Chiral Quaternary Ammonium Salts as Solid State Catalysts for the Enantioselective Addition of Diethylzinc to Aldehydes

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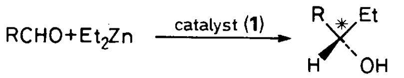
(1*S*, 2*R*)-*N*-Benzyl-*N*-methylephedrinium halides in the solid state revealed much higher enantioselectivities than those in solution during the enantioselective addition of diethylzinc to aldehydes.

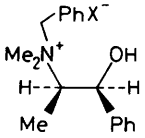
Relations between homogeneous and heterogeneous chiral catalysts is a problem which needs solving in a general way. In almost all cases, homogeneous chiral catalysts afford higher enantioselectivities than heterogeneous chiral catalysts.[1]

We report an unusual asymmetric reaction in which chiral catalysts of the *solid state* afford much higher enantioselectivities than those in *solution*. When benzaldehyde was treated with diethylzinc in hexane using (**1a**)[2] as chiral *solid state* catalyst (6 mol%), (*S*)-1-phenylpropanol (**3a**) was obtained in 90% yield and in 74% enantiomeric excess (e.e.) (Table 1, entry 1). Reactions run in other hydrocarbon solvents such as toluene–hexane and benzene–hexane, where the catalyst (**1a**) was the *solid state*, also afforded (*S*)-(**3a**) in good e.e. (entries 4 and 5). In contrast, the catalyst was soluble in *N*,*N*-dimethylformamide (DMF), and the reaction in DMF–hexane using the catalyst in solution (**1a**) gave only *racemic* (**3a**) in 71% yield (entry 6) [without the catalyst, the reaction in DMF–hexane was very slow (36%)]. This dramatic difference in the enantioselectivity of the same chiral catalyst (**1a**) regarding its solid or dissolved state was also the case in other catalysts (**1b**)[3] and solvents. *The solid state* catalyst (**1b**) in hexane afforded (*S*)-(**3a**) in moderate (62%) e.e. (entry 7), whereas *a solution* of (**1b**) in dimethyl sulphoxide (DMSO)–hexane and acetonitrile (MeCN)–hexane showed almost no enantioselectivity (0–2% e.e.) (entries 8 and 9). Although a strict measurement was not attempted, the relative rates of the catalysts in hexane and the other oxygen or nitrogen containing solvents are comparable. The catalyst (**1a**) in hexane for 3 days and in DMF–hexane for 2 days afforded (**3a**) in 90 and 71%, respectively (entries 1 and 6). The catalyst (**1b**) in hexane for 4 days, in DMSO–hexane for 3 days, and in MeCN–hexane for 7 days afforded (**3a**) in 72, 71, and 91% yield, respectively.



(**2**)
a; R = Ph
b; R = 4-MePh

(**3**)
a; R = Ph
b; R = 4-MePh



(**1**)
a; X = Cl
b; X = Br

We do not mean to imply that there is no catalyst in the hydrocarbon solvent. Some small amounts of the catalyst may be present in hydrocarbon solvents as the result of the interaction of the catalyst either with Et_2Zn or aldehydes. Most probably, Et_2Zn reacts with (**1**) to produce zinc alkoxide, and this species may be more soluble in hydrocarbon solvents. However, judging from the observations of the reaction mixtures, most of the catalyst (even though it reacts with Et_2Zn) is not soluble in the hydrocarbon reaction mixtures. The situation was the same when the lithium alkoxide of (**1a**), prepared *in situ*, was used (Table 1, entry 3).

Although the exact mechanism of the ammonium salt catalysed addition of dialkylzinc to aldehyde is not clear at present,[4] the effect described above may be explained by the difference in the degree of solvation to ammonium cations of the catalysts (**1a, b**). Hydrocarbons have very little effect on solvation. On the other hand, the oxygen or nitrogen atom of

Table 1. Enantioselective addition of diethylzinc to aldehydes using chiral quaternary ammonium catalysts.[a]

					Alcohol (**3**)				
Entry	Aldehyde (**2**)	Catalyst (**1**)	Solvent[b]	*t*/days		$[\alpha]_D$° (*c*, solvent)	Yield/%	E.e./%	Configuration
1	**a**	**a**	H	3	**a**	$[\alpha]^{26}$ −33.4 (5.18, $CHCl_3$)	90	74[e]	(*S*)
2[c]	**a**	**a**	H	6	**a**	$[\alpha]^{25}$ −27.5 (4.15, $CHCl_3$)	55	61	(*S*)
3[d]	**a**	**a**	H	3	**a**	$[\alpha]^{25}$ −31.0 (5.19, $CHCl_3$)	100	68	(*S*)
4	**a**	**a**	T–H	3	**a**	$[\alpha]^{24}$ −29.0 (5.22, $CHCl_3$)	84	64	(*S*)
5	**a**	**a**	B–H	3	**a**	$[\alpha]^{24}$ −33.0 (5.23, $CHCl_3$)	76	73	(*S*)
6	**a**	**a**	DMF–H	2	**a**	$[\alpha]^{27}$ 0 (4.74, $CHCl_3$)	71	0	—
7	**a**	**b**	H	4	**a**	$[\alpha]^{26}$ −28.8 (5.14, $CHCl_3$)	72	62	(*S*)
8	**a**	**b**	DMSO–H	3	**a**	$[\alpha]^{25}$ 0 (4.83, $CHCl_3$)	71	0	—
9	**a**	**b**	MeCN–H	7	**a**	$[\alpha]^{23}$ −0.97 (3.60, $CHCl_3$)	91	2	(*S*)
10	**b**	**a**	H	4	**b**	$[\alpha]^{25}$ −23.9 (5.85, PhH)	81	61[f]	(*S*)

[a] Molar ratio, aldehyde : catalyst : Et_2Zn = 1.0 : 0.06 : 2.2. Unless otherwise noted, reactions were run at room temperature. [b] H = hexane; T = toluene; B = benzene; THF = tetrahydrofuran. [c] Reaction was run at 0 °C. [d] Lithium alkoxide of (**1a**), prepared *in situ* by treatment with an equimolar amount of n-butyl-lithium, was used. [e] Reported value for (*S*)-1-phenylpropanol is $[\alpha]_D$ −45.45° (*c* 5.15, $CHCl_3$): R. H. Pikard and J. Kenyon, *J. Chem. Soc.*, 1914, 1115. [f] $[\alpha]_D$ −39.2° (PhH) for (*S*)-1-(4-methylphenyl)propanol: P. A. Chaloner and S. A. R. Perera, *Tetrahedron Lett.*, 1987, **26**, 3013.

DMF, DMSO, and MeCN strongly solvates the ammonium cation. The present results suggest that an ammonium cation with very little solvation is essential for the asymmetric induction. In addition, by using a chiral quaternary ammonium catalyst, the present method in our opinion is a new approach to the recent catalytic asymmetric addition of dialkylzinc to aldehydes.[5]

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References

1 For the use of polymer-bound heterogeneous chiral catalysts, see K. Soai, S. Niwa, and M. Watanabe, *J. Org. Chem.*, 1988, **53**, 927; *J. Chem. Soc., Perkin Trans. 1*, 1989, 109; S. Itsuno and J. M. J. Frechet, *J. Org. Chem.*, 1987, **52**, 4142; N. Kobayashi and K. Iwai, *J. Polym. Sci., Polym. Chem. Ed.*, 1980, **18**, 923; G. Parrinello and J. K. Stille, *J. Am. Chem. Soc.*, 1987, **109**, 7122.

2 S. Julia, A. Ginebreda, J. Guixer, J. Masana, A. Tomas, and S. Colonna, *J. Chem. Soc., Perkin Trans. 1*, 1981, 574.

3 Compound (**1b**) has been used as a chiral phase transfer catalyst in asymmetric alkylation of β-keto ester with alkyl halide in 5—6% e.e. See, J.-C. Fiaud, *Tetrahedron Lett.*, 1975, 3495.

4 M. Chastrette and R. Amouroux, *Tetrahedron Lett.*, 1970, 5165.

5 K. Soai, S. Niwa, Y. Yamada, and H. Inoue, *Tetrahedron Lett.*, 1987, **28**, 4841; K. Soai, A. Ookawa, T. Kaba, and K. Ogawa, *J. Am. Chem. Soc.*, 1987, **109**, 7111; M. Kitamura, S. Okada, S. Suga, and R. Noyori, *ibid.*, 1989, **111**, 4028; M. Yoshioka, T. Kawakita, and M. Ohno, *Tetrahedron Lett.*, 1989, **30**, 1657; K. Soai, M. Watanabe, and M. Koyano, *J. Chem. Soc., Chem. Commun.*, 1989, 534, and references cited therein.