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New Polymer Bound Chiral Catalyst with Methylene Spacer for the Enantioselective Addition of Diethylzinc to Aldehydes

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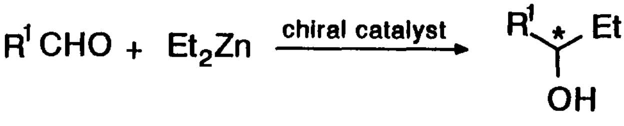
Abstract: Optically active sec-alcohols in good to high e.e.'s were obtained from the enantioselective addition of diethylzinc to both aliphatic and aromatic aldehydes using a polymer attached chiral catalyst with a methylene spacer.

Although chiral polymer catalyst has attracted much attention because of their easy recovery, reuse, and relation to biological macromolecular catalyst (i e., enzyme), the number of examples of their use in catalytic asymmetric carbon-carbon bond forming reaction is limited.[1] We previously reported an enantioselective addition of dialkylzincs to aldehydes using norephedrine derivatives attached to polystyrene.[2] However, e e. of the addition to aliphatic aldehyde is not adequately high. One of the reasons of moderate e.e.'s of the polymer catalyst against aliphatic aldehyde[2] is considered to be the severe limitation of freedom and mobility of the reactive site of the polymer catalyst. This is probably because the nitrogen atom of norephedrine is directly attached to the chloromethylated benzene ring. On the other hand, we previously reported that N,N-dibutylnorephedrine (DBNE) is a highly enantioselective chiral catalyst for the addition of dialkylzincs to not only aromatic but also aliphatic aldehydes.[3] One of the possible way to synthesize an enantioselective polymer chiral catalyst may be to realize the similar chiral environment in polymeric catalyst with that of monomeric catalyst (DBNE).

Here we report the synthesis of polymer attached chiral catalyst



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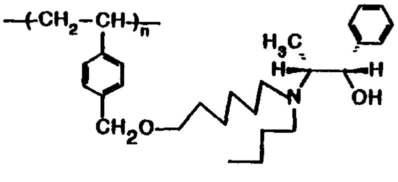
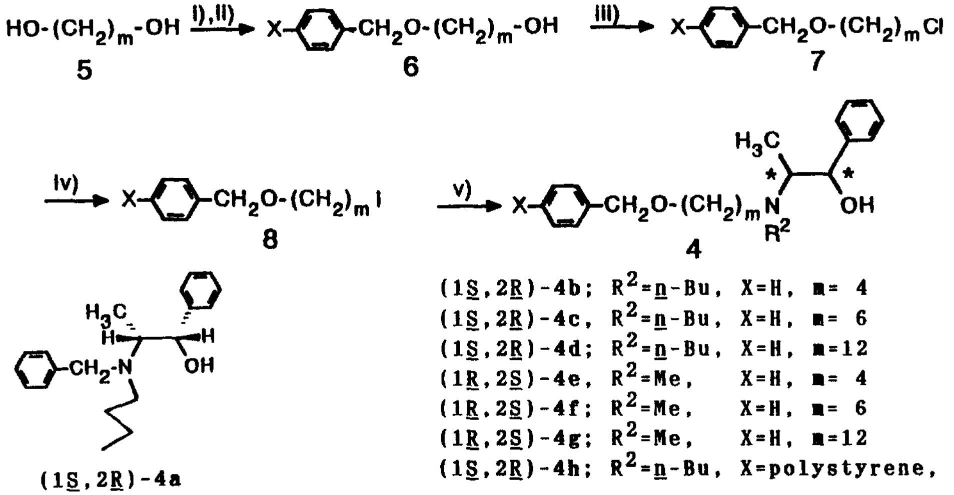
Polymer catalyst (1S,2R)-4h





(1S,2R)-4b; R^2=n-Bu, X=H, m= 4
(1S,2R)-4c, R^2=n-Bu, X=H, m= 6
(1S,2R)-4d; R^2=n-Bu, X=H, m=12
(1R,2S)-4e, R^2=Me, X=H, m= 4
(1R,2S)-4f; R^2=Me, X=H, m= 6
(1R,2S)-4g; R^2=Me, X=H, m=12
(1S,2R)-4h; R^2=n-Bu, X=polystyrene, m=6

Scheme 1. i) NaH/DMF, ii) x-C_6H_4-CH_2Cl, iii) $SOCl_2$, iv) NaI/Me_2CO, v) N-alkylnorephedrine, K_2CO_3/toluene

possessing a methylene spacer, and a highly enantioselective addition of diethylzinc to aldehydes.

In the first place, effect of the substituents on the nitrogen atom of norephedrine was examined using monomer catalysts (4a-g) which were synthesized as shown in Scheme 1. 1, ω-Alkanediol (5) was converted to monobenzyloxyalcohol (6) 6 was converted to chloroether (7) then to iodoether (8) Monomer catalysts (4b-g) were obtained by the reaction of 8 with (1S, 2R)-N-butylnorephedrine (for 4b,c,d,h) and (1R, 2S)-N-methylnorephedrine (for 4e,f,g), respectively.[4]

Effect of these monomeric chiral catalysts (4a-g) was examined in the enantioselective addition of diethylzinc (2) to benzaldehyde. The results are shown in Table 1. When N-butyl series (4a-d) (entries 2-4) and N-methyl series (4e-g) (entries 6-8) are compared, e.e 's of 1-phenylpropanol were higher in the N-butyl series than in the N-methyl series Then, effect of spacer was examined. Among N-butyl series, catalysts with N-benzyloxyalkyl substituents (entries 2,3,5) are more enantioselective than that with N-benzyl substituent (4a) (entry 1). Because the catalyst (4c) was the most enantioselective, polymeric catalyst (4h) with a methylene spacer like monomeric 4c was designed. Using chloromethylated polystyrene (cross linked with 1% divinylbenzene; chlorine content 0 8 mmol/g, 100 - 200 mesh) instead of benzyl chloride, polymer catalyst (1S, 2R)-4h was synthesized from 1,6-hexanediol.

Results of the enantioselective addition of Et_2Zn to aldehydes using the polymer catalyst (4h) are shown in Table 2 Aromatic

Table 1. Effect of the structure of monomer catalysts in the enantioselective addition of diethylzinc to benzaldehyde.

Entry	Aldehyde	Cat	Alcohol (3)			
			$[\alpha]_D$ (temp , *c*, $CHCl_3$)	Yield(%)	E.e.(%)	Config.
1	PhCHO	4a	-40.26 (23, 4.3, $CHCl_3$)	87	89[a]	*S*
2	PhCHO	4b	-43.58 (24, 5.0, $CHCl_3$)	91	96[a]	*S*
3	PhCHO	4c	-44.94 (24, 4.9, $CHCl_3$)	88	99[a]	*S*
4	*n*-$C_8H_{17}CHO$	4c	+6.57 (26, 6.0, EtOH)	79	73[b]	*S*
5	PhCHO	4d	-42.12 (25, 4.6, $CHCl_3$)	91	93[a]	*S*
6	PhCHO	4e	+37 39 (24, 4.8, $CHCl_3$)	93	82[a]	*R*
7	PhCHO	4f	+35.57 (25, 5.3, $CHCl_3$)	81	78[a]	*R*
8	PhCHO	4g	+36.21 (24, 3.9, $CHCl_3$)	92	80[a]	*R*

a) Molar ratio. R^1CHO : Cat. . Et_2Zn = 1.0 : 0.06 : 2 2. Reactions were run in hexane at 0 °C for 40 - 72 h. b) Based on the reported value of optical rotation $[\alpha]_D$ -45.45 (*c* 5.15, $CHCl_3$), R. H. Pickard and J Kenyon, J Chem. Soc., 1914, 1115. c) Based on the reported value of optical rotation. $[\alpha]^{29}_D$ +7.79 (2.1, EtOH) for 87% e.e. (determined by NMR analysis of the corresponding MTPA[5] ester using $Eu(fod)_3$, see ref 3.

Table 2. Enantioselective addition of diethylzinc to aldehydes using polymer catalyst [(1*S*, 2*R*)-4h].

Entry	Aldehyde	$[\alpha]_D$ (temp., *c*, $CHCl_3$)	Yield(%)	E.e.(%)	Config.
1	PhCHO	-37.09 (26, 5.1, $CHCl_3$)	91	82[a]	*S*
2	*n*-$C_8H_{17}CHO$	+6.22 (25, 6 2, EtOH)	75	69[b]	*S*
3[c]	*n*-$C_8H_{17}CHO$	+6.31 (21, 5.2, EtOH)	80	70[b]	*S*
4	$PhCH_2CH_2CHO$	+20.17 (23, 4.7, EtOH)	77	75[d]	*S*

a) See footnote a in Table 1. b) See footnote b in Table 1. c) Recycled catalyst (4h) was used. d) Based on the reported value of optical rotation. $[\alpha]_D$ +26.8 (*c* 5 0, EtOH). T. Sato, Y. Gotoh, Y. Wakabayashi, and T. Fujisawa, Tetrahedron Lett., 1983, *24*, 4123.

aldehyde was ethylated in high e.e (82%, entry 1) and aliphatic aldehyde was ethylated in moderate e e (70%, entries 2,3). There is very little difference in e.e. between those obtained with polymeric 4h and monomeric 4c Among the polymer catalysts so far reported,[1d-f, 2] the present catalyst (4h) is the most enantioselective in the addition of Et_2Zn to aliphatic aldehyde The polymer catalyst (4h) was easily recovered and the recovered catalyst showed no loss of the enantioselectivity (entry 3). The reason of the higher enantioselectivity of 4h than other polymer catalysts in the ethylation of aliphatic aldehyde may be the presence of a methylene spacer which assures the freedom of active site (i e., aminoalcohol).

General procedure: aldehyde (1 mmol) was added to a suspension of polymer catalyst (4h, 0.298 g) in hexane (2 ml) at 0 $^{\circ}$C. The mixture was stirred for 15 min, then Et$_2$Zn (2 2 mmol, 2.2 ml of 1 M hexane solution) was added Stirring was continued for 1 - 8 d, then the reaction was quenched with 1 M hydrochloric acid (5 ml). The catalyst was filtered off, and the filtrate was extracted with dichloromethane The extract was dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure Purification of the residue by silica gel TLC (developing solvent, EtOAc/hexane = 1/4) afforded optically active *sec*-alcohols (3). Optical rotation was measured after the bulb-to-bulb distillation. The recovered catalyst was regenerated as follows. it was treated with THF-3 M HCl(4 1, *v/v*) for 4 h, and filtered, washed with water and THF Then, it was treated with THF-2 M aq NaOH (4 : 1, *v/v*) for 4 h, filtered, and washed with water, THF, and methanol, successively It was dried at 40 $^{\circ}$C in vacuo (2 mm Hg) for 2 h [6]

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4 Satisfactory results were obtained from ^{1}H-NMR, IR, and high resolution mass spectrometric analyses of 4a-g

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