHg) to give 8.4 g (72%) of a colorless oil: $[\alpha]^{25}_D$ +72.6° (c 2.09, $CHCl_3$); IR (neat) 3314 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.30-1.59 (m, 6), 1.97 (s, 1), 2.10-2.49 (m, 6), 2.46 (s, 3), 2.53 (m, 1), 2.80 (m, 2), 7.25 (m, 5); MS *m/z* 232 (M^+). Anal. Calcd for $C_{15}H_{24}N_2$: C, 77.53; H, 10.41; N, 12.06. Found: C, 77.29; H, 10.27; N, 11.89.

(*S*)-N-Methyl-1-(methylthiomethyl)-2-(1-piperidinyl)ethanamine, 26. THF solutions of DCC (13 g, 64 mmol) and piperidine (4.8 g, 57 mmol) were added to a solution of (*S*)-N-carbobenzoxymethylcysteine (19 g, 64 mmol) in THF (70 mL) at 0°C under Ar. The resulting suspension was stirred for 3 hrs at 0°C and for 24 hrs at RT. A precipitate was removed by filtration. The filtrate was concentrated and chromatographed (silica gel, 1:2 ethyl acetate-hexanes) to give 14.8 g (78%) of **26a**: IR (neat) 3284, 1706, 1639 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.47-1.72 (m, 6), 2.13 (s, 3), 2.72 (dd, 1), 2.88 (dd, 1), 3.57 (m, 4), 4.87 (dd, 1), 5.11 (s, 2), 5.81 (d, 1), 7.38 (m, 5).

Amide **26a** (5.5 g, 16 mmol) was reduced with $LiAlH_4$ (5.0 g, 130 mmol) according to the procedure for **13**. The crude product was purified by column chromatography (silica gel, ether followed by 8:1:0.2 ether-MeOH-NH_4OH) and by Kugelrohr distillation (95°C, 0.01 mmHg) to give 2.0 g (60%) of a colorless oil: $[\alpha]^{25}_D$ +71.7° (c 2.48, $CHCl_3$); IR (neat) 3313 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.35-1.61 (m, 6), 1.95 (s, 1), 2.14 (s, 3), 2.24-2.49 (m, 6), 2.44 (s, 3), 2.60 (dd, 2), 2.70 (m, 1); MS *m/z* 202 (M^+ +1). Anal. Calcd for $C_{10}H_{22}N_2S$: C, 59.36; H, 10.96; N, 13.84. Found: C, 59.48; H, 11.02; N, 14.04.

(*S*)-N-Benzyl-1-isopropyl-2-(1-piperidinyl)ethanamine, 27. Pd-C (10%, 0.15 g) was added to a solution of amide **23a** (4.5 g, 14 mmol) in 70 mL of MeOH under Ar. The suspension was shaken under H_2 (30 psi) for 1.5 hrs. The Pd-C was removed by filtration and the filtrate was concentrated to afford 2.5 g (96%) of a colorless oil: IR (neat) 3376, 1636 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.91 (dd, 6), 1.45-1.72 (m, 6), 1.83 (m, 1), 1.94 (br s, 2), 3.34-3.62 (m, 5).

Amide **23a** (2.4 g, 13 mmol) was reduced with $LiAlH_4$ (2.0 g, 53 mmol) to afford 2.0 g (90%) of an oil, **27a**, which was used for the next reaction without further purification: IR (neat) 3288 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.92 (dd, 6), 1.35-1.65 (m, 6), 1.83 (m, 1), 1.86 (br s, 2), 2.04-2.75 (m, 6), 3.68 (dt, 1).

Amine **27a** (1.9 g, 11 mmol) and benzaldehyde (1.2 g, 11 mmol) were dissolved in benzene (20 mL). The reaction mixture was refluxed with removal of water using a Dean-Stark trap for 2.5 hrs, and concentrated to afford an oily product. Without further purification, the imine, **27b**, was dissolved in MeOH (45 mL). Pd-C (5%, 0.1 g) was added under Ar. The reaction mixture was shaken under H_2 (30 psi) for 12 hrs. The catalyst was removed by filtration and the filtrate was concentrated to afford 2.4 g of an oily product which was added to 40 mL of 1 N HCl and washed with ether (2 x 50 mL). The water layer was treated with 5 N KOH followed by extraction with ether (3 x 50 mL). The ether layer was dried (Na_2SO_4) and concentrated to afford 2.1 g of an oily product, which was purified by Kugelrohr distillation (140°C, 0.05 mmHg) to afford 1.0 g (34%) of pure a colorless oil: $[\alpha]^{25}_D$ +76.2° (c 2.04, $CHCl_3$); IR (neat) 3300 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.97 (d, 6), 1.40-1.68 (m, 6), 1.97 (m, 1), 2.14-2.51 (m, 7), 2.59 (dt, 1), 3.85 (dd, 2), 7.40 (m, 5); MS *m/z* (relative intensity) 261 (M^+ +1). Anal. Calcd for $C_{17}H_{28}N_2$: C, 78.41; H, 10.84; N, 10.76. Found: C, 78.27; H, 10.99; N, 10.59.

(*S*)-N^2-Methyl-N^2-(N,N-dimethyl-2-aminoethyl)-1-phenyl-1,2-ethanediamine, 28. Pd-C (10%, 0.7 g) was added to a solution of amide **29a** (15.9 g, 43.1 mmol, see below) in 190 mL of MeOH under Ar. The suspension was stirred under H_2 for 18 hrs. The Pd-C was removed by filtration and the filtrate was concentrated to afford 9.3 g (92%) of **28a**: IR (neat) 3356, 1631 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.19 (d, 6), 2.18 (br s, 2), 2.41 (t, 2), 2.91 (d, 3), 3.49 (m, 2), 5.71 (d, 1), 7.31 (m, 5).

Amide **28a** (9.0 g, 38 mmol) was reduced with $LiAlH_4$ (7.3 g, 190 mmol) to afford an oily residue which was purified by column chromatography (silica gel, 3:1:0.2 ethyl acetate-MeOH-NH_4OH) and by Kugelrohr distillation (155° C, 0.07 mmHg) to afford 5.9 g (70%) of a colorless oil: $[\alpha]^{26}_D$ +62.6° (c 2.22, $CHCl_3$); IR (neat) 3368 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.90 (s, 2), 2.25 (s, 6), 2.33 (s, 3), 2.50 (m, 6), 4.10 (dd, 1), 7.35 (m, 5). Anal. Calcd for $C_{13}H_{23}N_3$: C, 70.54; H, 10.47; N, 18.98. Found: C, 70.39; H, 10.30; N, 18.81.

(*S*)-N^1,N^2-Dimethyl-N^2-(2-(N,N-dimethylamino)ethyl)-1-phenyl-1,2-ethanediamine, 29. A solution of (*S*)-N-carbobenzoxyphenylglycine (16.7 g, 58.6 mmol) in THF (75 mL) and DCC (11.5 g, 55.8 mmol) in THF (7 mL) at 0° C was stirred 5 min under Ar. To the resulting suspension was added 5.2 g (51 mmol) of N^1,N^1,N^2-trimethyl-1,2-ethanediamine. The mixture was stirred for 3 hrs at 0°C and for 24 hrs at RT. A precipitate formed which was removed by filtration. The filtrate was concentrated and chromatographed (silica gel, ethyl acetate followed by 1:1 ethyl acetate-Et_3N) to afford 16.1 g of a white crystalline solid, **28a** (86%): IR (neat) 3298, 1703, 1634 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.14 (d, 6), 2.38 (t, 2), 2.90 (d, 3), 3.44 (t, 2),

5.03 (dd, 2), 5.58 (t, 1), 6.34 (br t, 1), 7.34 (m, 10).

Amide **28a** (11.0 g, 29.8 mmol) was reduced with $LiAlH_4$ (11.1 g, 292 mmol). The resulting oil was purified by column chromatography (silica gel, ethyl acetate followed by 1:1 ethyl acetate-Et_3N) and Kugelrohr distillation (145-50°C, 0.07 mmHg) to afford 4.4 g (63%, 91% ee) of a colorless oil: $[\alpha]^{25}_D$ +117.6° (c 1.31, $CHCl_3$); IR (neat) 3329 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.25 (s, 6), 2.29 (s, 3), 2.31 (s, 3), 2.53 (m, 6), 2.28-2.35 (s, 1), 3.59 (dd, 1), 7.35 (m, 5); HRMS (M^+ +1) calcd. 236.2127, found 236.2122. Anal. Calcd for $C_{14}H_{25}N_3$: C, 71.44; H, 10.71; N, 17.85. Found: C, 71.51; H, 10.81; N, 17.72.

(*S*)-N¹-Cyclohexyl-N²-(2-(N,N-dimethylamino)ethyl)-N²-methyl-1-phenyl-1,2-ethanediamine 30. Using the procedure for **6**, amine **28** (2.1 g, 9.5 mmol) and cyclohexanone (1.1 g, 11 mmol) were converted to an oily residue, which was purified by Kugelrohr distillation (200°C, 0.05 mmHg) to give 2.4 g (83%) of a colorless oil: $[\alpha]^{26}_D$ +82.4° (c 1.94, $CHCl_3$); IR (neat) 3291 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.12 (m, 6), 1.52-1.75 (m, 4), 1.85-2.09 (m, 3), 2.24 (s, 6), 2.29 (s, 3), 2.32-2.68 (m, 5), 3.92 (dd, 1), 7.30 (m, 5); MS *m/z* 303 (M^+). Anal. Calcd for $C_{19}H_{33}N_3$: C, 75.20; H, 10.96; N, 13.85. Found: C, 75.15; H, 10.90; N, 13.82.

(*S*)-N¹,N²-Di-(2-(N,N-dimethylamino)ethyl)-N²-methyl-1-phenyl-1,2-ethanediamine, 31. N-carbobenzoxysarcosine (2.2 g, 9.9 mmol) and amide **28b** (2.0 g, 8.5 mmol) were converted to the corresonding amide using the procedure for **28a**. The product was purified by column chromatography (silica gel, ethyl acetate followed by ethyl acetate : methanol : NH_4OH = 6 : 1 : 0.2) to give 3.3 g (88%) of **31a**; IR (neat) 3308, 1713, 1644 cm^{-1}; ^1H NMR (200MHz, $CDCl_3$) δ 2.19 (d, 6) 2.43 (t, 2), 2.92 (d, 6), 3.30-3.70 (m, 2), 3.93 (br s, 2), 5.12 (br d, 2), 5.83 (t, 1), 7.40 (m, 11).

Amide **31a** (3.2 g, 7.3 mmol) was reduced with $LiAlH_4$ (3.9 g, 100 mmol) in refluxing THF to the corresponding amine, which was purified by column chromatography (silica gel, ethyl acetate : Methanol : NH_4OH = 5 : 1 : 0.2) followed by Kugelrohr distillation (200°C, 0.02 mm Hg) to give 1.13 g (52%) of a colorless oil: $[\alpha]^{25}_D$ +47.74° (c, 2.00, $CHCl_3$); IR (neat) 3310 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.15 (s, 6), 2.21 (s, 6), 2.29 (s, 3), 2.20-2.65 (m, 10), 3.69 (dd, 1), 7.30 (m, 5); MS *m/z* 293 (M^+ +1). Anal. Calcd for $C_{17}H_{32}N_4$: C, 69.82; H, 11.03; N, 19.16. Found: C, 70.00; H, 11.09; N, 19.14.

(*R*)-N-Methyl-1-phenyl-2-(1-piperidinyl)ethanamine, 13. Piperidine (9.4 g, 110 mmol) and (*R*)-styrene oxide (12,0 g, 100 mmol, Aldrich) were combined neat and heated to 70° C for 0.5 h giving, after recrystallization from hexane, 15 g of (*R*)-1-phenyl-2-(1-piperidinyl)ethanol, **33** (mp 67-69°C, 73%).[18] To a stirred solution of **33** (2.1 g, 10 mmol) in anhyd ether (15 ml), were added, dropwise at 0° C, Et_3N (3.0 g, 30 mmol) and CH_3SO_2Cl (2.3 g, 20 mmol). The stirring was continued for 0.5 h and the reaction mixture was analyzed for completion of the reaction (GC,TLC). To this solution was added, with stirring at room temperature overnight, Et_3N (2.0 g 20 mmol) and CH_3NH_2 in water (10 mL of a 40% solution). The organic layer was separated and aqueous layer was extracted with ether. The combined ether extracts were washed successively with 5% $NaHCO_3$ and water, dried over anhyd Na_2SO_4 and filtered. The crude product solution was concentrated and the product distilled under vacuum to give 1.0 g (65%): bp 150-155° C (0.1 mmHg), $[\alpha]^{25}_D$ -107° (c 1.23 $CHCl_3$).

General Procedure for the Formation and Use of Chiral Cuprate Reagents. (*S*)-*N*-methyl-1-phenyl-2-(1-piperidinyl)ethanamine, **13**, (139.0 mg, 0.638 mmol) was dissolved in DMS (4 mL) and *n*-butyl lithium (2.5 M in hexanes, 0.255 mL, 0.638 mmol) was added to the solution at -65°C. The solution was stirred for 5 min at -65°C, gradually warmed to 0°C and stirred for 10 min. In a separate flask, *n*-butyl lithium (0.17 mL, 0.425 mmol) was added via syringe to a solution of CuI (81 mg, 0.425 mmol) solution in DMS (4 mL) at -70°C, to give a suspension of *n*-BuCu. The lithium amide solution was cooled to -35°C and added via canula to the suspension of *n*-BuCu at -40°C. The resulting solution was stirred for 25 min at -35°C and then cooled to -78°C. After 30 min, 2-cyclohexenone (40.8 mg, 0.425 mmol) was added slowly to the cuprate solution at -78°C. After 1 hr, the reaction was quenched with 4 N NH_4Cl (15 mL) and extracted with ether (15 mL). The extract was washed with 1 N HCl (15 mL), dried (Na_2SO_4) and concentrated. The oily residue was purified by column chromatography (silica gel, 10:1 hexanes-ethyl acetate) to afford (*S*)-3-*n*-butylcyclohexanone (37.1 mg, 60%, 83% ee, $[\alpha]^{25}_D$ -7.10° (c 1.00, toluene).

Ketal from 3-*n*-butylcyclohexanone and (+)-diethyltartrate. 3-*n*-Butylcyclohexanone (703 mg, 4.57 mmol), (+)-diethyltartrate (1.88 g, 9.12 mmol) and ca. 50 mg of toluenesulfonic acid were dissolved in 15 mL of benzene. The solution was refluxed with removal of water using a Dean-Stark trap for 24 hs, concentrated, and purified by column chromatography (silica gel, 4:1 hexanes-ethyl acetate) to give 1.4 g (90%) of product: IR (neat) 1745 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.83 (br t, 3), 1.28 (m, 14), 1.40-1.89 (m, 7), 4.27 (dt, 4), 4.77 (m, 2); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.23, 23.02, 23.14, 23.23, 29.14, 31.72, 35.42, 35.51, 35.58, 36.06, 36.78, 42.36, 42.76, 62.10, 76.98, 77.44, 115.41, 170.49, 170.61; HRMS calcd for $C_{18}H_{30}O_6$ 342.2042, found 342.2064.

Ketal from 3-phenylcyclohexanone and (+)-diethyltartrate. Using the procedure above, 3-phenylcyclohexanone (500 mg, 2.87 mmol) was converted to the corresponding ketal (900 mg, 87%): IR (neat) 1745, 1729 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.27 (m, 6), 1.51-2.10 (m, 8), 2.96 (m, 1), 4.27 (dt, 4), 4.82 (m, 2), 7.23 (m, 5); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.27, 23.61, 23.67, 33.06, 33.45, 35.36, 35.78, 41.68, 41.89, 42.94, 43.10, 62.24, 77.13, 77.61, 115.18, 115.23, 126.71, 127.29, 128.94, 146.26, 146.35, 170.41, 170.50, 170.58, 170.63; MS *m/z* (relative intensity) 362 (M^+, 11), 319, HRMS calcd for $C_{20}H_{26}O_6$ 362.1729, found 362.1720.

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