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Structural Requirements of An External, Chiral Amidophosphine Ligand for Asymmetric Reaction of An Organocopper Reagent

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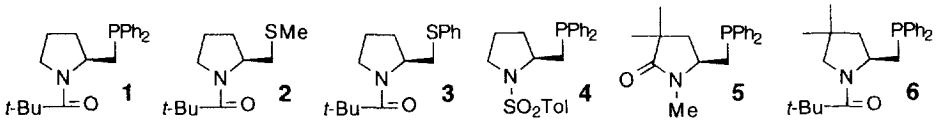
Abstract: Three types of an external, chiral amide ligand, **2-6**, were prepared and examination of their behavior in an asymmetric conjugate addition reaction of lithium dimethylcuprate with chalcone revealed the possibility for steric tuning to realize high selectivity. Copyright © 1996 Elsevier Science Ltd

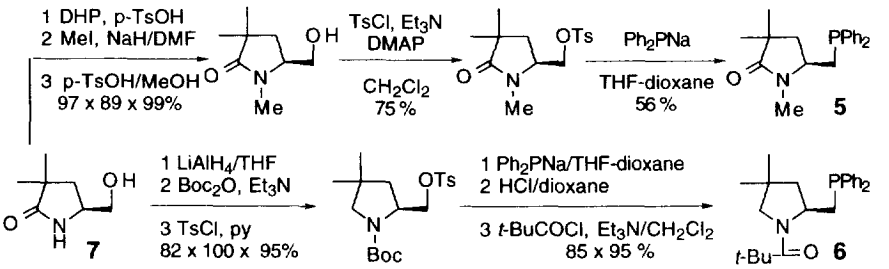
We have been involved in the development of an external, chiral ligand for asymmetric reaction of organometallics.[1] A chiral amidophosphine **1** was developed for organocuprate to provide an efficient asymmetric carbon-carbon bond-forming reaction with α,β-unsaturated carbonyl compounds.[2] In contrast to chirally modified heterocuprates,[3] metal-selective coordination is essential for the design of external, chiral ligands for organocopper.[4] The amidophosphine **1** was designed based on the metal-differentiating coordination, whose phosphorus and carbonyl oxygen atoms selectively coordinate to copper and lithium or magnesium of the organocopper species, respectively. Powerful external ligands bearing chiral phosphorus have been reported.[5] Other than phosphorus,[6] sulfur is a known coordinating atom to copper. Indeed, sulfur-based ligands have been used for the efficient reaction of organocopper.[7]



Investigation of structural requirements and improvement of our ligand **1** were expected to be carried out in three ways, (1) replacement of phosphorus to sulfur, (2) position tuning of the carbonyl oxygen atom, and (3) steric tuning of the pyrrolidine ring. We prepared three types of ligand based on **1**, the first types **2** and **3** have sulfur in place of phosphorus, the second types **4** and **5** have an oxygen atom for lithium at a different or remote position from phosphorus, the third type **6** has a steric bulk at the C4 of the pyrrolidine ring. Investigation of these ligands revealed that steric modification of **1** leads to promising tuning that is the subject of the present letter.

The sulfur-based ligands **2** and **3** were prepared by reaction of (*S*)-*N*-pivaloylprolinol with the corresponding disulfide-Bu_3P.[8] The tosylamide **4** was prepared from (*S*)-*N*-Boc-2-tosyloxymethyl-pyrrolidine[9] in three steps (i. $NaPPh_2$, ii. HCl, iii. TsCl-Et_3N). The amidophosphines **5** and **6** were prepared

from L-glu through 7[10] as shown below.



The reaction of lithium dimethylcuprate with chalcone in the presence of the first type ligands, **2** and **3** bearing methylthio and phenylthio groups respectively, in ether at -20 °C gave the corresponding addition product in high yields, but in significantly poor enantioselectivity as shown in Table 1.[11] These unsatisfactory ees indicate that the sulfur atom is not appropriate for coordination to formally anionic copper of organocuprate.

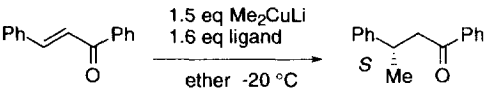
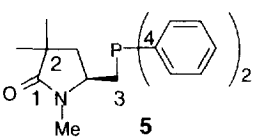


Table 1. Enantioselective Addition Reaction of Me_2CuLi with Chalcone

ligand	**1**	**2**	**3**	**4**	**5**	**6**
ee/%	84	4	4	8	1	90
confign	*S*	*R*	*S*	*S*	*R*	*S*
yield/%	79	99	91	80	90	99

The second type ligand, tosylamidophosphine **4** gave the product in 8% ee, indicating the selectivity is significantly affected by the nature or position of the oxygen atom.

The direction of the carbonyl oxygen also affects enantioselectivity, and the ligand **5** gave the product in marginal ee. However, as shown below, ^{13}C-NMR large chemical shift changes of **5** in toluene-ether (0.1 M) were observed at the carbonyl and its adjacent carbons upon addition of 1 eq $LiClO_4$, and at the carbons bonded to phosphorus upon addition of 1 eq CuBr, indicating that **5** maintains metal-selective coordination.

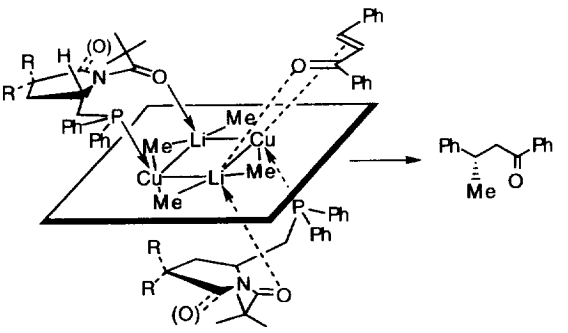


	δ (ppm)	+ $LiClO_4$ Δδ (ppm)	+CuBr•SMe_2 Δδ (ppm)
C-1	178.3	+ 2.3	+ 0.1
C-2	40.0	+1.0	+ 0.3
C-3	34.7	- 0.7	- 1.6
C-4	138.4	+ 0.3	- 5.8
	139.3	+ 0.2	- 4.7

^1H-NMR of **1** showed 16% nOe enhancement between the *t*-Bu protons and C5 protons of the pyrrolidine ring, indicating the carbonyl oxygen is *syn* to the phosphine moiety.[12] From the results above, it is apparent that phosphorus is the coordinating atom of choice for copper, and oxygen is aligned in the appropriate position for lithium coordination that would be essential in forming 1:1 complex or its dimer

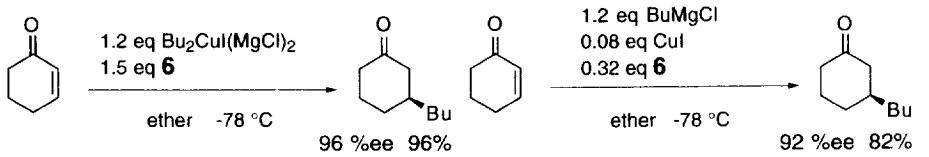
with lithium dimethylcuprate.

Finally we examined the third type ligand **6** and were pleased to find that **6** gave the product in improved 90% ee and quantitative yield.



As shown in the figure, the position shift of the carbonyl oxygen causes failure in forming tight coordination of both oxygen and phosphorus atoms to lithium and copper atoms of the established dimer structure of lithium dimethylcuprate.[13] A more steric bulk of the pyrrolidine ring may disturb the down face-approach of chalcone to result in the improved enantiofacial selection.

The reaction of magnesium butylcuprate with cyclohexenone was controlled by **6** to afford 3-butylcyclohexanone in 96% ee, whereas it gave 89% ee when controlled by **1**.[14] The catalytic asymmetric reaction afforded the product in 92% ee, higher than 80% ee controlled by **1**.[15] On the other hand, the same stoichiometric and catalytic reactions controlled by **5** gave the product in 38 (81% yield) and 48 (62% yield) % ees, respectively.



Thus, steric tuning of the amidophosphine is a promising guide for the design of external, chiral ligands for an organocopper reagent.

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14. Ee was determined by ^{13}C-NMR analysis of the corresponding diastereomeric ketals prepared with (*R,R*)-2,3-butanediol. The absolute configuration was determined by specific rotation. See reference 3 by Corey *et al.*
15. Typical procedure: CuI (0.08 mmol) and **6** (0.30 mmol) was suspended in ether (8 mL) at rt for 20 min. The suspension was cooled to -78 °C and BuMgCl (1.13 mmol) in ether was added. After 20 min stirring, a solution of 2-cyclohexenone (0.94 mmol) in ether (2 mL) was added dropwise. The reaction mixture was stirred for 1 h at -78 °C. Usual workup and purification by column chromatography (SiO_2, hexane:EtOAc 4:1) followed by distillation afforded (*S*)-3-butylcyclohexanone ($[\alpha]_{405}^{25}$ -74.8 (c 1.30, $CHCl_3$)) in 92% ee and 82% yield.

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