

Asymmetric Conjugate Addition Reactions with Chiral Amidocuprates: The Effect of Cu(I) Salts and Coordinating Heteroatoms

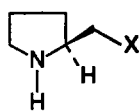
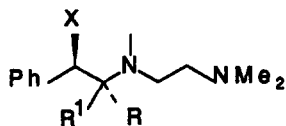
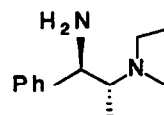
R. Karl Dieter*, Bharat Lagu, Niranjan Deo and Janice W. Dieter

Howard L. Hunter Chemistry Laboratory, Clemson University, Clemson, South Carolina 29634-1905

Abstract: Chiral amidocuprates with methyl or *n*-butyl transferable ligands containing additional heteroatoms afforded higher asymmetric induction with CuBr than with CuI, although reactivity and chemical yields are generally higher with CuI. The enantiomeric excess generally increases with the number of heteroatoms in the chiral amine ligand available for coordination and was low and extremely variable for the bidentate system 1a.

Although organocopper conjugate addition reactions play a very significant role in organic synthesis¹, they are extremely sensitive to a variety of parameters including thermal stability and reactivity of the cuprate², substrate structure, solvent, and Cu(I)³ precursor. The structure of the cuprates, reaction mechanism and extent of aggregation is largely unknown further complicating reagent design. We have examined several specifically designed chiral amidocuprates in an effort to probe ligand structural effects and have observed several facets of cuprate preparation and reaction conditions that significantly affect the efficiency of asymmetric induction. Although some understanding of the relative importance of ligand structural features and reaction parameters in promoting asymmetric induction is necessary for the development of synthetically useful procedures, the interplay of these factors is not readily apparent.

We examined the influence of the number of coordinating heteroatoms (O or N) in the amine ligand. Systems that were structurally similar to previously reported chiral amidocuprates or less thermally stable alkoxycuprates⁴ were examined. The enantiomeric excesses (ee's) were obtained by ketalization of the 3-alkylcyclohexanones with (+) diethyl tartrate and determination of the resultant diastereomer ratios by ¹³C NMR measurements. Methoxymethylprolidine 1a provided variable results that were inconsistent with the earlier report⁵ (Table 1.). Enantiomeric excesses of 30% (R_T = Me) and 22% (R_T = *n*-Bu) could

1 a X = OCH₃b X = OCH₂OCH₃2 a X = NH₂; R¹ = Me; R = H (R,S)b X = NH₂; R¹ = H; R = Me (R,R)c X = *n*-BuNH; R¹ = H; R = Me (R,R)

3 (R,R)

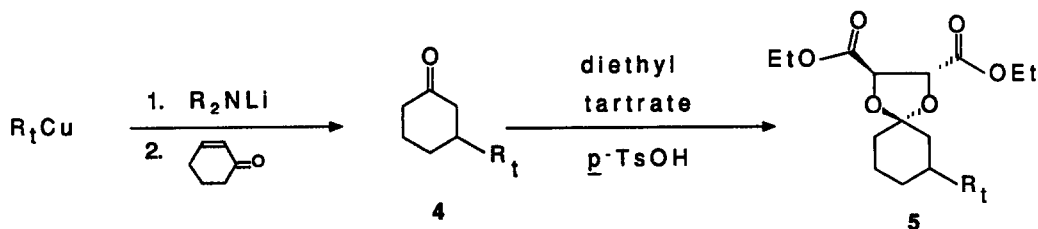


Table 1. Asymmetric Induction in Chiral Amidocuprate Conjugate Addition Reactions.

amine	R _t	solvent	additive	de ^a (% Yield) ^b		Conf ^c	Method ^d	
				CuI	CuBr			
1a	Me	Et ₂ O		0-20 (-) ^e	0-30 (-) ^e	R	B	
	<i>n</i> Bu	Et ₂ O		0-8 (98)	0-22 (56)	R	A	
1b	Me	Et ₂ O		20 (55)	47 (38)	R	B	
				30 (100)	46 (95)	R	A	
		20-33 (-) ^e	53-56 (-) ^e	R	B			
		17 (-)	40 (-)	R	B			
		PhCH ₃	0 (29)	-	A			
		THF	22 (45)	R	B			
	<i>n</i> Bu	Et ₂ O		10 (100)	R	A		
				12 (88)	R	A		
2a	<i>n</i> Bu	THF	Et ₂ O		12 (66)	R	A	
					0 (100)	-	A	
					30 (75)	70 (-)	R	A
					37	68 (63)	R	A
						58 (79) ^f	R	A
2b	<i>n</i> Bu	Et ₂ O	<i>n</i> -Bu ₃ P ^g		60 (57) ^f	R	A	
					12-52 (84)	R	A	
					25 (-)	66 (-)	R	A
					12 (84) ^f	56 (70)	R	A
						0 (91)	-	A
3	<i>n</i> Bu	Et ₂ O	TMSCl ^g		0 (91)	-	A	
					26 (82)	28 (60) ^f	S	A
					24 (91)	20 (54)	S	A
						30 (54)	S	A

^a Determined from measurements on the C-2 absorption peak in ¹³C NMR spectra (± 3-4%) of 5 unless otherwise noted. ^b Yields were determined by glc using dodecane as internal standard unless otherwise noted. ^c Configuration was determined from ¹³C chemical shifts (see reference 4) or by capillary glc retention time against a standard (for R_t = Me only). ^d A = i. RLi + CuX, (0°C 20-30 min. for MeLi; -78 to -60°C for *n*-BuLi). ii. R₂NLi, -78 to -35°C, 1.5 h. iii. enone, -78°C 1 h, then quench at -20°C. B = R₂NLi + CuX, 0°C to rt, 15 min. ii. RLi (-40 to -10°C, MeLi; -78 to -35°C, *n*-BuLi), 30-45 min. iii. enone, -78°C, 1 h then quench at -20°C. ^e Determined by capillary glc (supelcowax 10, 0.53 mm ID, 30 m, 1.0 μm film). ^f Yields are based upon the isolated yield of the diastereomeric ketals 5. ^g These reagents were introduced after cuprate formation and prior to enone addition.

be obtained but just as often little or no asymmetric induction was observed. The ee's were extremely variable and CuBr consistently gave better asymmetric induction than CuI. Interestingly, use of the CuBr·SMe₂ complex gave the opposite enantiomer (S) with 10% ee (R_T = n-Bu). The methoxymethoxy derivative 1b provided more consistent results and afforded ee's of 46-56% (CuBr) with methyl as the transferable ligand and 20-28% with CuI. The enantiomeric excess proved far more variable for R_T = n-Bu ranging from 12-34% for CuBr and 10-12% for CuI. No asymmetric induction was observed in THF and toluene gave results similar to diethyl ether.

Triamine 2a⁶ gave the highest enantiomeric excesses with the least variability and displayed significant differences between the Cu(I) salts. CuBr gave ee's of 58-70% with 2a and only 10-30% with CuI for R_T = n-Bu. The reproducibility of the optical yields required purification of the triamine prior to use via distillation and very careful preparation of the amidocuprate reagent. If the n-butylcuprate reagent was allowed to warm to greater than -30°C during preparation or prepared at -78°C without warming a significant decrease in optical yield was observed. The source⁷ of CuBr appeared to have very little influence upon the optical yields although the age of the CuBr did. Purified CuBr (light green color) generally gave reproducible results while darker colored material resulted in a diminution in optical yields. Introduction of n-Bu₃P produced variable results. Addition of 1.0 eq of n-Bu₃P subsequent to cuprate formation (from 2a) gave ee's ranging from 12-52% (4 runs). The observed ee appeared to depend, in part, upon the time elapsed before addition of the enone. Consistent with the above observations, addition of 3.0 eq of n-Bu₃P to the amidocuprate derived from 2a or addition of 1.0 eq to dissolve CuBr prior to amidocuprate formation (from 2b) yielded no or little (0-5 % ee) asymmetric induction.

Triamine 2b having the same configuration at the benzylic carbon atom and differing in configuration at the methyl bearing C-atom gave results quite similar to those obtained for 2a with a generally slight decrease (5-10%) in ee's. The cuprate derived from secondary amine 2c gave very low induction (6 % ee, CuBr).

Diamine 3 gave low ee's, the highest of which were significantly lower than those obtained with 2a-b. Interestingly, the opposite configuration (S) was obtained for the 3-alkylcyclohexanone, although the configuration at the benzylic C-atom was the same as in amines 2a-b.

These results point to several difficulties in understanding the variability in optical yields observed for chiral amidocuprates. First, the efficiency of CuBr vs CuI is consistent through the series of amidocuprates containing two additional heteroatoms in the side chains (e.g. cuprates derived from 1b, 2a, or 2b). Amidocuprates derived from amines 1a or 3 containing a single heteroatom in the side chain afford rather similar ee's with both CuBr and CuI. Amidocuprates containing a phenyl transferable group

are reported⁸ to give higher optical yields with CuI than with CuBr in contrast to our work with alkyl transferable ligands. Second, in diethyl ether optical yields generally increase with the number of coordinating ligands available. This is supported by the additive experiments which saw a loss of asymmetric induction upon addition of the strongly coordinating ligand $n\text{-Bu}_3\text{P}$ or trimethylsilyl chloride which can coordinate with the side chain heteroatoms interfering with chelation. Steric hindrance to chelation could also account for the poor asymmetric induction obtained with 2c. The influence of temperature during cuprate preparation suggests a very delicate balance between amidocuprate formation and decomposition. The importance of stability and chelation is suggested by the triamines 2a-b which give similar results although they differ in configuration at the stereogenic center bearing the methyl substituent. These results are consistent with the model proposed by Corey.⁴ Cuprates derived from the amino ether 1a uniformly afforded variable results which we have been unable to control while the MOM ether 1b with an additional coordinating heteroatom afforded modest ee's with $R_T = \text{Me}$ and poor ee's with $R_T = n\text{-Bu}$.

These results indicate that considerable caution is required when examining potential ligands as suitable candidates for effecting asymmetric induction in cuprate conjugate addition reactions. The stability profile of the amidocuprate appears to vary from system to system and the Cu(I) precursor has a significant effect upon the optical yields. The variability of optical yield with Cu(I) salt requires caution in attributing asymmetric induction efficiency solely to topological aspects of the chiral ligand. These observations suggest a complex reaction process perhaps involving a dynamic equilibrium of several cuprate species where one is responsible for the observed asymmetric induction.

Acknowledgement: Support for this work by the NSF (CHE-8614665) is gratefully acknowledged.

References

1. (a) Lipshutz, B. H.; Wilhem, R. S.; Kozlowski, J. A. Tetrahedron, 1984, **40**, 5005. (b) Posner, G. H. "An Introduction to Synthesis Using Organocopper Reagents"; Wiley: New York, 1980; references cited therein.
2. Bertz, S. H.; Dabbagh, G. J. Chem. Soc., Chem. Commun., 1982, 1030.
3. Bertz, S. H.; Gibson, C. P.; Dabbagh, G. Tetrahedron Lett., 1987, **28**, 4251.
4. Corey, E. J.; Nef, R.; Hannon, F. J. J. Am. Chem. Soc., 1986, **108**, 7114.
5. Dieter, R. K.; Tokles, M. J. Am. Chem. Soc., 1987, **109**, 2040.
6. Dieter, R. K.; Lagu, B.; Dieter, J. W.; Deo, N.; Pennington, W. T. Synlett., 1990, 109.
7. CuBr from France was kindly provided by Professor Jean-F. Normant, Universite' P. et M. Curie.
8. Bertz, S. H.; Dabbagh, G. J. Org. Chem., 1986, **51**, 4953.

(Received in USA 2 May 1990)