Highly Enantioselective Alkylation of Carbon–Nitrogen Double Bonds. Catalytic and Stoichiometric Asymmetric Synthesis of Optically Active Amines by the Enantioselective Addition of Dialkylzinc Reagents to *N*-Diphenylphosphinoyliminest†

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The first highly enantioselective alkylation of carbon–nitrogen double bonds (of *N*-diphenylphosphinoylimines) with dialkylzinc reagents promoted by chiral amino alcohols afforded optically active phosphoramides (precursors of amines) in up to 91% enantiomeric excess.

Alkylation of imines is an important method for the synthesis of amines because it encompasses the partial construction of carbon frameworks. However, to the best of our knowledge, only a few reports have appeared on the *enantioselective* alkylation of *N*-arylimines[1] (77% enantiomeric excess, e.e., in the presence of 2.6 equiv. of a chiral amino ether) and *N*-silylimines[2] (62% e.e. in the presence of 4 equiv. of a chiral diol) using alkyllithium reagents, with moderate enantioselectivities. Thus, the highly enantioselective alkylation of carbon–nitrogen double bonds is a challenging problem. Despite the recent progress in catalytic enantioselective addition of dialkylzinc reagents to aldehydes,[3] diethylzinc does not add to *N*-silyl-[2] or *N*-phenyl-imines[4] in the presence of chiral amino alcohols.

During our continuing studies on the catalytic enantioselective addition of dialkylzinc reagents to aldehydes[5] and the conjugate addition to enones,[6] we found that these reagents add to *N*-diphenylphosphinoylimines with high enantioselecti-

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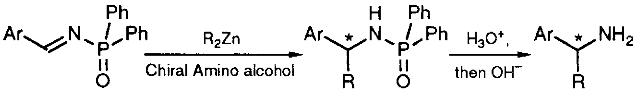
Table 1 Asymmetric synthesis of *N*-diphenylphosphoramides **3** by the enantioselective alkylation of *N*-diphenylphosphinoylimines **1**[a]

Entry	Ar	R	Chiral catalyst (equiv.)	Time/h	*N*-Diphenylphosphoramides **3** Yield (%)		E.e.[b] (%)
1	Ph	Et	**2a** (1.0)	22	**3a**	89	90 (98) (*S*)
2	Ph	Et	**2a** (0.5)	99	**3a**	69	85 (*S*)
3	Ph	Et	**2b** (1.0)	19	**3a**	61	84 (*S*)
4	2-Naphthyl	Et	**2a** (1.0)	112	**3b**	84	91
5	2-Naphthyl	Et	**2a** (0.5)	96	**3b**	57	85
6	4-MeC_6H_4	Et	**2a** (1.0)	90	**3c**	75	90
7	4-MeC_6H_4	Et	**2a** (0.5)	112	**3c**	69	87
8	Ph	Me	**2a** (1.0)	113	**3d**	46	85 (>99) (*S*)
9	Ph	Bu^n	**2a** (1.0)	22	**3e**	56	87
10	Ph	Et	**2b** (0.1)	8	**3a**	12	75 (*S*)

[a] Molar ratio **1** : R_2Zn : **2** = 1 : 0.5–1.0 : 3. [b] E.e.s in parentheses are those after recrystallization.



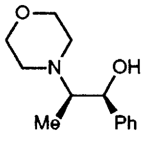
1

a; Ar = Ph
b; Ar = 2-Naphthyl
c; Ar = 4-MeC_6H_4

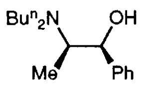
3

a; Ar = Ph, R = Et
b; Ar = 2-Naphthyl, R = Et
c; Ar = 4-MeC_6H_4, R = Et
d; Ar = Ph, R = Me
e; Ar = Ph, R = Bu^n

Chiral Amino alcohol



(1*S*,2*R*) - **2a**



(1*S*,2*R*) - **2b**

vities in the presence of a catalytic or a stoichiometric amount of chiral β-amino alcohols.

When the *N*-diphenylphosphinoylimine **1a**,[7] derived from benzaldehyde and diphenylphosphinic amide, was treated with Et_2Zn (3 mol. equiv.) in the presence of a stoichiometric amount (1 equiv.) of (1*S*,2*R*)-2-morpholino-1-phenylpropan-1-ol **2a**, the corresponding (*S*)-phosphoramide **3a** with 90% e.e. (determined by HPLC analysis using a chiral column) was obtained in 89% yield (Table 1, entry 1).‡ (1*S*,2*R*)-*N*,*N*-Dibutylnorephedrine (DBNE)[5a,d] also afforded (*S*)-**3a** with 84% e.e. (entry 3). The e.e. of phosphoramide **3b** reached 91% when the diphenylphosphinoylimine **1b** derived from 2-naphthaldehyde was ethylated in the presence of **2a** (entry 4). This is the first example of the highly enantioselective (>90% e.e.) alkylation of a carbon–nitrogen double bond. The phosphoramides **3a–c** were obtained in 85–87% e.e. when 0.5 equiv. of **2a** was used (entries 2, 5 and 7). The phosphoramide **3a** was obtained in 75% e.e. when a catalytic amount (0.1 equiv.) of **2b** was used (entry 10). Enantioselective methylation and butylation of **1a** with Me_2Zn and $Bu^n{}_2Zn$ using 1 equiv. of **2a** also afforded the corresponding phosphoramides (**3d–e**) in 85–87% e.e.s (entries 8 and 9).

Optically active amines were easily obtained without any racemisation by the acidic hydrolysis (3 mol dm^{-3} hydrochloric acid and tetrahydrofuran) of the phosphoramides **3**.[8] It should be noted that all the phosphoramides **3** obtained are crystalline and that their optical purity could be enhanced by recrystallization. For example, the e.e. of **3d** (85%, entry 8) was increased to >99% by one recrystallization from hexane–dichloromethane.

The enantioselective alkylation of *N*-diphenylphosphinoylimines[9] with dialkylzinc reagents promoted by chiral β-amino alcohols thus provides a convenient method for the preparation of optically active amines of high e.e.s.§

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References

1 K. Tomioka, I. Inoue, M. Shindo and K. Koga, *Tetrahedron Lett.*, 1990, **31**, 6681; 1991, **32**, 3095.
2 S. Itsuno, H. Yanaka, C. Hachisuka and K. Ito, *J. Chem. Soc., Perkin Trans. 1*, 1991, 1341.
3 Reviews: R. Noyori and M. Kitamura, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 49; K. Soai and S. Niwa, *Chem. Rev.*, in the press.
4 Unpublished observations.
5 (*a*) K. Soai, A. Ookawa, K. Ogawa and T. Kaba, *J. Chem. Soc., Chem. Commun.*, 1987, 467; (*b*) K. Soai, S. Yokoyama, K. Ebihara and T. Hayasaka, *J. Chem. Soc., Chem. Commun.*, 1987, 1690; (*c*) K. Soai, A. Ookawa, T. Kaba and K. Ogawa, *J. Am. Chem. Soc.*, 1987, **109**, 7111; (*d*) K. Soai, S. Yokoyama and T. Hayasaka, *J. Org. Chem.*, 1991, **56**, 4264.
6 K. Soai, T. Hayasaka and S. Ugajin, *J. Chem. Soc., Chem. Commun.*, 1989, 561; K. Soai, M. Okudo and M. Okamoto, *Tetrahedron Lett.*, 1991, **32**, 95.
7 W. B. Jennings and C. J. Lovely, *Tetrahedron*, 1991, **47**, 5561.
8 R. Ramage, D. Hopton, M. J. Parrott, G. W. Kenner and G. A. Moore, *J. Chem. Soc., Perkin Trans. 1*, 1984, 1357.
9 For the enantioselective reduction of diphenylphosphinoyl ketimines, see R. O. Hutchins, A. Abdel-Magid, Y. P. Stercho and A. Wambsgans, *J. Org. Chem.*, 1987, **52**, 702.

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‡ To a mixture of the phosphinoylimine **1a** (0.0767 g, 0.25 mmol) and (1*S*, 2*R*)-**2a** (0.0767 g, 0.251 mmol), toluene (1.5 ml) was added and the mixture stirred for 10 min at room temperature. A hexane solution of Et_2Zn (1.0 mol dm^{-3}; 0.75 ml) was added at 0 °C, and the stirring was continued for 22 h. The reaction was quenched with saturated aqueous ammonium chloride (5 ml). The mixture was extracted with dichloromethane (4 × 10 ml) and dried (Na_2SO_4) and the solvent was evaporated off. Purification of the residue by silica gel TLC (developing solvent, acetone–hexane, 1 : 2 v/v) afforded optically active (*S*)-phosphoramide **3a** (0.0745 g, 0.222 mmol) in 89% yield. The e.e. of **3a** was determined to be 90% by HPLC analysis using a chiral column (Chiralcel OD); 254 nm UV detector; eluent, 3% propan-2-ol in hexane; flow rate, 1.0 ml min^{-1}; column temperature, *ca.* 20 °C; retention time, 14 min for the minor (*R*)-isomer, 20 min for the major (*S*)-isomer. The absolute configuration of **3a** was determined to be (*S*) because its hydrolysis afforded optically active (*S*)-1-phenylpropylamine.

§ While this manuscript was in preparation, enantioselective addition of diethylzinc to *N*-(amidobenzyl)benzotriazoles (masked *N*-acylimines) promoted by DBNE[5a,d] (1 equiv.) was reported to afford *N*-(1-phenylpropyl)amides with 76% e.e. See A. R. Katritzky and P. A. Harris, *Tetrahedron: Asymm.*, 1992, **3**, 437.