Chiral N,N-Dialkylnorephedrines as Catalysts of the Highly Enantioselective Addition of Dialkylzincs to Aliphatic and Aromatic Aldehydes. The Asymmetric Synthesis of Secondary Aliphatic and Aromatic Alcohols of High Optical Purity[1]

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The chiral *N,N*-dialkylnorephedrine-catalyzed addition of dialkylzincs to aliphatic and aromatic aldehydes afforded secondary alcohols of high optical purity (to >95% ee). Among the *N,N*-di(*primary* alkyl)norephedrines, *N,N*-di-*n*-butylnorephedrine (DBNE, **3d**) was found to be the most effective catalyst. 1-Phenyl-2-(1-pyrrolidinyl)propan-1-ol (**3i**) and *N,N*-diallylnorephedrine (**3j**) were also highly effective catalysts. The method described provides optically active secondary *aliphatic* alcohols of high optical purity which cannot be prepared by conventional methods.

Introduction

Compared to optically active secondary *aromatic* alcohols, optically active secondary *aliphatic* alcohols are difficult to synthesize. The number of secondary aliphatic alcohols that have been prepared by the asymmetric reduction of ketones[2] or by the asymmetric hydroboration of alkenes[3] is somewhat limited. Only methyl ketones and ketones with a side chain at the α- or β-position have been reduced.[2] Asymmetric hydroboration is most typically applied to symmetric olefins like, for example, *cis*-2-butene, which affords 2-butanol (ethylmethylcarbinol).[3]

On the other hand, most of the enantioselective additions of dialkylzincs to aldehydes involving the use of chiral catalysts[4,5] have utilized *aromatic* aldehydes, which afford optically active secondary *aromatic* alcohols. The enantioselectivity of the addition of diethylzinc to *aliphatic* aldehydes is usually low to moderate.[5c,g] One exception is the (*S*)-(+)-diphenyl(1-methylpyrrolidin-2-yl)-methanol-catalyzed enantioselective addition of diethylzinc to heptanal to yield optically active (*S*)-3-nonanol in 91% enantiomeric excess.[4b] However, the optical purity that is produced depends on the structure of aliphatic aldehyde. For example, the enantiomeric excess produced by the ethylation of 3-methylbutanal is only moderate (73% ee).[4b] Thus, the development of a generally applicable catalytic enantioselective synthesis of optically active secondary *aliphatic* alcohols is a challenging problem.

Here, we describe the synthesis of optically active secondary *aliphatic* and *aromatic* alcohols of high optical purity by the chiral *N,N*-dialkylnorephedrine-catalyzed

Scheme I

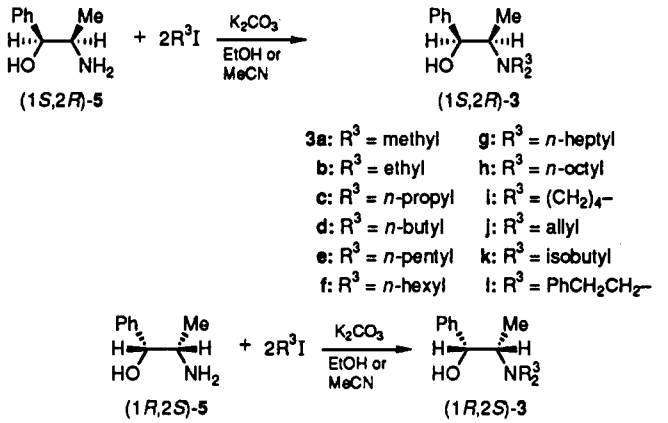

Table I. The Effect of the *N*-Alkyl Substituents of (1*S*,2*R*)-*N*,*N*-Dialkylnorephedrine Chiral Catalysts (3a-i) on the Addition of Diethylzinc to 3-Methylbutanal To Yield (*S*)-5-Methylhexan-3-ol

	N-alkyl substituent	(*S*)-5-methylhexan-3-ol		
entry[a]	(R_3)	yield (%)	$[\alpha]_D$, deg (*T* (°C), *c*, EtOH)	% ee[b]
1	methyl (**3a**)	53	+12.62 (27, 3.18)	53
2	ethyl (**3b**)	95	+19.62 (26, 4.69)	83
3	*n*-propyl (**3c**)	90	+20.65 (26, 4.00)	87
4	*n*-butyl (**3d**)	92	+22.10 (24, 4.57)	93
5	*n*-pentyl (**3e**)	91	+20.22 (25, 4.32)	85
6	*n*-hexyl (**3f**)	85	+19.69 (30, 3.44)	83
7	*n*-heptyl (**3g**)	80	+18.78 (26, 3.09)	79
8	*n*-octyl (**3h**)	53	+18.08 (24, 2.29)	76
9	$-(CH_2)_4-$ (**3i**)	81	+16.52 (25, 1.55)	70

[a] Reactions were run at 0 °C in hexane in the presence of 6 mol % of chiral catalyst (**3**). [b] For entry 4, the ee was determined from the ^1H NMR spectrum of the MTPA ester[18] recorded in the presence of a chiral shift reagent [Eu(fod)$_3$]. For the other entries, the ee was based on an optical rotation of +22.10° for 93% ee (entry 4).

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Et_2Zn adds to benzaldehyde in the presence of chiral β-amino alcohol derivatives to afford 1-phenylpropanol. See: Sato, T.; Soai, K.; Suzuki, K.; Mukaiyama, T. *Chem. Lett.* **1978**, 601. Mukaiyama, T.; Soai, K.; Sato, T.; Shimizu, H.; Suzuki, K. *J. Am. Chem. Soc.* **1979**, *101*, 1455.

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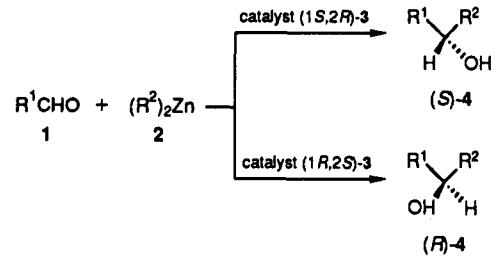
Figure 1. Relationship between the ee's of the product aliphatic alcohols and the carbon number of the *N*-alkyl substituents (R^3) of the chiral catalyst [(1*S*,2*R*)-*N*,*N*-di-*n*-alkylnorephedrines (**3a–h**)] in the enantioselective addition of Et_2Zn to 3-methylbutanal and nonanal: (○) (*S*)-5-methylhexan-3-ol, (▲) (*S*)-3-undecanol.

enantioselective addition of dialkylzincs to aldehydes.[6] This method is more generally applicable to the synthesis of optically active secondary *aliphatic* alcohols than conventional methods[2,3] are.[7,8]



Results and Discussion

Synthesis of Chiral Catalysts. Both (1*S*,2*R*)- and (1*R*,2*S*)-*N*,*N*-disubstituted norephedrines (**3b–l**) are easily obtained by the one-step reaction of the appropriate norephedrine with 2 equiv of alkyl halide or 1 equiv of α,ω-dihalide in refluxing ethanol or acetonitrile in the presence of potassium carbonate (Scheme I).

Effect of the Structure of the Chiral Catalyst. It was found that the enantioselectivity of the addition of dialkylzincs to aldehydes is very sensitive to the structure of the chiral catalyst. The effect that the *N*-alkyl substituents of the (1*S*,2*R*)-*N*,*N*-di-*n*-alkylnorephedrines (**3a–i**) had on the enantioselectivity of the addition of Et_2Zn to 3-methylbutanal is summarized in Table I and Figure 1. Some conclusions can be drawn from the results. (*S*)-5-Methylhexan-3-ol was obtained when the catalysts (1*S*,2*R*)-**3a–i** was used. The chain length of the *N*-*n*-alkyl substituent is important. The optical purity of the product increases as the chain length of the *N*-alkyl substituent increases and peaks at a chain length of four carbons (93% ee, entry 4). Thus, *N*,*N*-di-*n*-butylnorephedrine (DBNE) gave the best results. Catalysts with *N*-alkyl substituents of a chain length greater than four carbons gave alcohols of lower optical purity. In the addition of Et_2Zn to nonanal, a similar effect was observed (Table II, Figure 1). Here again, DBNE gave the best results (87% ee, entry 4) among the catalysts (**3a–h**) bearing straight-chain *N*-alkyl substituents (entries 1–8). Unsymmetrical *N*,*N*-disubstituted catalysts (i.e., one substituent was methyl) gave aliphatic alcohols of only low optical purity.[9] The reaction was slow when a catalyst bearing two *N*-isobutyl substituents (branched at the β-position) (**3k**) or two *N*-(2-phenylethyl) substituents (which possess a phenyl substituent at the β-position) (**3l**) were used. More importantly, no asymmetric induction was observed (entries 11 and 12). The low enantioselectivity of the additions catalyzed by **3k** and **3l** is probably a result of the bulkiness of the *N*-alkyl substituents. Thus, two *N*-*n*-butyl substituents efficiently control the enantioselectivity.[10]

On the other hand, the addition of Et_2Zn to nonanal catalyzed by the chiral norephedrine bearing a pyrrolidine ring (**3i**) was found to be more enantioselective (Table II, entry 9) than that catalyzed by DBNE (87% ee, entry 4), affording (*S*)-3-undecanol in >95% ee. The pyrrolidine ring is conformationally rigid and has been used to construct chiral auxiliaries for use in other asymmetric syntheses.[8a] However, the DBNE-catalyzed addition of

Table II. The Effect of the *N*-Alkyl Substituents of (1*S*,2*R*)-*N*,*N*-Dialkylnorephedrines Chiral Catalysts (3a–l) on the Addition of Diethylzinc to Nonanal To Yield (*S*)-3-Undecanol

		(*S*)-3-undecanol		
entry[a]	*N*-alkyl substituent (R^3)	yield (%)	$[\alpha]_D$, deg (*T* (°C), *c*, EtOH)	% ee[b]
1	methyl (**3a**)	95	+4.09 (33, 7.49)	46
2	ethyl (**3b**)	97	+6.74 (33, 8.10)	75
3	*n*-propyl (**3c**)	95	+7.02 (33, 7.42)	78
4	*n*-butyl (**3d**)	95	+7.79 (26, 8.63)	87
5	*n*-pentyl (**3e**)	91	+7.38 (32, 4.47)	82
6	*n*-hexyl (**3f**)	99	+7.11 (28, 8.70)	79
7	*n*-heptyl (**3g**)	96	+6.57 (33, 6.58)	73
8	*n*-octyl (**3h**)	83	+6.04 (32, 4.02)	67
9	$-(CH_2)_4-$ (**3i**)	87	+9.02 (27, 5.43)	>95
10	allyl (**3j**)	61	+7.87 (24, 5.09)	88
11	isobutyl (**3k**)	26	0.00 (27, 0.61)	0
12	$C_6H_5CH_2CH_2$ (**3l**)	36	0.00 (27, 2.54)	0

[a] Reactions were run at 0 °C in hexane in the presence of 6 mol % of chiral catalyst (**3**). [b] For entry 4, the ee was determined from the ^1H NMR spectrum of the MTPA ester[18] recorded in the presence of a chiral shift reagent [Eu(fod)$_3$]. For the other entries, the ee was based on an optical rotation of +7.79° for 87% ee (entry 4).

(6) The results have been reported in communication form. See: Soai, K.; Yokoyama, S.; Ebihara, K.; Hayasaka, T. *J. Chem. Soc., Chem. Commun.* **1987**, 1690.

(7) Since the publication of ref 6, the following reports describing the synthesis of secondary *aliphatic* alcohols of moderate optical purity (except in the case of ref 7c) have appeared: (a) Tanaka, K.; Ushio, H.; Suzuki, H. *J. Chem. Soc., Chem. Commun.* **1989**, 1700. (b) Joshi, N. N.; Srebnik, M.; Brown, H. C. *Tetrahedron Lett.* **1989**, *30*, 5551. (c) Takahashi, H.; Kawakita, T.; Yoshioka, M.; Kobayashi, S.; Ohno, M. *Ibid.* **1989**, *30*, 7095. (d) Noyori, R.; Suga, S.; Kawai, K.; Okada, S.; Kitamura, M.; Oguni, N.; Hayashi, M.; Kaneko, T.; Matsuda, Y. *J. Organomet. Chem.* **1990**, *382*, 19. (e) Itsuno, S.; Sakurai, Y.; Ito, K.; Maruyama, T.; Nakahama, S.; Fréchet, J. M. J. *J. Org. Chem.* **1990**, *55*, 304. (f) Corey, E. J.; Yuen, P.-W.; Hannon, F. J.; Wierda, D. A. *Ibid.* **1990**, *55*, 784.

(8) For the diastereoselective synthesis of chiral tertiary *aliphatic* alcohols, see: (a) Mukaiyama, T. *Tetrahedron* **1981**, *37*, 4111. (b) Eliel, E. L.; Soai, K. *Tetrahedron Lett.* **1981**, 2859.

(9) The use of (1*R*,2*S*)-*N*-*n*-hexyl-*N*-methylnorephedrine (*n*-hexylephedrine) as a chiral catalyst lowered the enantioselectivity of the addition of Et_2Zn to *aliphatic* aldehydes. The enantiomeric excesses of the products, (*R*)-5-methylhexan-3-ol and (*R*)-3-undecanol, were 28% and 48%, respectively.

(10) For the use of *N*,*N*-di-*n*-butylnorephedrine (DBNE) in nickel-catalyzed conjugate additions, see: Soai, K.; Yokoyama, S.; Hayasaka, T.; Ebihara, K. *J. Org. Chem.* **1988**, *53*, 4148. Soai, K.; Hayasaka, T.; Ugajin, S.; Yokoyama, S. *Chem. Lett.* **1988**, 1571. Soai, K.; Hayasaka, T.; Ugajin, S. *J. Chem. Soc., Chem. Commun.* **1989**, 516.

Table III. The DBNE-Catalyzed Addition of Dialkylzincs to Various Aldehydes

entry	aldehyde	dialkylzinc	enantiomer of DBNE used	yield (%) of alcohol	[α], deg (λ, T (°C), c, solvent)	% ee	config
1	heptanal	Me_2Zn	(−)	70	+11.15 (D, 29, 2.1, EtOH)	90[a]	S
2	heptanal	Et_2Zn	(−)	95	+9.07 (D, 24, 7.2, $CHCl_3$)	88[a]	S
3	heptanal	$(n\text{-}Pr)_2Zn$	(−)	100	+2.20 (365, 23, 8.2, $CHCl_3$)	90[a]	
4	nonanal	Me_2Zn	(−)	28	+13.44 (D, 27, 0.90, EtOH)	89[a]	S
5	nonanal	Et_2Zn	(−)	95	+7.79 (D, 26, 8.7, EtOH)	87[a]	S
6	nonanal	$(n\text{-}Pr)_2Zn$	(−)	100	+2.35 (365, 24, 10.5, $CHCl_3$)	89[a]	
7	nonanal	Et_2Zn	(+)	99	−7.83 (D, 25, 8.8, EtOH)	87[a]	R
8	3-methylbutanal	Et_2Zn	(−)	92	+22.10 (D, 24, 4.6, EtOH)	93[a]	S
9	cyclohexanecarboxaldehyde	Et_2Zn	(−)	94	−6.32 (D, neat)	78[a]	S
10	benzaldehyde	Et_2Zn	(−)	100	−40.74 (D, 26, 5.2, $CHCl_3$)	90[b]	S
11	o-methoxybenzaldehyde	Et_2Zn	(−)	100	−50.63 (D, 27, 3.0, $PhCH_3$)	94[c]	S
12	3-phenylpropanal	Et_2Zn	(−)	94	+25.52 (D, 25, 5.0, EtOH)	95[d]	S
13	benzaldehyde	$(i\text{-}Pr)_2Zn$	(−)	53	−35.54 (D, 28, 3.8, Et_2O)	75[e]	S

[a] Determined from the ^1H NMR spectrum of the MTPA ester[18] recorded in the presence of a chiral shift reagent [Eu(fod)$_3$]. [b] Based on the reported value of $[\alpha]_D$ −45.45° (c 5.2, $CHCl_3$). See: Pickard, R. H.; Kenyon, J. *J. Chem. Soc.* **1914**, 1115. [c] Based on the reported value of $[\alpha]^{20}_D$ +47.0° (c 1.2, $PhCH_3$) for 87% ee. See: ref 5a. [d] Based on the reported value of $[\alpha]_D$ +26.8° (c 5.0, EtOH). See: Sato, T.; Gotoh, T.; Wakabayashi, Y.; Fujusawa, T. *Tetrahedron Lett.* **1983**, *24*, 4123. [e] Based on the reported value of $[\alpha]^{20}_D$ +47.7° (c 7, Et_2O). See: MacLeod, R.; Welch, F. J.; Mosher, H. S. *J. Am. Chem. Soc.* **1960**, *82*, 876.

Et_2Zn to 3-methylbutanal (which is a branched-chain aliphatic aldehyde) was more enantioselective (93% ee, Table I, entry 4) than that catalyzed by the pyrrolidinyl-substituted catalyst (**3i**) (70% ee, Table I, entry 9).

In conventional asymmetric syntheses, rings like pyrrolidine,[8a] oxazoline,[11] 1,3-oxathiane,[8b] oxazolidin-2-one,[12] and thiazolidine-2-thione[13] are used to construct chiral auxiliaries for reasons often having to do with precisely locating (in a stereochemical sense) the controlling heteroatoms that coordinate with the substrates, metals, etc. In the enantioselective additions described here, as mentioned in the preceding paragraph, the pyrrolidinyl-substituted chiral catalyst (**3i**) is also very effective. However, it should be emphasized that the control over the enantioselectivity exerted by the catalyst bearing conformationally mobile *acyclic N-n*-butyl substituents is unique in asymmetric synthesis. The *n*-butyl substituent is conformationally mobile compared to the pyrrolidine ring. Therefore, the *n*-butyl substituent may be able to differentiate the enantiotopic faces of the various aldehydes to a greater degree than does the pyrrolidine ring.

Also, both enantiomers of each secondary alcohol were synthesized by using the appropriate enantiomer of DBNE. The addition catalyzed by *N,N*-diallylnorephedrine (**3j**), which bears two unsaturated allyl substituents, was also found to be highly enantioselective, possibly because the allyl groups are structurally similar to the *n*-butyl groups of DBNE (Table II, entry 10).

One advantage to using compounds **3** as the chiral catalysts is that they are readily available in both enantiomeric forms. Thus, by using the appropriate enantiomer of DBNE, either enantiomer of 3-undecanol can be synthesized in a predictable manner, with the same ee and in the same chemical yield, within experimental error (Table III, entries 5 and 7).

Effect of Temperature and the Amount of Catalyst. Greater enantioselectivity was observed when the reaction of benzaldehyde and Et_2Zn catalyzed by 6 mol % DBNE was performed at 0 °C (90% ee, Table III, entry 10) than when it was performed at lower temperatures, i.e., −30 to −10 °C (78% ee). The enantioselective addition of Et_2Zn to 3-methylbutanal in hexane catalyzed by 6 mol % (−)-DBNE at 0 °C and at room temperature afforded the (*S*)-alcohol in 93% ee (Table III, entry 8) and 91% ee, respectively. Thus, the optimum reaction temperature was 0 °C.

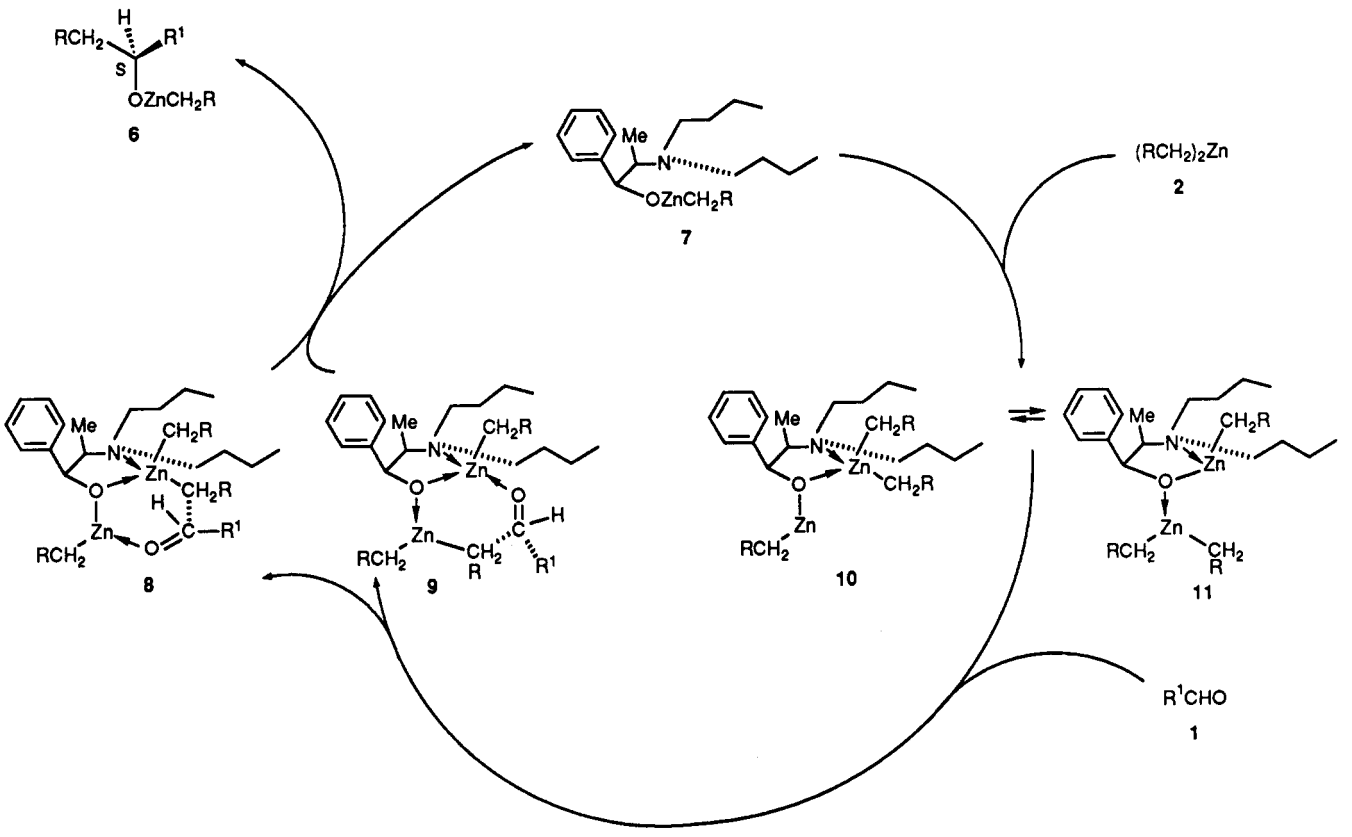
The effect of the amount of catalyst was examined in the case of the DBNE-catalyzed addition of Et_2Zn to benzaldehyde. When 2 mol % of (−)-DBNE (relative to benzaldehyde) was used, (*S*)-1-phenylpropanol (77% ee) was obtained in 84% yield. The ee increased to 89% when 4 mol % of DBNE was used. The optical purity remained constant (89–90% ee) when the amount of catalyst was increased to 6–10 mol %. The addition of Et_2Zn to 3-methylbutanal in hexane at 0 °C catalyzed by 2 mol %, 4 mol %, 6 mol %, and 10 mol % of (−)-DBNE (relative to aldehyde) afforded (*S*)-5-methylhexan-3-ol in 85% ee, 90% ee, 93% ee (Table III, entry 8) and 89% ee, respectively. Thus, the optimum amount of chiral catalyst (DBNE) (relative to aldehyde) was 4 mol % or more.

DBNE-Catalyzed Enantioselective Addition of Dialkylzincs to Various Aldehydes. The results of the DBNE-catalyzed enantioselective addition of dialkylzincs to various aliphatic and aromatic aldehydes are shown in Table III. Optically active secondary *aliphatic* alcohols of high optical purity (87–93% ee) were obtained from the enantioselective addition of dimethyl-, diethyl-, and di-*n*-propylzinc to aliphatic aldehydes (entries 1–7). Unlike the aliphatic alcohols synthesized by conventional methods,[2,3] the optically active aliphatic alcohols prepared by the DBNE-catalyzed addition of dialkylzincs to aliphatic aldehydes bear straight chains of various lengths. When an aliphatic aldehyde branched at the α-position was employed, the ee of the product alcohol was 78% (entry 9). The highly enantioselective DBNE-catalyzed addition of diethylzinc to aromatic aldehydes afforded optically active aromatic alcohols of high optical purity (90–95% ee) (entries 10–12). When diisopropylzinc was allowed to react with benzaldehyde, the ee of the product benzylic alcohol was 75% (entry 13).

A tentative mechanism which explains the stereochemical course of the reaction is shown in Scheme II. Thus, it was reported that diethylzinc reacts rapidly with alcohols to afford the corresponding zinc monoalkoxides.[14] Further reaction of the monoalkoxide with secondary alcohols is

(11) Lutomski, K. A.; Meyers, A. I. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, Chapter 3.
(12) Evans, D. A.; Emis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.
(13) Mukaiyama, T.; Iwasawa, N. *Chem. Lett.* **1982**, 1903. Nagao, Y.; Ikeda, T.; Yagi, M.; Fujita, E.; Shiro, M. *J. Am. Chem. Soc.* **1982**, *104*, 2079.
(14) Ishimori, M.; Tsuruta, T. *Makromol. Chem.* **1963**, *64*, 190.

Scheme II



slow at room temperature. However, zinc dialkoxide is formed by the reaction of zinc monoalkoxide with a secondary alcohol at higher temperatures.[14] In the reactions described here, the formation of an alkylzinc monoalkoxide (**7**) by the reaction of the dialkylzinc and the chiral catalyst (DBNE) at room temperature is very probable. To determine whether the catalytic zinc alkoxide is the mono- or the dialkoxide, a mixture of Et_2Zn and 2 molar equiv of catalyst **3i** was refluxed in hexane. The zinc dialkoxide that was produced did not catalyze the addition of Et_2Zn to aldehydes at 0 °C. Thus, it is believed that the zinc monoalkoxide **7** is the catalytic species.

The structure of the zinc monoalkoxide–dialkylzinc complex is believed to be that depicted by either **10** or **11**. In both, the coordination geometry of the zinc atom is essentially tetrahedral.[15] The nucleophilicity of the alkyl group of the dialkylzinc would be increased by coordination of the zinc atom with the oxygen or the nitrogen atom of the catalyst.[16] It is believed that it is the alkyl group of the dialkylzinc and not that of **7** that adds to the aldehyde, because the alkoxy(methoxy or ethoxy)ethylzinc (prepared by the reaction of ROH and Et_2Zn)[14] itself did not ethylate benzaldehyde, and also because the lithium alkoxide derived from DBNE also catalyzes the addition of dialkylzincs to aldehydes.[17]

The aldehyde (**1**) is attacked at the *si* face via a six-center transition state (**8**[4b] or **9**,[5d] respectively) to afford chiral alkylzinc alkoxide (**6**). The intermediacy of a six-center transition state **8** or **9** may explain the stereochemical course of additions. Examination of molecular models and the data in Figure 1 and Tables I and II suggests that the substituents on the nitrogen atom of chiral catalyst may affect the formation and stability of the six-center transition states **8** and **9**. There is a large difference between the optical purities of the alcohols prepared by the *N*-methyl-**3a**-catalyzed additions (46–53% ee) and those of the alcohols prepared by the **3b–h**-catalyzed additions (67–93% ee). These results show that the *N*-alkyl substituent must possess at least one β-carbon atom to insure enantioselective addition. When the *N*-alkyl substituents are large, they may block the approach at the attacking species to one of the enantiotopic faces of the aldehyde. However, when the *N*-alkyl substituents are bulkier than *n*-butyl, the formation of **8** and **9** may be more or less inhibited. Thus, reaction was slow, and no asymmetric induction was observed when either catalyst **3k** (with two isobutyl substituents, each branched at the β-position) or the catalyst **3l** (with two alkyl substituents, each bearing a phenyl group at the β-position) was employed. The same trend is apparent when the straight-chain *N*-alkyl substituents are longer (i.e., bulkier) than *n*-butyl. Thus, the optical purities of the alcohols that were obtained when catalysts with *N*-alkyl substituents larger than *n*-butyl were used were lower than those of the alcohols obtained from the DBNE-catalyzed additions. On the other hand, when the *N*-alkyl substituent is smaller (methyl in **3a**, for example) than *n*-butyl (DBNE), it may not be sufficiently bulky to hinder the approach of the attacking species. It may also be possible that, when the *N*-alkyl substituents are too small, **8** and **9** may be less stable.

Thus, DBNE (**3d**), which bears two *N*-*n*-butyl groups, may be the optimum catalyst. However, the pyrrolidine ring of the catalyst **3i** may be a more suitably sized blocking group, because higher enantioselectivity was observed in the **3i**-catalyzed addition of Et_2Zn to nonanal (a straight-chain aldehyde) than in the DBNE-catalyzed

(15) An X-ray crystallographic study of the pentadienylzinc chloride–*N,N,N',N'*-tetramethylethylenediamine (TMEDA) complex showed that the coordination geometry of the zinc atom is essentially tetrahedral. See: Yasuda, H.; Ohnuma, Y.; Nakamura, A.; Kai, Y.; Yasuoka, N.; Kasai, N. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1101.

(16) Dialkylzinc adds to aldehydes in the presence of TMEDA. See: Soai, K.; Watanabe, M.; Koyano, M. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2124.

(17) See also refs 4b and 5d.

addition (Table II, entry 9). On the other hand, the conformational rigidity of the pyrrolidine ring may slightly destabilize the congested transition state complex with 3-methylbutanal (a branched-chain aldehyde). In this case, the DBNE-catalyzed addition was more enantioselective. The moderate optical purity of the product of the addition of diisopropylzinc (a branched-chain dialkylzinc) (Table III, entry 13) may be a result of the instability of the complexes 8 and 9.

Finally, after the dialkylzinc added to the aldehyde, 7 was regenerated and the chiral zinc monoalkoxide (6) was produced. Hydrolysis of 6 affords the optically active alcohol 4, the configuration of which is *S* when the priority order of the substituents is $R^1 > RCH_2$.

Conclusion

Optically active secondary aliphatic and aromatic alcohols of high optical purity were synthesized by the chiral *N,N*-dialkylnorephedrine-catalyzed enantioselective addition of dialkylzinc reagents to aldehydes. The method afforded optically active secondary aliphatic alcohols of high optical purity that cannot be synthesized by other methods.

Experimental Section

General Procedure for the Synthesis of *N,N*-Dialkylnorephedrines (3b–l). A mixture of (1*S*,2*R*)-(+)-norephedrine (10 mmol), alkyl halide (20 mmol), K_2CO_3 (20 mmol), and EtOH or CH_3CN (10 mL) was refluxed for 2–24 h. The reaction mixture was cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on alumina (EtOAc). Some *N,N*-dialkylnorephedrines were purified further by bulb-to-bulb distillation.

(1*S*,2*R*)-(−)-2-(*N,N*-Diethylamino)-1-phenylpropan-1-ol (3b): yield 43%; colorless oil; bp 160 °C (2 mmHg) (bath temperature); $[\alpha]^{27}_D$ −9.50° (*c* 2.00, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.76–1.17 (m, 9 H), 2.47 (q, *J* = 7.0 Hz, 4 H), 2.95 (m, 1 H), 3.90 (s, 1 H), 4.65 (d, *J* = 5.0 Hz, 1 H), 7.25 (s, 5 H); IR (neat) 3425, 2980, 1455, 1390, 1200, 700 cm^{-1}; HRMS (M^+ − H) calcd for $C_{13}H_{20}NO$ 206.1072, found 206.1042.

(1*S*,2*R*)-(−)-2-(*N,N*-Di-*n*-propylamino)-1-phenylpropan-1-ol (3c): yield 45%; colorless oil; bp 165 °C (2 mmHg) (bath temperature); $[\alpha]^{26}_D$ −12.30° (*c* 2.00, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.77–1.13 (m, 9 H), 1.13–1.87 (m, 4 H), 2.10–3.13 (m, 6 H), 4.65 (d, *J* = 4.0 Hz, 1 H), 7.25 (s, 5 H); IR (neat) 3425, 2980, 1455, 1390, 1210, 700 cm^{-1}; HRMS (M^+ − H) calcd for $C_{15}H_{24}NO$ 234.1308, found 234.1312.

(1*S*,2*R*)-(−)-2-(*N,N*-Di-*n*-butylamino)-1-phenylpropan-1-ol (DBNE, 3d): yield 67%; colorless oil; bp 170 °C (2 mmHg) (bath temperature); $[\alpha]^{22}_D$ −24.4° (*c* 2.00, hexane); ^1H NMR ($CDCl_3$) δ 0.67–1.03 (m, 9 H), 1.03–1.83 (m, 8 H), 2.10–2.67 (m, 4 H), 2.75–3.25 (m, 1 H), 3.80 (br, 1 H), 4.65 (d, *J* = 5.0 Hz, 1 H), 7.25 (s, 5 H); IR (neat) 3425, 2950, 1450, 1380, 1190, 700 cm^{-1}; HRMS (M^+ − H) calcd for $C_{17}H_{28}NO$ 262.2144, found 262.2178.

(1*R*,2*S*)-(+)-2-(*N,N*-Di-*n*-butylamino)-1-phenylpropan-1-ol (DBNE, 3d). This compound was synthesized from (1*R*,2*S*)-norephedrine. **3d:** yield 66%; colorless oil; bp 170 °C (2 mmHg) (bath temperature); $[\alpha]^{25}_D$ +24.4° (*c* 2.05, hexane); the ^1H NMR and IR spectra were identical with those of (1*S*,2*R*)-**3d**; HRMS (M^+ − H) calcd for $C_{17}H_{28}NO$ 262.2144, found 262.2180.

(1*S*,2*R*)-(−)-2-(*N,N*-Di-*n*-pentylamino)-1-phenylpropan-1-ol (3e): yield 44%; colorless oil; bp 170 °C (1 mmHg) (bath temperature); $[\alpha]^{26}_D$ −13.25° (*c* 2.00, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.77–1.13 (m, 9 H), 1.13–1.87 (m, 12 H), 2.10–3.13 (m, 6 H), 4.65 (d, *J* = 4.0 Hz, 1 H), 7.25 (s, 5 H); IR (neat) 3425, 2950, 1450, 1380, 1190, 700 cm^{-1}; HRMS (M^+ − H) calcd for $C_{19}H_{32}NO$ 290.2580, found 290.2584.

(1*S*,2*R*)-(−)-2-(*N,N*-Di-*n*-hexylamino)-1-phenylpropan-1-ol (3f): yield 46%; colorless oil; $[\alpha]^{26}_D$ −11.75° (*c* 2.00, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.67–1.05 (m, 9 H), 1.20 (m, 16 H), 1.87–2.67 (m, 4 H), 3.00 (m, 1 H), 3.47 (s, 1 H), 4.65 (d, *J* = 5.0 Hz, 1 H), 7.25 (s, 5 H); IR (neat) 3400, 2945, 1450, 1380, 1200, 700 cm^{-1}; HRMS (M^+ − H) calcd for $C_{21}H_{36}NO$ 318.2816, found 318.2810.

(1*S*,2*R*)-(−)-2-(*N,N*-Di-*n*-heptylamino)-1-phenylpropan-1-ol (3g): yield 40%; colorless oil; $[\alpha]^{27}_D$ −9.50° (*c* 2.00, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.67–1.05 (m, 9 H), 1.20 (m, 20 H), 2.13–2.67 (m, 4 H), 3.00 (m, 1 H), 3.40 (br, 1 H), 4.65 (d, *J* = 5.0 Hz, 1 H), 7.25 (s, 5 H); IR (neat) 3425, 2950, 1455, 1390, 1200, 700 cm^{-1}; HRMS (M^+ − H) calcd for $C_{23}H_{40}NO$ 346.3352, found 346.3354.

(1*S*,2*R*)-(−)-2-(*N,N*-Di-*n*-octylamino)-1-phenylpropan-1-ol (3h): yield 41%; colorless oil; $[\alpha]^{27}_D$ −7.50° (*c* 2.00, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.58–1.03 (m, 9 H), 1.25 (m, 24 H), 2.08–2.58 (m, 4 H), 2.58–3.15 (m, 2 H), 4.65 (d, *J* = 5.0 Hz, 1 H), 7.25 (s, 5 H); IR (neat) 3425, 2950, 1460, 1390, 1200, 700 cm^{-1}; HRMS (M^+ − H) calcd for $C_{25}H_{44}NO$ 374.3888, found 374.3890.

(1*S*,2*R*)-(−)-1-Phenyl-2-(1-pyrrolidinyl)propan-1-ol (3i): yield 33%; colorless oil; bp 155 °C (3 mmHg); $[\alpha]^{24}_D$ −7.25° (*c* 2.00, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.80 (d, *J* = 6.4 Hz, 3 H), 1.40–2.27 (m, 4 H), 2.27–3.07 (m, 5 H), 3.60 (s, 1 H), 4.98 (d, *J* = 3.0 Hz, 1 H), 7.25 (s, 5 H); IR (neat) 3400, 2950, 2800, 1450, 1385, 1200, 750, 700 cm^{-1}; HRMS (M^+ − H) calcd for $C_{13}H_{18}NO$ 204.1384, found 204.1381.

(1*S*,2*R*)-(+)-2-(*N,N*-Diallylamino)-1-phenylpropan-1-ol (3j): yield 61%; colorless oil; bp 160 °C (2 mmHg); $[\alpha]^{24}_D$ +8.90° (*c* 2.00, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.95 (d, *J* = 7.0 Hz, 3 H), 2.86–3.67 (m, 6 H), 4.56–6.13 (m, 7 H), 7.25 (s, 5 H); IR (neat) 3400, 3080, 2980, 2800, 1650, 1460 cm^{-1}; HRMS (M^+) calcd for $C_{15}H_{21}NO$ 231.1624, found 231.1606.

(1*S*,2*R*)-(+)-2-(*N,N*-Diisobutylamino)-1-phenylpropan-1-ol (3k): yield 19%; colorless oil; bp 130 °C (2 mmHg); $[\alpha]^{27}_D$ +9.90° (*c* 2.00, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.70–1.17 (m, 15 H), 1.33–2.00 (m, 2 H), 2.37–2.47 (m, 4 H), 2.47–3.07 (m, 1 H), 4.65 (d, *J* = 4.0 Hz, 1 H), 7.25 (s, 5 H); IR (neat) 3400, 2950, 1450, 1390, 1200, 720 cm^{-1}; HRMS (M^+ − H) calcd for $C_{17}H_{28}NO$ 262.2144, found 262.2166.

(1*S*,2*R*)-(+)-2-(*N,N*-Bis(2-phenylethyl)amino)-1-phenylpropan-1-ol (3l): yield 33%; colorless crystals; mp 72.5–73.5 °C. $[\alpha]^{27}_D$ +4.50° (*c* 2.00, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.80 (d, *J* = 6.6 Hz, 3 H), 1.93–2.50 (m, 4 H), 2.63–3.16 (m, 6 H), 4.67 (d, *J* = 4.0 Hz, 1 H), 7.10–7.45 (m, 15 H); IR (KBr) 3050, 2850, 1425, 1350, 1140, 1100, 1000, 900, 750 cm^{-1}; HRMS (M^+ − H) calcd for $C_{25}H_{28}NO$ 358.2524, found 358.2520.

General Procedure for the Chiral *N,N*-Dialkylnorephedrine-Catalyzed Addition of Dialkylzincs to Aldehydes. To a mixture of the chiral catalyst (0.06 mmol, 6 mol %) and hexane (2 mL) was added the aldehyde (1 mmol) at room temperature. The mixture was stirred for 20 min and then was cooled to 0 °C. Dialkylzinc (2.2 mL of a 1 M hexane solution, 2.2 mmol) was added. The mixture was stirred for 16 h at 0 °C. The reaction was quenched by the addition of dilute aqueous HCl. The mixture was then extracted with CH_2Cl_2. The extract was dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the residue by preparative silica gel TLC afforded the optically active secondary alcohol. The optical rotation was measured after the alcohol was further purified by bulb-to-bulb distillation. The enantiomeric excesses of aliphatic alcohols were determined from the ^1H NMR spectra of the corresponding MTPA esters[18] recorded in the presence of a chiral shift reagent [Eu(fod)$_3$]. The ee's were calculated from the peak areas of the respective methoxy group proton signals. The enantiomeric excesses of aromatic alcohols were calculated from the reported optical rotations.

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Supplementary Material Available: ^1H NMR spectra of **3b–l** (12 pages). Ordering information is given on any current masthead page.

(18) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.