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ENANTIOSELECTIVE CONJUGATE ADDITION TO CYCLIC ENONES WITH (*S*)-MAPP-CUPRATES.

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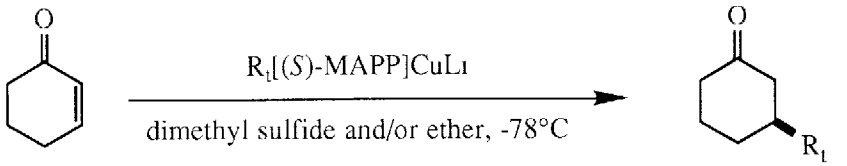
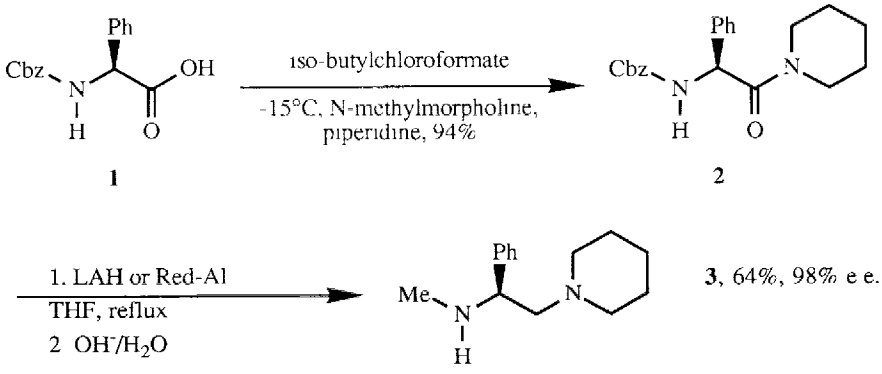
Summary Chiral amidocuprates, formed from CuI, n-butyl or methyl lithium and (*S*)-*N*-methyl-1-phenyl-2-(1-piperidinyl)ethanamine, (*S*)-MAPP, react enantioselectively with 5, 6, 7 and 8-membered cyclic enones to give products with up to 97% e e The synthesis of (*S*)-MAPP is also reported.

Recently, we reported a study in which we screened a number of chiral amidocuprates, derived from CuI, n-butyl or phenyl lithium and several new chiral amines, relative to their ability to react enantioselectively with 2-cyclohexenone (eq 1).[1] The best ligand we found in this study is the chiral diamine, (*S*)-*N*-methyl-1-phenyl-2-(1-piperidinyl)ethanamine, **3**, to which we have given the acronym (*S*)-MAPP. Chiral amidocuprates formed using this ligand gave 3-phenylcyclohexanone in 97% ee and 3-n-butylcyclohexanone in 83% ee. At that time, few studies on enantioselective cuprate conjugate addition had been done on substrates other than 2-cyclohexenone [2] In principle, enantioselective conjugate addition to 2-cycloheptenones and 2-cyclooctenones and other medium and large ring α,β-unsaturated ketones is valuable in the synthesis of a variety of chiral, physiologically active substances including phorbol esters[3], guaianolides[4], pseudoguaianolides[5], dictyopterenes [6], taxanes[7], and ophiobolins[8] We report here the reaction of this reagent with cyclic enones of varying ring size. We also report an efficient synthesis of (*S*)-MAPP and a general synthetic protocol for performing these reactions.



(1)

We synthesized (*S*)-MAPP as shown in ca 64% overall yield. We observed <2% racemization with this procedure although we observed up to 10% racemization during attempts to scale up this reaction The enantiomeric purity of amide **2** can be upgraded to >99% ee by recrystallization. The ee of the **2** and **3** were checked by HPLC using a Daicel Chiracel OD column (10% isopropanol/hexanes)



The cuprate reagent is formed using the same protocol reported in our original communication. Addition of 1.0 equiv of enone to 1.0 equiv of cuprate results in a rapid reaction to yield the desired product. The enantiomeric purity of the products is conveniently monitored either by analysis of the chiral ketones directly using chiral GC columns or by converting the ketones to the corresponding ketals with (+)-diethyl tartrate or (*R*,*R*)-2,3-butanediol and analyzing the products by GC or by ^{13}C NMR. As shown in Table I, the enantiomeric purity of the products varies considerably with 3-methyl- and 3-*n*-butylcycloheptenone manifesting the highest ees. Surprisingly, the predominant enantiomer of 3-methylcyclopentanone is the R enantiomer.

Table I. Enantioselective Conjugate Addition of R[(*S*)-MAPP]CuLi with Cyclic Enones

Enone	R_t	% Yield	% ee	R/S
2-cyclopentenone	methyl	40	32[a]	R[e]
	n-butyl	51	45[c]	S[f]
2-cyclohexenone	methyl	57	58[b]	S[e]
	n-butyl	92	83[a,c]	S[f]
2-cycloheptenone	methyl	60	97[b]	S[f]
	n butyl	63	96[b]	ND
2-cyclooctenone	methyl	48	67[a]	ND
	n-butyl	50	86[d]	ND

Methods for determination of ee and absolute configuration a 30m Chiraldex APH column, Astec Inc Whippany, NJ, b 30m Chiraldex BPH column, Astec Inc Whippany, NJ, c (+)-diethyl tartrate ketal, 25m SB-SMECTIC column, Lee Scientific Inc , Salt Lake City, UT d (R,R)-2,3-butanediol ketal, 30m SE 54 column, Hewlett-Packard e determined by comparing GC elution time with that of the authentic R enantiomer f determined by comparing the optical rotation to literature values [9]

We have made an observation with important mechanistic implications When (*n*-butyl)[(*S*)-MAPP]CuLi is formed using (*S*)-MAPP which is 84% ee and reacted with 2-cycloheptenone, 3-*n*-butylcycloheptanone is obtained in 94% ee. This suggests that at some point in the reaction pathway, a dimeric complex[10] is involved. We are continuing to investigate the synthetic scope and mechanism of this reaction

Experimental

Synthesis of (*S*)-*N*-Methyl-1-phenyl-2-(1-piperidinyl)ethanamine, (*S*)-MAPP.

4-Methylmorpholine (14.4 g, 142 mmol) and isobutyl chloroformate (19.4 g, 142 mmol) were added to a solution of (*S*)-*N*-carbobenzoxyphenylglycine[11] (40.6 g, 0.142 mol) in THF (350 mL) at -15 °C with stirring for 5 min. A THF solution of piperidine (12.1 g, 142 mmol) was added to the reaction mixture at -15 °C yielding a white precipitate. After 1 hr at -15 °C and 4 hrs at RT, the reaction mixture was concentrated and dissolved in ethyl acetate (650 mL) and water (100 mL). The two-phase mixture was partitioned and the organic layer was washed with 1 N HCl (2 X 250 mL), water (100 mL), 5% $NaHCO_3$ (2 X 250 mL), water (250 mL) and saturated NaCl (200 mL). The organic layer was dried (Na_2SO_4) and concentrated to afford the crude carbobenzoxyamide as an oil which crystallizes on standing (47.2 g, 134 mmol, 94%). The product can be purified by preparative HPLC (silica gel, 3:1 hexanes-ethyl acetate) or by recrystallization (ethyl acetate-hexanes) giving white crystals (mp 76.5-77.5 °C). IR (neat) 3306, 1724, 1650 cm^{-1}, ^1H NMR (200 MHz, $CDCl_3$) δ 1.52 (m, 6, C-CH_2-C), 3.50 (m, 4, N-CH_2-C), 5.04 (dd, 1, $C_6H_5C\underline{H}$), 5.59 (d, 1, $C_6H_5C\underline{H}$), 6.46 (d, 1, NH), 7.40 (m, 10, C_6H_5).

The crude carbobenzoxyamide (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 THF (350 mL) at 0°C under Ar. The suspension was refluxed for 12 hrs, cooled to 0°C and treated with THF (300 mL) and water (50 mL) followed sequentially by 50 mL of 15% NaOH and 30 mL of water. The resulting suspension was filtered and the solid residue washed with 200 mL of THF. The THF washings and filtrate were combined and concentrated to afford an oily residue which was dissolved in 1N HCl (280 mL) and washed with ether (2 X 400 mL). The water layer was treated with 5N KOH and extracted with ether (2 X 400 mL). The ether layer was dried ($MgSO_4$), concentrated and the residue vacuum distilled (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}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.40 (m, 2, C-CH_2-C), 1.58 (m, 4, C-CH_2-C), 2.37 (s, 3, CH_3-N), 2.20-2.65 (m, 7, -CH_2-N and NH), 3.60 (dd, 1, $C_6H_5C\underline{H}$), 7.35 (m, 5, C_6H_5). MS *m/z* (relative intensity) 219 (M^++1, 0.2). 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.

General Procedure for the Formation and Use of (*S*)-MAPP-Cuprates

(*S*)-MAPP, **3**, (348 mg, 1.6 mmol) was dissolved in ether (12 mL, distilled from Na/benzophenone) and *n*-butyl lithium (2.5 M in hexanes, 0.61 mL, 1.53 mmol) was added to the solution at -65°C. The solution was stirred for 5 min at -65 °C and warmed gradually to 0°C. In a separate flask, n-butyl lithium (0.51 mL, 1.28 mmol) was added to a CuI (254 mg, 1.33 mmol) in ether (10 mL) at -70°C forming a suspension of n-butylcopper. The lithium amide solution was cooled to -35 °C and added via canula to the suspension of n-BuCu also at -35°C. After several minutes, the resulting solution was cooled to -78°C. After 30 min, 2-cycloheptenone (141 mg, 1.28 mmol) was added dropwise via syringe. The reaction mixture was quenched

after 1 hr by adding 4 N NH_4Cl (15 mL) and extracted with 20 mL of ether The extract was washed with 15 mL of 1 N HCl, dried (Na_2SO_4) and concentrated. The oily residue was chromatographed (silica gel, 10:1 hexanes-ethyl acetate) to afford (*S*)-3-*n*-butylcycloheptanone (136 mg, 63%, 96% e.e.). $[\alpha]_D$ = -33.0 (c 3.20, $CHCl_3$); IR (neat) 1701 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0 88 (t, 3, CH_3), 1.16-1.98 (m, 13, CH_2 and CH), 2.47 (m, 4, CH_2). HRMS calcd for $C_{11}H_{20}O$ (M^+) 168 1514, found 168 1514.

Acknowledgements

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