



N-Alkyl-*N*-vinylbenzylnorephedrine and Their Copolymers as Chiral Ligands for the Highly Enantioselective Ethylation of *N*-Diphenylphosphinylimine

Takefumi Suzuki, Naoyuki Narisada, Takanori Shibata and Kenso Soai*

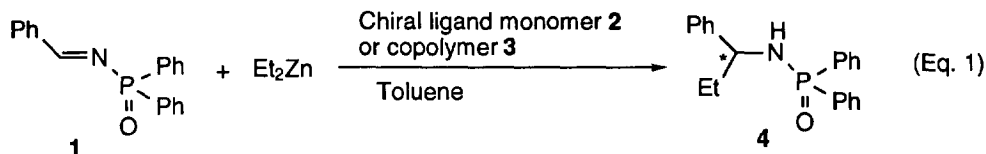
Department of Applied Chemistry, Faculty of Science, Science University of Tokyo, Shinjuku, Tokyo, 162 Japan

Abstract: Enantioselective addition of diethylzinc to *N*-diphenylphosphinylimine in the presence of a stoichiometric amount of *N*-alkyl-*N*-vinylbenzylnorephedrine and their copolymers as chiral ligands affords optically active *N*-diphenylphosphinylamine with up to 95% e.e. Copyright © 1996 Published by Elsevier Science Ltd

Enantioselective alkylation of imines is a direct method for providing optically active amines. Some diastereoselective alkylations have been reported, however, there are only a few enantioselective ones; alkylation of *N*-arylimine,^{1a} *N*-silylimine^{1b} and *N*-acylimine^{1c} using homogeneous chiral ligands (or catalysts). We previously reported enantioselective alkylation of *N*-diphenylphosphinylimine with diethylzinc in the presence of *N,N*-dialkylnorephedrine which has the same substituent on the nitrogen atom.² On the other hand, heterogeneous chiral ligands can facilitate separation processes of the product from the reaction mixture more than homogeneous chiral ligands. However, only very few reports have appeared where heterogeneous chiral ligands are utilized in the enantioselective alkylation of imine.³

We here report highly enantioselective alkylation of *N*-diphenylphosphinylimine **1** with diethylzinc using chiral ligands, namely *N*-vinylbenzyl-*N*-alkylnorephedrine and their copolymers with styrene and divinylbenzene (DVB) (Eq. 1).

Chiral monomeric ligands **2a-d** were prepared by the reaction of *N*-(alkyl)norephedrine hydrochloride⁴ (2 mmol) with vinylbenzyl chloride (2 mmol) in the presence of potassium carbonate (4 mmol) in refluxing EtOH for 7 h (Eq. 2).⁵⁻⁷ Imine **1**⁸ reacted with Et₂Zn in the presence of an equimolar amount of **2a-d** as chiral monomeric ligands in toluene at 0 °C. The results are shown in Table 1. In all cases, e.e.'s of the obtained *N*-



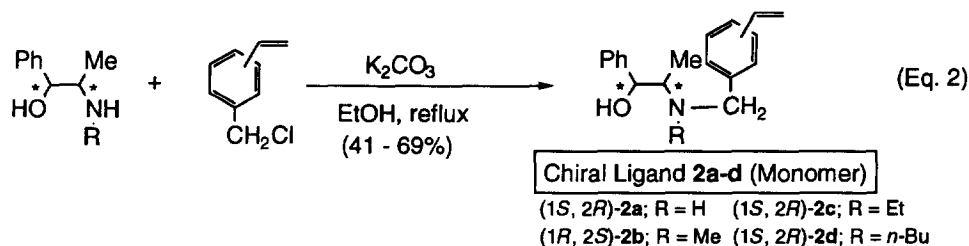


Table 1. Enantioselective Addition of Diethylzinc to Diphenylphosphinylimine **1** using Monomeric Chiral Ligands **2a-d**.

Entry ^a	Chiral Ligand 2 (Monomer)	Time (d)	Temp.(°C)	<i>N</i> -Diphenylphosphinylamine 4		
				Yield (%)	E.e.(% e.e.) ^b	Config.
1	(1 <i>S</i> , 2 <i>R</i>)- 2a	2	0	14	88	<i>S</i>
2	(1 <i>R</i> , 2 <i>S</i>)- 2b	1	0	81	95	<i>R</i>
3	(1 <i>S</i> , 2 <i>R</i>)- 2c	1	0	76	90	<i>S</i>
4	(1 <i>S</i> , 2 <i>R</i>)- 2d	1	0	59	89	<i>S</i>

^a Molar ratio. **1** : Et₂Zn : **2** = 1 : 3 : 1. ^b Determined by HPLC analysis using a chiral column (Chiralcel OD).

diphenylphosphinylamine **4** were high. Among chiral monomeric ligands, (1*R*, 2*S*)-*N*-vinylbenzylephedrine **2b**⁷ gave the best enantioselectivity. In the presence of chiral ligand **2b**, (*R*)-**4** with 95% e.e. was obtained in 81% (Entry 2). It should be noted that this enantioselectivity (95% e.e.) is the highest in the enantioselective alkylations of imines reported.¹⁻³

Copolymerized chiral ligands **3a-d** were synthesized by the copolymerization of chiral monomer **2a-d** with styrene and DVB (molar ratio. **2a-d** : styrene : DVB = 1 : 7 : 2) (Eq. 3).^{9, 10}

In the presence of copolymerized chiral ligands **3a-d**, imine **1** was reacted with Et₂Zn in toluene at room temperature. As shown in Table 2, *N*-diphenylphosphinylamine **4** with good or high (64-88%) e.e.'s was obtained. (*R*)-**4** and (*S*)-**4** with 88% e.e. were obtained by using (1*R*, 2*S*)-**3b** and (1*S*, 2*R*)-**3c**, respectively as chiral catalysts (Entries 2 and 4). The enantioselectivities of copolymerized **3b** and **3c** were comparable with those of the corresponding monomeric chiral ligands **2b** and **2c**. It should be emphasized that the enantioselectivity of 88% e.e. (Entries 2 and 4) is the highest in the enantioselective alkylations of imines using polymer ligands.³ Copolymerized **3b** was easily separated from the reaction mixture by filtration and was recovered. When the recycled **3b** was employed as a chiral ligand, (*R*)-**4** with 86% e.e. was obtained (Entry 3). Thus chiral ligand **3b** can be reused as a chiral catalyst without any loss (within an experimental error) of the enantioselectivity. In addition, *N*-diphenylphosphinylamine **4** is known to be derived into the corresponding optically active amine by acidic hydrolysis.²

General procedure for the enantioselective ethylation of imine **1** is as follows: Et₂Zn (0.6 mmol, 1M hexane

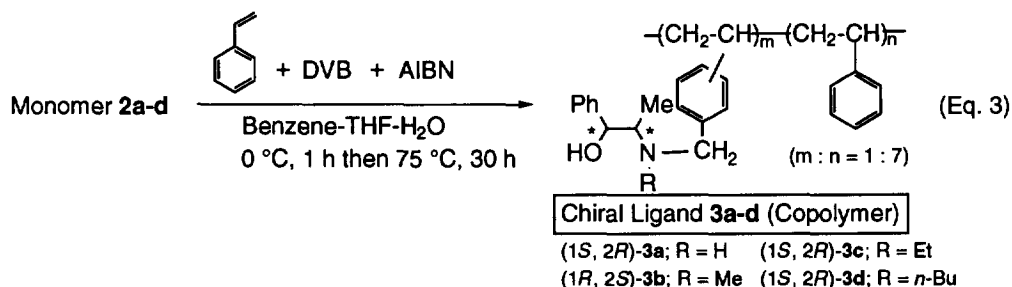


Table 2. Enantioselective Addition of Diethylzinc to Diphenylphosphinylimine **1** using Copolymerized Chiral Ligands **3a-d**.

Entry ^a	Chiral Ligand 3 (Copolymer)	Time (d)	<i>N</i> -Diphenylphosphinylamine 4		
			Yield (%)	E.e. (% e.e.) ^b	Config.
1	(1 <i>S</i> , 2 <i>R</i>)- 3a	3	45	73	<i>S</i>
2	(1 <i>R</i> , 2 <i>S</i>)- 3b	2	56	88	<i>R</i>
3 ^c	(1 <i>R</i> , 2 <i>S</i>)- 3b	2	48	86	<i>R</i>
4	(1 <i>S</i> , 2 <i>R</i>)- 3c	2	60	88	<i>S</i>
5	(1 <i>S</i> , 2 <i>R</i>)- 3d	2	30	64	<i>S</i>

^a Molar ratio. Imine : Et₂Zn : Chiral ligand **3** (based on the content of the nitrogen atom) = 1 : 3 : 1. The reactions were run at room temperature. ^b Determined by HPLC analysis using a chiral column (Chiralcel OD).

^c Recycled **3b** was used.

solution 0.6 ml) was added to a mixture of **1** (0.061g, 0.2 mmol) and chiral ligand **2a-d** (0.2 mmol) or **3a-d** (0.2 mmol, based on the content of the nitrogen atom by elemental analysis of **3a-d**) at 0 °C. The mixture was stirred at 0 °C (for **2a-d**) or at room temperature (for **3a-d**) for the appropriate time. The reaction was quenched by adding satd. aq. ammonium chloride, the precipitate was filtered, and the filtrate was extracted with dichloromethane. The extract was dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, and the purification of the residue with silica gel TLC (developing solvent in hexane/acetone = 3/2) gave pure **4**.

As described, *N*-alkyl-*N*-vinylbenzylnorephedrine and their copolymers are highly enantioselective chiral ligands for the addition of diethylzinc to *N*-diphenylphosphinylimine.

Acknowledgment

We thank H. Miyata for experimental assistance. This work was supported by a Grant-in-Aid for Scientific Research in Priority Areas of "New Polymers and Their Nano-organized Systems" (No. 08246250) from the Ministry of Education, Science, Sports and Culture.

References and Notes

1. (a) K. Tomioka, I. Inoue, M. Shindo and K. Koga, *Tetrahedron Lett.*, **1991**, *32*, 3095; K. Tomioka, I. Inoue, M. Shindo and K. Koga, *Tetrahedron: Asymmetry*, **1993**, *4*, 1603; S. E. Denmark, N. Nakajima and O. J.-C. Nicaise, *J. Am. Chem. Soc.*, **1994**, *116*, 8797; I. Inoue, M. Shindo, K. Koga and K. Tomioka, *Tetrahedron*, **1994**, *50*, 4429. (b) S. Itsuno, H. Yanaka, C. Hachisuka and K. Ito, *J. Chem. Soc., Perkin Trans. 1*, **1991**, 3095; (c) A. R. Katritzky and P. A. Harris, *Tetrahedron: Asymmetry*, **1992**, *3*, 437.
2. K. Soai, T. Hatanaka and T. Miyazawa, *J. Chem. Soc., Chem. Commun.*, **1992**, 1097.
3. K. Soai, T. Suzuki and T. Shono, *J. Chem. Soc., Chem. Commun.*, **1994**, 317; S. Itsuno, M. Sasaki, S. Kuroda and K. Ito, *Tetrahedron: Asymmetry*, **1995**, *6*, 1507.
4. K. Soai, S. Niwa and M. Watanabe, *J. Chem. Soc., Perkin Trans. 1*, **1989**, 109.
5. M. Watanabe and K. Soai, *J. Chem. Soc., Perkin Trans. 1*, **1994**, 837.
6. cf. Z. Zhengpu, P. Hodge and P. W. Stratford, *Reactive Polymers*, **1991**, *15*, 71.
7. General procedure for the synthesis of **2a-d**. Vinylbenzyl chloride (0.305g, 2 mmol, mixture of *m*- and *p*-isomers) was added to a mixture of *N*-(alkyl)norephedrine hydrochloride⁴ (2 mmol) and potassium carbonate (0.55g, 4 mmol) in EtOH (8 ml). The mixture was refluxed for 7 h, and EtOH was evaporated under reduced pressure. 10 ml of 2 M NaOH was added and the mixture was extracted with ether (10 ml x 5). The extract was dried over anhydrous sodium sulfate, evaporated, and purified with silica gel TLC (developing solvent hexane/acetone = 3/1). Compounds **2a-d** were obtained in 41-69%.
8. W. B. Jennings and C. J. Lovely, *Tetrahedron*, **1991**, *47*, 5561.
9. cf. S. Itsuno, Y. Sakurai, K. Ito, T. Maruyama, S. Nakahama and J. M. J. Fréchet, *J. Org. Chem.*, **1990**, *55*, 304.
10. A procedure for the preparation of (1*R*, 2*S*)-**3b**. To a water solution (25 ml) of poly(vinyl alcohol) (0.1g) was added (1*R*, 2*S*)-**2b** (0.56g, 2 mmol),⁶ styrene (1.46g, 14 mmol, 1.6 ml), DVB (0.52g, 4 mmol, 0.57 ml), α , α' -azobisisobutyronitrile (AIBN, 0.065g, 0.4 mmol), benzene (6 ml) and THF (6 ml). The mixture was stirred at 0 °C for 1 h and then at 75 °C for 30 h. The reaction mixture was filtered, washed successively with water, MeOH, THF-MeOH, THF and MeOH (50 ml each). The polymer was dried at 40 °C *in vacuo* for 5 h. (1*R*, 2*S*)-**3b** (2.05g) was obtained. Elemental analysis of **3b**: C 88.32%, H 7.43%, N 1.20%. Therefore the content of the nitrogen atom of (1*R*, 2*S*)-**3b** was 0.899 mmol/g.

(Received in Japan 13 July 1996)