



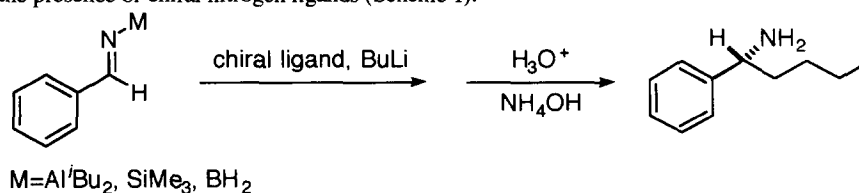
Asymmetric Addition of Butyllithium to N-Metallo Imines of Benzaldehyde

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Abstract: *N*-Metallo imines derived from benzaldehyde such as *N*-aluminium imine, *N*-boryl imine and *N*-silyl imine were asymmetrically alkylated with butyllithium in the presence of chiral ligands including (-)-sparteine and proline-derived amino alcohols to give optically active 1-phenylpentyl-1-amine in up to 74 % enantiomeric excess. Polymer-supported chiral ligands were also used for the asymmetric addition.

The asymmetric addition of organometallic reagent to imine functions constitutes an important method for the preparation of chiral amines that are important substrates for the synthesis of bioactive compounds. Although the impressive progress on the intramolecular asymmetric induction by using chiral imines¹ and hydrazones² as substrates has been made, there are only a handful of reports for external chiral ligand-controlled addition of organometallic reagents to achiral imines³ and nitroene.⁴ Asymmetric addition of organometallic reagents to *N*-metallo imines as masked imine derivatives of ammonia is one of the most useful method to obtain optically active primary amines. We have previously reported the asymmetric addition of organometallic reagents to *N*-trimethylsilyl imines in the presence of external chiral ligands such as chiral alcohols and diols.⁵ Here we report an asymmetric addition of butyllithium to *N*-metallo imines including *N*-(diisobutylaluminio)benzaldehyde imine, *N*-borylbenzaldehyde imine, and *N*-(trimethylsilyl)benzaldehyde imine in the presence of chiral nitrogen ligands (Scheme 1).



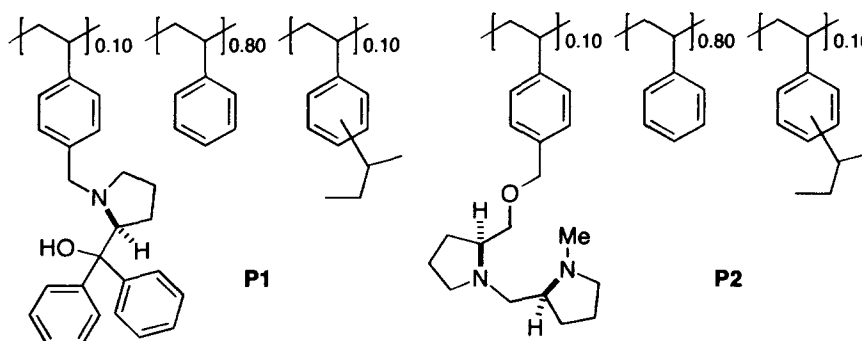
Scheme 1

We examined the reactions of butyllithium with *N*-(diisobutylaluminio)benzaldehyde imine by using (-)-sparteine as external chiral bidentate ligand. (-)-Sparteine is an inexpensive and commercially available chiral diamine that has been used for several asymmetric syntheses such as deprotonation⁶ and polymerization of methacrylate esters.⁷ The *N*-aluminium imine was prepared from partial reduction of benzonitrile with diisobutylaluminium hydride according to the reported procedure.⁸ The *N*-aluminium imine thus generated was added to the preformed (-)-sparteine-butyllithium complex at -78 °C in THF (Method A). Hydrolytic workup of the reaction mixture gave the corresponding primary amine, 1-phenylpentylamine, in 78% yield

Table I Asymmetric Addition of Butyllithium to *N*-Metallo Imine

Entry	Chiral ligand	Imine ^a	Solvent	Method ^b	Temp. °C	1-Phenylpentylamine	
						Yield ^c (%)	%ee ^d (Config.)
1	(-)-Sparteine	Al	THF	A	-78	78	16 (<i>R</i>)
2	(-)-Sparteine	Si	THF	A	-78	57	8 (<i>R</i>)
3	(-)-Sparteine	Al	THF	B	-78	52	1 (<i>R</i>)
4	(-)-Sparteine	Al	ether	A	-78	72	52 (<i>R</i>)
5	(-)-Sparteine	Al	ether	A	-35	71	44 (<i>R</i>)
6	(-)-Sparteine	Al	ether	A	0	69	32 (<i>R</i>)
7	(-)-Sparteine	Al	pentane	A	-78	70	74 (<i>R</i>)
8	(-)-Sparteine	B	THF	A	-78	52	9 (<i>S</i>)
9	(-)-Sparteine	B	THF	B	-78	83	28 (<i>R</i>)
10	(-)-Sparteine	B	ether	B	-78	68	50 (<i>R</i>)
11	(-)-Sparteine	B	THF/ether	B	-78	70	43 (<i>R</i>)
12	1	B	THF	B	-78	72	33 (<i>R</i>)
13	P1	B	THF	B	-78	85	44 (<i>R</i>)
14	P1	Si	THF	A	-78	64	12 (<i>R</i>)
15	P2	B	THF	B	-78	80	26 (<i>R</i>)

^a Al: *N*-(diisobutylaluminio)benzaldehyde imine, B: *N*-borylbenzaldehyde imine, Si: *N*-(trimethylsilyl)benzaldehyde imine. ^b Method A: Imine was added to chiral ligand-butyllithium, Method B: Butyllithium was added to chiral ligand-imine. ^c Yields referred to isolated pure materials. ^d Determined by chiral HPLC analysis.



with enantiomeric excess of 16% (Table I, entry 1). On the other hand, when butyllithium was added to the mixture of (-)-sparteine and the *N*-aluminium imine (Method B), enantioselectivity decreased significantly (entry 3). In order to maximize the complexation of the nucleophile with the ligand, ether and pentane was employed in Method A. Much higher enantioselectivity of 74 %ee was obtained using pentane as solvent (entry 7). Enantioselectivities decreased with a rise in reaction temperature (entries 4-6). *N*-trimethylsilyl imine was also alkylated under the reaction conditions to give the same amine with low enantioselectivity (entry 2).

We have already reported that *N*-boryl imines were readily alkylated with organometallic reagents such as alkyllithiums and Grignard reagents to give primary amines.⁹ Thus asymmetric addition of butyllithium to *N*-boryl imine was performed in the presence of (-)-sparteine. Contrary to the reactions with *N*-aluminium imine and *N*-silyl imine, Method B gave better results in enantioselectivities in the case of *N*-boryl imine (entries 8, 9). In Method B, (-)-sparteine and *N*-borylbenzaldehyde imine would form chiral amine-borane complex. This chirally modified imine was then alkylated with butyllithium to give the chiral amine. In this manner the *N*-boryl imine was alkylated with butyllithium in ether to give the corresponding primary amine with 50 %ee (entry 3). Asymmetric addition of butyllithium to the *N*-boryl imine also occurred with proline-derived chiral diamino alcohol (entry 12), (2*S*, 2'*S*)-2-hydroxymethyl-1-[(pyrrolidin-2-yl)methyl]pyrrolidine (**1**) that was used as effective chiral ligand for the addition of butyllithium to aldehyde.¹⁰

It is always important to separate the used chiral auxiliary effectively and reuse it.¹¹ The polymer supported chiral ligands **P1**¹² and **P2** were prepared by copolymerization method¹³ and used for the asymmetric addition of butyllithium to the *N*-boryl imine. In the presence of these polymers **P1** and **P2**, asymmetric alkylation of the *N*-boryl imine gave the primary amine in 44 and 26%ee, respectively (entries 13, 15). The use of insoluble polymeric chiral ligands markedly facilitated the separation process.

Asymmetric addition of butyllithium to *N*-(diisobutylaluminio)benzaldehyde imine was performed according to the following procedure (Method A). To a stirred solution of 1.03g (10 mmol) of benzonitrile in 10 ml of dry pentane under nitrogen atmosphere was added 10 mmol of diisobutylaluminium hydride at -78 °C. The solution was stirred for 3 hours at the same temperature, and the generation of the *N*-aluminium imine was detected by TLC analysis.⁵ To the pentane solution of (-)-sparteine (10 mmol, 2.34g) and 10 mmol of butyllithium (1.6 M hexane solution, 6.25 ml), was added the *N*-aluminium imine obtained as described above at -78 °C. The resulting solution was stirred for a further 4 hours at the same temperature, and then cautiously hydrolyzed with water and 2M HCl. The organic layer was removed and the aqueous layer was neutralized with NH₄OH and extracted with ether. The combined extracts were dried (MgSO₄) and concentrated under reduced pressure. The enantioselectivity was determined by chiral HPLC analysis {Daicel Chiralcel OD-H, hexane-isopropyl alcohol-diethylamine (90 : 10 : 0.1)} of the crude product. The yield of the product was determined after purification by a silica gel column chromatography (ethanol).

Further investigations of this enantioselective alkylation of other masked imine derivatives are now in progress.

This work was supported by a Grant-in-Aids for Scientific Research from the Ministry of Education, Science and Culture, Japan.

REFERENCES AND NOTES

1. Polniaszec, R. P., Dillard, L. W. *Tetrahedron Lett.*, **1990**, 31, 797. Takahashi, H., Inagaki, H. *Chem. Pharm. Bull.* **1982**, 30, 922. Solladie-Carallo, A., Frankhani, D. *Tetrahedron Lett.*, **1986**, 27, 1331. Clark, R. D., Jahangir, Souchet, M., Kern, J. R. *J. Chem. Soc., Chem. Commun.*, **1989**, 930. Matsubara, S., Ukita, H., Kodama, T., Utimoto, K. *Chem. Lett.*, **1994**, 831. Ukaji, Y., Sumi, T., Fujisawa, T. *Chem. Lett.*, **1991**, 1555. Reetz, M. T., Jager, R., Drewlies, R., Hübel, M. *Angew. Chem., Int. Ed. Engl.*, **1991**, 30, 103. Laschat, S., Kuntz, H. *J. Org. Chem.*, **1991**, 56, 5883.
2. Denmark, S. E., Weber, T., Poitrowski, D. W. *J. Am. Chem. Soc.* **1987**, 109, 2224. Takahashi, H., Tomioka, K., Otomatsu, H. *J. Chem. Soc., Chem. Commun.*, **1979**, 668. Enders, D., Schubert, H. *Angew. Chem., Int. Ed. Engl.*, **1986**, 25, 2224. Weber, T., Edwards, J. P., Denmark, S. E. *Synlett*, **1988**, 20. Alexakis, A., Lensen, N., Tranchier, J. -P., Mangeney, P. *J. Org. Chem.*, **1992**, 57, 4563. Thiam, M., Chastrette, F. *Tetrahedron Lett.*, **1990**, 31, 1429. Clareman, D. A., Lumna, P. K., Philips, B. T. *J. Am. Chem. Soc.*, **1986**, 108, 8265.
3. Denmark, S. E., Nakajima, N., Nicaise, O. J.-C. *J. Am. Chem. Soc.*, **1994**, 116, 8797. Soai, K., Hatanaka, T., Miyazawa, T. *J. Chem. Soc., Chem. Commun.*, **1992**, 1097. Katritzky, A. R., Harris, P. A. *Tetrahedron: Asymmetry*, **1992**, 3, 437. Tomioka, K., Inoue, I., Shindo, M., Koga, K. *Tetrahedron Lett.*, **1990**, 31, 6681. Tomioka, K., Inoue, I., Shindo, M., Koga, K. *Tetrahedron Lett.*, **1991**, 32, 3095. Inoue, I., Shindo, M., Koga, K., Tomioka, K. *Tetrahedron: Asymmetry*, **1993**, 4, 1603. Inoue, I., Shindo, M., Koga, K., Tomioka, K. *Tetrahedron*, **1994**, 50, 4429.
4. Ukaji, Y., Hatanaka, T., Ahmed, A., Inomata, K. *Chem. Lett.*, **1993**, 1313.
5. Itsuno, S., Yanaka, H., Hachisuka, C., Ito, K. *J. Chem. Soc., Perkin Trans. 1*, **1991**, 1341.
6. Kerrick, S. T., Beak, P. *J. Am. Chem. Soc.*, **1991**, 113, 9708. Hoppe, D., Hintze, F., Tebben, P. *Angew. Chem., Int. Ed. Engl.*, **1990**, 29, 1422.
7. Okamoto, Y., Suzuki, K., Ohta, K., Hatada, K. *J. Am. Chem. Soc.*, **1979**, 101, 4763. Okamoto, Y., Suzuki, K., Yuki, H. *J. Polym. Sci., Polym. Chem. Ed.*, **1980**, 18, 3043.
8. Andreoli, P., Billi, L., Cainelli, G., Panunzio, M., Martelli, G., Spunta, G. *J. Org. Chem.*, **1990**, 55, 4199.
9. Itsuno, S., Hachisuka, C., Ito, K. *J. Chem. Soc., Perkin Trans. 1*, **1991**, 1767.
10. Mukaiyama, T., Soai, K., Sato, T., Shimizu, H., Suzuki, K. *J. Am. Chem. Soc.*, **1979**, 106, 1455.
11. Itsuno, S. *Macromolecules* **1992**, J. Kahovec (Ed.) VSP, Utrecht, **1993**, 413.
12. **P1** was obtained as follows; To a well stirred solution of poly(vinyl alcohol) (degree of polymerization: 2000, degree of saponification: 78-82% hydrolyzed) in 230 ml of water was added a solution of the chiral monomer, (*S*)-(+)-*N*-(4-vinylbenzyl)- α,α -diphenyl-2-pyrrolidinemethanol, 10 mmol of divinylbenzene, 80 mmol of styrene, and benzoyl peroxide (1 mmol) as radical initiator in benzene/THF at 0 °C. Obtained suspension was stirred at 0 °C for 30 min and the temperature was raised to 80 °C and the reaction mixture was stirred vigorously for 24 hours. The resulting polymer beads were filtered and washed with water, water-methanol, THF, methanol followed by drying under reduced pressure at 40 °C afforded **P1**. The amino alcohol content was determined by elemental analysis.
13. Itsuno, S., Watanabe, K., Koizumi, T., Ito, K. *Reactive Polymers*, **1995**, 24, 219.

(Received in Japan 20 April 1995; accepted 7 June 1995)