Enantioselective Addition of Diethylzinc to Aldehydes using Chiral Polymer Catalysts Possessing a Methylene Spacer

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N-Butylnorephedrine supported on polystyrene resin *via* a six-methylene spacer catalyses the enantioselective addition of diethylzinc to both aromatic and aliphatic aldehydes, providing optically active secondary alcohols in good to high enantiomeric excesses. In the enantioselective addition of diethylzinc to an aliphatic aldehyde, polymer catalyst with a six-methylene spacer is more enantioselective than other previously reported polymer catalysts.

Polymer-supported chiral catalysts have attracted increasing interest.[1] It is possible to achieve the enantioselective carbon–carbon bond-forming reaction using a synthetic polymer catalyst.[2] Furthermore, it has attracted our attention in view of its easy separation from the reaction mixture and the recyclability of the polymer-supported chiral catalyst. These catalysts are also considered to be simplified analogues of biologically active macromolecules, *i.e.*, enzymes. However, the catalytic activity and enantioselectivity of polymer catalysts are often lower than those of the corresponding monomer chiral catalysts. For example, quinine (monomer)-catalysed asymmetric Michael addition for 5 h affords the product with 55% e.e. in 93% yield, whereas the corresponding polymeric quinine-catalysed asymmetric Michael addition requires a much longer reaction time (48 h) and affords the product with only 24% e.e.[2a] This is probably because the steric hindrance of the polymer matrix may restrict the freedom and mobility of the catalytic site.

Enantioselective addition of dialkylzincs to aldehydes using chiral catalysts is of current interest.[3] We have reported highly enantioselective reactions using chiral catalysts such as *N*,*N*-dibutylnorephedrine (DBNE),[4a,c] diphenyl(1-methylpyrrolidin-2-yl)methanol (DPMPM),[4b,c] chiral ammonium salts,[5] and chiral piperazines.[6] Among these chiral catalysts, DBNE is a highly efficient catalyst not only for aromatic aldehydes but also for aliphatic aldehydes. Moreover, we reported the enantioselective addition of dialkylzincs to aldehydes using *N*-alkylnorephedrine directly attached to a polystyrene resin.[7,8] However, the enantioselectivity of the addition to aliphatic aldehydes remains only moderate (56% e.e.).[7b]† Because *N*-alkylnorephedrine is directly attached to the benzyl group of the polystyrene resin, the freedom of the catalytic site of these catalysts may be limited by the framework of polystyrene.

In this paper, we describe the enantioselective addition of dialkylzincs to both aromatic and aliphatic aldehydes using polymer-bound chiral catalysts having a spacer.[10] In order to eliminate the restriction of the freedom of the catalytic site, we synthesized chiral polymer catalysts with a methylene spacer that can separate the catalytic site from the polystyrene resin.

† In our previous paper,[7b] we reported that the e.e. of the obtained (*S*)-undecan-3-ol **6b** $\{[\alpha]_D^{25}$ +4.99° (*c* 7.6, EtOH)$\}$ was 80% e.e. based on the reported value for the optical rotation $\{[\alpha]_D^{26}$ −6.22° (EtOH) (ref. 9)$\}$. However, based on the value of footnote *a* in Table 1, the e.e. should be corrected to 56% e.e.

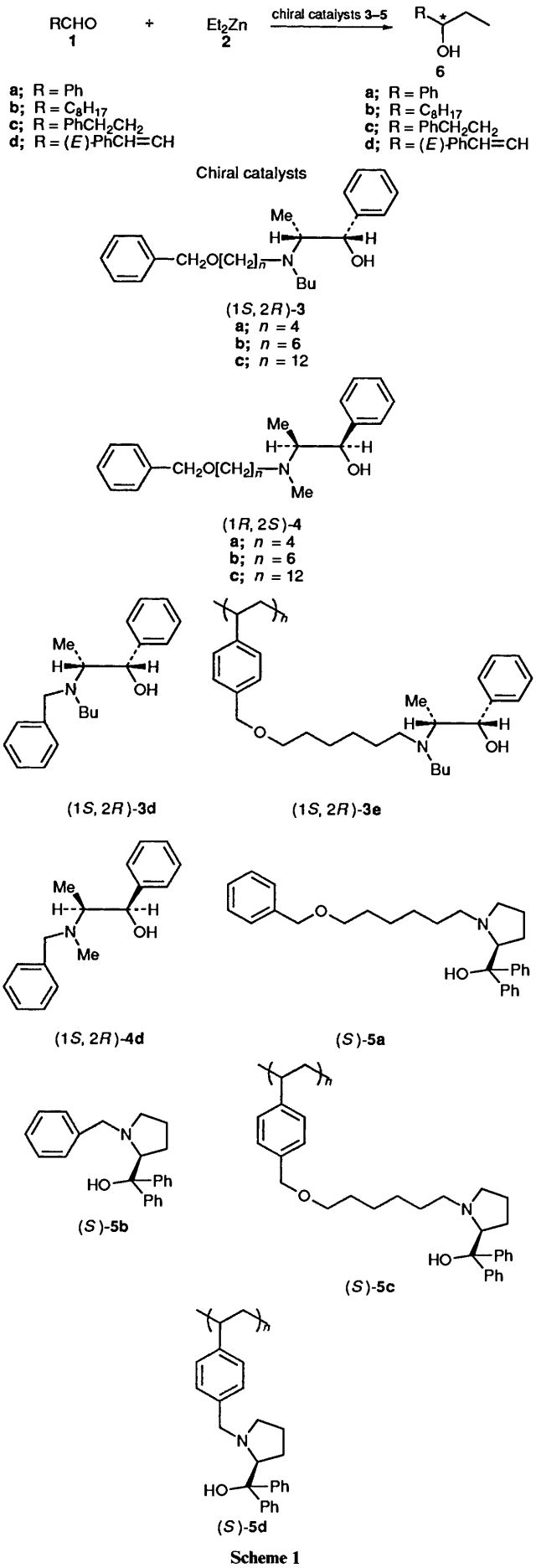
‡ Polystyrene resin contains aromatic rings at a concentration of ~9.6 mmol g^{-1}. Therefore, a chlorine content of 0.8 mmol g^{-1} means that ~8% of the aromatic rings are chloromethylated.

Results and Discussion

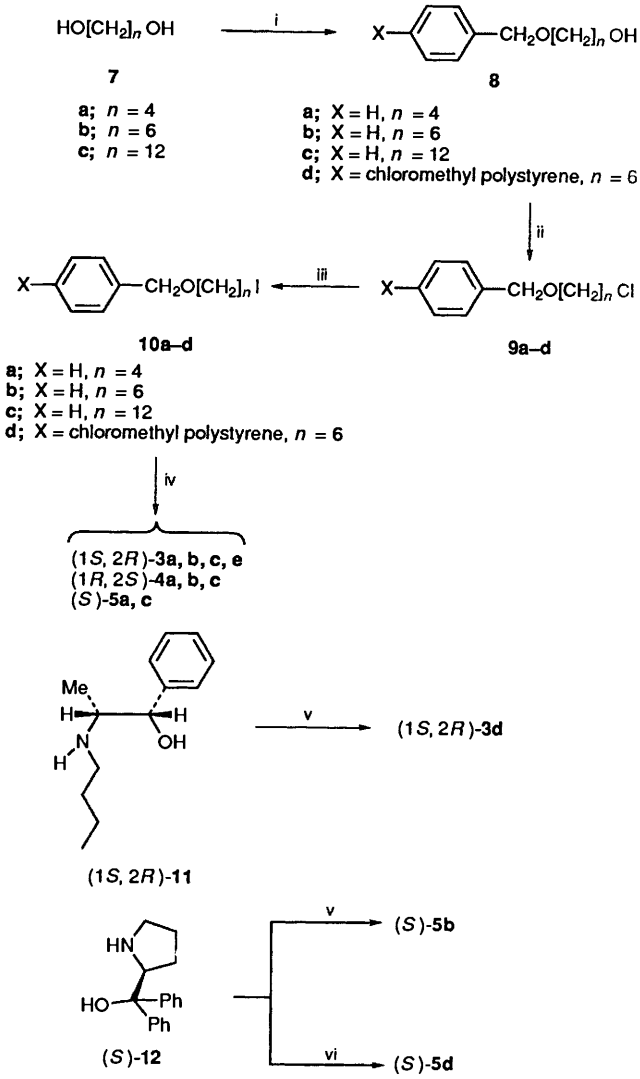
The enantioselectivities of the addition of dialkylzincs to aldehydes are highly dependent on the structures of the substituents on the nitrogen atom of the monomer catalyst.[4a,b] In designing chiral polymer catalysts, it is necessary to consider the related monomer catalysts. In order to determine the most suitable spacer between the benzyl group of the polystyrene resin and the nitrogen atom of the chiral amino alcohol, we first elucidated the relationship between the structures of monomer catalysts and their enantioselectivities.

Chiral monomer catalysts having substituents with various chain lengths on the nitrogen atom were synthesized by the following procedures (Scheme 2); (i) Alkane-1,ω-diols **7a–c** were converted into the corresponding monobenzyloxy alcohols **8a–c** by the reaction with benzyl chloride in the presence of sodium hydride. (ii) Compounds **8a–c** were converted into the corresponding chloro ethers **9a–c** in refluxing thionyl dichloride, then into the iodo ethers **10a–c** with sodium iodide. (iii) Chiral catalysts **3a–c**, **4a–c**, **5a** were obtained by the reactions of iodides **10a–c** with (1*S*,2*R*)-*N*-butylnorephedrine **11** for **3a–c** and (1*R*,2*S*)-*N*-methylnorephedrine (ephedrine) for **4a–c** and (*S*)-diphenyl(pyrrolidin-2-yl)methanol **12** for **5a**, respectively. Polystyrene-derived iodo ether **10d** was synthesized in the same manner as the preparation of monomer iodo ethers **10a–c** using chloromethylated polystyrene (1% divinylbenzene; chlorine content 0.8 mmol g^{-1}; 100–200 mesh)‡ instead of benzyl chloride. We adopted this chloromethylated polystyrene because it is commercially available and is widely utilized in solid-phase peptide synthesis. Reactions of compound **10d** with (1*S*,2*R*)-**11** and (*S*)-**12** afforded chiral polymer catalysts (1*S*,2*R*)-**3e** (content of amino alcohol moiety is up to 0.085 mmol g^{-1}) and (*S*)-**5c** (content of amino alcohol moiety is up to 0.25 mmol g^{-1}), respectively. Polymer catalyst (*S*)-**5d** was prepared from compound (*S*)-**12** and chloromethylated polystyrene.

We examined the enantioselective addition of diethylzinc **2** to benzaldehyde **1a** at 0 °C in the presence of 5–6 mol% monomer catalyst. The results are shown in Table 1. When comparing the butyl and methyl substituents on the nitrogen atom of the norephedrine-derived chiral catalysts, all of the catalysts possessing a butyl substituent on the nitrogen atom (**3a–c**) (entries 1–3) gave 1-phenylpropan-1-ol **6a** with higher (93–99%) e.e.s than did the chiral catalysts possessing a methyl substituent on the nitrogen atom (**4a–c**) (78–82% e.e.s) (entries 5–7). *N*-Alkyl-*N*-benzylnorephedrines **3d** and **4d** were also examined for comparison (entries 4 and 8). As a result, the most enantioselective (99% e.e.) monomer chiral catalyst was found to be compound **3b** that possesses butyl and 6-benzyloxyhexyl (six-



Scheme 1



Scheme 2 Synthesis of chiral catalysts **3**–**5**. *Reagents:* i, NaH–$PhCH_2Cl$ or chloromethylated polystyrene–DMF; ii, $SOCl_2$; iii, NaI–acetone; iv, *N*-alkylnorephedrine or **12**–K_2CO_3; v, $PhCH_2Br$–K_2CO_3; vi, chloromethylated polystyrene–K_2CO_3.

methylene spacer) substituents on the nitrogen atom of the catalyst (entry 2). Catalyst **3b** was also effective for the enantioselective addition of Et_2Zn to an aliphatic aldehyde (nonanal). (*S*)-Undecan-3-ol **6b** with 73% e.e. was obtained in 79% yield (entry 11).

The chiral pyrrolidinylmethanol derivative **5a** with a 6-benzyloxyhexyl (six-methylene spacer) substituent on the nitrogen atom was then examined. The effect of the methylene spacer of the substituent on the nitrogen atom was again significant. The catalyst **5a** afforded (*S*)-**6a** with a much higher e.e. (81% e.e., entry 9) than did the catalyst **5b** with a benzyl substituent on the nitrogen atom (43% e.e., entry 10).

Based on the above mentioned results, the six-methylene, *i.e.*, hexyl, group was chosen as the best spacer to introduce the polystyrene resin.

We examined the enantioselective ethylation of benzaldehyde and an aliphatic aldehyde in the presence of 3 mol% (based on the amino alcohol moiety) chiral polymer catalysts **3e**. The polymer catalyst doesn't swell in hexane and does swell in toluene. We previously observed that the yield and e.e. of the obtained alcohols are higher in the reaction run in hexane than in the reaction run in toluene in the enantioselective addition of dialkylzinc to aldehydes using ephedrine supported on polystyrene.[7b] Based on the previous results, the swelling of the

Table 1 Enantioselective addition of diethylzinc **2** to aldehydes by using chiral monomer catalysts

Entry	Aldehyde **1**		Catalyst	Number of methylene groups (*n*)	Time (*t*/h)	Alcohol **6** Yield (%)	$[\alpha]_D$ (*c*, solvent)	E.e.[a] (%)	Config.
1	Ph	**1a**	**3a**	4	48	**6a** 91	$[\alpha]^{24}$ −43.58 (4.96, $CHCl_3$)	96	*S*
2	Ph	**1a**	**3b**	6	40	**6a** 88	$[\alpha]^{24}$ −44.94 (4.91, $CHCl_3$)	99	*S*
3	Ph	**1a**	**3c**	12	48	**6a** 91	$[\alpha]^{25}$ −42.12 (4.59, $CHCl_3$)	93	*S*
4	Ph	**1a**	**3d**		72	**6a** 87	$[\alpha]^{23}$ −40.26 (4.32, $CHCl_3$)	89	*S*
5	Ph	**1a**	**4a**	4	48	**6a** 93	$[\alpha]^{24}$ +37.39 (4.75, $CHCl_3$)	82	*R*
6	Ph	**1a**	**4b**	6	48	**6a** 81	$[\alpha]^{25}$ +35.57 (5.34, $CHCl_3$)	78	*R*
7	Ph	**1a**	**4c**	12	40	**6a** 92	$[\alpha]^{24}$ +36.21 (3.98, $CHCl_3$)	80	*R*
8	Ph	**1a**	**4d**		45	**6a** 98	$[\alpha]^{25}$ +41.62 (5.28, $CHCl_3$)	92	*R*
9	Ph	**1a**	**5a**	6	21	**6a** 92	$[\alpha]^{25}$ −36.61 (5.19, $CHCl_3$)	81	*S*
10	Ph	**1a**	**5b**		16	**6a** 100	$[\alpha]^{24}$ −19.45 (5.19, $CHCl_3$)	43	*S*
11	$Me[CH_2]_7$	**1b**	**3b**	6	30	**6b** 79	$[\alpha]^{26}$ +6.57 (5.99, EtOH)	73	*S*
12	$Me[CH_2]_7$	**1b**	**5a**	6	24	**6b** 90	$[\alpha]^{21}$ +5.80 (9.81, EtOH)	65	*S*

[a] Based on the reported values of optical rotation $[\alpha]_D$ −45.45 (*c* 5.15, $CHCl_3$) for (*S*)-**6a** (ref. 11); $[\alpha]_D^{29}$ +7.79 (*c* 2.1, EtOH) for (*S*)-**6b** with 87% e.e. which was determined by NMR analysis of the corresponding MTPA ester by using $Eu(fod)_3$. See ref. 4*a*.

Table 2 Enantioselective addition of diethylzinc **2** to aldehydes by using chiral polymer catalysts

Entry	Aldehyde **1**		Catalyst	Time (*t*/h)	Alcohol **6** Yield (%)	$[\alpha]_D$ (*c*, solvent)	E.e.[a] (%)	Config.
1	Ph	**1a**	**3e**	45	**6a** 91	$[\alpha]^{26}$ −37.09 (5.12, $CHCl_3$)	82	*S*
2	$Me[CH_2]_7$	**1b**	**3e**	96	**6b** 75	$[\alpha]^{25}$ +6.22 (6.15, EtOH)	69	*S*
3[b]	$Me[CH_2]_7$	**1b**	**3e**	192	**6b** 80	$[\alpha]^{21}$ +6.31 (5.24, EtOH)	71	*S*
4	$PhCH_2CH_2$	**1c**	**3e**	24	**6c** 77	$[\alpha]^{23}$ +20.17 (4.72, $CHCl_3$)	75	*R*
5	(*E*)-PhCH=CH	**1d**	**3e**	24	**6d** 53	$[\alpha]^{22}$ −5.81 (3.53, $CHCl_3$)	51	*S*
6	Ph	**1a**	**5c**	24	**6a** 91	$[\alpha]^{25}$ −27.59 (5.12, $CHCl_3$)	61	*S*
7	$Me[CH_2]_7$	**1b**	**5c**	72	**6b** 70	$[\alpha]^{24}$ +4.37 (6.51, EtOH)	49	*S*
8	Ph	**1a**	**5d**	77	**6a** 68	$[\alpha]^{23}$ −10.94 (5.01, $CHCl_3$)	24	*S*

[a] Based on the reported values of optical rotation. See footnote *a* in Table 1 for compounds **6a** and **6b**. $[\alpha]_D$ +26.8 (*c* 5.0, EtOH) for (*R*)-**6c** (ref. 12); $[\alpha]_D^{22}$ −5.7 ($CHCl_3$) for (*S*)-**6d** in 96% e.e. determined by HPLC analysis using a chiral column (ref. 13). [b] Recycled catalyst **3e** was used.

polymer catalyst should be avoided in the enantioselective addition of dialkylzincs to aldehydes. Therefore, we chose hexane as a solvent. The results are shown in Table 2. The reaction of benzaldehyde **1a** and diethylzinc **2** in hexane for 45 h with compound **3e** as chiral polymer catalyst afforded (*S*)-(−)-1-phenylpropan-1-ol **6a** with 82% e.e. in 91% yield (entry 1). Chiral polymer catalysts didn't swell in hexane. Enantioselective ethylation of an aliphatic aldehyde (nonanal) using chiral polymer catalyst **3e** afforded (*S*)-undecan-3-ol **6b** with 69% e.e. in 75% yield (entry 2). Furthermore, catalyst **3e** was easily removed from the reaction mixture by simple filtration after the reaction. The recycled catalyst **3e** was successfully used again without any loss in catalytic activity and enantioselectivity (80%, 71% e.e., entry 3). To the best of our knowledge, the present enantioselectivity (71% e.e.) is the highest for the addition of a dialkylzinc to an aliphatic aldehyde using a chiral polymer catalyst. 3-Phenylpropanal **1c** was also ethylated in 75% e.e. (entry 4). On the other hand, in the reactions using chiral polymer catalysts containing an (*S*)-diphenyl(pyrrolidin-2-yl)methanol moiety, the effect of the methylene spacer was also remarkable. Thus, ethylation of benzaldehyde using polymer catalyst **5c** (8 mol% based on the amino alcohol moiety) with a six-methylene spacer afforded an optically active alcohol with moderate (61%) e.e. (entry 6), whereas catalyst **5d** without a spacer afforded an alcohol with only a low e.e. (entry 8).

The relationship between the structures of the monomer and polymer chiral catalysts and their enantioselectivities in the addition of Et_2Zn to benzaldehyde and nonanal is shown in Fig. 1.

In a comparison of compound (1*R*,2*S*)-**4d** and the corresponding polymer-supported compound (1*R*,2*S*)-**13**, the enantioselectivities of both in catalysing the addition to benzaldehyde **1a** is seen to be high (92 and 89% e.e.). However, the enantioselectivity of catalyst **13** *without* a six-methylene spacer in the addition to nonanal **1b** is low. In a comparison between (1*S*,2*R*)-**3d** and the corresponding polymer-supported catalyst (1*S*,2*R*)-**14** *without* a six-methylene spacer, the enantioselectivities of compound **3d** in the addition to both benzaldehyde and nonanal are much higher than those of catalyst **14**. In these cases, the enantioselectivities of polymer catalysts **13** and **14** for the alkylation of aliphatic aldehydes drop considerably. One of the reasons for the result may be that aliphatic nonanal cannot be orientated in a sterically effective direction in the transition state because of the steric repulsion between the alkyl substituent of nonanal and polystyrene.

In contrast to the results described above, the enantioselectivities of (1*S*,2*R*)-**3b** and the corresponding polymer-supported (1*S*,2*R*)-**3e** possessing a six-methylene spacer are, in all cases, good to high. Surprisingly, the enantioselectivities of catalysts **3b** and **3e** for the formation of aliphatic alcohol (*S*)-**6b** are almost the same (73 and 71% e.e.). Thus, the chiral polymer catalyst possessing the six-methylene spacer is effective for high enantioselectivities especially in the reaction of an aliphatic aldehyde. It is admitted that distinguishing the enantioface of aliphatic aldehydes especially with a straight-chain substituent is more difficult than that for aromatic aldehydes. The role of the six-methylene spacer in polymer catalyst **3e** is considered to be two-fold. (1) A methylene spacer prevents the steric repulsion between the active site of the catalyst (*N*-butylnorephedrine)

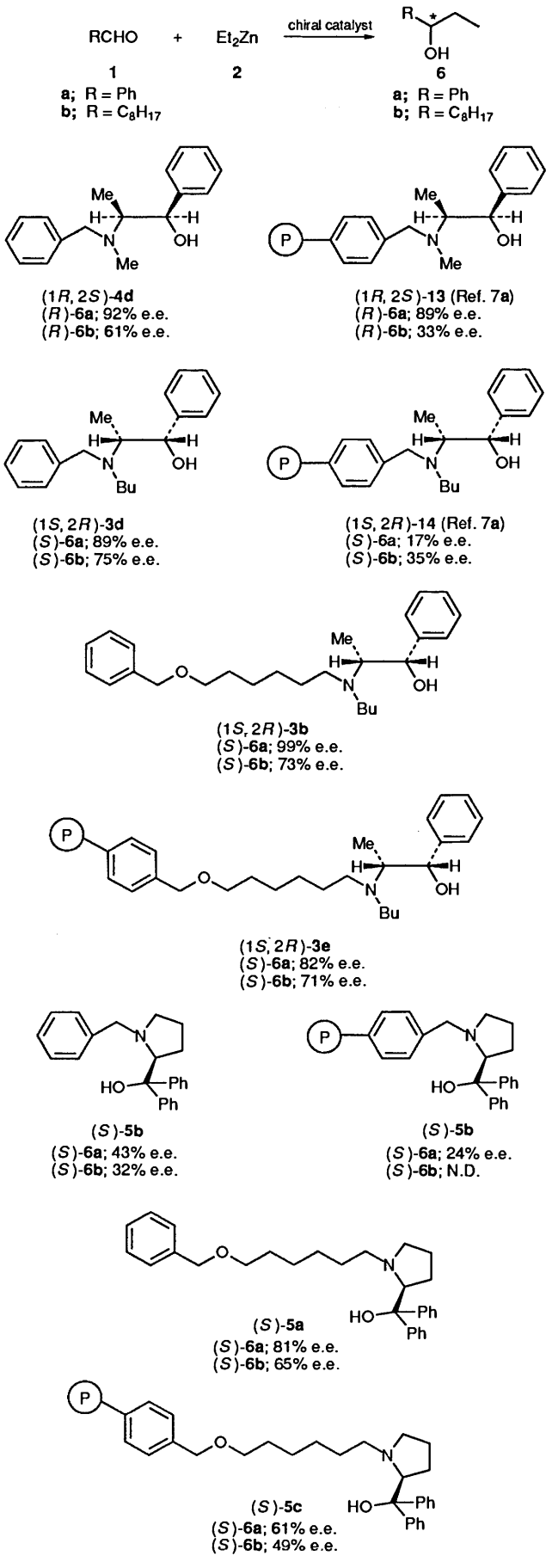


Fig. 1 Relationship between the structure of chiral catalysts and the e.e. of the obtained alcohols

and the polystyrene. (2) A methylene spacer as a substituent on the nitrogen atom of *N*-butylnorephedrine assists the stereochemical control of the reaction. This is supported by the fact that DBNE[4a] is an highly enantioselective chiral catalyst for aliphatic aldehydes. The effect of the six-methylene spacer also occurs in polymer catalysts (*S*)-**5c** and (*S*)-**5d**. Enantioselectivities of compound **5c** with a six-methylene spacer is higher than that of analogue **5d** without the six-methylene spacer, although the level of enantioselectivity of catalyst **5c** is lower than that of compound **3e**.

In conclusion, optically active secondary alcohols of high e.e.s were obtained from the enantioselective addition of Et_2Zn to both aromatic and aliphatic aldehydes when using a chiral polymer catalyst possessing a six-methylene spacer. The polymer catalyst is recyclable.

Experimental

General.—IR spectra, ^1H NMR spectra, and optical rotations (given in units of 10^{-1} deg cm^2 g^{-1}) were recorded with an Hitachi 260-10 spectrophotometer, a JEOL JNM-PMX-60 spectrometer and a JASCO DIP-181 polarimeter, respectively. Bulb-to-bulb distillation was carried out with a Shibata Glass Tube Oven GTO-250. Hexane was distilled over lithium aluminium hydride. All reactions were carried out under argon.

Materials.—Diethylzinc **2** in hexane was purchased from Kanto Chemical Co. (1*S*,2*R*)-*N*-Butylnorephedrine **11**,[7b] (1*R*,2*S*)-*N*-benzylephedrine **4d**,[8a,d] and (*S*)-diphenyl(pyrrolidin-2-yl)methanol **12**[14] were prepared according to the respective literature procedure. Chloromethylated polystyrene resin (1% divinylbenzene; chlorine content 0.8 mmol g^{-1}; 100–200 mesh) was purchased from Wako Pure Chemical Industries.

Synthesis of (1S,2R)-2-{N-[4-(*Benzyloxy*)*butyl*]-N-*butylamino*}-1-*phenylpropan*-1-*ol* **3a**.—To a cold solution of butane-1,4-diol **7a** (2.72 g, 30.1 mmol) in dry dimethylformamide (DMF) (15 cm^3) was added sodium hydride (0.422 g, 10.5 mmol) at 0 °C, then benzyl chloride (1.15 cm^3, 10.0 mmol) was added. The reaction mixture was heated at 60 °C for 2 h, quenched with water (100 cm^3) at 0 °C, and extracted with diethyl ether (75 cm^3 × 3). The ethereal layer was dried over sodium sulfate and was then evaporated under reduced pressure. The residue was purified by silica gel column chromatography to afford 4-(benzyloxy)butan-1-ol **8a** (1.49 g, 83%).

A mixture of the alcohol **8a** (1.49 g, 8.24 mmol), thionyl dichloride (1.2 cm^3, 16.5 mmol) and pyridine (0.8 cm^3, 9.89 mmol) was refluxed for 2 h. The reaction mixture was poured into crushed ice–water, and was extracted with diethyl ether (25 cm^3 × 4). The combined extracts were dried over sodium sulfate and then evaporated under a reduced pressure. The residue was purified by silica gel column chromatography to afford 1-benzyloxy-4-chlorobutane **9a** (1.11 g, 68%).

To a solution of sodium iodide (0.976 g, 16.5 mmol) in acetone (5 cm^3) was added a solution of the chloride **9a** (0.603 g, 3.04 mmol) in acetone (2 cm^3) at room temperature, then the reaction mixture was refluxed for 3 h. The solvent was evaporated off under reduced pressure. The residue was extracted with diethyl ether (25 cm^3 × 3), washed with aq. sodium hydrogen sulfite, dried over sodium sulfate, and evaporated under reduced pressure. 1-Benzyloxy-4-iodobutane **10a** was obtained (0.763 g, 87%).

A mixture of (1*S*,2*R*)-**11** (0.103 g, 0.498 mmol),[7b] the iodide **10a** (0.153 g, 0.527 mmol) and potassium carbonate (0.094 g, 0.681 mmol) in acetonitrile (2.5 cm^3) was refluxed for 22 h. The reaction mixture was extracted with diethyl ether (10 cm^3 × 3) and the combined organic layer was dried over sodium sulfate

and evaporated under reduced pressure. The residue was purified by silica gel column chromatography to afford *title compound* (1*S*,2*R*)-**3a** in 49% yield (0.089 g), $[\alpha]_D^{24}$ −7.17 (*c* 1.47, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3410, 3040, 3010, 2920, 2850, 1495, 1450, 1365, 1210 and 1095; δ($CDCl_3$) 0.63–1.78 (14 H, m), 2.13–3.21 (5 H, m), 3.21–4.00 (3 H, m), 4.48 (2 H, s), 4.54–4.78 (1 H, m) and 7.00–7.54 (10 H, m) (Found: M^+, 369.2653. Calc. for $C_{24}H_{35}NO_2$: *M*, 369.2670).

Synthesis of (1S,2R)-2-{N-[6-(*Benzyloxy*)*hexyl*]-N-*butylamino*}-1-*phenylpropan*-1-*ol* **3b**.—Compound **3b** was synthesized from (1*S*,2*R*)-*N*-butylnorephedrine **11** and 1-benzyloxy-6-iodohexane **10b** according to the same procedure as that described in the synthesis of its analogue **3a**. Yield of product **3b** was 36%; $[\alpha]_D^{20}$ −10.84 (*c* 2.03, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3440, 3050, 2945, 2860, 1500, 1460 and 1370; δ($CDCl_3$) 0.66–1.79 (18 H, m), 2.20–3.12 (5 H, m), 3.12–3.86 (3 H, m), 4.53 (2 H, s), 4.63–4.79 (1 H, d) and 7.28–7.48 (10 H, m) (Found: M^+, 397.2983. Calc. for $C_{26}H_{39}NO_2$: *M*, 397.2983).

Synthesis of (1S,2R)-2-{N-[12-(*Benzyloxy*)*dodecyl*]-N-*butylamino*}-1-*phenylpropan*-1-*ol* **3c**.—Compound **3c** was synthesized from (1*S*,2*R*)-**11** and 1-benzyloxy-12-iodododecane **10c** according to the same procedure as described in the synthesis of compound **3a**. Yield of product **3c** was 26%; $[\alpha]_D^{25}$ −7.42 (*c* 2.09, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3400, 3000, 2905, 2825, 1485, 1440 and 1345; δ($CDCl_3$) 0.69–2.00 (30 H, m), 2.17–3.86 (8 H, m), 4.46 (2 H, s), 4.56–4.74 (1 H, d) and 7.17–7.40 (10 H, m) (Found: M^+, 481.3953. Calc. for $C_{32}H_{51}NO_2$: *M*, 481.3923).

Synthesis of (1R,2S)-2-{N-[4-(*Benzyloxy*)*butyl*]-N-*methylamino*}-1-*phenylpropan*-1-*ol* **4a**.—Compound **4a** was synthesized from (1*R*,2*S*)-ephedrine and 1-benzyloxy-4-iodobutane **10a** according to the same procedure as that described in the synthesis of compound **3a**. Yield of product **4a** was 64%; $[\alpha]_D^{25}$ −1.01 (*c* 2.27, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3420, 3025, 2945, 2855, 1500, 1455 and 1370; δ($CDCl_3$) 0.66–1.03 (3 H, d), 1.40–2.73 (4 H, m), 2.17–3.03 (3 H, m), 2.23 (3 H, s), 3.30–3.73 (3 H, m), 4.50 (2 H, s), 4.73–4.89 (1 H, d) and 7.13–7.51 (10 H, m) (Found: M^+, 327.2155. Calc. for $C_{21}H_{29}NO_2$: *M*, 327.2200).

Synthesis of (1R,2S)-2-{N-[6-(*Benzyloxy*)*hexyl*]-N-*methylamino*}-1-*phenylpropan*-1-*ol* **4b**.—Compound **4b** was synthesized from (1*R*,2*S*)-ephedrine and 1-benzyloxy-6-iodohexane **10b** according to the same procedure as that described in the synthesis of compound **3a**. Yield of compound **4b** was 68%; $[\alpha]_D^{25}$ −2.72 (*c* 2.02, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3430, 3030, 2945, 2855, 1500, 1460 and 1360; δ($CDCl_3$) 0.76–1.07 (3 H, d), 1.03–1.89 (8 H, m), 2.07–3.07 (3 H, m), 3.23 (3 H, s), 3.26–3.77 (3 H, m), 4.49 (2 H, s), 4.68–4.86 (1 H, d) and 7.03–7.43 (10 H, m) (Found: M^+, 355.2494. Calc. for $C_{23}H_{33}NO_2$: *M*, 355.2516).

Synthesis of (1R,2S)-2-{N-[12-(*Benzyloxy*)*dodecyl*]-N-*methylamino*}-1-*phenylpropan*-1-*ol* **4c**.—Compound **4c** was synthesized from (1*R*,2*S*)-ephedrine and 1-benzyloxy-12-iodododecane **10c** according to the same procedure as that described in the synthesis of compound **3a**. Yield of compound **4c** was 33%; $[\alpha]_D^{20}$ −2.90 (*c* 2.07, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3450, 3050, 2945, 2860, 1510, 1475 and 1385; δ($CDCl_3$) 0.73–1.03 (3 H, d), 1.03–1.96 (20 H, m), 2.18–2.92 (6 H, m), 3.30–3.68 (3 H, m), 4.45 (2 H, s), 4.69–4.86 (1 H, d) and 7.13–7.36 (10 H, m) (Found: M^+, 439.3440. Calc. for $C_{29}H_{45}NO_2$: *M*, 439.3453).

Synthesis of (S)-{1-[6-(*Benzyloxy*)*hexyl*]*pyrrolidin*-2-*yl*}*diphenylmethanol* **5a**.—Compound **5a** was synthesized from (*S*)-**12** and 1-benzyloxy-6-iodohexane **10b** according to the same procedure as that described in the synthesis of compound **3a**. Yield of product **5a** was 65%; $[\alpha]_D^{26}$ +24.51 (*c* 3.24, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3300, 3050, 3020, 2920, 2850, 1495, 1445 and 1370; δ($CDCl_3$) 0.69–2.56 (15 H, m), 2.96–3.86 (4 H, m), 4.46 (2 H, s), 4.25–4.67 (1 H, br s) and 6.86–7.69 (15 H, m) (Found: M^+, 443.2815. Calc. for $C_{30}H_{37}NO_2$: *M*, 443.2826).

General Procedure for the Preparation of Polymer-bound Chiral Catalysts with Methylene Spacer.—To a cold solution of hexane-1,6-diol **7b** (4.52 g, 38.3 mmol) in DMF (30 cm^3) was added sodium hydride (0.522 g, 13.0 mmol) at 0 °C. After the mixture had been stirred for 30 min, chloromethylated polystyrene (6.52 g) was added. The reaction mixture was heated at 60 °C for 50 h and the reaction mixture was then quenched with water at 0 °C. The polymer was collected by filtration and was washed successively with water, benzene and methanol. After being dried *in vacuo* at 40 °C for 4 h, the polymer **8d** (6.71 g) was obtained.

A suspension of polymer **8d** (6.39 g) in thionyl dichloride (40 cm^3) was refluxed for 48 h. Then the thionyl dichloride was evaporated off under reduced pressure and the polymer was washed successively with water, tetrahydrofuran (THF) and methanol. After being dried *in vacuo* at 40 °C for 4 h, the chlorinated polymer **9d** (6.33 g) was obtained.

To a solution of sodium iodide (2.84 g, 18.9 mmol) in acetone (35 cm^3) was added compound **9d** (5.81 g). The reaction mixture was refluxed for 48 h. The polymer was collected by filtration and was then washed successively with water, THF and methanol. After being dried *in vacuo* at 40 °C for 4 h, the polymer **10d** (5.97 g) was obtained.

A mixture of (1*S*,2*R*)-*N*-butylnorephedrine **11** (0.443 g, 2.14 mmol), the polymer **10d** (1.44 g), and potassium carbonate (0.278 g, 2.0 mmol) in toluene (5 cm^3) was refluxed for 100 h. The polymer was collected by filtration and was then washed successively with water, THF and methanol. After being dried *in vacuo* at 40 °C for 4 h, chiral polymer **3e** (1.28 g) was obtained. (1*S*,2*R*)-*N*-Butylnorephedrine **11** was recovered (0.420 g), which indicates that 0.023 g (0.443 − 0.420 = 0.023) of compound **11** was supported on chiral polymer **3e** (1.28 g). Thus, the content of amino alcohol moiety of chiral polymer **3e** is considered to be up to 0.085 mmol g^{-1}. Chiral polymer **5c** (the content of amino alcohol moiety is considered to be up to 0.25 mmol g^{-1}) was synthesized by the reaction of polymer **10d** and compound (*S*)-**12** according to the same procedure as described above.

Synthesis of (1S,2R)-N-*Benzyl*-N-*butylnorephedrine* **3d**.—A mixture of compound (1*S*,2*R*)-**11** (0.207 g, 1 mmol), benzyl bromide (0.171 g, 1 mmol) and potassium carbonate (0.138 g, 1 mmol) in ethanol was refluxed for 17 h. Ethanol was evaporated off under reduced pressure, and water was added. The mixture was extracted with diethyl ether. The organic layer was dried (Na_2SO_4), evaporated, and purified by silica gel TLC. Title compound (1*S*,2*R*)-**3d** was obtained in 91% yield; $[\alpha]_D^{24}$ +12.86 (*c* 5.00, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3420, 3060, 3020, 2960, 2930, 2870, 1500, 1455 and 1380; δ($CDCl_3$) 0.5–1.80 (10 H, m), 2.17–2.53 (2 H, m), 2.76–3.66 (4 H, m), 4.53–4.73 (1 H, d) and 6.89–7.50 (10 H, m).

Synthesis of (S)-(1-*Benzylpyrrolidin*-2-*yl*)*diphenylmethanol* **5b**.—Compound (*S*)-**5b** was prepared in a similar manner to compound (1*S*,2*R*)-**3d** by using (*S*)-**12** instead of compound (1*S*,2*R*)-**11**. Yield was 97%; $[\alpha]_D^{22}$ +96.34 (*c* 2.02, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3260, 3030, 2960, 2790, 1600, 1500, 1450 and 1390; δ($CDCl_3$) 1.31–3.31 (8 H, m), 3.76–4.01 (1 H, m), 4.40–4.87 (1 H, m) and 6.87–7.84 (15 H, m).

General Procedure for the Enantioselective Addition of Aldehydes by using a Chiral Monomer Catalyst.—To a cold solution of monomer catalyst **3b** (0.0177 g, 0.045 mmol) in hexane (1.5 cm^3) was added the appropriate aldehyde (0.738 mmol) at

0 °C. After the mixture had been stirred for 10 min, diethylzinc **2** (1.6 cm^3 of a 1 mol dm^{-3} hexane solution) was added dropwise. The reaction mixture was stirred at 0 °C for 40 h and was then quenched with 1 mol dm^{-3} HCl (3 cm^3). The organic layer was separated and the aqueous layer was extracted with dichloromethane (15 cm^3 × 3). The combined extracts were dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue purified by silica gel TLC. Optically active secondary alcohols **6** with 43–99% e.e.s were obtained in 79–100% yield.

General Procedure for the Enantioselective Addition of Aldehydes by using a Chiral Polymer Catalyst.—To a cold suspension of polymer catalyst **3e** (3 mol% based on the amino alcohol moiety) in hexane (2 cm^3) was added the appropriate aldehyde (0.984 mmol) at 0 °C. After the mixture had been stirred for 10 min, diethylzinc **2** (2.2 cm^3 of 1 mol dm^{-3} hexane solution) was added dropwise. The reaction mixture was stirred at room temperature for 45 h and was then quenched with 1 mol dm^{-3} HCl (3 cm^3). The polymer catalyst was removed by filtration and was washed with dichloromethane. The filtrate was extracted with dichloromethane (15 cm^3 × 3). The combined extracts were dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was purified by silica gel TLC. Optically active secondary alcohols **6** with 49–82% e.e.s were obtained in 51–91% yield.

Recovery of Polymer Catalyst **3e**.—The recovery and recycling of polymer catalyst was carried out by the same procedure as previously described.[7b] The recovered polymer catalyst was stirred for 4 h in a 4:1 mixture of THF–2 mol dm^{-3} HCl. The polymer was filtered off and was washed successively with water and a 4:1 mixture of THF–2 mol dm^{-3} HCl. Then the polymer was stirred again for 4 h in a 4:1 mixture of THF–2 mol dm^{-3} NaOH, filtered off, and washed successively with water, MeOH, THF, aq. THF, THF and MeOH. After being dried *in vacuo* at 40 °C, the recycled polymer catalyst was used in the enantioselective addition of diethylzinc to aldehyde.

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