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Enantioselective addition of diethylzinc to *N*-diphenylphosphinoylimines employing *N*,*N*-dialkyl-1,2-diphenyl-2-aminoethanols as chiral ligands

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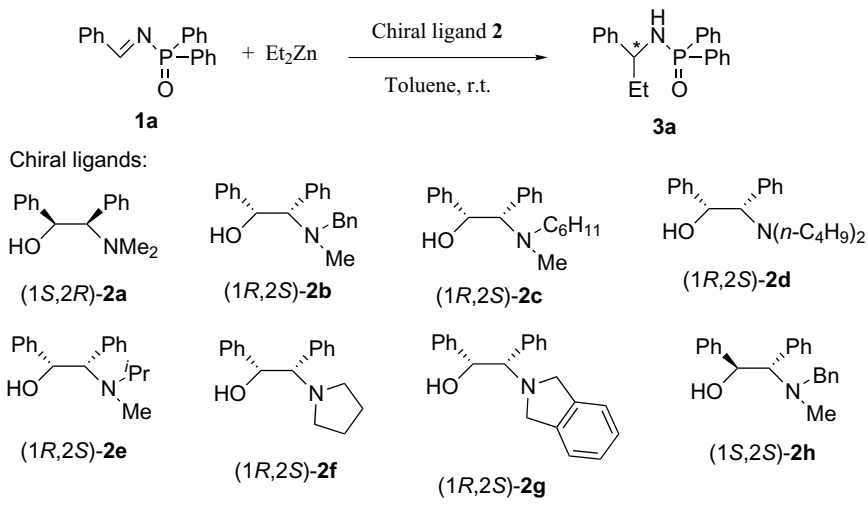
Abstract—By fine-tuning the substituents on the nitrogen of (1*S*,2*R*) and (1*R*,2*S*)-1,2-diphenyl-2-aminoethanols, a chiral ligand **2b** was obtained, which showed excellent enantioselectivity, with up to 94% e.e, for the asymmetric addition of diethylzinc to *N*-diphenylphosphinoylimines **1**. In one example, the optically active amide **3c** was converted into a new amine **5** with 98% e.e. by a reaction sequence involving Suzuki coupling and hydrolysis without racemization.

As is widely known, optically active amines play important roles in the synthesis of natural products and physiologically active substances.[1] Moreover, optically active amines are employed extensively as resolving reagents[2] and as chiral auxiliaries in asymmetric synthesis.[3] Enantioselective addition of dialkylzinc reagents to imines is a convenient route to optically active amines. There have been several reports of enantioselective addition of dialkylzincs to imines employing chiral aminoalcohols,[4] polymeric chiral aminoalcohols[5] and



Scheme 1. Asymmetric diethylzinc addition to *N*-diphenylphosphinoylimine **1a** promoted by **2a**–**h**.

Keywords: diethylzinc addition; imines; aminoalcohols; Suzuki coupling.

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chiral dendrimers[6] as ligands. Generally, conformationally restricted aminoalcohols exhibit higher enantioselectivity.[4d,f] Recently, Tomioka and co-workers reported their work on the copper–amidophosphine catalyzed asymmetric addition of organozincs to imines with excellent results.[7]

The complexes of chiral 1,2-diphenyl-2-aminoethanol and its derivatives have been investigated for promoting several reactions in our laboratory, and have exhibited high enantioselectivities in most cases.[8] Prompted by these results and the fact that the size of the substituent on chiral aminoalcohols bonded to the nitrogen might play an important role in the enantioselectivity,[4c,d] we have proposed that highly enantioselective ligands for asymmetric diethylzinc addition to *N*-diphenylphosphinoylimines **1** might be obtained by fine-tuning of the substituents on the nitrogen of the chiral 1,2-diphenyl-2-aminoethanol.

Chiral ligands **2a**–**h** were prepared from 1,2-diphenyl-2-aminoethanol according to the literature.[9] The results of imine **1a** reacting with Et_2Zn in the presence of a stoichiometric amount of **2a**–**h** in toluene at room temperature[10] (Scheme 1) are presented in Table 1.

It was found that the size of the substituents bonded to the nitrogen on ligands **2** was very important for achieving high enantioselectivity in the reactions. The ligand (1*S*,2*R*)-**2a**, which is excellent for enantioselective diethylzinc addition to aldehydes,[8a] also directed addition to **1a** with 91% e.e. (entry 1). A slight improvement on the enantioselectivity was realized when the reaction was catalyzed by **2b**. Further increase in the steric hindrance of the substituents on nitrogen of the chiral ligands led to a significant decrease in enantioselectivity (entries 4–8). Unlike the known conformationally restricted aminoalcohols,[4d,f] the use of nitrogen constrained ligands **2f** and **2g** as promoters resulted in a dramatic drop in both yields and enantioselectivities (entries 7 and 8), perhaps due to the rigidity of the pyrrolidine ring in the ligands that made it difficult for ligand–zinc alkoxides to coordinate with the substrates. A comparison of entries 2 and 9 shows that the configuration of the product depends on the configuration of the carbon bonded to the hydroxyl group in the ligands. When the configuration of this carbon is inverted, but that of the carbon bonded to nitrogen remained, as shown by **2b** and **2h**, the configuration of the product is inverted from *R* to *S*. The *erythro* ligand **2b** showed much better enantioselectivity than the *threo* ligand **2h**. Lowering the catalyst loading from stoichiometric to 50 mol% led to a decrease in yield, even if the reaction was prolonged to 72 h, but the e.e. remained high (entry 3).

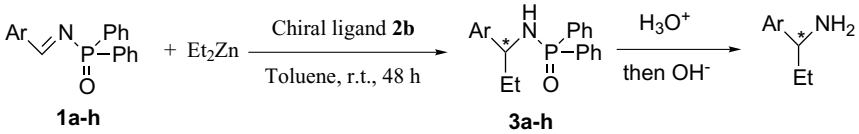
The optimal ligand (1*R*,2*S*)-**2b** was utilized for the asymmetric addition of diethylzinc to various imines (Scheme 2). As shown in Table 2, most of the reactions proceeded smoothly to provide the corresponding chiral diphenylphosphinoyl amides **3** in good yields with enantiomeric excesses higher than 90%. The poor yield and low e.e. of the adduct from the imine **1h** may be due to the steric hindrance imposed by the di-*ortho*-substituted benzene ring (entry 8). A variety of optically active amines may be easily obtained by acidic hydrolysis of the diphenylphosphinoyl amides **3**.[11]

Through a simple Suzuki coupling,[15] **3c** was converted to **4**[16] without racemization. After hydrolysis of **4**, the optically active amine **5** was obtained with 98% e.e. (Scheme 3). This sequence of reactions provides a promising method to synthesize a wide range of optically active amines.

Table 1. Asymmetric diethylzinc addition to *N*-diphenylphosphinoylimine **1a** promoted by the ligands **2a**–**h**[a]

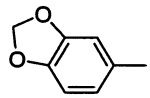
Entry	Ligand (equiv.)	Time (h)	Yield (%)[b]	E.e. (%)[c]	Config.[d]
1	(1*S*,2*R*)-**2a** (1.0)	48	76	91	*S*
2	(1*R*,2*S*)-**2b** (1.0)	48	90	94	*R*
3	(1*R*,2*S*)-**2b** (0.5)	72	67	90	*R*
4	(1*R*,2*S*)-**2c** (1.0)	48	72	89	*R*
5	(1*R*,2*S*)-**2d** (1.0)	48	75	88	*R*
6	(1*R*,2*S*)-**2e** (1.0)	48	91	85	*R*
7	(1*R*,2*S*)-**2f** (1.0)	48	65	80	*R*
8	(1*R*,2*S*)-**2g** (1.0)	48	69	78	*R*
9	(1*S*,2*S*)-**2h** (1.0)	48	92	40	*S*

[a] Molar ratio **1a**:Et_2Zn:**2** = 1:4:0.5–1
[b] Isolated yield.
[c] Determined by HPLC analysis on a chiral column (Chiralcel OD).
[d] Determined by comparison of the retention time with the literature.[4]

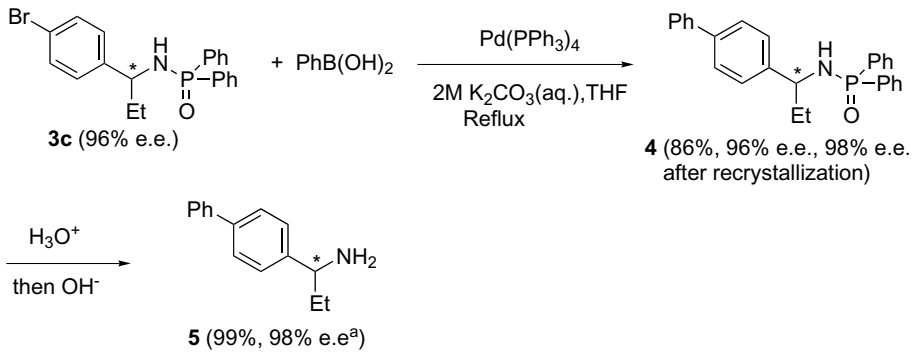


Scheme 2. Asymmetric diethylzinc addition to *N*-diphenylphosphinoylimines **1a–h** promoted by **2b**.

Table 2. Asymmetric diethylzinc addition to *N*-diphenylphosphinoylimine **1a–h** promoted by the ligand **2b**

Entry	Ar	Imine	Adduct	Yield (%)	E.e. (%)[a]
1	C_6H_5-	**1a**	**3a**	90	94
2	*p*-ClC_6H_4-	**1b**	**3b**	84	92
3	*p*-BrC_6H_4-	**1c**	**3c**	90	91(96)[b]
4	*p*-$CH_3OC_6H_4$-	**1d**	**3d**	59	93
5		**1e**	**3e**[12]	86	93
6	*p*-$CH_3C_6H_4$-	**1f**	**3f**	79	94
7	*m*-$CH_3C_6H_4$-	**1g**	**3g**[13]	90	92
8	2,4,6-tri $CH_3C_6H_2$-	**1h**	**3h**[14]	22	76

[a] Determined by HPLC analysis on a chiral column (Chiralcel OD or Chiralcel AD).
[b] E.e was obtained after recrystallization.



[a] Determined by HPLC analysis using a chiral column (Chiralcel AD) after derivation of the amine to the corresponding acetamide.

Scheme 3. Preparation of chiral amine **5** from **3c** by a reaction sequence of Suzuki coupling and hydrolysis.

In summary, we have demonstrated the use of a series of *N*,*N*-dialkyl-1,2-diphenyl-2-aminoethanols for the asymmetric addition of diethylzinc to *N*-diphenylphosphinoylimines. The chiral ligand **2b** which is effective in asymmetric induction was obtained by fine-tuning of the substituents bonded to the nitrogen on the chiral aminoalcohols. The configuration of the product depended upon the configuration of the carbon bonded to the hydroxyl group in the ligand. Further conversion of *N*-(1-*p*-bromophenylpropyl)-*P*,*P*-diphenylphosphinoylamide to optically active 1-*p*-phenylphenylpropylamine, without racemization, by a reaction sequence involving a Suzuki coupling and hydrolysis provided a potentially facile method to synthesize a wide range of chiral amines.

Acknowledgements

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10. Typical experimental procedure for the enantioselective addition of diethylzinc to *N*-diphenylphosphinoyl imine **1a** in the presence of **2b**: Imine **1a** (30.5 mg, 0.1 mmol) and ligand **2b** (31.7 mg, 0.1 mmol) were dissolved in toluene (1.5 mL) under argon. To the mixture was added Et_2Zn in hexane (1 M, 0.5 mL, 0.5 mmol) at rt. After stirring for 48 h, the reaction was quenched with saturated aqueous ammonium chloride, the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine, and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residue was purified by column chromatography on silica gel to give **3a** (30.3 mg, 0.090 mmol, 90%) as a white solid. The enantiomeric excess of 94% with *R*-enantiomer predominating was determined by HPLC (Chiracel OD column, hexane/propan-2-ol = 95:5); flow rate 1 mL/min; *R*-isomer, t_R 12.58 min and *S*-isomer, t_R 18.15 min)
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12. ***N*-(1-Piperonylpropyl)-*P*,*P*-diphenylphosphinoylamide 3e**: ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.78 (t, 3H, $J = 7.4$ Hz, CH_3CH_2), 1.73–1.85 (m, 1H, CH_2CH_3), 1.91–2.05 (m, 1H, CH_2CH_3), 3.25 (m, 1H, NH), 4.02–4.04 (m, 1H, CHNH), 5.94–5.95 (m, 2H, OCH_2O), 6.55–6.59 (m, 1H, Ar-H), 6.69–6.71 (m, 2H, Ar-H), 7.35–7.48 (m, 6H, Ar-H), 7.75–7.95 (m, 4H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 10.5 (CH_3), 32.4 (CH_2), 56.9 (CHNH), 100.9 (OCH_2O), 106.7 (Ar), 107.9 (Ar), 119.9 (Ar), 128.1 (Ar), 128.2 (Ar), 128.3 (Ar), 128.4 (Ar), 131.5 (Ar), 131.6 (Ar), 131.7 (Ar), 131.8 (Ar), 132.3 (Ar), 132.4 (Ar), 132.5 (Ar), 134.0 (Ar), 137.5 (Ar), 146.4 (Ar), 147.6 (Ar).
13. ***N*-[1-(3-Methylphenyl)propyl]-*P*,*P*-diphenylphosphinoylamide 3g**: ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.78 (t, 3H, $J = 7.3$ Hz, CH_3CH_2), 1.79–1.91 (m, 1H, CH_2CH_3), 1.95–2.06 (m, 1H, CH_2CH_3), 2.32 (s, 3H, CH_3Ar), 3.30–3.33 (m, 1H, NH), 4.02–4.09 (m, 1H, CHNH), 6.92–7.07 (m, 3H, Ar-H), 7.20–7.27 (m, 1H, Ar-H), 7.35–7.48 (m, 6H, Ar-H), 7.77–7.88 (m, 4H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 10.5 (CH_3), 21.4 (CH_3Ar), 32.3 (CH_2), 57.1 (CHNH), 123.4 (Ar), 127.3 (Ar), 127.7 (Ar), 128.1 (Ar), 128.2 (Ar), 128.3 (Ar), 128.4 (Ar), 131.6 (Ar), 131.7 (Ar), 131.8 (Ar), 132.5 (Ar), 132.6 (Ar), 137.9 (Ar), 143.2 (Ar), 143.3 (Ar).
14. ***N*-[1-(2,4,6-Trimethylphenyl)propyl]-*P*,*P*-diphenylphosphinoylamide 3h**: ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.89 (t, 3H, $J = 7.8$ Hz, CH_3CH_2), 1.70 (s, 3H, CH_3Ar), 1.88–1.98 (m, 1H, CH_2CH_3), 2.00–2.12 (m, 1H, CH_2CH_3), 2.25 (s, 3H, CH_3Ar), 2.52 (s, 3H, CH_3Ar), 3.37 (m, 1H, NH), 4.49–4.59 (m, 1H, CHNH), 6.65 (s, 1H, Ar-H), 6.84 (s, 1H, Ar-H), 7.26–7.28 (m, 2H, Ar-H), 7.42–7.46 (m, 4H, Ar-H), 7.67–7.71 (m, 2H, Ar-H), 7.90–7.93 (m, 2H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 11.3 (CH_3), 20.4 (CH_3Ar), 20.6 (CH_3Ar), 20.8 (CH_3Ar), 30.1 (CH_2), 52.8 (CHNH), 128.0 (Ar), 128.1 (Ar), 128.3 (Ar), 128.5 (Ar), 129.0 (Ar), 130.9 (Ar), 131.1 (Ar), 131.5 (Ar), 131.7 (Ar), 132.6 (Ar), 132.7 (Ar), 135.9 (Ar), 136.1 (Ar), 136.2 (Ar).
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16. ***N*-(1-Biphenylpropyl)-*P*,*P*-diphenylphosphinoylamide 4**: ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.84 (t, 3H, $J = 7.3$ Hz, CH_3CH_2), 1.84–1.94 (m, 1H, CH_2CH_3), 1.96–2.10 (m, 1H, CH_2CH_3), 3.43–3.44 (m, 1H, NH), 4.14–4.16 (m, 1H, CHNH), 7.23–7.62 (m, 15H, Ar-H), 7.76–7.94 (m, 4H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 10.6 (CH_3), 32.8 (CH_2), 57.2 (CHNH), 126.9 (Ar), 127.1 (Ar), 127.2 (Ar), 128.1 (Ar), 128.5 (Ar), 128.7 (Ar), 131.7 (Ar), 131.9 (Ar), 139.8 (Ar), 140.7 (Ar), 143.8 (Ar), 143.9 (Ar); 98% ee, $[\alpha]_D^{20} = +80.4$ ($c = 1.0$, $CHCl_3$).