Remarkable Effect of Alkylbenzenes as Solvents in Enantioselective Alkylation of *N*-Diphenylphosphinoylimines with Diethylzinc using Polystyrene Supported Ephedrine

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Diethylzinc adds to *N*-diphenylphosphinoylimines highly enantioselectively using chiral ephedrine supported on polystyrene, the enantioselectivities of the reaction in alkylbenzenes are much higher than those in individual aromatic (benzene) and aliphatic (hexane) hydrocarbons.

Polymer supported chiral reagents have attracted increasing interest.[1] Easy separation from the reaction mixture and the easy reuse are major advantages of polymer supported chiral reagents over homogeneous chiral reagents. However, the number of asymmetric C–C bond forming reactions of high enantioselectivity is very limited. It is only recently that high enantioselectivities in C–C bond forming reactions using polymer supported chiral reagents have been reported in asymmetric hydroformylation of olefins[2] and alkylation of aldehyde.[3] Although enantioselective alkylation of imines with dialkylzinc[4] and alkyllithium[5] have been very recently reported, no report has appeared on the enantioselective alkylation of imines using chiral polymer supported reagent.

We now report an highly enantioselective alkylation of *N*-diphenylphosphinoylimines **1** with diethylzinc using (1*R*,2*S*)-ephedrine supported on polystyrene **2**. The results are shown in Table 1. When **1a**[6] was treated with diethylzinc (1 mol dm^{-3} hexane solution) in the presence of (1*R*,2*S*)-ephedrine supported on polystyrene[7] in benzene for 5 days, the corresponding phosphoramide (*R*)-(**3**) with only 22% enantiomeric excess (e.e.) was obtained in only 4% yield (entry **4**). When the same reaction was run in hexane for 2 days, **3** with only 2% e.e. was obtained in 55% yield (entry 3). Thus, neither individual aromatic- nor aliphatic-hydrocarbon solvent was effective in the reaction.

However, when toluene was employed in the reaction, the yield and e.e. of **3** increased dramatically to 70 and 84% e.e., respectively (entry 1).† When toluene solution (1 mol dm^{-3}) of diethylzinc was employed in the reaction run in toluene, a comparable result was obtained (80, 80% e.e., entry 2). The generality of effectiveness of alkylbenzene as solvent is exemplified by the reactions run in *o*- (85% e.e.), *m*- (85% e.e.), *p*-xylene (78% e.e.) and ethylbenzene (85% e.e.) (entries 5–8). Thus, hydrocarbon possessing aliphatic and aromatic moiety in the same molecule, *i.e.*, alkylbenzene is particularly effective in the present enantioselective reaction. The present unusual effect of solvent observed in the reaction using chiral polymer catalyst **2** is not observed in the corresponding reaction using a monomer chiral catalyst which affords **3** in either hexane (84% e.e.) or toluene (84% e.e.).[4a,b] To the best of our knowledge, such a dramatic difference in enantioselectivity between alkylbenzene (toluene) and benzene has not been reported in an asymmetric reaction. Chiral polymer reagent **2** was easily recovered and was used again without the loss of the enantioselectivity and with slight loss of reactivity (entry 9). Imine **1b** was also ethylated in 85% e.e. (entry 10). The obtained chiral phosphoramides **3a, b** are known to be easily derived into the corresponding optically active amines **4** by acidic hydrolysis without racemization.[4a,8]

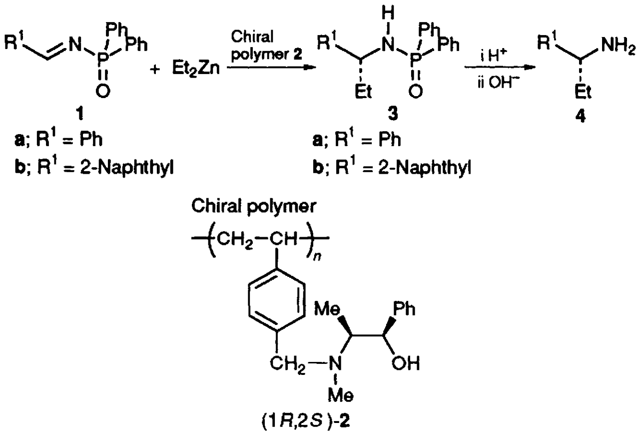
Table 1 Enantioselective addition of diethylzinc to *N*-diphenylphosphinoylimines **1** using chiral polymer reagent **2**

Entry[a]	R¹	Solvent		Yield (%)	E.e. (%)[b]	Config.
1	Ph	Toluene	a	70	84	*R*
2	Ph	Toluene	a	80	80	*R*
3	Ph	Hexane	a	55	2	*R*
4	Ph	Benzene	a	4	22	*R*
5	Ph	*o*-Xylene	a	56	85	*R*
6	Ph	*m*-Xylene	a	43	85	*R*
7	Ph	*p*-Xylene	a	28	78	*R*
8	Ph	Ethylbenzene	a	48	85	*R*
9[c]	Ph	Toluene	a	45	81	*R*
10	2-Naphthyl	Toluene	b	61	85	—

[a] Reactions were run at room temp. for 2 days (5 days for entry 4). Hexane solution (1 mol dm^{-3}) of Et_2Zn was used. For only entry 2, toluene solution (1 mol dm^{-3}) of Et_2Zn was used. [b] Determined by HPLC analyses using a chiral column (Chiralcel OD, 4.6 × 250 mm); 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, **3a**: 15 min for the major (*R*)-isomer, 24 min for the minor (*S*)-isomer; **3b**: 27 min for the major isomer, 44 min for the minor isomer. [c] Recycled chiral polymer reagent **2** was used.

The *N*-diphenylphosphinoylimines **1** employed in the present enantioselective reaction have two advantages over common imines such as *N*-aryl-, *N*-trimethylsilyl- or *N*-benzylimines. One is the presence of a diphenylphosphinoyl group as an electron-withdrawing group which facilitates the increased reactivity of **1** with diethylzinc in the presence of chiral **2**. On the contrary, *N*-aryl-,[9] *N*-trimethylsilyl-[5b] and *N*-benzylimines[9] are hardly reactive with diethylzinc even in the presence of catalysts. The other advantage is that the *N*-diphenylphosphinoyl group is very easily handled. *N*-Diphenylphosphinoyl group is more stable than *N*-trimethylsilyl group against moisture, therefore **3** can be isolated by aqueous work up. Moreover, diphenylphosphinoyl group is easily removed by acidic hydrolysis,[4a,8] whereas *N*-aryl-[10] and *N*-benzyl-groups[11] require oxidative and reductive cleavages, respectively.

Although the mechanism of the effect of alkylbenzenes is not yet clear, we have observed that the shape of chiral polymer reagent **2** differs according to the solvent employed. Chiral polymer reagent **2** swells considerably in benzene, whereas it does not seem to swell in hexane. In alkylbenzenes, the degree of swell of **2** seems between benzene and hexane. The difference in the degree of swell of **2** and the subsequent possible change in the environment of the chiral reactive site



may be some of the reasons for the differences of enantioselectivities in various solvents. A suitable degree of swell in alkylbenzenes may afford the environment of the chiral reactive site of high enantioselectivities.

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Footnote

† Typical experimental procedure (Table 1, entry 1): To a mixture of *N*-diphenylphosphinoylimine **1a** (0.061 g, 0.2 mmol) and chiral polymer reagent **2** (0.25 g, up to 0.2 mmol of chiral aminoalcohol moiety) [prepared from (1*R*, 2*S*)-ephedrine and chloromethylated polystyrene resin (1% divinylbenzene; chlorine content 0.8 mmol g^{-1}; 100–200 mesh)][7] in toluene (3 ml) was added a hexane solution (1.0 mol dm^{-3}, 0.6 ml) of diethylzinc (0.6 mmol) at 0 °C over 10 min. The reaction mixture was stirred for 2 d at room temp., and the reaction was quenched with saturated aq. NH_4Cl. Chiral polymer catalyst was removed by a filtration, and the filtrate was extracted with dichloromethane (3 × 10 ml). The extract was dried (Na_2SO_4), evaporated under a reduced pressure. The residue was purified by silica gel TLC (developing solvent: hexane–acetone (7/3). (*R*)-**3a** (0.046 g) was obtained in 70%.

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