

ENANTIOSELECTIVE CONJUGATE ADDITION WITH CHIRAL AMIDOCUPRATES, PART III.1 STUDIES ON THE SYNTHETIC OPTIMIZATION OF MAPP-CUPRATES.

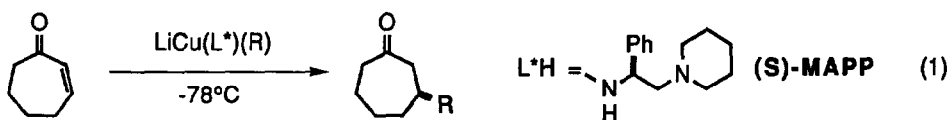
Bryant E. Rossiter*, Guobin Miao, Nicole M. Swingle, Masakatsu Eguchi,
Amelia E. Hernández and R. Greg Patterson

Department of Chemistry, Brigham Young University, Provo, Utah 84602

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Summary: The influence of Cu(I) salt, solvent, TMSCl and ligand ee on the reactivity and selectivity of LiCu(MAPP)(*n*-Bu) in conjugate addition to 2-cycloheptenone has been examined.

We have previously shown that chiral amidocuprates, whose formula is LiCu(L*)(R) where L* is (*R*)- or (*S*)-*N*-methyl-1-phenyl-2-(1-piperidiny)ethanamine (MAPP) and R is methyl, *n*-butyl or phenyl, conjugate add R to the β carbon of cyclic enones with ee's as high as 97% (eq 1).^{1b,2} While we were pleased with the high ee's achieved in some cases, we were dismayed with the low yields and poor ee's obtained in others. Studies have shown that some cuprate reactions manifest significant improvements in chemical yields and selectivities when run with various additives such as TMSCl³ or cyanide.⁴ We have found that the performance of our amidocuprates is subject to the influence of solvent. In an effort to monitor and optimize the reactivity of these reagents, we have subjected them to a number of different experimental conditions. In addition, we have further explored an observation made relative to the non-linearity of asymmetric induction observed in these reactions. We believe these experiments shed light on important aspects of the mechanism of these reactions. Preliminary efforts are reported herein.



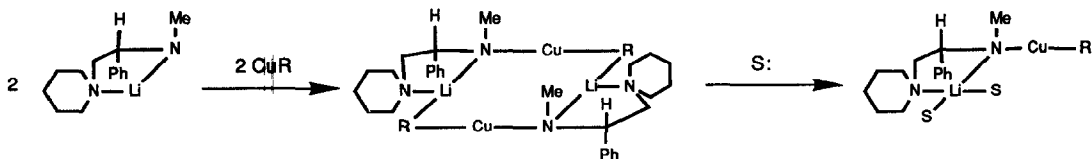
In this study we focused on the conjugate addition of *n*-butyl to 2-cycloheptenone using the reagent LiCu(MAPP)(*n*-Bu). We did this because under optimum conditions this reagent reacts with up to 97% ee and is readily analyzed by chiral GC. On the other hand, we have had problems reproducibly getting >80% yields in this reaction. Thus we felt this was a good reaction with which to monitor the impact of experimental modifications on both chemical yield and enantioselectivity.

We first looked at the affect of using more than one equivalent of reagent (Table I, entries 1-3) Not surprisingly, using increased amounts of reagent gave better yields with no significant loss of enantioselectivity.

Normally we add our ketone to the reaction mixture neat. We thought that diluting the enone and cooling the solution of enone to -78°C before addition might improve yields and enantioselectivity. As shown, doing such has a negligible effect on the reaction (entry 4).

We next monitored the effect of varying the solvent. Use of dimethyl sulfide (DMS) gives results roughly equivalent to ether (entry 5). Diisopropyl ether and *t*-butyl methyl ether (TBME), which are less polar than ether or DMS, give poor results (entries 6 and 7).⁵ Use of THF as solvent or adding 1 or more equivalents of HMPA to the reaction mixture (entries 8 and 9) results in poor yields and no enantioselectivity.⁶ Adding TMSCl to the reaction does not seem to appreciably help or hinder the reaction (entries 10-14). Interestingly however, running these reactions in ether with a mixture of TMSCl and HMPA gives results roughly equal to those without either additive except when HMPA occurs in excess of the TMSCl (entries 15-18). Use of CuBr-DMS results in a dramatic drop in enantioselectivity (entry 20) which contrasts with the work of Dieter *et al.* who found that CuBr tends to give higher ee's than CuI.⁷ Surprisingly, use of Cu(OTf) results in no product (entry 21). Use of CuCN results in a low yield and no enantioselectivity (entry 22).

In our first report concerning MAPP-cuprates,^{1a} we speculated these reagents react as dimers. We have observed that when this reaction is run and quenched at -78°C , it gives a product which has a higher ee than the ligand from which the cuprate was formed (Table II). This observation of asymmetric amplification suggests that somewhere in the reaction manifold a dimer is operating.⁸ Assuming this to be the case, our experimental results can be rationalized by first assuming that both enantiomers of MAPP and the organocuprate reagent self-assemble to form a statistical mixture of the SS, RR and SR (meso) dimeric complexes as shown and that the meso complex is unreactive.⁹ By determining the relative percent of the SS and RR complexes and factoring in the inherent enantioselectivity of this reaction (ca. 96 % ee) one can compute the expected ee of this reaction.¹⁰ As shown in Table II our results correlate well with the expected ee's. The major deviation in this trend occurs when the reaction is allowed to warm to -25°C (entry 5). In this case, the meso dimer may enter into the reaction manifold by reacting in a non-enantioselective manner or the R-ligand may leak into the reaction manifold by ligand exchange.¹¹ The observed solvent effects are also consistent with this dimer model if one also assumes that the monomeric complex is non-enantioselective. By increasing solvent polarity, one crosses a threshold in which the dimers break into monomers due to solvation of the lithium as shown.¹² While TMSCl by itself does not appreciably improve this reaction, it apparently helps overcome the deleterious effects of HMPA perhaps by forming a 1:1 adduct. We are continuing to investigate this interesting and potentially useful reaction.



Acknowledgements.

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Table I. Reaction of LiCu(MAPP)(*n*-Bu) with 2-Cycloheptenone

Entry	Solvent	Experimental	% Yield	% ee
1	ether	1 equiv cuprate	54	96
2	ether	2 equiv cuprate	52	97
3	ether	3 equiv cuprate	82	94
4*	ether	cold, dilute addition of enone	57	95
5	DMS	1 equiv cuprate	46	90
6	<i>i</i> -Pr ₂ O	1 equiv cuprate	20	84
7	<i>t</i> -BuOMe	1 equiv cuprate	6	39
8	THF	1 equiv cuprate	22	1
9	ether	HMPA (1 equiv)	29	1
10	ether	TMSCl (1 equiv)	60	97
11	ether	TMSCl (10 equiv)	34	94
12**	ether	1 equiv cuprate	35	46
13**	ether	TMSCl (2 equiv)	51	44
14	THF	TMSCl (4.6 equiv)	50	1
15	ether	HMPA (1 equiv)/TMSCl (1 equiv)	61	89
16	ether	HMPA (1 equiv)/TMSCl (10 equiv)	50	93
17	THF	TMSCl (1 equiv)/HMPA (1 equiv)	8	0
18	ether	HMPA (10 equiv)/TMSCl (1 equiv)	0	0
19	ether	BF ₃ •Et ₂ O	8	1
20	ether	CuBr•Me ₂ S	19	65
21	ether	CuOTf•0.5 C ₆ H ₆	0	0
22	ether	CuCN	28	0

Each reaction was performed as described in reference 1b in which the cuprate is formed at -40°C, cooled to -78°C and the enone is added to the cuprate neat. Except where noted, CuI is used as the source of copper(I). The products were analyzed using a 30m Chiraldex BPH GC column (Astec Inc.). TMSCl, HMPA and BF₃•Et₂O were added to the reaction mixture after the cuprate was formed and before the enone was added. Chemical yields were monitored by GC using dodecane as an internal standard.

* Cycloheptenone was dissolved in ether, cooled to -78°C and added via cannula to the reaction mixture.

** 2-Cyclopentenone was used as the substrate

Table II. Non-Linear Enantioselective Conjugate Addition of LiCu(MAPP)(*n*-Bu) to 2-Cycloheptenone at -78°C

Entry	% ee of MAPP	Observed % ee of Product	Expected % ee of Product
1	>99	96	96
2	84	94	94.6
3	78	88	93.1
4	56	81	81.9
5*	56	47	81.9

* This reaction was run from -78 to -25°C and quenched at -25°C.

References

1. For parts I and II see: a. Rossiter, B. E.; Eguchi, M. *Tetrahedron Lett.* **1990**, *31*, 965; b. Rossiter, B. E.; Eguchi, M.; Hernández, A. E.; Vickers, D.; Medich, J.; Marr, J.; Heinis, D. *Tetrahedron Lett.* **1991**, *32*, 3973.
2. For a review of enantioselective conjugate addition see Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* submitted for publication.
3. Alexakis, A.; Sedrani, R.; Mangeney, P. *Tetrahedron Lett.* **1990**, *31*, 345 and references cited therein.
4. Lipshutz, B. H. *Synth.* **1987**, 325.
5. Similar results are obtained when we attempt to form our reagents at -78°C instead of -40°C . We believe the ligand exchange and reagent self assembly necessary for proper reagent formation is either too slow or not possible under these conditions.
6. In general, polar solvents have been found to retard conjugate addition to enones. Hallnemo, G.; Ullenius, C. *Tetrahedron*, **1983**, *39*, 1621.
7. Dieter, R. K.; Lagu, B.; Deo, N.; Dieter, J. W. *Tetrahedron Lett.* **1990**, *31*, 4105.
8. For another example of asymmetric amplification in conjugate addition, see Bolm, C. *Tetrahedron Asymm.* **1991**, *2*, 701.

9. In our model of the dimeric complex, the SS and RR complexes have an open and closed face (Figure A).^{1a} Modeling studies suggest that the phenyl groups crowd underneath the complex, blocking the underside of the cuprate (Snyder, J. P.; Rossiter, B. E. unpublished results). We believe the meso complex will have two closed faces because of the presence of phenyl groups on both sides of the complex and will therefore be unreactive (Figure B).

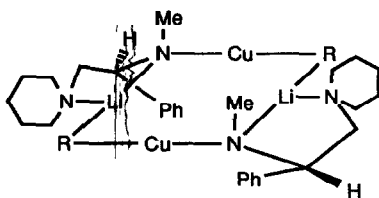


Figure A

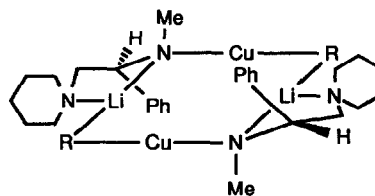


Figure B

10. For example, 56% ee of (*S*)-MAPP (78% *S* and 22% *R*) would form dimers consisting of $(0.78 \times 0.78) \times 100$ or 60.84 % *SS*, $2(0.78 \times 0.22) \times 100$ or 34.32 % *SR* and $(0.22 \times 0.22) \times 100$ or 4.84 % *RR* enantiomers. Ignoring the meso complex and recomputing the ee of the *SS/RR* dimers gives $[(60.84 - 4.84) + (60.84 + 0.484)] \times 100 = 85.26$ % ee. Factoring in the inherent enantioselectivity of 96 % gives $85.26 \times 0.96 = 81.85$. This simple model ignores several factors such as the degree to which the *R* and *S* isomers will self-assemble and the rate of ligand exchange.

11. For studies of ligand exchange in cuprates, see Van Koten, G.; Noltes, J. G. *J. Organomet. Chem.* **1979**, *174*, 367.

12. Note that cuprates recrystallized from ether or DMS have a dimeric structure whereas those recrystallized from THF are monomeric. a. Olmstead, M. M.; Power, P. P. *J. Am. Chem. Soc.* **1990**, *112*, 8008; b. Lorenzen, N. P.; Weiss, E. *Angew. Chem. Ed. Engl.* **1990**, *29*, 300; c. Hope, H.; Olmstead, M. M.; Power, P. P.; Sandell, J.; Xu, X. *J. Am. Chem. Soc.* **1985**, *107*, 4337.