ENANTIOSELECTIVE CONJUGATE ADDITION OF ORGANOCUPRATE USING A CHIRAL AMIDOPHOSPHINE LIGAND

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Summary: Based on the concept of a metal differentiating coordination, a new chiral amidophosphine ligand 2 was designed, synthesized, and applied in an enantioselective conjugate addition of lithium dimethylcuprate to chalcone providing the corresponding adduct in 84% ee.

Enantioselective conjugate addition is a rapidly developing area in organocopper chemistry.¹ Chiral modification of heterocuprates has been the representative of these approaches wherein chiral amides, alkoxides, and thiolates are employed as chiral components of the cuprates.² Another interesting, however, scarce approach is the use of chiral external ligands as an asymmetric controller.³ As part of our studies directed toward asymmetric reactions employing external chiral ligands,⁴ we have been involved in design and application of new chiral ligand for organocuprates. We describe herein the design, synthesis, and application of an amidophosphine in a conjugate addition of homocuprate to chalcone based on the concept of a metal differentiating coordination.

General idea of our study is a metal differentiating coordination of a bidentate ligand with lithium organocuprate by which asymmetric space is available around lithium organocuprateexternal ligand complexes. As such ligand, we designed an aminophosphine 1^5 and amidophosphines 2-5 of which phosphorus atom and amino nitrogen or amide oxygen atoms are expected to selectively coordinate with copper and lithium atoms, respectively.⁶ The ligands $1 \sim 5$ were synthesized by methylation or acylation of the corresponding amine prepared from L-proline.^{7,8}



We began our studies with a conjugate addition of lithium dimethylcuprate with chalcone in the presence of 1 in ether solvent at -20 °C for 1 h. As shown in Table I, the ligand 1 was found to be quite disappointing to give the corresponding adduct in only 2% ee. Fortunately it was found that the ligand 2 gave the desired (S)-product in 84% ee.⁹

It is surprising and implicative in that the two ligands 1 and 2 of similar skeleton structure exhibited contrasting outcome each other in enantiofacial differentiation. However, NMR studies revealed this discrepancy is rationalized by the concept of metal differentiating coordination.

Thus, upon an addition of one equivalent of copper bromide-dimethyl sulfide complex into a solution of 1 in ether-toluene- d_8 (1:2) at ambient temperature, large chemical shift changes in ¹³C

entry	Ligand	temp / °C	time / h	ee / %	R/S	yield / %
1	1	-20	1	2	S	89
2	2	-20	1	84	S	79
3	3	-20	1	71	S	88
4	4	-20	1	67	S	88
5	5	-20	1	40	S .	72

Table I. Enantioselective Conjugate Addition of Lithium Dimethylcuprate to Chalcone

NMR (Table II) were observed at the carbons both adjacent to nitrogen (C-1 and C-2) and phosphorus atoms (C-3 and C-4), implying non-selective coordination of both nitrogen and phosphorus atoms in 1 with copper atom.¹⁰ On the other hand, large chemical shift changes were observed only at the carbons adjacent to phosphorus atom, and quite small one at the carbonyl carbon of the amidophosphine 2. On the contrary, upon an addition of lithium perchlorate, large chemical shift changes were observed at the carbonyl carbon but not those adjacent to phosphorus atom of $2.^{11}$ These indicate strongly, for the amidophosphine 2, selective coordination of carbonyl oxygen with lithium and phosphorus with copper.

 Table II.
 13C-NMR chemical shift changes of 1 and 2

	$2 \sqrt{\frac{1}{CH_3}} P(1) $			$2 \sqrt{N} P(4) 2$			
	δ (ppm)	+ CuBr·SMe ₂ Δδ (ppm)		δ (ppm)	+ LiClO ₄ Δδ (ppm)	+ CuBr·SMe ₂ Δδ (ppm)	
C-1 C-2 C-3 C-4	40.2 57.4 34.6 140.1 141.0	+ 4.8 + 1.3 - 1.3 - 5.0 - 4.3	C-1 C-2 C-3 C-4	175.2 48.1 33.6 138.6 140.9	+ 2.6 + 1.0 - 0.8 - 0.7 - 1.1	+ 0.3 - 0.2 - 1.7 - 6.1 - 4.6	

Concentration was 0.07M in ether-toluene- d_8 (1:2). Values are referenced relative to the methyl carbon of toluene- d_8 as 20.4ppm.

These NMR data suggest the possibility in that lithium and copper atoms of lithium dimethylcuprate are selectively coordinated by carbonyl oxygen and phosphorus atoms of 2, respectively.¹² This circumstance is the minimal for the creation of the specific asymmetric space around organocuprate-chiral ligand complexes. Unfortunately, the aminophosphine 1 seems to be unsatisfactory by virtue of non-selective coordination with two atoms.

Further evidence that coordination of phosphorus atom of the amidophosphine 2 is operative in the asymmetric conjugate addition was obtained by a competitive experiment. Thus, conjugate addition of the lithium dimethylcuprate-2 complex to chalcone was affected by the presence of non-

chiral *tertiary* phosphine (three equivalents of tributylphosphine) to afford the adduct of the decreased ee of 18%. This fact clearly demonstrated that coordination of phosphorus atom of 2 with lithium dimethylcuprate is operative in the asymmetric conjugate addition.

Other amidophosphines 3~5 having coordinating oxygen atom also exhibited relatively high asymmetric induction, indicating the importance of the presence of metal differentiating coordinating sites.

A sense of enantiofacial differentiation in the present asymmetric conjugate addition seems to be estimated by the model depicted in Figure I. A metal selective coordination of phosphorus and carbonyl oxygen of 2 with copper and lithium of the reported dimeric structure of lithium dimethylcuprate¹³ would form a coordinated complex. The down face is shielded by the pyrrolidine ring of 2, allowing entry of chalcone from the upper face of the complex. Subsequent d,π^* -complexation of copper and C-C double bond¹⁴ would lead to the product with the (S)absolute configuration observed in the present asymmetric conjugate addition.



General procedure (Table I, entry 2): A solution of methyllithium (low halide, 1.3 ml, 1.88 mmol, 3 eq) in Et₂O was added dropwise to a suspension of CuI (179 mg, 0.94 mmol, 1.5 eq) in Et₂O 8 ml under Ar at -20 °C. The resulting colorless clear solution was stirred for 25 min, and then cooled to -78 °C. A solution of 2 (351 mg, 0.99 mmol) in Et₂O 3 ml was added to the solution and the whole was stirred at -78 °C for 20 min. The reaction mixture turned to a white suspension. A solution of chalcone (130 mg, 0.63 mmol) in Et₂O 5 ml was added dropwise over a period of 5 min and the resulting red suspension was stirred at -20 °C for 1 h. Usual workup and purification by silica gel column chromatography (benzene-hexane 4/1) gave the adduct (110 mg, 79%) as a colorless oil. The ee was determined to be 84% by HPLC analysis (Daicel ChiralPak AD, *i*-propylalcohol/hexane 1/30, 0.5 ml/min, (S) 14 min, (R) 17 min). The absolute configuration was determined to be S by optical rotation ($[\alpha]_{D}^{25} + 12.6$ °(c 2.62, CCL4)).⁹

Although further refinements of the ligand structure are necessary, we believe that the concept of a metal differentiating coordination will open a new guide for the design of much more efficient ligands for organocuprates.¹⁵

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