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Solvent-free catalytic enantioselective addition of diethylzinc to aldehydes

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Solvent-free enantioselective addition of diethylzinc to aldehydes using β-amino alcohols as chiral catalysts afford chiral *sec*-alcohols with high enantiomeric excesses, and the reaction in solvent-free system is faster than that using organic solvent.

Solvent-free organic synthesis has received much attention.[1,2] From an environmental point of view, potent toxic waste should be minimized and, obviously, bulk wastes in chemical reactions are often organic solvents. Thus, the development of solvent-free organic synthesis is important. Recent advances in this field include, for example, polymerization,[3] radical addition[4] and ionic reactions.[5]

Meanwhile, solvents often play an essential role in catalytic enantioselective synthesis. They not only make the reaction mixtures homogeneous but participate to construct the stereochemically preferable reactive transition state by coordinating with metals. Thus, the use of solvent is generally considered unavoidable in achieving high enantioselectivity in asymmetric reactions.[6] So far, only a few solvent-free enantioselective catalytic reactions are known.[7] We previously reported enantioselective addition of dialkylzincs to aldehydes in the presence of *N*,*N*-dialkylnorephedrines as chiral catalysts using organic solvents such as toluene and hexane.[8]

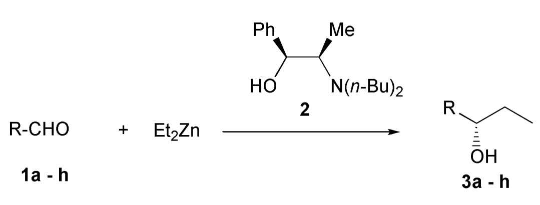
We here report a solvent-free catalytic enantioselective addition of diethylzinc (Et_2Zn) to aldehydes. In the presence of *N*,*N*-dialkylnorephedrines **2, 4** and **5** as chiral catalysts, aldehydes **1** were reacted with neat Et_2Zn without using any solvent. The reactions were homogeneous and proceeded in highly enantioselective manner to give optically active *sec*-alcohols **3** with high ees (Scheme 1).

The results of the enantioselective addition of Et_2Zn to benzaldehyde **1a** under the solvent-free conditions are summarized in Table 1. In the presence of (1*S*,2*R*)-*N*,*N*-dibutylnorephedrine (DBNE) **2**[8a] (10 mol%) as a chiral catalyst, neat Et_2Zn was added to aldehyde **1a** at 0 °C to give (*S*)-1-phenylpropanol **3a** with 87% ee in an almost quantitative yield (99%) (run 1). When the amount of DBNE **2** was 5 mol%, (*S*)-**3a** was obtained in 97% yield and 87% ee (run 2). The reaction using 3.4 mol% of DBNE **2** and 2.2 mol. equiv. of neat Et_2Zn afforded (*S*)-**3a** with 87% ee in 93% yield (run 3). It should be noted that solvent-free reactions at 0 °C were complete in 2 h (runs 1–3), whereas the same reaction in toluene takes longer time to complete.[8a] *N*,*N*-Dipropylnorephedrine **4**[8a] and 1-phenyl-2-(1-pyrrolidinyl)propan-1-ol **5**[8a,9] were also efficient chiral catalysts which afforded (*S*)-**3a** in 97–99% yields with 85% ee and 86% ee, respectively (runs 4 and 5). An acceleration of the reaction rate under solvent-free conditions is clearly seen in low-temperature reactions. Enantioselective addition of Et_2Zn using (1*S*,2*R*)-DBNE **2** as a chiral catalyst proceeded efficiently at −10 °C within 4 h to give **3a** with 89% ee in 98% yield (run 6). Moreover, the reaction even at −28 °C was complete within 6 h to afford **3a** with 87% ee in 99% yield (run 7). It should be noted that when a solvent (toluene) is used, the reaction hardly proceeds at −28 °C. The high reactivity of Et_2Zn under solvent-free conditions may be attributed to the higher concentration of neat Et_2Zn (*ca.* 9.5–10 M) than that in solvents. Thus, a strong acceleration of the reaction rate was observed in the present solvent-free enantioselective reaction without a decrease in enantioselectivity.[10] The catalytic species is, presumably, zinc monoalkoxide of **2**.[8a,11]

To clarify the generality of substrates, various aldehydes were subjected to the solvent-free enantioselective addition of diethylzinc using (1*S*,2*R*)-**2** (5 mol%) as a chiral catalyst (Table 2). *p*-Tolualdehyde **1b** and 1-naphthaldehyde **1c** were ethylated in a highly enantioselective manner to give the corresponding *sec*-alcohols **3b** and **3c** with *S* configuration in 90% ee and 91% ee, respectively (runs 1 and 2).[12] The reaction with 2-naphthaldehyde **1d** gave (*S*)-**3d** in 98% yield and 86% ee (run 3).

Cyclohexanecarbaldehyde **1g**, an aliphatic aldehyde, was ethylated enantioselectively to afford (*S*)-**3g** with 88% ee in 96% yield (run 6). Enantioselective addition of Et_2Zn to aldehyde **1h**, possessing hydrogen atoms on the α-carbon atom, gave **3h** with 84% ee in 92% yield (run 7).

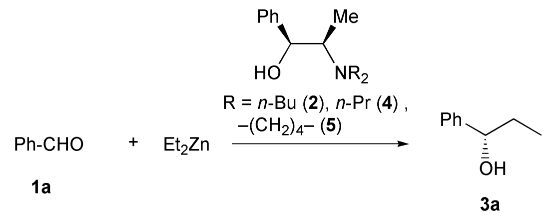
In conclusion, we have described a highly enantioselective ethylation of aldehydes under solvent-free conditions which is



a; R = Ph
b; R = Tolyl
c; R = 1-Naphthyl
d; R = 2-Naphthyl
e; R = *p*-ClC_6H_4
f; R = *p*-$MeOC_6H_4$
g; R = *c*-C_6H_{11}
h; R = $PhCH_2CH_2$

Scheme 1

Table 1 Solvent-free catalytic enantioselective addition of diethylzinc to benzaldehyde



Run[a]	Chiral catalyst (mol%)	*T*/°C	*t*/h	(*S*)-1-phenylpropanol **5a**[b] Yield (%)	Ee (%)
1	(1*S*,2*R*)-**2** (10)	0	2	99	87
2	(1*S*,2*R*)-**2** (5)	0	2	97	87
3[c]	(1*S*,2*R*)-**2** (3.4)	0	2	93	87
4	(1*S*,2*R*)-**3** (5)	0	2	99	85
5	(1*S*,2*R*)-**4** (5)	0	2	97	86
6	(1*S*,2*R*)-**2** (5)	−10	4	98	89
7	(1*S*,2*R*)-**2** (5)	−28	6	99	87

[a] Reactions were carried out using 3–5 mol. equiv. of neat Et_2Zn. [b] Ee was determined by HPLC analysis using a chiral stationary phase (Chiralcel OB-H). [c] Reaction was run using 2.2 mol. equiv. of neat Et_2Zn.

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Table 2 Solvent-free enantioselective addition of Et_2Zn to various aldehydes using (1*S*,2*R*)-*N*,*N*-dibutylnorephedrine **2** as a chiral catalyst

		(*S*)-**3**		
Run[a]	Aldehydes		Yield (%)	Ee (%)[b]
1	*p*-Tolualdehyde **1b**	**3b**	99	90
2	1-Naphthaldehyde **1c**	**3c**	80	91
3	2-Naphthaldehyde **1d**	**3d**	98	86[c]
4	*p*-Chlorobenzaldehyde **1e**	**3e**	99	85
5	*p*-Methoxybenzaldehyde **1f**	**3f**	98	89
6	Cyclohexanecarbaldehyde **1g**	**3g**	96	88[d]
7	3-Phenylpropanal **1h**	**3h**	92	84[c]

[a] Reactions were carried out for 2 h at 0 °C using 5 mol% of **2** and 3–5 mol. equiv. of Et_2Zn. [b] Unless otherwise noted, ee was determined by HPLC analysis using a chiral stationary phase (Chiralcel OB-H). [c] Chiralcel OD-H was used as a chiral stationary phase. [d] Ee was determined as *p*-bromobenzoate of **3g** using a chiral stationary phase (Chiralcel OJ-R).

accelerated with respect of the corresponding reaction in organic solvents.

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