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Enantioselective addition of diorganozincs to aldehydes catalyzed by β-amino alcohols *

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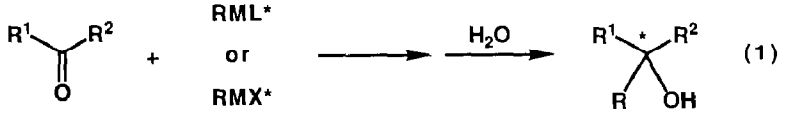
Abstract

Nucleophilic addition of dialkylzincs to aldehydes in hydrocarbon solvents is markedly accelerated by the presence of a catalytic amount of a β-dialkylamino alcohol. Use of certain sterically constrained chiral amino alcohols such as 3-*exo*-(dimethylamino)isoborneol or 1-t-butyl-2-piperidinoethanol effects highly enantioselective catalysis giving secondary alcohols in up to 99% ee. Dimethyl-, diethyl-, di-n-butyl-, and di-n-pentyl-zincs have been employed for the alkylation of substituted benzaldehydes and some olefinic or aliphatic aldehydes. Configurational correlation between the chiral auxiliary and alkylation products is discussed.

Introduction

Enantioselective alkylation of carbonyl compounds is a new domain of asymmetric catalysis [1]. Organometallic alkylation of aldehydes or ketones is a simple and very common synthetic operation, and development of a chiral version leading to optically active alcohols is obviously desirable because of its high synthetic utility (eq. 1). A non-racemic, chiral environment can be introduced to organometallic



(1)

M = metallic species
L* = chiral neutral ligand
X* = chiral heteroatom substituent

* Dedicated to Prof. G. Wilke on the occasion of his 65th birthday.

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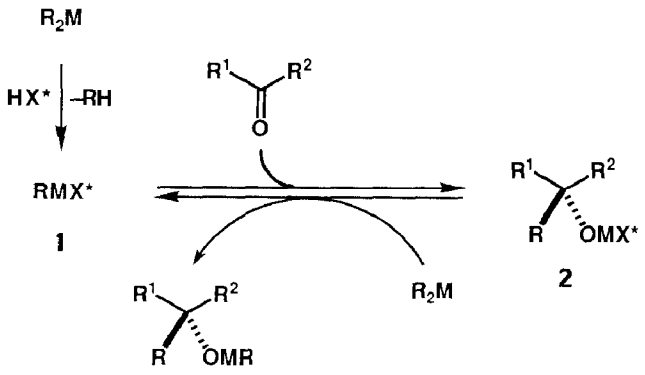


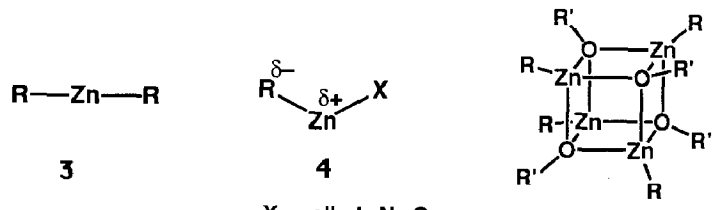
Scheme 1

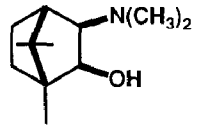
compounds by (1) coordination of an aprotic chiral complexing agent or solvent to the metallic center [2*] or (2) modification of organometallics by protic auxiliaries such as optically active hydroxy or amino compounds, giving organometallic alkoxides or amides, respectively [3*]. So far tremendous efforts have been made along these lines and indeed several highly enantioselective additions to prochiral aldehydes have been reported [4*]. For example, optical yields of $> 90\%$ were accomplished by use of, among others, a chiral 1,2-diamine/alkyllithium [5], diamino alcohol/alkyllithium [6], β-sulfonamido alcohol/alkyltitanium combined system [7], or organotitanium [8] or Li/Mg [9] binary organometallic agents modified by optically active 2,2′-dihydroxy-1,1′-binaphthol. However, these approaches generally suffer from necessity of employing stoichiometric or even excess amounts of chiral sources to organometallic reagents or carbonyl substrates, hampering their practical usefulness [10*]. We have aimed to realize a high level of enantioselective alkylation with a catalytic quantity of chiral auxiliary.

Rationale

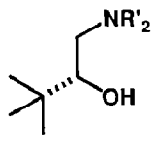
Scheme 1 illustrates enantioselective addition of an organometallic reagent R_2M to a prochiral carbonyl substrate catalyzed by a protic chiral auxiliary, HX*. Here, in order to secure an efficient chiral multiplication, the reaction system must satisfy several conditions. First, chiral anionic ligand X* must possess an appropriate three-dimensional structure which makes clear differentiation between diastereomeric transition states of the alkyl transfer step, **1** → **2**. Second, the rate of the chirally promoted alkylation process should exceed substantially that of uncatalyzed reaction with the achiral reagent R_2M. Accordingly, addition of HX* to R_2M, generating **1**, must accelerate the nucleophilic reaction toward carbonyl substrates, and X* must also be readily detached from the initially formed alkoxide **2** by the action of an alkyl donor or carbonyl substrate. This is a key issue in obtaining a high turnover efficiency. Actually the metallic compounds in Scheme 1 are not simple as formulated, but usually exist as aggregates or in forms associated with other molecules. Although a variety of well-shaped chiral auxiliaries are now accessible from natural products or by synthesis, the above kinetic requirements are not easily satisfied.

* Reference number with asterisk indicates a note in the list of references.



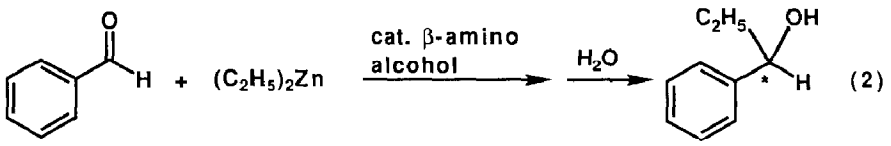


7, (−)-DAIB



8 **a:** R' = CH_3
b: R'—R' = $(CH_2)_5$
c: R'—R' = $(CH_2)_2O(CH_2)_2$

Diorganozincs serve as ideal alkyl donors in this context. Monomeric dialkylzincs (**3**) having an *sp*-hybridized linear geometry are inert to carbonyl compounds, because the alkyl–metal bond is rather nonpolar [11]. However, the bond polarity can be enhanced by creating a bent geometry where the Zn atom possesses a higher *p* character. A coordinatively unsaturated bent compound **4**, particularly with an electronegative substituent, has a strong donor property for the alkyl group and acceptor character at the Zn atom. Such auxiliary-induced structural perturbation would increase the reactivity toward carbonyl substrates. In addition, since alkylzinc alkoxides usually form stable cubic tetramers (**5**) in hydrocarbons [11], liberation of chiral anionic ligands from the initial alkylation products may be facilitated. Overall, organozinc chemistry provides an opportunity for stereoselective alkylation based on catalytic asymmetric induction. The validity of such a consideration was first shown in 1984 by Oguni and Omi reporting that reaction of diethylzinc and benzaldehyde was aided by a catalytic amount of (*S*)-leucinol to give (*R*)-1-phenyl-1-propanol [(*R*)-**6**] in 48.8% ee (eq. 2) [12*]. Two years later, the Noyori group



6

realized the first highly enantioselective alkylation, catalyzed by (−)-3-*exo*-(dimethylamino)isoborneol [(−)-DAIB] (**7**), leading to secondary alcohols including (*S*)-**6** in up to 99% ee [13]. We here describe the details of these investigations [14*].

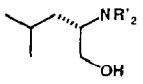
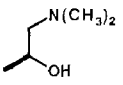
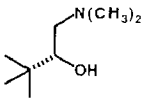
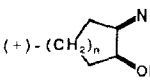
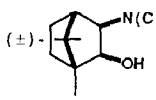
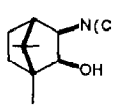
Results and discussion

Ligand acceleration of alkylation

When benzaldehyde and diethylzinc are mixed in toluene below room temperature, a yellow coloration occurs owing to reversible donor–acceptor complexation.

Table 1

Ligand acceleration of ethylation of benzaldehyde

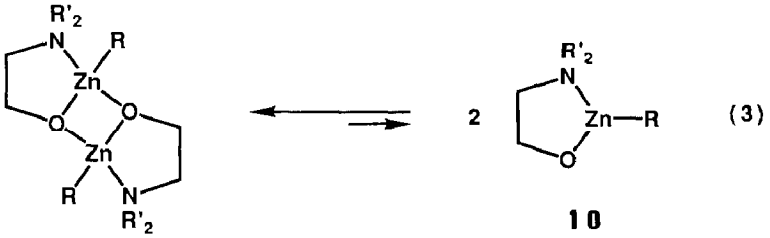
Entry	Additive	Type [a]	Yield [b] (%)
1	$HOCH_2CH_2OH$	5-O^-,O^-	0
2	$CH_3OCH_2CH_2OCH_3$	5-O,O	0
3	$H_2NCH_2CH_2NH_2$	5-N^-,N^-	4
4	$(CH_3)_2NCH_2CH_2N(CH_3)_2$	5-N,N	10
5	$(CH_3)_2NCH_2CH_2CH_2N(CH_3)_2$	6-N,N	3
6	$H_2NCH_2CH_2OH$	5-N^-,O^-	5
7	$(CH_3)HNCH_2CH_2OH$	5-N^-,O^-	10
8	$(CH_3)_2NCH_2CH_2OH$	5-N,O^-	9
9	$(C_2H_5)_2NCH_2CH_2OH$	5-N,O^-	18
10	 R' = H	5-N^-,O^-	3
11	R' = CH_3	5-N,O^-	8
12		5-N,O^-	4
13	 (8a)	5-N,O^-	66
14	 n = 1	5-N,O^-	59
15	n = 2	5-N,O^-	63
16	 ((±)-7)	5-N,O^-	20
17	 (7)	5-N,O^-	85
18	$(CH_3)_2NCH_2CH_2CH_2OH$	6-N,O^-	4

[a] Type of the expected Zn complex is designated as *n*-X,Y: *n*, the number of chelate ring size; X and Y, anionic alkoxo and amido ligand (O^-, N^-) or neutral ether or amine ligand (O, N). [b] The yield obtained when benzaldehyde and diethylzinc were mixed in toluene at 0 °C for 1 h in the presence of 2 mol% of the additive.

No chemical reaction, however, or even change in the NMR spectrum, is observed. At elevated temperatures, ethylation does occur, but very slowly. We screened a variety of bidentate aprotic ligands or protic auxiliaries in the hope of obtaining acceleration of this nucleophilic alkylation. Thus a 1: 1.2 mixture of benzaldehyde and diethylzinc in toluene containing 2 mol% of an additive was stirred at 0 °C for 1 h and the mixture was analyzed after aqueous workup. The results are summarized in Table 1.

Although dimethoxyethane had no effect, its nitrogen analogue, *N,N,N′,N′*-tetramethylethylenediamine, accelerated the ethylation to a considerable extent.

Ethylene glycol was ineffective but ethylene diamine was slightly active. The efficiency of amino alcohols is highly dependent on their structure and substitution pattern. β-Dialkylamino alcohols act better than the corresponding *N*-monoalkyl or non-alkylated compounds, where acidic protons on the nitrogen may cause complications; *N*,*N*-dimethylleucinol was ca. three-times more reactive than leucinol (entry 10 vs. 11). β-Dialkylamino alcohols like **8a** having a bulky α substituent appeared to be very effective (entry 12 vs. 13). Further, impressive rate enhancement was observed with sterically constrained α,β-disubstituted β-dialkylamino alcohols including DAIB (**7**) (entries 14–17). Reaction of 2-dimethylaminoethanol and dimethylzinc is known to evolve methane, giving a trimeric methylzinc alkoxide [15]. By contrast, the amino alcohols **7** and **8** which have a similar but sterically congested structure lead to dimeric compounds of type **9** [16], substantiated by single crystal X-ray analysis and/or molecular weight measurements. The dimeric alkylzinc alkoxide **9** does not alkylate benzaldehyde but acts as catalyst for reaction of alkylzincs and aldehydes [16]. Here, the steric constraint caused by the ligand backbone facilitates the dissociation to reactive monomer **10** [14b], resulting in great rate enhancement (eq. 3).



9 **10** (3)

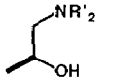
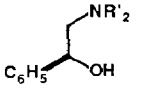
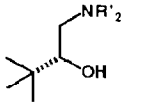
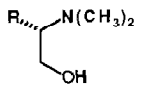
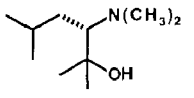
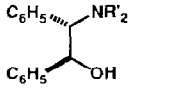
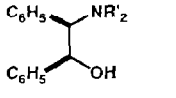
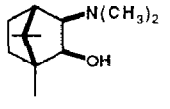
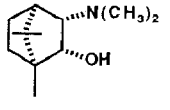
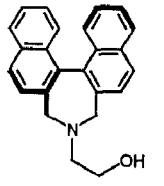
Enantioselective alkylation

Suitable reaction conditions were sought using diethylzinc, benzaldehyde, and a catalytic amount of a β-amino alcohol. Optically active β-alkyl β-aminoethanols can be prepared from the corresponding natural α-amino acids. Enantioselective hydrogenation of certain α-dialkylamino ketones catalyzed by BINAP–$Ru^{(II)}$ complexes leads to α-alkyl β-dialkylaminoethanols in up to 96% ee [17]. (−)- or (+)-DAIB is obtainable from camphor [18]. Table 2 illustrates examples of the enantioselective ethylation of benzaldehyde at 0 °C in the presence of various amino alcohols. A good correlation between the reactivity and enantioselectivity has been observed; higher enantioface selection is generally obtained along with faster reaction. Thus in the presence of 2 mol% of **7** or **8**, ethylation proceeded smoothly at 0 °C and **6** was obtained in 95–97% chemical yield in 98% ee. It should be added that, in sharp contrast to the catalysis by **7** leading to (*S*)-**6**, the reaction catalyzed by 3-*exo*-methylaminoisoborneol or its nonmethylated derivative at 20 °C gave slowly (*R*)-**6** in only 7 and 17% ee, respectively.

The enantioselective alkylation can be extended to a range of alkylating agents and aldehyde substrates, as illustrated in Table 3. Dimethyl-, diethyl- and other simple dialkylzinc agents can be used as alkylating agents. Methylation proceeded ca. 20-times slower than the ethylation, but gave an ee of > 90%. Divinylzinc may also be employed [19]. *para*-Substituted benzaldehydes gave carbinols of type **11**

Table 2

Enantioselective ethylation of benzaldehyde catalyzed by a β-amino alcohol [a]

Entry	β-Amino alcohol		Solvent	Time (h)	1-Phenyl-1-propanol		
					Yield (%)	% ee	Configuration
1		R' = CH_3	hexane	24	70	3	*R*
2		R' = C_2H_5	hexane	24	99	12	*S*
3		R' = CH_3	hexane	24	93	59	*S*
4		R' = C_2H_5	hexane	24	95	70	*S*
5		R'–R' = $(CH_2)_4$	hexane	24	91	67	*S*
6		R'–R' = $(CH_2)_5$	hexane	24	97	75	*S*
7		R' = CH_3 (**8a**)	hexane	24	90	93	*R*
8		R'–R' = $(CH_2)_5$ (**8b**)	hexane	24	95	98	*R*
9		R'–R' = $(CH_2)_2O(CH_2)_2$ (**8c**)	hexane	24	96	98	*R*
10		R = $(CH_3)_2CH$	hexane	120	75	49	*R*
11		R = $(CH_3)_2CHCH_2$	toluene	1	8	47	*R*
12		R = $C_6H_5CH_2$	hexane	120	80	48	*R*
13			toluene	1	12	88	*R*
14		R' = CH_3	hexane	24	88	66	*S*
15		R' = C_2H_5 (**18**)	hexane	24	97	81	*S*
16		R' = CH_3	hexane	24	99	73	*S*
17		R' = C_2H_5 (**19**)	hexane	24	93	94	*S*
18		((–)-**7**)	toluene	6	97	98	*S*
19		((+)-**7**)	toluene	6	94	98	*R*
20		(**20**)	toluene	48	71	49	*S*

[a] Reactions were carried out at 0 °C using 8 mM of a β-amino alcohol, 0.42 M of benzaldehyde, and 0.42 M of diethylzinc.

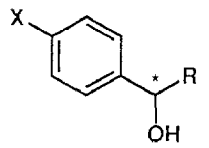
Table 3

Enantioselective addition of dialkylzinc to carbonyl compounds [a]

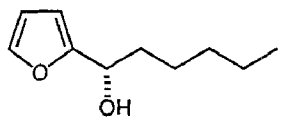
Carbonyl compound	Alkylating agent	Catalyst	Conditions		Alkylated product		
			Solvent	Time (h)	Yield (%)	% ee	Configuration
C_6H_5CHO	$(C_2H_5)_2Zn$	**7**	toluene	6	97	98	*S*
C_6H_5CHO	$(C_2H_5)_2Zn$	**7**	hexane/toluene (2/1)	6	94	98	*S*
C_6H_5CHO	$(C_2H_5)_2Zn$	**7**	ether/toluene (2/1)	6	98	99	*S*
C_6H_5CHO	$(C_2H_5)_2Zn$	**7**	THF/toluene (2/1)	64	44	91	*S*
C_6H_5CHO	$(C_2H_5)_2Zn$	**8b**	hexane	24	95	98	*R*
C_6H_5CHO	$(C_2H_5)_2Zn$	**8c**	hexane	24	96	98	*R*
C_6H_5CHO	$(CH_3)_2Zn$	**7**	toluene	70	59	91	*S*
C_6H_5CHO	$(n\text{-}C_4H_9)_2Zn$	**7**	toluene	13	88	95	*S*
C_6H_5CHO	$n\text{-}C_4H_9Li/ZnCl_2$ (2/1)	**7**	ether/hexane (4/3)	14	84	41	*S*
C_6H_5CHO	$n\text{-}C_4H_9Li/ZnCl_2$ (2/1)	**7**	hexane/toluene (3/4)	14	90	2	*R*
$p\text{-}ClC_6H_4CHO$	$(C_2H_5)_2Zn$	**7**	toluene	12	86	93	*S*
$p\text{-}CH_3OC_6H_4CHO$	$(C_2H_5)_2Zn$	**7**	toluene	12	96	93	*S*
2-furaldehyde	$(n\text{-}C_5H_{11})_2Zn$	**7**	toluene	12	80	> 95	*S*
ferrocenecarboxaldehyde	$(CH_3)_2Zn$	**7**	toluene	170	60	81 [b]	*S*
$(E)\text{-}C_6H_5CH{=}CHCHO$	$(C_2H_5)_2Zn$	**7**	toluene	6	81	96	*S*
$(E)\text{-}C_6H_5CH{=}CHCHO$	$(C_2H_5)_2Zn$	**8b**	hexane	24	86	84	*R*
$(E)\text{-}C_6H_5CH{=}CHCHO$	$(C_2H_5)_2Zn$	**8c**	hexane	24	79	86	*R*
$(E)\text{-}CH_3CH{=}CHCHO$	$(C_2H_5)_2Zn$	**8b**	hexane	24	90	90	*R*
$(E)\text{-}CH_3CH{=}CHCHO$	$(C_2H_5)_2Zn$	**8c**	hexane	24	95	86	*R*
$(E)\text{-}(n\text{-}C_4H_9)_3SnCH{=}CHCHO$	$(n\text{-}C_5H_{11})_2Zn$	**7**	toluene	24	84	85	*S*
$C_6H_5CH_2CH_2CHO$	$(C_2H_5)_2Zn$	**7**	toluene	12	80	90	*S*
$n\text{-}C_6H_{13}CHO$	$(C_2H_5)_2Zn$	**7**	toluene	24	81	61	*S*
$n\text{-}C_6H_{13}CHO$	$(C_2H_5)_2Zn$	**8b**	hexane	24	89	76	*R*
$n\text{-}C_6H_{13}CHO$	$(C_2H_5)_2Zn$	**8c**	hexane	24	85	75	*R*
$C_6H_5CH_2OCH_2CHO$	$(C_2H_5)_2Zn$	**7**	toluene	5	80	0	–
$C_6H_5COCH_3$	$(C_2H_5)_2Zn$	**7**	toluene	24	0	–	–
$n\text{-}C_3H_7OCOCOCH_3$	$(C_2H_5)_2Zn$	**7**	toluene	24	90	0	–
$n\text{-}C_4H_9OCOCH_2COCH_3$	$(C_2H_5)_2Zn$	**7**	toluene	24	0	–	–

[a] Reactions were carried out at 0 °C using 2 mol% catalyst. [b] Reaction at 20 °C.

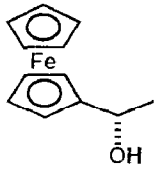
with consistently high enantioselectivity, indicating that the stereoselectivity is steric in origin. The reaction of 2-furaldehyde with di-n-pentylzinc afforded (*S*)-**12**, which is recognized as a versatile compound in organic synthesis [20], in > 95% optical yield. Optically active 1-ferrocenylethanol (**13**), a key compound for synthesis of a wide variety of chiral ferrocene derivatives [21], is also obtained in 81% optical yield by the reaction of ferrocenecarboxaldehyde and dimethylzinc. Certain α,β-unsaturated or aliphatic aldehydes can also be alkylated to give **14** in a moderate to



11, **a**: R = CH_3, X = H
b: R = C_2H_5, X = H (**6**)
c: R = C_2H_5, X = Cl
d: R = C_2H_5, X = OCH_3
e: R = *n*-C_4H_9, X = H



12



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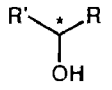
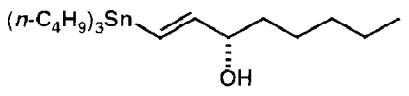


14, R = alkyl,
R' = alkenyl or alkyl



15

high ee's. Addition of di-n-pentylzinc to (*E*)-3-tributylstannylpropenal catalyzed by (−)-DAIB afforded **15**, which serves as a chiral building block of the three-component coupling prostaglandin synthesis [22], with $S/R = 93/7$ selectivity. Some functionalities present near to the carbonyl group affect reactivity and often diminish enantioselectivity, probably because heteroatom coordination to the metal facilitates the uncatalyzed achiral pathway. Benzyloxyacetaldehyde or propyl pyruvate was readily ethylated (even without amino alcohols) but the product was racemic. n-Butyl acetoacetate and acetophenone were not alkylated under the standard conditions.

In the DAIB-catalyzed ethylation of benzaldehyde, nonpolar solvents such as toluene, hexane, ether, or their mixtures gave the most satisfactory results. Use of THF retarded the reaction and lowered the product ee to 91%. With regard to the effect of temperature, the optical yields of **6** in toluene ranged from 98% at −20–0 °C to 89% at 50 °C. Decrease in the concentration of the catalyst or substrate lowered the rate but the optical yield remained virtually constant. Use of halide-free dialkylzincs is crucial for obtaining high ee values. The (−)-DAIB aided alkylation of benzaldehyde with a reagent formed from n-butyllithium and zinc chloride in a 2/1 mole ratio produces (*S*)-1-phenyl-1-pentanol in only 41% (4/3 ether/hexane, 0 °C) or the *R* enantiomer in 2% ee (4/3 toluene/hexane, 0 °C). No enantiomeric bias was obtained in the reaction of benzaldehyde and n-butyllithium (hexane/toluene), diethylmagnesium (THF/toluene), triethylaluminum (toluene) in

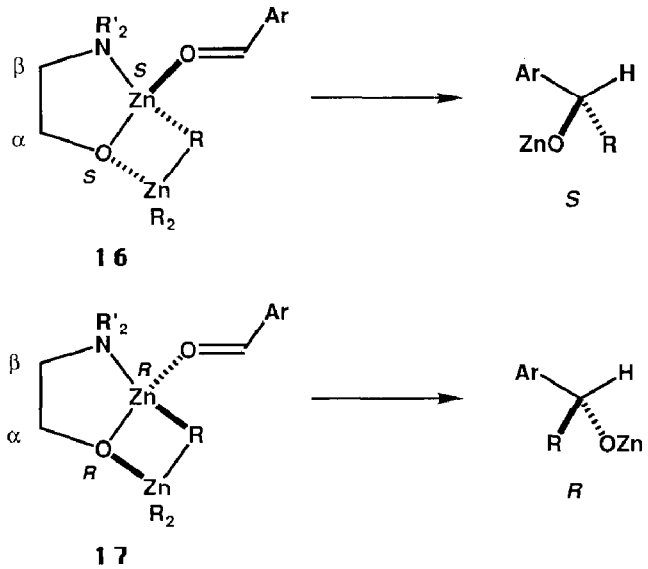
the presence of 2 mol% of **7** or a complex formed from equimolar amounts of **7** and diethylzinc.

Reaction of benzaldehyde and dialkylzincs gives benzyl alcohol as a major by-product, whose yield appears to increase with increasing aldehyde/alkylzinc ratio. Under the above described standard conditions using equimolar amounts of benzaldehyde and diethylzinc, benzyl alcohol was formed in only 1–2% yield. However, when the reaction was conducted using a benzaldehyde/diethylzinc/(−)-DAIB ratio of 100/50/1 (toluene, 0 °C, 170 h), the products obtained were (*S*)-**6** (98% ee), benzyl alcohol and propiophenone in 48 (based on benzaldehyde), 12, and 10% yields, respectively. Thus the ethylation product, ethylzinc 1-phenyl-1-propanoxide, can undergo a disproportionation with benzaldehyde giving propiophenone and ethylzinc benzyloxide. Indeed an independent experiment indicated that ethylzinc alkoxide **5** ($R = C_2H_5$, $R' = CH(C_2H_5)C_6H_5$) reacts slowly with benzaldehyde to give after aqueous workup benzyl alcohol and propiophenone in nearly equal amounts. Diorganozincs are not a major source of hydride, since the reaction with dimethylzinc also produces benzyl alcohol together with acetophenone.

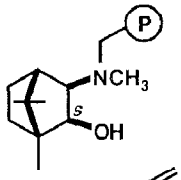
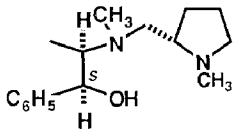
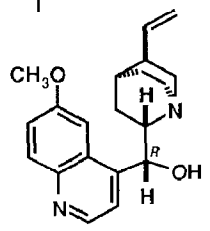
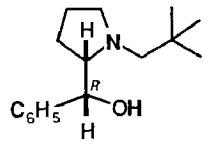
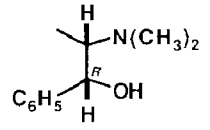
Sense of asymmetric induction

The enantioselective alkylation proceeds via a series of dinuclear Zn complexes and the sense of the asymmetric induction may be conceived as controlled by the chirality of the 5/4-fused bicyclic structures of type **16** and **17**, as illustrated in Scheme 2 [16]. The *S*-configured Zn alkoxide is basically derived from **16** having angular *S*-Zn and *S*-O atoms, while the *R* alkoxide is obtained from the *R*-Zn, *R*-O enantiomer **17**.

Table 2 classifies the auxiliaries by substitution pattern. The results indicate that the relative stabilities of the chiral bicyclic structures, **16** and **17**, are influenced profoundly by substituents at the α and β positions as well as the nitrogen substituents. The α-*S* or β-*R* configuration gives a preference to **16**, while **17** is



Scheme 2

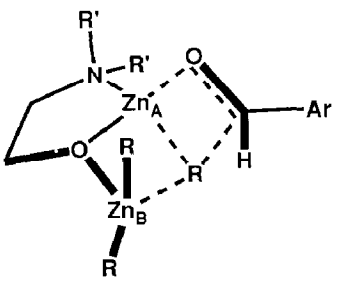
auxiliary	confign of **6**	auxiliary	confign of **6**
	*S* [14b]		*S* [14f]
	*R* [14a]		*R* [14d]
	*R* [14h]		

Scheme 3

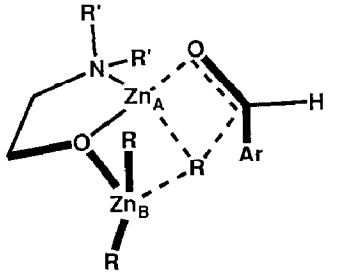
stabilized by the α-*R* or β-*S* configuration. The reaction with α-monoalkylated auxiliaries agrees with this view (entries 1–9). The degree of the asymmetric induction depends primarily on the bulkiness of the substituents of the α carbon, and indeed, amino alcohol **8** bearing a t-butyl group resulted in up to 98% optical yield in the ethylation of benzaldehyde. The reaction with β-monosubstituted β-amino alcohols also exhibits the expected sense of asymmetric induction (entry 10–12). *gem*-Dimethylation at the α position intensifies this effect (entry 13). Obviously, *cis*-α,β-disubstitution, as is seen with DAIB auxiliary (entry 18 and 19), is the most desirable, because the directing effects of the two substituents cooperate in keeping a single chiral integrity, either **16** or **17**, to accomplish a very high enantioselectivity. Many efficient auxiliaries so far recorded have this type of substitution pattern; some examples taken from the literature are given in Scheme 3. On the other hand, with *trans*-α,β-disubstitution, the directivities derived offset each other, but the α stereogenic center appears to be more influential than the β center (entries 14–17). Thus (1*S*,2*S*)-2-diethylamino-1,2-diphenylethanol (**18**) and (1*S*,2*R*)-2-diethylamino-1,2-diphenylethanol (**19**) exhibit the same asymmetric orientation, with the latter in higher enantioselectivity (81% ee vs. 94% ee) (entries 15 and 17). Substituents at the nitrogen atom also affect the enantioselectivity to some extent and, in most cases, the bulky alkyl groups tend to increase the stereoselectivity. Notably, even with **20**, in which the (*S*)-binaphthyl moiety is the only chiral element, a moderate enantioselection is generated (entry 20).

The alkyl transfer reaction was postulated to occur via a folded bicyclic transition structure [9,16,23]. As illustrated by the diastereomeric structures **21a** and **21b** arising from **16**, the stereochemical bias is provided by a nonbonded repulsion of the carbonyl substituents (Ar and H) from a terminal R group attached to Zn_B. The

S-generating geometry **21a** is obviously favorable compared with the *R*-generating transition state **21b**.



21a



21b

In summary, stereochemical information from the chiral auxiliaries defines the chirality of the stereo-determining 5/4-fused bicyclic intermediates, **16** and **17**, which in turn is transmitted to the aldehyde ligand in the alkyl transfer step. Direct steric interaction between carbonyl substituents and α- or β-substituents of β-amino alcohols is unimportant. The sense of the asymmetric induction in the reaction using other aldehydes can be interpreted in a like manner.

Conclusion

Highly enantioselective alkylation of aldehydes has been realized by combination of dialkylzinc reagents and a catalytic amount of chiral β-dialkylamino alcohol. Sterically congested auxiliaries such as **7** and **8** are particularly effective for obtaining high reactivity and excellent enantioselection. This stereoselective alkylation is complementary to asymmetric reduction of prochiral ketones and provides a useful tool for preparation of optically active secondary alcohols. It should be added that this type of reaction exhibits an enormous chiral amplification phenomenon [9,16,24]; catalysis using **7** or **8** in a low ee leads to the alkylation product in up to 98% ee. This effect has proved to be due to marked difference of chemical properties of the diastereomeric (chiral and achiral) catalyst precursors of type **9** [16].

Experimental

General

^{1}H NMR spectra were measured on a JEOL JNM-GX270 or Hitachi R-250H spectrometer using toluene-d_8 or chloroform-*d* as solvent. Chemical shifts are reported in ppm (δ) downfield from tetramethylsilane. IR spectra were obtained with a JASCO IR-810 or A-202 spectrometer. Optical rotation was measured on a JASCO DIP-4 or DIP-181 digital polarimeter. Liquid chromatographic analyses were conducted on a Shimadzu LC-6A, JASCO TWINCLE, or JASCO 8800PU instrument. Gas-liquid phase chromatography analyses were performed on a Hitachi 263-30 or Shimadzu GC-15A instrument. Flash chromatography was done on a column of silica gel (Fuji Davison BW300, 240–400 mesh). Elemental analyses were performed on Perkin–Elmer Model 240C at the Faculty of Agriculture, Nagoya University.

Materials

Toluene, hexane, ether, and THF for asymmetric alkylation were distilled from sodium benzophenone ketyl under argon and stored in 2-l Schlenk flasks. Dichloromethane and acetonitrile were freshly distilled from calcium hydride and phosphorus pentoxide, respectively. A stock solution of dialkylzincs was prepared by mixing toluene or hexane with either 99% dimethylzinc or 99% diethylzinc (Toyo Stauffer Chemical Co., Lot No DMZ EK-01 and DEZ 932) in a lecture bottle. Di-n-butyl- and di-n-pentyl-zinc were prepared by the Frankland method [25]. These solutions were kept in a 20-ml Schlenk tube equipped with a Young's tap. All substrates for alkylation were purified by distillation from 4Å molecular sieves and kept in Schlenk tubes. All alkylation experiments were performed under an argon atmosphere using standard Schlenk techniques. β-Alkyl- β-dialkylamino alcohols such as (*S*)-*N*,*N*-dimethylvalinol, (*S*)-*N*,*N*-dimethylleucinol, and (*S*)-*N*,*N*-dimethylphenylglycinol were prepared by known methods [26]. Racemic *cis*-2-(dimethylamino)cyclohexan-1-ol or *cis*-2-(dimethylamino)cyclopentan-1-ol were prepared by the osmium-catalyzed oxyamination of cyclohexene or cyclopentene [27] and Eschweiler–Clarke *N*-dimethylation method [28].

Preparation of β-dialkylamino alcohols

3-exo-(Dimethylamino)isoborneol (DAIB) (7). (−)- and (+)-DAIB were prepared on a 10–30 g scale by the reported method [18b] from (1*R*)-(+)-camphor (Nakarai Chemical Co., Lot No 070-07, $[\alpha]_D^{20}$ + 45.2° (*c* 9.7, ethanol)) and (1*S*)-(−)-camphor (Aldrich Chemical Co., Lot No 27,967-6, $[\alpha]_D^{20}$ −42.9° (*c* 10.0, ethanol)), respectively. The oily (−)-DAIB was mixed with an equimolar amount of (2*R*,3*R*)-(+)-tartaric acid in a hot 5/4 ethanol/methanol mixture and allowed to stand at 25 °C for 9 h and 5 °C for 5 h. The resulting crystals, m.p. 197–199 °C, $[\alpha]_D^{29}$ + 17.6° (*c* 2.03, CH_3OH), were separated and partitioned between dichloromethane and ice-cooled 2 *N* sodium hydroxide solution. The aqueous layer was further extracted twice with dichloromethane. The combined organic layers were washed with water and dried over anhydrous sodium sulfate. Evaporation of the solvent and bulb-to-bulb distillation (120 °C/18 mmHg) afforded pure (−)-DAIB (**7**): $[\alpha]_D^{28}$ −14.7° (*c* 4.58, C_2H_5OH). Elemental analysis of the HCl salt of **7**: Anal. Found C, 61.86; H, 10.41; N, 5.70. $C_{12}H_{24}ClNO$ calcd.: C, 61.65; H, 10.35; N, 5.99%. (+)-DAIB showing $[\alpha]_D^{28}$ + 14.6° (*c* 4.53, C_2H_5OH) was obtained in a similar manner via formation of a crystalline salt with (2*S*,3*S*)-(−)-tartaric acid.

These compounds were enantiomerically pure, as confirmed by HPLC analysis: 3,5-dinitrophenyl isocyanate (20 mg, 0.089 mmol) and pyridine (5 μl) were added to a toluene solution (2 ml) of DAIB (10 mg, 0.051 mmol). After vigorous stirring for 30 min at 20 °C, 2 μl of the reaction mixture containing the *N*-3,5-dinitrophenylcarbamate was analyzed by HPLC (column, Sumitomo Chemical Co. SUMIPAX OA-4000; eluent, 99.5/0.5 hexane/ethanol mixture; flow rate, 1.0 ml/min; detection, 254-nm light; t_R, 17.4 min (carbamate from (−)-DAIB) and 22.5 min (carbamate from (+)-DAIB)). The ee's of other β-dialkylamino alcohols were determined in a similar manner.

*1-t-Butyl-2-(dialkylamino)ethanols (**8**)*

The title compounds were prepared by epoxy opening of the known (*R*)-t-butylethylene oxide with a bromomagnesium dialkylamide [29] or BINAP–Ru-based asymmetric hydrogenation of a 1-(dialkylamino)-3,3-dimethylbutan-2-one [17].

*(R)-1-t-Butyl-2-(dimethylamino)ethanol (**8a**).* Yield: 4.0 g (80%). Purification: recrystallization of HCl salts (ethanol/ether) and distillation (65–67 °C/23 mmHg). Enantiomeric excess: 99%; t_R of (*R*)-carbamate, 10 min; t_R of (*S*)-carbamate, 11 min; eluent, 97/3 hexane/ethanol mixture. $[\alpha]_D^{25}$ −70.4° (*c* 1.2, $CHCl_3$). IR (neat) 3500 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$)) δ 0.9 (s, 9, $(CH_3)_3C$), 2.14 (dd, 2, *J* 3.0 Hz and 14.9 Hz, CH_2), 2.20 (s, 6, $N(CH_3)_2$), 3.25 (dd, 1, *J* 3.3 Hz and 14.3 Hz, C*H*OH), 3.6 (brs, 1, OH). Anal. Found C, 66.29; H, 13.12; N, 9.69. $C_8H_{19}NO$ calcd.: C, 66.16; H, 13.18; N, 9.64%.

*(R)-1-t-Butyl-2-piperidinoethanol (**8b**).* Yield: 610 mg (82%). Purification: distillation (59–61 °C/1 mmHg). Enantiomeric excess: 99%; t_R of (*R*)-carbamate, 9 min; t_R of (*S*)-carbamate, 11 min; eluent, 97/3 hexane/ethanol mixture. $[\alpha]_D^{25}$ −72.4° (*c* 1.8, $CHCl_3$). IR (neat) 3400 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 0.9 (s, 9, $(CH_3)_3C$), 2.2–2.3 (m, 4, $NCH_2 \times 2$), 2.5–2.6 (m, 6, $(CH_2)_3$), 2.7–2.8 (m, 2, CH_2), 3.3 (dd, 1, *J* 4.9 and 14.3 Hz, C*H*OH), 4.3 (brs, 1, OH). Anal. Found C, 71.24; H, 12.29; N, 7.68. $C_{11}H_{23}NO$ calcd.: C, 71.30; H, 12.51; N, 7.56%.

*(R)-1-t-Butyl-2-morpholinoethanol (**8c**).* Yield: 680 mg (90%). Purification: distillation (67 °C/1 mmHg). Enantiomeric excess: 99%; t_R of (*R*)-carbamate, 7.7 min; t_R of (*S*)-carbamate, 8.5 min; eluent, 97/3 hexane/ethanol mixture. $[\alpha]_D^{25}$ −69.2° (*c* 1.0, $CHCl_3$). IR (neat) 3400 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 0.9 (s, 9, $(CH_3)_3C$), 2.3–2.5 (m, 4, 2 NCH_2), 2.6–2.8 (m, 2, CH_2), 3.3–3.4 (m, 1, C*H*OH), 3.6 (brs, 1, OH), 3.7–3.8 (m, 4, $CH_2O \times 2$). Anal. Found C, 63.98; H, 10.99; N, 7.47. $C_{10}H_{21}NO_2$ calcd.: C, 64.17; H, 11.30; N, 7.48%.

(S)-1-(Dimethylamino)-2-propanol. Preparation: $LiAlH_4$ reduction of (*S*)-*O*-acetyl-*N*,*N*-dimethyllactamide [30]. Yield: 550 mg (80%). Purification: distillation (35 °C/40 mmHg). Enantiomeric excess: 96%; t_R of (*S*)-carbamate, 22 min; t_R of (*R*)-carbamate, 25 min; eluent, 97/3 hexane/ethanol mixture. $[\alpha]_D^{21}$ + 9.3° (*c* 2.17, C_2H_5OH). ^1H NMR (250 MHz, $CDCl_3$) δ 1.05 (d, 3, *J* 6.0Hz, CH_3), 2.25 (m, 8, $NCH_3 \times 2$ and CH_2), 3.0 (brs, 1, OH), 3.4–4.0 (m, 1, CH).

(S)-1-Phenyl-2-(dialkylamino)ethanols. The title compounds were prepared by the reported method [31] starting from (*S*)-mandelic acid (Aldrich Chemical Co., $[\alpha]_D^{20}$ + 154° (*c* 2.8, H_2O)).

(S)-1-Phenyl-2-(dimethylamino)ethanol. Yield: 4.0 g (68%). Purification: recrystallization of the HCl salt (ethanol/ether) and bulb-to-bulb distillation (63–64 °C/2 mmHg). Enantiomeric excess: 99%; t_R of (*S*)-carbamate, 22 min; t_R of (*R*)-carbamate, 27 min; eluent, 97/3 hexane/ethanol mixture. $[\alpha]_D^{21}$ + 74.8° (*c* 0.95, CH_3OH). ^1H NMR (250 MHz, $CDCl_3$) δ 2.35 (s, 6, $N(CH_3)_2$), 2.25–2.52 (d, 2, *J* 10.0 Hz, CH_2), 3.2–4.2 (br, 1, OH), 4.69 (dd, 1, *J* 3.6 Hz and 10.8 Hz, C*H*OH), 7.2–7.4 (m, 5, aromatics).

(S)-1-Phenyl-2-(diethylamino)ethanol [31]. Yield: 3.9 g (82%). Purification: recrystallization of the HCl salt (ethanol/ether) and bulb-to-bulb distillation (68–69 °C/2 mmHg). Enantiomeric excess: 98%; t_R of (*S*)-carbamate, 17 min; t_R of (*R*)-carbamate, 28 min; eluent, 97/3 hexane/ethanol mixture. $[\alpha]_D^{25}$ + 81.0° (*c* 1.03, CH_3OH). ^1H NMR (250 MHz, $CDCl_3$) δ 1.07 (t, 6, *J* 7.0 Hz, $CH_3 \times 2$), 2.4–2.8 (m, 6, $NCH_2 \times 3$), 3.7–4.5 (br, 1, OH), 4.63 (dd, 1, *J* 3.8 Hz and 8 Hz, C*H*OH), 7.2–7.4 (m, 5, aromatics).

(S)-1-Phenyl-2-pyrrolidinoethanol [31]. Yield: 2.8 g (77%). Purification: recrystallization from hexane (m.p. 75 °C). Enantiomeric excess: 99%; t_R of (*S*)-carbamate, 18 min; t_R of (*R*)-carbamate, 35 min; eluent, 97/3 hexane/ethanol mixture.

$[\alpha]_D^{27} + 43.8°$ (*c* 0.96, CH_3OH). ^1H NMR (250 MHz, $CDCl_3$) δ 1.8 (brm, 4, $CH_2 \times 2$), 2.4–2.8 (m, 6, $NCH_2 \times 3$), 3.2–4.4 (br, 1, OH), 4.70 (dd, 1, *J* 3.1 Hz and 10.4 Hz, C*H*OH), 7.25–7.45 (m, 5, aromatics).

(S)-1-Phenyl-2-piperidinoethanol [31]. Yield: 3.5 g (85%). Purification: recrystallization from hexane (m.p. 84–84.5 °C). Enantiomeric excess: 99%; t_R of (*S*)-carbamate, 18 min; t_R of (*R*)-carbamate, 31 min; eluent, 97/3 hexane/ethanol mixture. $[\alpha]_D^{24} + 57.2°$ (*c* 0.99, CH_3OH). ^1H NMR (250 MHz, $CDCl_3$) δ 1.6–1.8 (m, 6, $CH_2 \times 3$), 2.3–2.5 (m, 4, $NCH_2 \times 2$), 2.6–2.8 (brm, 2, CH_2), 3.9–4.5 (br, 1, OH), 4.72 (dd, 1, *J* 3.7 Hz and 10.4 Hz, C*H*OH), 7.2–7.4 (m, 5, aromatics).

(1S,2S)-(−)-threo-2-(Dimethylamino)-1,2-diphenylethanol and (1S,2R)-(+)-erythro-2-(dimethylamino)-1,2-diphenylethanol

The title compounds were prepared by the reported method [32] starting from benzoin oxime. The ee's were determined to be > 99% by the same method as described in preparation of **7**. (1*S*,2*S*)-(−)-*threo*-2-(Dimethylamino)-1,2-diphenylethanol: m.p. 59–60 °C; $[\alpha]_D^{22} -128.0°$ (*c* 1.48, C_2H_5OH); HPLC analysis, t_R, 28.2 min ((*S*)-carbamate) and 54.8 min ((*R*)-carbamate). (1*S*,2*R*)-(+)-*erythro*-2-(Dimethylamino)-1,2-diphenylethanol: m.p. 88–89.5 °C; $[\alpha]_D^{25} + 121.0°$ (*c* 1.44, C_2H_5OH); HPLC analysis, t_R, 34.1 min ((1*S*,2*R*)-carbamate) and 74.5 min ((1*R*,2*S*)-carbamate).

*(1S,2S)-(−)-threo-2-(Diethylamino)-1,2-diphenylethanol (**18**) and (1S,2R)-(+)-erythro-2-(diethylamino)-1,2-diphenylethanol (**19**)*

(1*S*,2*S*)-*threo*-2-Amino-1,2-diphenylethanol or (1*S*,2*R*)-*erythro*-2-amino-1,2-diphenylethanol (1.2 g, 5.6 mmol), prepared by the reported method [32], was dissolved in acetonitrile (50 ml) containing ethyl iodide (1.35 ml, 16.8 mmol) and sodium carbonate (4.4 g, 40 mmol). The mixture was refluxed for 71 h. After being cooled to room temperature, the mixture was extracted three times with dichloromethane (50 ml). The combined organic layers were washed with water (30 ml) and brine (10 ml), dried over anhydrous sodium sulfate, and evaporated under reduced pressure to give the corresponding diethyl compound (1.25 g, 75% yield). The ee's were determined to be > 99% by the same method as described in the preparation of **7**. **18**: $[\alpha]_D^{23} -59.9°$ (*c* 0.848, C_2H_5OH); ^1H NMR (250 MHz, $CDCl_3$) δ 1.16 (3, t, *J* 7.02 Hz, CH_2CH_3), 1.16 (3, t, *J* 7.32 Hz, CH_2CH_3), 2.1–2.3 (2, m, CH_2CH_3), 2.7–2.9 (2, m, CH_2CH_3), 3.75 (1, d, *J* 10.4 Hz, $NCHC_6H_5$), 5.00 (1, d, *J* 10.4 Hz, $OCHC_6H_5$), 5.3–5.5 (1, brs, OH), 7.1–7.3 (10, m, aromatics); HPLC analysis, t_R, 19.2 min ((*S*)-carbamate) and 37.9 min ((*R*)-carbamate). **19**: m.p. 73.5–74.5 °C; $[\alpha]_D^{23} + 35.8°$ (*c* 0.886, C_2H_5OH); ^1H NMR (250 MHz, $CDCl_3$) δ 1.01 (3, t, *J* 6.71 Hz, CH_2CH_3), 1.01 (3, t, *J* 7.32 Hz, CH_2CH_3), 1.4–2.0 (1, brs, OH), 2.6–2.9 (4, m, $CH_2CH_3 \times 2$), 3.76 (1, d, *J* 4.88 Hz, $NCHC_6H_5$), 5.27 (1, d, *J* 4.28 Hz, $OCHC_6H_5$), 6.95–7.2 (10, m, aromatics); HPLC analysis, t_R, 20.6 min ((1*S*,2*R*)-carbamate) and 22.3 min ((1*R*,2*S*)-carbamate).

*(S)-2,2′-[2-(2-Hydroxyethyl)-2-azapropane-1,3-diyl]-1,1′-binaphthalene (**20**).* (*S*)-2,2′-Bis(bromomethyl)-1,1′-binaphthyl [33] (100 mg, 0.23 mmol), benzene (3.0 ml), and ethanolamine (68.8 μl, 1.14 mmol) were placed in a 10 ml round-bottomed flask equipped with a condenser. The resulting white suspension was refluxed for 4 h under argon and cooled to room temperature. 1 *N* aqueous sodium hydroxide solution (5 ml) was added and the aqueous layer was extracted with three 4-ml

portions of chloroform. The combined organic layers were washed with water (5 ml) and saturated aqueous sodium chloride solution (5 ml), dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography (1/40 and then 1/20 methanol/dichloromethane) to give **20** (70.8 mg, 91.6% yield): $[\alpha]_D^{23} + 363.0°$ (*c* 0.71, $CHCl_3$). ^1H NMR (270 MHz, $CDCl_3$) δ 2.86 (m, 1, NC*H*H), 3.15 (m, 1, NCH*H*), 3.59 (d, 2, *J* 13.5 Hz, NCH_2), 3.98 (t, 2, *J* 5.4 Hz, CH_2O), 4.10 (d, 2, *J* 13.5 Hz, NCH_2), 7.3–8.05 (m, 12, aromatics).

General procedure for the asymmetric alkylation

In general, 300 mg of an aldehyde was used. The concentrations of catalyst, dialkylzinc, and aldehyde were adjusted to 8 m*M*, 0.42 *M*, and 0.42– 0.50 *M*. The reaction scale could be increased without problems. A typical procedure for a 10-g scale ethylation of benzaldehyde was as follows: a dry 250-ml Schlenk tube containing a Teflon-coated stirring bar and argon atmosphere was charged with optically active (−)-DAIB (371 mg, 1.88 mmol) and toluene (200 ml). A 4.19 *M* toluene solution of diethylzinc (27.0 ml, 113 mmol) was added at 15 °C. The mixture was stirred for 15 min and then cooled to −78 °C. To this was added benzaldehyde (10.0 g, 94.2 mmol) in one portion. The reaction mixture was stirred at 0 °C for 6 h. Then saturated aqueous ammonium chloride solution (100 ml) was added. The mixture was extracted three times with ether (100 ml). The combined organic layers were washed with 1 *N* aqueous hydrochloric acid solution (100 ml), water (100 ml), and brine (100 ml), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude mixture was distilled to give (*S*)-1-phenyl-1-propanol in 98% ee (12.4 g, 97% yield). For details of the determination of enantiomeric excess and absolute configuration, see below.

Determination of enantiomeric excesses and absolute configurations

The enantiomeric excesses were determined by HPLC analysis of alkylated products on chiral stationary phases, or their (*R*)-MTPA esters ((*R*)-α-methoxy-α-(trifluoromethyl)phenylacetates) or (*R*)-1-(1-naphthyl)ethyl carbamates on ordinary (achiral) stationary phases. In the preparation of these esters or carbamates, no noticeable kinetic resolution of the chiral alcohols took place. In most cases, the peaks of the diastereomers gave base-line separation. Conditions of HPLC analysis for secondary alcohols: column, Bakerbond DNBPG covalent or Daicel Co. CHIRALCEL OB; eluent, hexane/2-propanol mixture; flow rate, 1.0 ml/min; detection, 254-nm light. Conditions of HPLC analysis for (*R*)-MTPA esters: column, Develosil 100-5; eluent, ethyl acetate/hexane mixture; flow rate, 1.0 ml/min; detection, 254-nm light. Conditions of HPLC analysis for (*R*)-1-(1-naphthyl)ethyl carbamates: column, Develosil 100-3; eluent, ether/hexane mixture; flow rate, 1.0 ml/min; detection, 254-nm light. The absolute configurations were determined by comparison of the rotation values with those reported in the literature.

(*R*)-MTPA esterification procedure, exemplified by (*S*)-1-phenyl-1-ethanol, was as follows: synthetic (*S*)-1-phenyl-1-ethanol (23 mg, 0.188 mmol) was dissolved in dichloromethane (0.5 ml) containing pyridine (50 μl, 0.63 mmol). To this solution was added (*R*)-MTPACl (60 mg, 0.24 mmol) and the mixture was kept at 20 °C for 6 h. To this was added ether (2 ml) and water (1 ml) and the mixture was vigorously stirred for 15 min. The aqueous layer was extracted with two 2-ml portions of ether

and the combined organic layers were successively washed with 1 *N* hydrogen chloride solution (3 ml), 1 *N* sodium hydroxide solution (3 ml), water (3 ml), and brine (3 ml). After drying over anhydrous sodium sulfate, evaporation of the solvent under reduced pressure afforded the (*R*)-MTPA esters (61 mg, 95% yield).

Preparation of (*R*)-1-(1-naphthyl)ethyl carbamates is exemplified by conversion of (*S*)-decan-3-ol: synthetic (*S*)-decan-3-ol (10.0 mg, 0.0698 mmol), benzene (1.0 ml) and (*R*)-1-(1-naphthyl)ethyl isocyanate (Aldrich, 16.6 mg, 0.0842 mmol) were placed in a small glass tube. The whole mixture was frozen and the tube was sealed under reduced pressure. After being heated at 120 °C for 48 h and cooled to room temperature, the tube was opened and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (silica gel, 1.5 g; eluent, hexane and then 1/2 ether/hexane mixture) to afford the carbamates (20.0 mg, 97% yield).

The properties of the alkylated products listed in Table 3 are as follows.

*(S)-1-Phenyl-1-ethanol (**11a**).* Yield: 136 mg (59%). In addition, benzyl alcohol was obtained in 0.5% yield. Purification: bulb-to-bulb distillation, 80–85 °C/18 mmHg. Enantiomeric excess: 91% assayed as the (*R*)-MTPA ester (1/100 ethyl acetate/hexane; t_R of (*R*,*R*)-isomer, 15.1 min; t_R of (*R*,*S*)-isomer, 16.2 min). $[\alpha]_D^{22}$ −49.7° (*c* 2.01, c-C_5H_{10}) [lit. [34]: $[\alpha]_D^{20}$ +43.1° (*c* 7.19, c-C_5H_{10}) for the *R* enantiomer].

*(S)-1-Phenyl-1-propanol (**11b**).* Yield: 12.4 g (97%). Benzyl alcohol was obtained in 1% yield. Purification: distillation, 150 °C/20 mmHg. Enantiomeric excess: 98% by HPLC analysis (column, Bakerbond DNBPG covalent; 99.75/0.25 hexane/2-propanol; t_R of (*S*)-isomer, 47.8 min; t_R of (*R*)-isomer, 50.0 min). $[\alpha]_D^{22}$ −47.6° (*c* 6.11, $CHCl_3$) [lit. [35] $[\alpha]_D$ −45.45° (*c* 5.15, $CHCl_3$) for the *S* enantiomer].

*(R)-1-Phenyl-1-propanol (**11b**).* Yield: 5.9 g (95%) obtained with **8b**. Purification: distillation, 142 °C/17 mmHg. Enantiomeric excess: 98% by HPLC analysis (column, Daicel CHIRALCEL OB; 100/0.2 hexane/2-propanol; t_R of (*S*)-isomer, 12 min; t_R of (*R*)-isomer, 13 min). $[\alpha]_D^{25}$ +45.4° (*c* 2.0, C_2H_5OH).

*(S)-1-p-Chlorophenyl-1-propanol (**11c**).* Yield: 338 mg (86%). *p*-Chlorobenzyl alcohol was obtained in 2% yield. Purification: flash chromatography (1/5 ether/hexane) and bulb-to-bulb distillation. Enantiomeric excess: 93% (column, Bakerbond DNBPG covalent; 99.5/0.5 hexane/2-propanol; t_R of (*S*)-isomer, 17.6 min; t_R of (*R*)-isomer, 18.7 min). $[\alpha]_D^{22}$ −23.5° (*c* 0.82, C_6H_6) [lit. [36] $[\alpha]_D^{22}$ −10.4° (*c* 5, C_6H_6) for the *S* enantiomer in 43% ee].

*(S)-1-p-Methoxyphenyl-1-propanol (**11d**).* Yield: 346 mg (96%). *p*-Methoxybenzyl alcohol was obtained in 2% yield as by-product. Purification: flash chromatography (ether/hexane 1/5) and bulb-to-bulb distillation. Enantiomeric excess: 93% (Bakerbond DNBPG covalent; 99.5/0.5 hexane/2-propanol; t_R of (*S*)-isomer, 28.9 min; t_R of (*R*)-isomer, 30.8 min). $[\alpha]_D^{22}$ −32.1° (*c* 1.25, C_6H_6) [lit. [36] $[\alpha]_D^{22}$ −17.2° (*c* 5, C_6H_6) for the *S* enantiomer in 51% ee].

*(S)-1-Phenyl-1-pentanol (**11e**).* Yield: 414 mg (88%). Benzyl alcohol was obtained in 5% yield. Purification: flash chromatography (1/3 ether/hexane) and bulb-to-bulb distillation. Enantiomeric excess: 95% (Bakerbond DNBPG covalent; 99.5/0.5 hexane/2-propanol; t_R of (*S*)-isomer, 13.3 min; t_R of (*R*)-isomer, 14.1 min). $[\alpha]_D^{22}$ −35.2° (*c* 1.08, C_6H_6) [lit. [5,37] $[\alpha]_D^{25}$ +35.7° (*c* 3, C_6H_6) for the R enantiomer].

*(S)-1-(2-Furyl)-1-hexanol (**12**).* Yield: 280 mg (80%). In addition, furfuryl al-

cohol was obtained in 5% yield. Purification: flash chromatography (ether/hexane 1/10) and bulb-to-bulb distillation (100 °C/20 mmHg). Optical yield: > 95%. $[\alpha]_D^{23}$ −14.4° (*c* 1.18, $CHCl_3$) [lit. [20] $[\alpha]_D^{25}$ +13.8° (*c* 1.07, $CHCl_3$) for the *R* enantiomer in > 95% ee].

(S)-1-Ferrocenylethanol (13). Yield: 180 mg (60%). Purification: flash chromatography (dichloromethane/hexane 2/1). Optical yield: 81%. $[\alpha]_D^{25}$ +24.4° (*c* 1.10, C_6H_6) [lit. [38] $[\alpha]_D^{25}$ +30.1° (*c* 1.2, C_6H_6) for the *S* enantiomer]. $[\alpha]_{546}^{25}$ +30.7° (*c* 1.00, C_6H_6) [lit. [39] $[\alpha]_{546}^{22}$ −30° (*c* 5, C_6H_6) for the *R* enantiomer in at least 82 ± 2% ee].

(S,E)-1-Phenyl-1-penten-3-ol. Yield: 297 mg (81%). In addition, (*E*)-3-phenyl-2-propen-1-ol was obtained in 4% yield. Purification: flash chromatography (ether/hexane 1/7) and bulb-to-bulb distillation. Enantiomeric excess: 96% (Bakerbond DNBPG covalent; 99.5/0.5 hexane/2-propanol; t_R of (*S*)-isomer, 32.2 min; t_R of (*R*)-isomer, 33.3 min). $[\alpha]_D^{22}$ −5.7° (*c* 1.00, $CHCl_3$) [lit. [40] $[\alpha]_D^{23}$ −6.6° (*c* 3.18, $CHCl_3$) for the *S,E* enantiomer in 75% ee].

(R,E)-4-Hexene-3-ol. Yield: 387 mg (90%) using (*R*)-1-t-butyl-2-piperidinoethanol as catalyst. Purification: bulb-to-bulb distillation. Enantiomeric excess: 90% (determined by the same method as described in preparation of **7**: HPLC analysis, t_R, 36 min (carbamate from (*R,E*)-4-hexene-3-ol) and 42 min (carbamate from (*S,E*)-4-hexene-3-ol); eluent, 100/1.5 hexane/ethanol mixture)). $[\alpha]_D^{25}$ +1.0° (*c* 2.0, $(C_2H_5)_2O$). Hydrogenation (1 atm H_2, C_2H_5OH, 5% Pd/C) gave (*R*)-(−)-3-hexanol, $[\alpha]_D^{22}$ −7.3° (*c* 2.7, C_2H_5OH) [41].

(S)-1-Phenyl-3-pentanol. Yield: 293 mg (80%). In addition, 3-phenylpropanol was obtained in 3% yield. Purification: flash chromatography (ether/hexane 1/8). Enantiomeric excess: 90% determined as the (*R*)-1-(1-naphthyl)ethyl carbamate (1/2 ether/hexane; t_R of (*R,S*)-isomer, 6.87 min; t_R of (*R,R*)-isomer, 7.96 min). $[\alpha]_D^{22}$ +23.9° (*c* 1.44, C_2H_5OH) [lit. [40] $[\alpha]_D$ +26.8° (*c* 5.0, C_2H_5OH) for the S enantiomer].

(S)-3-Nonanol. Yield: 226 mg (81%). Purification: flash chromatography (ether/hexane 1/8). Enantiomeric excess: 61% determined as the (*R*)-1-(1-naphthyl)ethyl carbamate (1/2 ether/hexane; t_R of (*R,S*)-isomer, 5.5 min; t_R of (*R,R*)-isomer, 6.4 min). $[\alpha]_D^{22}$ + 5.1° (*c* 1.31, $CHCl_3$) [lit. [42] $[\alpha]_D^{24}$ +9.6° (*c* 8.3, $CHCl_3$) for the *S* enantiomer].

(S,E)-1-Tri-n-butylstannyl-1-octen-3-ol (15). Yield: 207 mg (84%). Purification: flash chromatography (ether/hexane 1/12). Enantiomeric excess: 85% assayed as the (*R*)-MTPA ester (1/100 ether/hexane; t_R of (*R,R*)-isomer, 6.2 min; t_R of (*R,S*)-isomer, 6.6 min). The absolute configuration was determined by comparison of HPLC behavior of the synthetic and authentic material prepared by the known method [43].

Ligand acceleration effects

A 0.05 *M* toluene solution of an appropriate ligand listed in Table 1 (0.376 ml, 0.0188 mmol), toluene (1.0 ml), and diethylzinc (1.21 ml of a 1.17 *M* solution in toluene, 1.41 mmol) were placed in a 20-ml Schlenk tube by means of a tight syringe. The mixture was stirred for 10 min at 20 °C and cooled to −78 °C. Benzaldehyde (100 mg, 0.942 mmol) was added and the apparatus was immersed in an ice bath. After 1 h stirring of the mixture at 0 °C, the usual workup afforded a crude mixture. A 1.0 *M* toluene solution of 1-phenyl-1-ethanol (0.41 ml, 50.1 mg) as

an internal standard was added and the mixture was subjected to HPLC analysis to determine the yield of 1-phenyl-1-propanol and benzyl alcohol. The conditions of HPLC were: column, Develosil 100-5; flow rate, 1 ml/min; eluent, 1/2 ether/hexane mixture; detection, 254-nm light; t_R of benzyl alcohol, 15.41 min (factor 0.8541); t_R of 1-phenyl-1-ethanol, 11.7 min (factor 1.0000); t_R of 1-phenyl-1-propanol, 8.17 min (factor 1.0964); t_R of benzaldehyde, 4.85 min (factor 0.0226).

Reaction of benzaldehyde and ethylzinc 1-phenyl-1-propanoxide

(*S*)-1-Phenyl-1-propanol (173 mg, 1.27 mmol) in toluene (3 ml) was placed into a 20-ml Schlenk tube. To this was added diethylzinc (0.495 ml of a 2.56 *M* toluene solution, 1.27 mmol) at 25 °C. Benzaldehyde (0.13 ml, 1.29 mmol) was added and kept at 25 °C for 24 h. The crude product, obtained by a usual workup of an aliquot of the mixture (0.5 ml), was subjected to GLC analysis (column, PEG-20M bonded 25 m × 0.25 mm i.d.; column temp, 100 °C; injection temp, 130 °C; flow rate of helium carrier gas, 50 ml/min; detection, FID; t_R of benzyl alcohol, 36.7 min (2%); t_R of 1-phenyl-1-propanol, 38.0 min (53%); t_R of propiophenone, 16.9 min (3%); t_R of benzaldehyde, 7.3 min (42%).

In a similar manner, (*S*)-1-phenyl-1-ethanol, dimethylzinc, and benzaldehyde were mixed at 25 °C for 24 h and the product was analyzed by GLC (column, PEG-20M on 20% Chromosorb (3 m); column temp, 200 °C; injection temp, 220 °C; flow rate of nitrogen carrier gas, 2.0 kg/cm^2; detection, FID; t_R of benzyl alcohol 23.4 min (5%); t_R of 1-phenyl-1-ethanol, 19.2 min (49%); t_R of acetophenone, 13.6 min (4%); t_R of benzaldehyde, 9.6 min (41%).

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