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Asymmetric synthesis of *N*-diphenylphosphinoylamines by solvent-free enantioselective addition of dialkylzincs to *N*-diphenylphosphinoylimines

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Solvent-free enantioselective addition of dialkylzincs to *N*-diphenylphosphinoylimines in the presence of chiral 2-morpholino-1-phenylpropan-1-ol affords *N*-diphenylphosphinoylamines with up to 97% ee. The reaction in the solvent-free system is faster than in organic solvents.

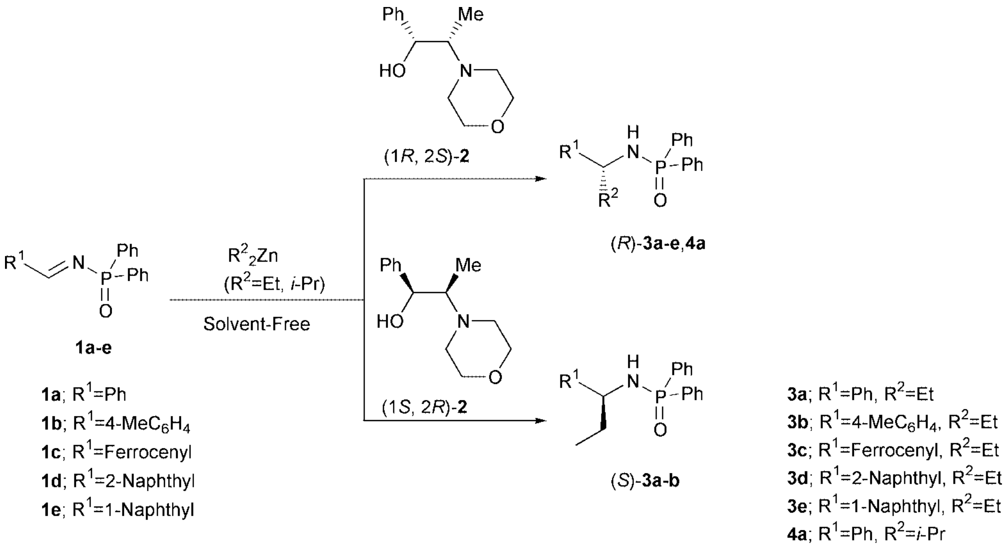
The development of solvent-free organic synthesis is of current interest.[1,2] Although solvent-free synthesis is reported, for example, in polymerization,[3] radical addition[4] and ionic reactions,[5] the number of solvent-free *enantioselective* syntheses has been very few.[6,7] In many enantioselective syntheses, the solvents are of paramount importance to achieve high enantioselectivity. Solvents are considered to play a crucial role in the enantioselection by coordinating, more or less, to the chiral reaction intermediates. Indeed, the enantioselectivity of a chiral ligand or chiral catalyst often differs significantly with the change of the structure of the solvent.[8]

Enantioselective alkylation of imines is one of the challenges in asymmetric synthesis. We previously reported the enantioselective alkylation of *N*-diphenylphosphinoylimines with diethylzinc in toluene in the presence of chiral β-amino alcohols.[9,10] Subsequent removal of the diphenylphosphinoyl group by acid hydrolysis[11] affords enantiomerically enriched secondary amines. Compared to the enantioselective addition of dialkylzincs to aldehydes,[12] less attention has been paid to the enantioselective addition of organometallic reagents to imines.[13]

We wish to report here a solvent-free enantioselective addition of dialkylzincs to *N*-diphenylphosphinoylimines. In the presence of (1*R*,2*S*)-2-morpholino-1-phenylpropan-1-ol **2**,[9a] *N*-diphenylphosphinoylimines **1a**–**e** react with *neat* dialkylzincs without any solvent (Scheme 1).

Enantioselective addition of diethylzinc (Et_2Zn) to *N*-diphenylphosphinoylimine **1a** was examined (Table 1). In the presence of (1*R*,2*S*)-**2**, neat Et_2Zn was added to imine **1a** at 0 °C to give (*R*)-*N*-diphenylphosphinoylamine **3a** with 88% ee in an isolated yield of 75% (entry 1). The reaction was homogeneous and was complete within 2 h. Compared to the enantioselective addition of Et_2Zn to imine **1a** using **2** in toluene (0 °C, 22 h),[9a] the reaction without solvent is much faster. Presumably, the high concentration of Et_2Zn due to the absence of solvent is responsible for the acceleration of the reaction rate. Coordination between Et_2Zn, zinc alkoxide of **2**, and imine is considered to be enhanced because of the absence of the solvation. Even at lower temperatures (−10 °C and −20 °C), the reaction gave (*R*)-**3a** with 84 and 80% ee in 75 and 71% yields, respectively (entries 3 and 4).

Enantioselective synthesis of various *N*-diphenylphosphinoylamines **3** is summarized in Table 2. By using the chiral ligand (1*R*,2*S*)- and (1*S*,2*R*)-**2**, amines (*R*)-**3a** and (*S*)-**3a** with high ee were synthesized, respectively (entries 1 and 2). Enantioselective addition of Et_2Zn to **1b** in the presence of (1*R*,2*S*)-**2** afforded (*R*)-**3b** with 93% ee in a yield of 82% (entry 3). It is noteworthy that the reaction of ferrocenylimine **1c** in the presence of (1*R*,2*S*)-**2** proceeded in a highly enantioselective manner to give **3c** with as high as 97% ee (entry 5). This ee was much higher compared with the reaction of ferrocenylimine **1c** in toluene (0 °C, 119 h, 90% ee).[9b] Alkylation of imines **1d** and **1e** also gave amines **3d** and **3e** with high (91 and 80%) ee's, respectively (entries 6 and 7). Next, enantioselective addition of



Scheme 1

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Table 1 Solvent-free enantioselective addition of diethylzinc to *N*-diphenylphosphinoylimine **1a** in the presence of (1*R*,2*S*)-**2**

				(*R*)-*N*-Diphenylphosphinoylamine **3a**[b]	
Entry[a]	**2** (mol equiv.)	*T*/°C	*t*/h	Yield (%)	Ee (%)
1	(1*R*,2*S*)-**2** (1.0)	0	2	75	88
2	(1*R*,2*S*)-**2** (0.5)	0	24	42	75
3	(1*R*,2*S*)-**2** (1.0)	−10	4	75	84
4	(1*R*,2*S*)-**2** (1.0)	−20	6	71	80

[a] Reactions were carried out on a 0.5 mmol scale using 6–8 mol equivalents of neat Et$_2$Zn. [b] The ee was determined by HPLC analysis using a chiral stationary phase (Chiralcel OD). For the absolute configuration, see ref. 9*a*.

Table 2 Solvent-free enantioselective synthesis of various *N*-diphenylphosphinoylamines

				N-Diphenylphosphinoylamine **3**[b]	
Entry[a]	*N*-Diphenylphosphinoylimine **1**	Chiral ligand	$R^2{}_2$Zn	Yield (%)	Ee (%) (config.)
1	**1a**	(1*R*,2*S*)-**2**	Et$_2$Zn	**3a** 75	88 (*R*)
2	**1a**	(1*S*,2*R*)-**2**	Et$_2$Zn	**3a** 76	84 (*S*)
3	**1b**	(1*R*,2*S*)-**2**	Et$_2$Zn	**3b** 82	93 (*R*)
4	**1b**	(1*S*,2*R*)-**2**	Et$_2$Zn	**3b** 82	89 (*S*)
5	**1c**	(1*R*,2*S*)-**2**	Et$_2$Zn	**3c** 58	97 (*R*)
6	**1d**	(1*R*,2*S*)-**2**	Et$_2$Zn	**3d** 88	91 (*R*)
7	**1e**	(1*R*,2*S*)-**2**	Et$_2$Zn	**3e** 84	80 (*R*)
8	**1a**	(1*R*,2*S*)-**2**	*i*-Pr$_2$Zn	**4a** 89	84 (*R*)[c]

[a] Reactions were carried out in 0.5 mmol scale at 0 °C using 1.0 mol equivalent of (1*R*,2*S*)-**2** and 6–8 mol equivalent of $R^2{}_2$Zn. [b] Ee's were determined by HPLC analyses using chiral stationary phases (Chiralcel OD for **3a**,**b**,**d**,**e** and Chiralpak AS for **3c**). Absolute configurations of **3b**–**e** are tentatively assigned based on the analogy with (*R*)-**3a**. [c] The ee was determined by HPLC analysis using a chiral stationary phase (Chiralcel OD). The configuration of **4a** is tentatively assigned by analogy with (*R*)-**3a**.

neat diisopropylzinc was examined. In the presence of (1*R*,2*S*)-**2**, addition of diisopropylzinc to *N*-diphenylphosphinoylimine **1a** gave the corresponding amine **4a** with 84% ee in a yield of 89% (entry 8).

A typical experimental procedure is as follows (Table 2, entry 5): to an ice-cooled 2-necked flask containing *N*-diphenylphosphinoylimine **1c** (0.21 g, 0.5 mmol) and (1*R*,2*S*)-2-morpholino-1-phenylpropan-1-ol **2** (0.11 g, 0.5 mmol), *neat* Et$_2$Zn (0.49 g, 4 mmol) was transferred through a cannula under an argon atmosphere. After the mixture was stirred at 0 °C for 2 h, the completion of the reaction was confirmed by TLC analysis. After additional stirring for 2.5 h, excess Et$_2$Zn was removed under reduced pressure and saturated aq. ammonium chloride was added to the residue. The mixture was extracted with dichloromethane and the combined organic layer was dried over anhydrous sodium sulfate. Concentration of the organic layer and purification of the residue on silica gel TLC gave (*R*)-**3c** (0.13 g, 58%). The ee was determined to be 97% by HPLC analysis using a chiral stationary phase (Chiralpak AS).

As described, enantioselective addition of dialkylzincs to *N*-diphenylphosphinoylimine under solvent-free conditions proceeds more rapidly than the reaction in toluene and the corresponding amines with high ee's are obtained.[14]

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