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Enantioselective Conjugate Addition, Part V.[1] Synthesis and Testing of Scalemic[2] Tetraamines as Chiral Cuprate Ligands.

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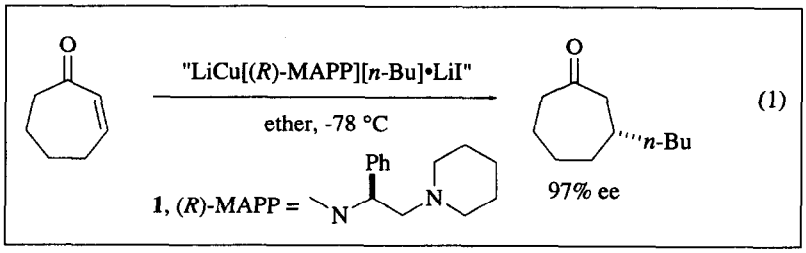
Abstract: Reported herein is the enantioselective conjugate addition of *n*-butyl to 2-cyclopentenone, 2-cyclohexenone, 2-cycloheptenone and 2-cyclooctenone using scalemic amidocuprates derived from copper(I) iodide, *n*-butyllithium and a homologous series of 5 scalemic tetraamines referred to as DIMAPP-2 through -6. Cuprates derived from DIMAPP-4 manifest the highest enantioselectivities (up to 78%) and the same sense of enantioselectivity as the MAPP cuprates upon which these new cuprates are based. A previously developed mechanistic proposal has been revised to account for the observations made.

INTRODUCTION

The development of methods for enantioselective conjugate addition of organic moieties to α,β-unsaturated substrates using chiral reagents or catalysts is a problem which has still to be solved in a general sense.[4] While a number of research groups, including our own,[1] have reported a variety of methods for this type of transformation, there is still no single method by which this transformation can be accomplished efficiently and in high enantiomeric excess for a broad variety of α,β-unsaturated substrates.[5]

We have introduced a cuprate which uses as its chiral auxiliary the diamine we refer to as MAPP, **1**.[1] Using this cuprate, we have been able to achieve ee's of up to 97% in conjugate additions to 2-cyclohexenone and 2-cycloheptenone (eq 1). Even though our reagent is highly enantioselective for some reactions, for many others, the enantioselectivity is poor. Our reagent, like all other reagents reported to date,[4] manifests poor enantioselectivity in its reaction with 2-cyclopentenone.[1b,d] It also seems to work poorly with non-cyclic enones such as 4-phenyl-3-buten-2-one.[6] This has motivated us to seek an improved chiral cuprate. One of the problems in developing an enantioselective cuprate is that, in spite of recent advances in the elucidation of the structure of cuprates,[7] there is still much which is not known about the structural parameters of heterocuprates such as their ligand exchange equilibria and aggregation properties. We have proposed that the structure of our cuprate is that of a dimer reminiscent of homocuprates (Figure 1a).[1] This model is supported by the observation of non-linear asymmetric induction with these reagents.[1d] Some of the assumptions underpinning the stereochemical and coordination features of this model are 1. that the organo and amido ligands alternate in



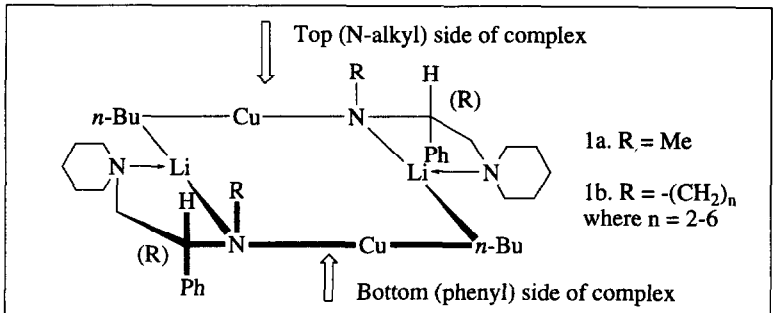


Figure 1. Proposed Structure of MAPP and DIMAPP Cuprates

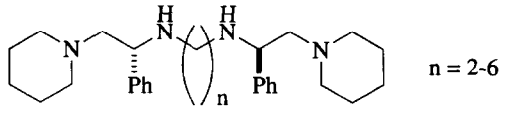


Figure 2. DIMAPPs-**2** through **6**

bridging between lithium and copper(I),[8] 2. that the tertiary nitrogen of the piperidine rings prefers to bind to lithium rather than copper[9] and 3. that the N-methyl and phenyl groups will be as far apart from one another as possible in order to minimize unfavorable steric interactions. The top side of this dimer, as shown in Figure 1a, is characterized by the presence of two N-methyl groups and the bottom side by two phenyl groups which define the chiral topology of this complex. Each pair of substituents is situated so as to render the complex C_2 symmetric in its idealized form.

In the course of trying to improve this reagent, we decided to synthesize a series of chiral ligands in which we linked the two benzylic nitrogens with methylene bridges, as shown in Figure 2. We assumed that such ligands would form dimers analogous to our model of the MAPP-cuprates with the linking group bridging across the dimeric complex. Our rational for doing so was two-fold, namely, to promote and stabilize the formation of a dimer and to block one face of the dimer. As part of our original structural and mechanistic proposal for MAPP-cuprates, we suggested that reaction occurs from the N-alkyl side of the complex (Figure 1). Linking the benzylic nitrogens with a methylene bridge should block approach of the cuprate from this side of the complex. In fact, we have found this not to be the case. This has prompted us to revise our mechanistic proposal for this reaction. The results of this study are reported herein.

EXPERIMENTAL RESULTS

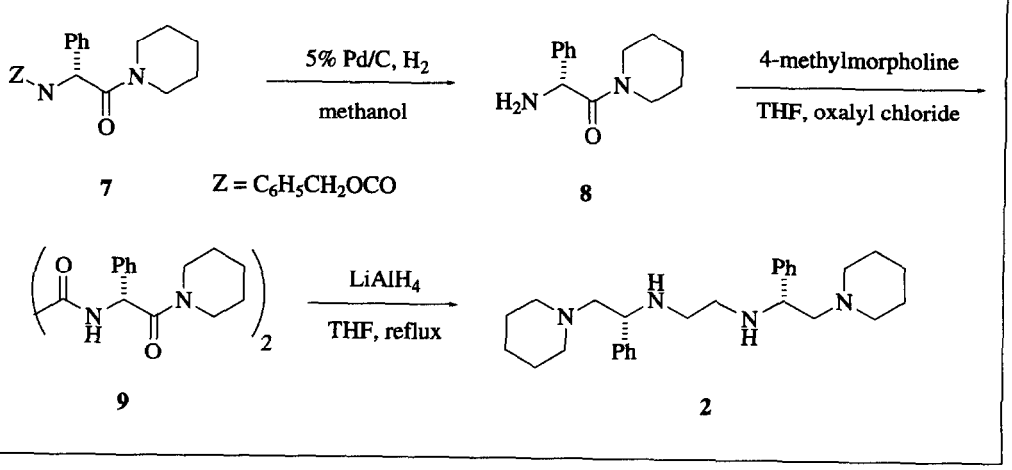
Synthesis of the Chiral Tetraamine Ligands

We began this project by synthesizing five scalemic tetraamines which we refer to as DIMAPP-n where n equals the number of methylene groups linking the two benzylic amines (Figure 2). Two synthetic routes were employed in the synthesis of the DIMAPP ligands. The first method, a five step procedure from (*R*)-phenylglycine, was used to make DIMAPPs-2 and -4 and is illustrated for DIMAPP-2 (Scheme 1). Compound **7** is obtained in two steps and in good yield from (*R*)-phenylglycine as reported in reference 1d. The benzyloxycarbonyl group was removed via palladium-catalyzed hydrogenation to give the amino amide **8**. One mmol of **8** was then coupled with 0.5 mmol of oxalyl chloride to form **9**. The tetraamide **9** was reduced to the tetraamine DIMAPP-2, **2**, with lithium aluminum hydride in refluxing THF. Crude (*R,R*)-DIMAPP-2 is an oil which solidifies on standing to form a low melting, waxy solid which is difficult to recrystallize. We purified this material by first forming a solution of the tetrahydrochloride salt with concentrated hydrochloric acid, concentrating this solution to dryness to form a white, crystalline salt and then recrystallizing the salt from acetonitrile/methanol. We then treated the salt with reagent grade NaOH dissolved in dionized water to obtain the free base and extracted the product with freshly distilled ether. Upon concentration, the purified (*R,R*)-DIMAPP-2 solidifies slowly to a waxy solid which gave a clean NMR spectrum. (*R,R*)-DIMAPP-4 was synthesized using an analogous procedure and purified first by chromatography and then by recrystallization from pentane/ether.

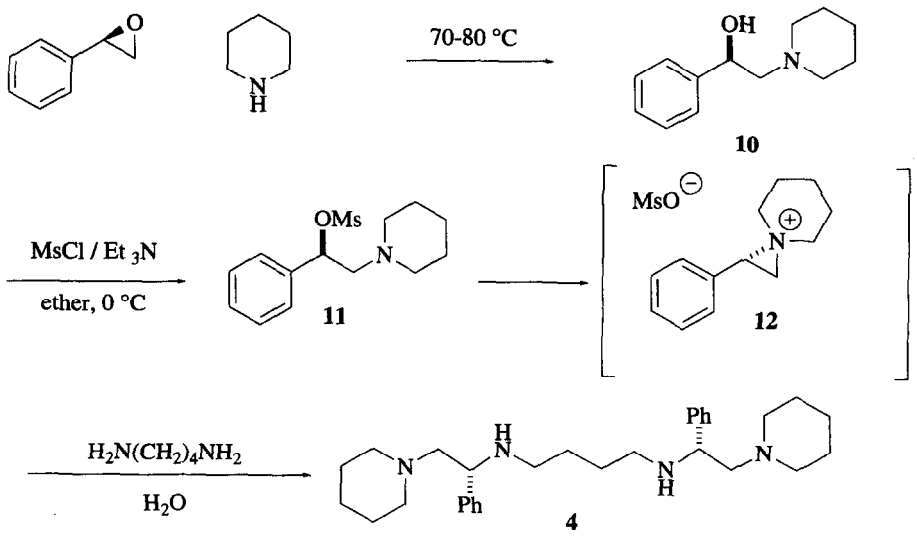
The second and preferred method for synthesizing these tetraamines consists of two steps starting from commercially available (*R*)-styrene oxide and is illustrated for the synthesis of (*R,R*)-DIMAPP-4 (Scheme 2). For reasons of economy, we synthesized (*R*)- styrene oxide from styrene using the method of Kolb and Sharpless.[10] Reaction of (*R*)-styrene oxide with piperidine opens the epoxide ring to yield (*R*)-1-phenyl-2-(1-piperidinyl)ethanol, **10**.[11] Using a procedure developed by Dieter et al.,[12] the amino alcohol was then reacted with methanesulfonyl chloride and triethylamine to form mesylate **11.** Treatment of the crude mesylate in ether with aqueous 1,4-butanediamine affords (*R,R*)-DIMAPP-4. This final step proceeds with retention of configuration, presumably through an intermediate aziridinium species **12**. (*R,R*)-DIMAPPs 3, 4, 5, and 6 were synthesized using this procedure.

We had difficulty determining unambiguously the exact enantiomeric and diastereomeric purity of tetraamines **2-6** by chiral HPLC. The NMR spectra in each case were free of resonances not readily attributable to the tetraamines and did not manifest diastereomeric resonances. Furthermore, the optical rotations for

Scheme 1.



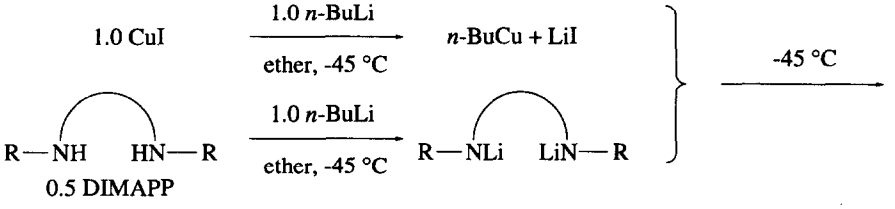
Scheme 2.



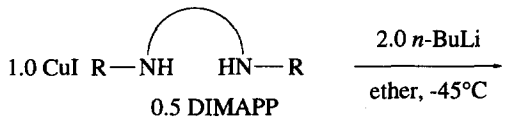
DIMAPP-4, synthesized using the two methods described above, are identical. The optical rotations of the other DIMAPP ligands are of the same order of magnitude as DIMAPP-4. We therefore concluded that the enantiomeric and diastereomeric purities of these ligands were >90%.

Conjugate Addition Reaction Procedure Using Chiral Organo(DIMAPP)Cuprates

As part of this work with the DIMAPP ligands, we found it necessary to optimize the conjugate addition reaction conditions. Because of the high sensitivity of organocopper reagents toward water and air, all reactions were performed in Schlenk glassware under a N_2 atmosphere. In addition, because of thermal instability, the cuprate reagents were always prepared at temperatures lower than -30 °C. In our initial experiments, the cuprates were prepared by first forming, in separate Schlenk flasks, the lithium amides from the DIMAPP ligands, and *n*-butyllithium and *n*-butylcopper from CuI and *n*-butyllithium (eq 2). The ether solution of the lithium amide was then transferred via canula to the Schlenk tube containing the *n*-butylcopper. We later found that we obtained nearly identical results by adding two equivalents of *n*-butyllithium directly to a mixture of CuI and the DIMAPP ligand in ether at -45 °C (eq 3). The experimental results reported in this paper were obtained using the latter procedure for forming the cuprate.



0.5 "Li_2Cu_2(DIMAPP)(*n*-Bu)$_2$•(LiI)$_2$" (2)



0.5 "Li_2Cu_2(DIMAPP)(*n*-Bu)$_2$•(LiI)$_2$" (3)

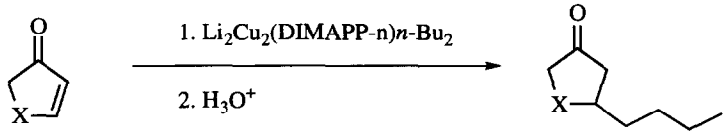
We also found that the temperature at which the cuprate is formed affects the enantioselectivities of subsequent reactions. In our initial experiments, the temperature at which the cuprates were formed was maintained below -30 °C and was not kept constant. We were not able to obtain consistent results with these reactions and decided to determine if the temperature differential could be at the heart of the inconsistencies. Four test reactions were performed simultaneously, each involving the conjugate addition of *n*-butyl to 2-cycloheptenone using (*R,R*)-DIMAPP-4 as the ligand. The reagents for two of these reactions were formed at -28 °C whereas the reagents for the other two reactions were formed at -45 °C. In all four cases, once the reagent was formed, the reaction mixture was cooled to -78 °C in preparation for carrying out the conjugate addition. The first two reactions yielded nearly identical results, i.e. 27% yield and 64% ee for the product in one reaction and 28% yield and 64% ee in the other. Likewise, the two reactions using reagent formed at -45 °C gave results which were nearly identical to one another but superior to the reactions performed with reagent formed at -28 °C, i.e. 53% yield and 74% ee, and 52% yield and 74% ee. Attempts to form the reagents at -60 °C and -78 °C gave a mixture which was unreactive. The cuprates used in the reactions reported herein were formed at -45 °C and reacted with enones at -78 °C.

We also discovered that we generally obtained better and more reproducible results if DIMAPP ligands were introduced as azeotroped, standard benzene solutions. These materials tend to be waxy solids or thick oils which are difficult to recrystallize and/or distill. By carefully purifying the ligands, dissolving them in benzene,

azeotroping each solution using a Dean-Stark trap, and then adding sufficient dry, degassed benzene to form standard solutions of the tetraamines used in these reactions, we were able to observe optimum and reproducible results. Most likely, the azeotoping procedure serves to remove traces of water and possibly other low boiling impurities dissolved in the ligand. Chemical yields were determined by GC using dodecane as an internal standard. Enantiomeric purities were also determined by GC.

DIMAPP-2, 3, 4, 5, and 6 were all evaluated relative to their ability to effect enantioselective conjugate addition of *n*-butyl to 2-cyclopentenone, 2-cyclohexenone, 2-cycloheptenone, and 2-cyclooctenone (Table 1). These results are compared to results obtained using (*S*)-MAPP as the chiral ligand.[1] In general, the DIMAPP ligands did not improve upon the results obtained with MAPP. Of the ligands tested, DIMAPP-4 is the best overall tetraamine ligand. Interestingly, (*R,R*)-DIMAPP-4 reacts to give a fairly consistent level of enantioselectivity with the different enones except for 2-cyclopentenone. It is also noteworthy that DIMAPP-4 is superior to DIMAPPs with both longer and shorter linking groups except with 2-cyclopentenone. In one case, we observed an enantioselectivity superior to that achieved with the MAPP ligand. Addition of *n*-butyl to 2-cyclopentenone using (*S*)-MAPP as the chiral ligand gives 2-*n*-butylcyclopentanone in 45% ee. In contrast, the reaction of 2-cyclopentenone using a cuprate formed with DIMAPP-6 occurred in 71% ee. Unfortunately the yield was very poor.

Table 1. Conjugate Addition of Cyclic Enones Using (*R,R*)-DIMAPP Cuprates*



X = $(CH_2)_m$ where m = 1-4

Ligand	2-Cyclopentenone			2-Cyclohexenone			2-Cycloheptenone			2-Cyclooctenone		
	% ee	% yield	R/S	% ee	% yield	R/S	% ee	% yield	R/S	% ee	% yield	R/S
(*R,R*)-**2**	47	74	S	22	69	R	6	56	R	18	52	ND
(*R,R*)-**3**	38	51	R	27	53	R	57	20	R	12	34	ND
(*R,R*)-**4**	27	55	S	77	64	R	78	39	R	76	46	ND
(*R,R*)-**5**	37	44	R	23	53	R	42	26	R	11	41	ND
(*R,R*)-**6**	71	15	R	34	70	R	42	72	R	55	34	ND
(*S*)-MAPP	45	51	S	83	92	S	97	63	S	86	50	ND

* Reactions were typically run on a one mmole scale. The cuprate reagents were formed by forming a suspension of CuI (1 mmol) and the ligand dissolved in benzene (0.5 mmol) in ether. The mixture was cooled to -45°C and treated with 2 mmols of *n*-BuLi in hexane. The reaction mixture was cooled to -78°C and enone was added next to the reaction mixture.

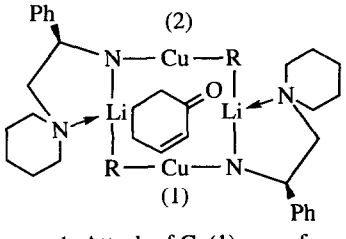
DISCUSSION

We previously proposed a mechanism to account for the origin of enantioselectivity with MAPP cuprates. Such mechanisms are, of course, tenuous in the absence of good structural data. We originally assumed that the phenyl groups of our ligand would block one side of the complex and that conjugate addition would occur from the N-alkyl side of the complex.[1d] The results using DIMAPP ligands argue against this proposal in that these

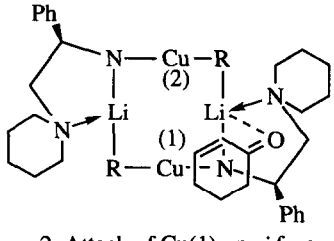
ligands should form complexes similar to that shown in Figure 1b. In these complexes the bridging methylene chains are expected to block the N-alkyl side of the complex. The exact nature of the complexes using different DIMAPP ligands is expected to vary as a function of the length of the bridging group. DIMAPP-2, for example, most likely does not have a long enough methylene chain to form a complex like that shown in Figure 1b. DIMAPP-4 performs similar to MAPP and is superior to DIMAPP ligands with both longer and shorter linking groups. This is consistent with the notion that DIMAPP-4 is forming a cuprate complex which is similar in nature to that using MAPP.

The stereochemical course of the reaction using DIMAPP-4 can be justified in the following manner. We believe this same rational applies for the MAPP ligands. The first step most likely consists of complexation of the enone oxygen with a lithium in order to tether the enone to the cuprate and to activate the enone towards conjugate addition.[13] Either Cu(1) or Cu(2) may react at the β-carbon of the enone to begin the process of carbon-carbon bond formation.[14] The phenyl groups undoubtedly serve to define the stereochemical topology on this face of the complex. The enone then has four ways in which a copper (I) atom can interact with the β-carbon of the enone i.e. 1. Cu(1) interacts with the *re* face; 2. Cu(1) interacts with the *si* face; 3. Cu(2) interacts with the *re* face; 4. Cu(2) interacts with the *si* face. In order to observe high enantioselectivity, one pathway will most likely be favored over the other three. We can likely dismiss situations 2 and 3 since both require that the aliphatic side of the enone push either into the phenyl group of the ligand (2) or the transferable R group (3). In situation 1, the enone is poised in a way which appears to minimize steric interaction with either phenyl groups or R groups. In addition, the R group is exo relative to the enone. This seems like an inherently good position for the R group to be in since it requires little movement of R to add to the enone following oxidative addition of the copper. In situation 4, the enone, for proper alignment with the copper, must impose its steric bulk into the sterically crowded quadrant occupied by the amide group.

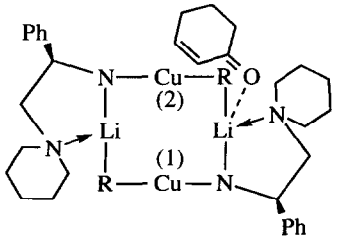
Other unanticipated cuprate complexes involving the DIMAPP ligands, particularly those such as DIMAPP-2 and -3 with linking groups too small to adequately bridge across the complex shown in Figure 1b, may exist. We will have to wait until we have more definitive data on the structure of these structures to judge. One thing these results do suggest is that with further ligand design, we may find a DIMAPP ligand which is superior to MAPP.



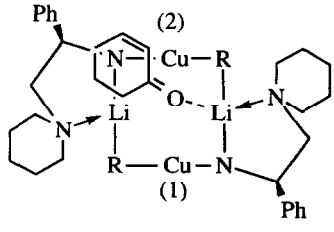
1. Attack of Cu(1) on *re* face



2. Attack of Cu(1) on *si* face



3. Attack of Cu(2) on *re* face



4. Attack of Cu(2) on *si* face

One set of results which is rather curious is that involving 2-cyclopentenone. For this enone, enantioselectivities are poorest when DIMAPP-4 is used and best when DIMAPP-2 and DIMAPP-6 are used. Furthermore, unlike the other enones, the predominant enantiomer formed with 2-cyclopentenone changes depending on which of the DIMAPPs is used. We are currently at a loss to explain this observation. We note however that similar behavior has been observed previously with 2-cyclopentenone when MAPP is used as the chiral ligand.[1d] We are encouraged by the observation that the cuprate formed with DIMAPP-6 gives a higher ee than that obtained using MAPP. Unfortunately the chemical yield is poor. We have found in the past however that higher yields can often be obtained if the all chemical reagents are carefully purified, something which was difficult to do for DIMAPP-6, and if effort is put into optimizing the reaction. This is the first time we have observed a reaction in which results superior to those obtained with MAPP have been realized. This encourages us to believe further progress in this area can be made.

CONCLUSIONS

We have screened a series of scalemic tetraamines, referred to as DIMAPP ligands, as chiral cuprate ligands for conjugate addition to cyclic enones. We found that one of those tetraamines, DIMAPP-4, gave results similar to those observed for MAPP cuprates. Further refinements in the ligand structure of these tetraamines may result in the discovery of chiral ligands superior to MAPP for enantioselective conjugate addition.

EXPERIMENTAL

General

IR spectra were obtained using a Perkin-Elmer FT-IR model 1600. NMR spectra were obtained using a Varian 200 MHz Gemini spectrometer. Melting points were measured with a Thomas Hoover Unimelt melting point apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer 241 Polarimeter. GC analyses were performed using a Hewlett-Packard Model 5890 gas chromatograph with FID detector and He as the carrier gas. The enantiomeric purity of 3-*n*-butylcycloheptanone was determined by GC using a 30 m, 0.25 mm i.d. β-cyclodextrin 120 column (Supelco). The diastereomeric purities of the ketals formed from 3-*n*-butylcyclopentanone and (+)-diethyltartrate and from 3-*n*-butylcyclooctanone and (2*S*,3*S*)-(+)-2,3-butanediol were determined by GC using a 30 m, 0.25 mm i.d. SE-54 column. The diastereomeric purity of the ketal formed from 3-*n*-butylcyclohexanone and (+)-diethyltartrate was determined by GC using a 30 m, 0.2 mm i.d. meta, meta-cyanobiphenyl column (25%, prepared by Abdul Malik, Brigham Young University).[15] The R/S designations of the predominant enantiomers of 3-*n*-butylcyclopentanone and 3-*n*-butylcyclohexanone were determined by comparing the optical rotations of the products with literature values.[16] (*R*)-Benzyloxycarbonylamide **7** and the the ketal formed from 3-*n*-butylcyclohexanone and (+)-diethyltartrate were prepared according to the procedure of Rossiter et al.[1d] (*R*)-Styrene oxide was prepared according to the procedure of Kolb and Sharpless.[9] Diethyl ether was freshly distilled from Na/benzophenone immediately before use.

(R,R)-N,N'-Di-(1-phenyl-2-(1-piperidinyl)ethyl)-1,2-ethanediamine, **2**, *(DIMAPP-2)*

(*R*)-Benzyloxycarbonylamide **7** (32.4 g, 91.9 mmol) was added to a methanol (200 mL) suspension of Pd/C (5%, 2 g) in a Parr flask under N_2. The suspension was shaken under 45 psi of H_2 until no more H_2 was taken up. The solution was filtered through Celite™ and concentrated to yield 19.8 g (90.7 mmol, 99%) of an oil: IR (neat) 3364, 3297, 1628, 1449 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.83-1.08 (m, 1H), 1.23-1.62 (m, 5H), 1.96-2.12 (s, 2H), 3.18-3.29 (m, 2H), 3.37-3.53 (m, 1H), 3.63-3.79 (m, 1H), 4.68-4.76 (s, 1H), 7.19-7.41 (m, 5H).

A solution of amino carboxamide **8** in THF (200 mL) was treated dropwise with 4-methylmorpholine (16.3

g, 161 mmol) dissolved in THF (60 mL) and then with oxalyl chloride (9.97g, 78.5 mmol) also dissolved in THF (60 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 3 h and then quenched with 50 mL of water. Concentration of the solution yielded a yellow solid that was dissolved in ethyl acetate (650 mL). The ethyl acetate fraction was washed with 1N HCl (3 x 125 mL), water (100 mL), 5% $NaHCO_3$ (3 x 125 mL), water (150 mL) and saturated NaCl solution (150 mL) and then dried (anhyd Na_2SO_4) and concentrated to yield an off-white solid. The solid was recrystallized from ethyl acetate/isopropyl ether to yield slightly off-white crystals of tetraamide **9** (25.1 g, 51.2 mmol, 65%): mp 173-177.5 °C; $[\alpha]_D$ -249° (c 1.00, $CHCl_3$); IR (KBr) 3360, 1679, 1640 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.82-1.04 (m, 2H), 1.23-1.65 (m, 10H), 1.70 (s, 2H), 3.16-3.82 (m, 8H), 5.75(d, 2H, J = 7.8 Hz), 7.16-7.43 (m, 10H), 8.75 (d, 2H, J = 7.8 Hz).

Tetraamide **9** (24.7 g, 50.3 mmol) was dissolved in THF and added to a suspension of $LiAlH_4$ (30 g, 0.79 mol) at 0 °C. The suspension was refluxed for 11 hs and then cooled to 0 °C. The reaction was quenched by diluting the reaction mixture with THF (250 mL) and then adding 4N NaOH (75 mL). The resulting suspension was gently heated on the Rotavap to break up the aluminum salts and then filtered. Concentration of the filtrate yielded a thick, orange oil (22 g). Addition of 6N HCl to form the hydrochloride salt and subsequent concentration afforded a crystalline yellow solid. Stirring in boiling acetone followed by hot filtration yielded an insoluble white solid (21.9 g). Recrystallization of this solid from acetonitrile/methanol afforded white crystals (17.2 g). The free amine was recovered by addition of a 3N NaOH solution (reagent grade NaOH in deionized water) followed by extraction with a total of 450 mL of freshly distilled ether. The ether solution was dried (anhyd Na_2SO_4) and concentrated to yield the amine as a slightly yellow oil (10.9 g, 25.0 mmol, 50%) which slowly crystallized upon standing: $[\alpha]_D$ -112° (c 1.02, $CHCl_3$); mp 58-60 °C; IR (neat) 3309, 1602, 1492 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.35-1.67 (m, 12H), 2.17-2.62 (m, 18H), 3.64-3.75 (dd, 2H, J_1 = 3.9Hz, J_2 = 11.4Hz), 7.16-7.37 (m, 10H); CIMS (M+1, 435); Anal. Calcd. for $C_{28}H_{42}N_4$: C, 77.37; H, 9.74, N, 12.89; Found: C, 77.58; H, 9.47; N, 12.95.

(R,R)-N,N'-Di-(1-phenyl-2-(1-piperidinyl)ethyl)-1,4-butanediamine, **4**, *(DIMAPP-4)*

(*R*)-Styrene oxide (51.6 g, 0.429 mol) and piperidine (44 g, 0.52 mol) were combined without solvent and heated for 1 h at 70-80 °C. The solid material obtained after cooling was recrystallized from hexane to yield 53 g (0.26 mol, 60%) of (*R*)-1-phenyl-2-(1-piperidinyl)ethanol, (*R*)-**10**: $[\alpha]_D$ -73.9° (c 2.0, $CHCl_3$); mp 81 °C; IR (KBr) 3110, 1489, 1454 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.40-1.55 (m, 2H), 1.55-1.70 (m, 4H), 2.30-2.50 (m, 4H), 2.65-2.80 (m, 2H), 4.74 (dd, 1H, J_1 = 4.0Hz, J_2 = 10.2Hz), 7.20-7.41 (m, 5).

Methanesulfonyl chloride (11.2 g, 97.8 mmol) was added to a solution of (*R*)-**10** (10 g, 49 mmol) and triethylamine (14.8 g, 146 mmol) in diethyl ether (150 mL) at 0 °C. The reaction mixture was warmed to room temperature, stirred for an additional 30 min and then washed with water. A solution of 1,4-butanediamine (2.15 g, 24.4 mmol) in 15 mL water was added to the ether solution of crude mesylate and the mixture was stirred for two days at room temperature. The ether phase was separated from the aqueous phase and washed with water. The aqueous phase was extracted with ether, and the combined ether fractions were dried over anhyd Na_2SO_4 and concentrated to yield 7.9 g (17 mmol, 70%) of a white solid: mp 99-101 °C; $[\alpha]_D$ -110.7° (c=0.187, $CHCl_3$); IR (KBr) 3310, 3298, 1490, 1448 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.36-1.68 (m, 16H), 2.08-2.62 (m, 18H), 3.67-3.78 (dd, 2H, J_1 = 3.5 Hz, J_2 = 11 Hz), 7.18-7.39 (m, 10H). Anal. Calcd. for $C_{30}H_{46}N_4$: C, 77.87; H, 10.02; N, 12.11. Found: C, 78.04; H, 9.76; N, 12.20.

(R,R)-N,N'-Di-(1-phenyl-2-(1-piperidinyl)ethyl)-1,3-propanediamine, **3**, *(DIMAPP-3)*

Methanesulfonyl chloride (2.3 g, 20 mmol) was added to a solution of (*R*)-**10** (2.05 g, 9.99 mmol) and triethylamine (3.04 g, 30.0 mmol) in diethyl ether at room temperature. The ether solution was washed with water, combined with a solution of 1,3-propanediamine (0.4 g, 5 mmol) in water and stirred at room temperature for 12 hs. The reaction mixture was then washed with a saturated NaCl solution, dried over anhyd Na_2SO_4,

filtered and concentrated to yield 1.8 g (4.0 mmol, 80%) of a solid. The crude DIMAPP-3 was then recrystallized from hexane: $[\alpha]_D$ -114° (c 0.54, $CHCl_3$); mp 150-154 °C; IR (KBr) 3303, 1602, 1492 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.33-1.75 (m, 14H), 2.14-2.61 (m, 18H), 3.65-3.78 (dd, 2H, J_1 = 3.6Hz, J_2 = 10.8Hz), 7.15-7.40 (m, 10H). Anal. Calcd. for $C_{29}H_{44}N_4$: C, 77.63; H, 9.88; N, 12.49. Found: C, 77.38; H, 9.77; N, 12.85.

(R,R)-N,N'-Di-(1-phenyl-2-(1-piperidinyl)ethyl)-1,5-pentanediamine, **5**, *(DIMAPP-5)*

Triethylamine (3.03 g, 29.9 mmol) was added to a solution of (*R*)-**10** (2.05 g, 9.99 mmol) in anhyd ether at 0 °C. Methanesulfonyl chloride (2.3 g, 20 mmol) was slowly added, and the reaction mixture was then warmed to room temperature. The ether solution was washed with water, combined with a solution of 1,5-pentanediamine (0.5 g, 5 mmol) in water (10 mL) and stirred vigorously at room temperature for 2 days. The reaction mixture was then washed with water, brine and then dried over anhyd Na_2SO_4 and concentrated to yield 1.5 g (3.1 mmol, 60%) of a yellow oil. The product was purified by flash chromatography (99:1 EtOAc-Et_3N): $[\alpha]_D$ -95.9° (c 6.33, benzene); IR (neat) 3305, 1602, 1492 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.23-1.72 (m, 18H), 2.18-2.64 (m, 18H), 3.67-3.81 (dd, 2H, J_1 = 3.5Hz, J_2 = 10.8Hz), 7.16-7.42 (m, 10H). Anal. Calcd. for $C_{31}H_{48}N_4$: C, 78.10; H, 10.15; N, 11.75. Found: C, 77.91; H, 10.27; N, 11.82.

(R,R)-N,N'-Di-(1-phenyl-2-(1-piperidinyl)ethyl)-1,6-hexanediamine, **6**, *(DIMAPP-6)*

Methanesulfonyl chloride (16.8 g, 147 mmol) was added to a solution of (*R*)-**10** (15 g, 73 mmol) and triethylamine (22.2 g, 219 mmol) in diethyl ether at 0 °C. The reaction mixture was warmed to room temperature and stirred for an additional 30 min. A solution of 1,6-hexanediamine (4.25 g, 36.6 mmol) in water (20 mL) was added to the ether solution of crude mesylate, and the mixture was stirred for 2 days at room temperature. The ether phase was separated from the aqueous phase and washed with water. The aqueous phase was extracted with ether, and the combined ether fractions were dried over anhyd Na_2SO_4 and concentrated to yield 11.7 g of a thick oil (23.8 mmol, 65%). The product was purified by flash chromatography (99:1 EtOAc-Et_3N) : $[\alpha]_D$ -85.1° (c 0.33, $CHCl_3$); IR (neat) 3307, 1602, 1492 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.23-1.68 (m, 20H), 2.19-2.62 (m, 18H), 3.68-3.79 (dd, 2H, J_1 = 3.4Hz, J_2 = 10.9Hz), 7.15-7.42 (m, 10H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 25.0, 26.7, 27.7, 30.3, 48.2, 55.1, 60.6, 66.8, 126.2, 127.6, 127.9, 128.9. Anal. Calcd. for $C_{32}H_{50}N_4$: C, 78.32; H, 10.27; N, 11.41. Found: C, 78.12; H, 10.41; N, 11.47.

General Procedure for Conjugate Addition Reactions Using Chiral Cuprate Reagents

CuI (75.4 mg, 0.396 mmol) was added to an oven-dried Schlenk flask which was then equipped with a stir bar and rubber septum and purged with several vacuum/N_2 cycles. (*R,R*)-DIMAPP-4 (51 mM in benzene, 3.9 mL, 0.20 mmol) and ether (10 mL) were added via syringe. The solution was cooled to -45 °C and *n*-butyllithium (0.50 mL, 0.79 mmol) was added via syringe. The reaction mixture was stirred at -45 °C for 30 min. The reaction mixture was then cooled to -78 °C in a dry ice/acetone bath and 2-cyclohexenone (0.038 mL, 0.39 mmol) was added neat via syringe. After ca. 1 h, the reaction mixture was slowly warmed to ca. -20 °C and quenched with a 9:1 NH_4Cl:NH_4OH solution (15 mL). Dodecane (50 μL) was added as an internal standard and the product was extracted into diethyl ether. The ether extract was washed with 1 N HCl, dried (anhyd Na_2SO_4), and analyzed by GC to obtain the yield of 3-*n*-butylcyclohexanone (64%).

Ketal from 3-n-butylcyclopentanone and (+)-diethyltartrate

Racemic 3-*n*-butylcyclopentanone (71 mg, 0.51 mmol), (+)-diethyltartrate (300 mg, 1.45 mmol), and toluenesulfonic acid (54 mg) were dissolved in benzene (30 mL) and refluxed with removal of water using a Dean-Stark trap for 24 hs. The reaction solution was then washed with a saturated $NaHCO_3$ solution, dried (anhyd Na_2SO_4), concentrated and purified by column chromatography (silica gel, 97:3 hexanes-ethyl acetate).

Analysis of the product by GC (30m SE-54) showed two well-defined, baseline resolved peaks whose integrated areas where nearly identical: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.73-0.86 (t, 3H, J = 8Hz), 1.10-1.30 (m, 12H), 1.33-1.63 (m, 2H), 1.67-2.23 (m, 3H), 4.12-4.28 (q, 4H, J = 8Hz), 4.61 (s, 1H), 4.68 (s, 1H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 12.9, 21.7, 28.0, 34.3, 35.8, 36.5, 36.7, 42.2, 60.8, 121.6, 168.4.

Ketal from 3-n-butylcyclooctanone and (2S, 3S)-(+)-2,3-butanediol

Racemic 3-*n*-butylcyclooctanone (311 mg, 1.70 mmol), (2S, 3S)-(+)-2,3-butanediol (390 mg, 4.33 mmol), and toluenesulfonic acid (62 mg) were dissolved in benzene (30 mL) and refluxed with removal of water using a Dean-Stark trap for 24 hs. The reaction solution was then washed with a saturated $NaHCO_3$ solution, dried (anhyd Na_2SO_4), concentrated and purified by column chromatography (silica gel, 99:1 hexanes-ethyl acetate). Analysis of the product by GC (30m SE-54) showed two well-defined, baseline resolved peaks whose integrated areas where nearly identical: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.70-0.90 (bs, 5H), 1.0-1.3 (16H), 1.35-1.70 (m, 7H), 3.35-3.60 (m, 2H).

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