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Chiral ligands derived from abrine. Part 6: Importance of a bulky *N*-alkyl group in indole-containing chiral β-*tertiary* amino alcohols for controlling enantioselectivity in addition of diethylzinc toward aldehydes

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Abstract

A number of chiral β-amino alcohols possessing a 3-indolylmethyl group have been synthesized from the alkaloid (*S*)-abrine and elucidated for potency in the catalytic enantioselective ethylation of PhCHO with Et_2Zn. In general, the *secondary* amines **15a–d** bearing a dialkylhydroxymethyl group induced (*R*)-1-phenyl-1-propanol, whereas **15e–g** and **18** bearing a diarylhydroxymethyl group favored the (*S*)-enantiomer. In contrast, the β-*tertiary* amino alcohols **20b–d** and **21** produced (*R*)-1-phenyl-1-propanol, regardless of the substituents at the carbon bearing the hydroxy group. Enantiomeric excess of 87.5% was obtained for (*R*)-1-phenyl-1-propanol using ligand **21** as the promoter. Eleven substituted benzaldehydes and naphthaldehydes were examined for enantioselective ethylation by using **21** and the chiral alcohols were obtained in 93–97% ee, except for *o*-BrC_6H_4CHO and *p*-$Me_2NC_6H_4CHO$. Excellent enantioselectivity was also observed in the ethylation of cyclohexanecarboxaldehyde (94.8% ee) and 2-thiophenecarboxaldehyde (94.9% ee) by using catalytic **21**. The *anti* 5/4/4-fused tricyclic TS **I** was proposed to rationalize the asymmetric induction. The diethylhydroxymethyl and *N*-2-*t*-butylethyl groups are believed to enforce the preference for the *anti*-TS(*R*) **I** and it results in high enantioselectivity.

1. Introduction

The organic molecules isolated from the extracts of plants have been extremely valuable to humans in curing diseases such as cancer.[1,2] Because the molecules produced through plant biosynthesis are commonly homochiral, natural products are also the most important source of the homochiral ligands and auxiliaries used in contemporary asymmetric synthesis.[3] A well-known

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example is the use of the alkaloids, dihydroquinidine and dihydroquinine, and their derivatives in the catalytic asymmetric dihydroxylation.[4] Recently, we were able to isolate the alkaloid, (*S*)-abrine **1b**,[5] the *N*-methylated α-amino acid of (*S*)-tryptophan **1a** in multi-gram quantity from the red beans (Rosary pea or Xiang Si Zi in Chinese) of *Abrus precatorius* L., which were collected in the Yunnan Province located in the southwestern part of China. We were particularly interested in exploring the application of (*S*)-abrine in catalytic enantioselective reactions by taking advantage of the indole moiety and the *N*-methyl group. After searching the literature, we found only a small number of precedents in utilizing (*S*)-tryptophan derivatives as the chiral ligands in catalytic enantioselective reactions (Fig. 1). The Zn(II) complex formed from (*S*)-tryptophan ethyl ester and $Zn(NO_3)_2 \cdot 6H_2O$ was used to catalyze the asymmetric aldol reaction.[6a] Inoue and co-workers reported that the chiral Ti(IV) species derived from the dipeptide **2** and $Ti(O\textit{i}\text{-}Pr)_4$ promoted the addition of HCN to aldehydes in up to 90% ee.[6b] A number of chiral oxazaborolidines obtained from *N*-tosyl-(*S*)-tryptophan **3a** and *N*-tosyl-(α*S*,β*R*)-β-methyltryptophan **3b** and boron compounds were demonstrated to be excellent catalysts for asymmetric Diels–Alder reaction.[6c–e] Various 2-substituted 2,3-dihydro-4*H*-pyran-4-ones were prepared in 67–82% ee via the aldol reaction catalyzed by the chiral oxazaborolidine of **3a** followed by treatment with CF_3CO_2H.[6f] The chiral oxazaborolidine formed from **3b** and (*p*-chlorophenyl)dibromoborane catalyzed the enantioselective ring cleavage of 1,3-dioxolanes with enol silyl ethers in 86–93% ee.[6g] Very recently, Engberts and co-workers reported the (*S*)-abrine–Cu(II) complex that catalyzed the Diels–Alder reaction of 3-phenyl-1-(2-pyridyl)-2-propen-1-one with cyclopentadiene in 74% ee.[7] It was suggested that both the 3-indolylmethyl and the *N*-methyl groups in (*S*)-abrine are important for stereochemistry control in the transition state.[7]

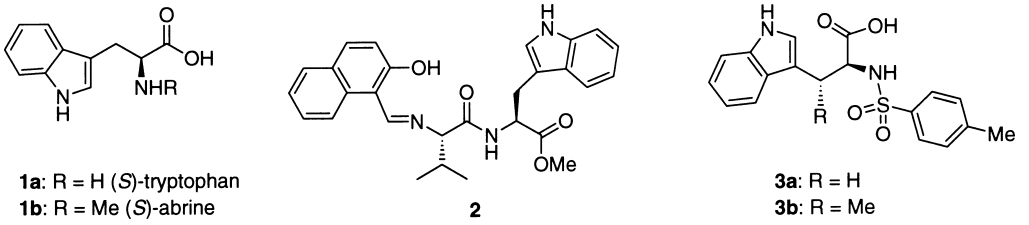


Figure 1. Chiral indole-containing ligands used in catalytic enantioselective reactions

Enantioselective addition of dialkylzincs to aldehydes in the presence of a chiral promoter, such as chiral β-amino alcohols, has been shown to be an attractive and synthetically useful carbon–carbon bond-forming reaction.[8] A vast number of chiral promoters including β-amino alcohols, β-amino thiols, diamines, and diols has been accumulated since the first report by Oguni and Omi in 1984,[8a] some representative chiral β-amino alcohols and the ee percentages of the ethylation of PhCHO with Et_2Zn are given in Fig. 2.[9] In general, enantioselectivities of 90–100% ee can be achieved for aromatic aldehydes using dialkylzincs. Starting from (*S*)-abrine, we prepared three classes of chiral ligands possessing an indole moiety, and examined their catalysis in the ethylation of aldehydes with Et_2Zn.[10] They are *secondary* and *tertiary* β-amino alcohols,[10a] 2,4-*cis*-substituted 1,3-oxazolidines,[10b,d] and 1,2,3,4-tetrahydro-β-carbolines.[10c] In this article, we disclose a full account of the synthesis and catalysis of chiral acyclic β-*secondary* and β-*tertiary* amino alcohols possessing a 3-indolylmethyl group. Emphasis will be put on the elucidation of the effect of a bulky *N*-alkyl chain on the enantioselectivity. A crystalline β-*tertiary* amino alcohol **21** has been found to promote the addition of Et_2Zn to aldehydes in high ee's.

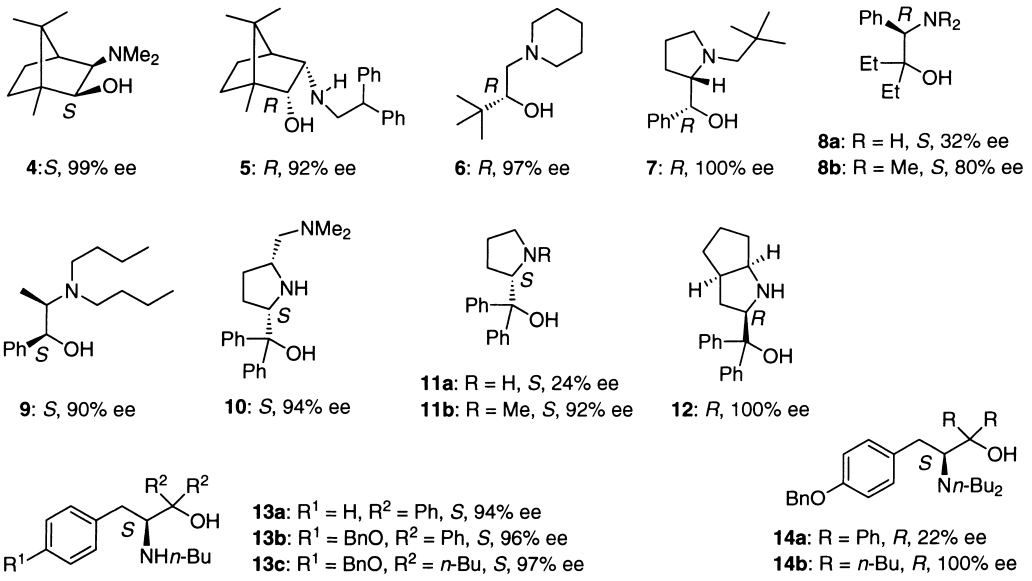


Figure 2. The configuration and ee percentage of 1-phenyl-1-propanol formed from ethylation of PhCHO promoted by chiral ligands **4**–**14**

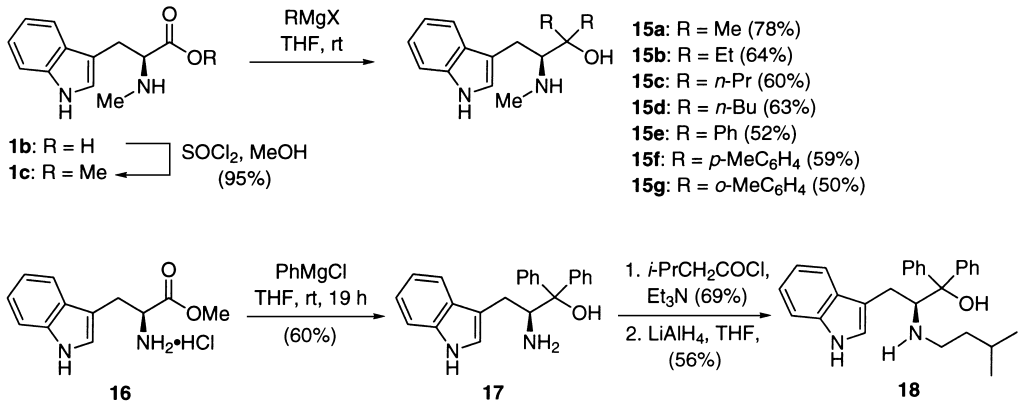
2. Results and discussion

2.1. Secondary *amino alcohols*

An examination on the chiral ligands illustrated in Fig. 2 revealed that both *secondary* and *tertiary* amines were used. A diphenylhydroxymethyl group was found in **10**–**13a**,**b** and **14a**.[9d,j–m,o,q,r] Because of the enhanced stereoselectivity in catalytic reactions, the 'diarylhydroxymethyl group' is called the 'magic group' in catalyst design and synthesis and has been used with increasing frequency in recent years.[11a] In contrast, chiral ligands possessing a dialkylhydroxymethyl group rarely provide high enantioselectivity.[11b] In 1995, we disclosed the chiral compound **21** (vide infra) containing the diethylhydroxymethyl group for use in the ethylation of aromatic aldehydes with >90% ee's.[10a] Very recently, several groups also demonstrated the effect of the dialkylhydroxymethyl group in chiral compounds **8b**,[9g] **13c**,[9p] **14b**,[9p] and others[9k,m,r–t] on enantioselectivity. It is known that β-*secondary* amino alcohols **5** and **12** possessing a bicyclic skeleton and **10** having an additional chelating site induce high enantioselectivity, whereas **11a**[9l] and others[9g,r–t] usually give low enantioselectivity. Chiral amino alcohol **13a**[9o] gives an impressively high level of ee and this encouraged us to undertake the following investigations.

Our initial effort was to design and synthesize a number of β-*secondary* amino alcohols **15a**–**g** bearing either a di-*n*-alkylhydroxymethyl or diarylhydroxymethyl group (Scheme 1). Conversion of (*S*)-abrine **1b** into the methyl ester **1c** was achieved by treatment of **1b** with excess $SOCl_2$ in MeOH in 95% yield. Addition of various Grignard reagents (in excess) to the ester **1c** provided the *tertiary* alcohols **15a**–**g** in 50–78% yield. An analogous compound **18** of **13a** was also synthesized for comparison of the effect of the 3-indolylmethyl group in **18** with the benzyl group in **13a**. Treatment of (*S*)-tryptophan methyl ester hydrochloride **16** with large excess PhMgCl in THF gave the alcohol **17** in 60% yield. Selective acylation of the primary amino group in **17** with isovaleryl

chloride–Et_3N at room temperature formed the corresponding amide in 69% yield. Finally, the amide was reduced by excess $LiAlH_4$ in refluxing THF to furnish the β-*secondary* amino alcohol **18** in 56% yield (Scheme 1).

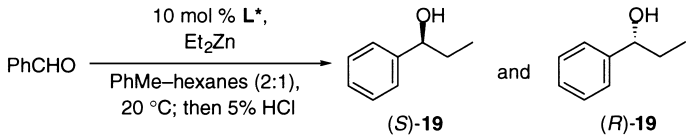


Scheme 1.

Catalysis of the above synthesized chiral ligands **15a–g** and **18** was examined with PhCHO as the substrate under the standard conditions (entries 1–8 in Table 1). The ethylation was carried out in dry PhMe:hexanes (2:1) in the presence of 10 mol% chiral ligand at room temperature, and the reaction mixture was then quenched by 5% aqueous HCl in an ice–water bath. The product, 1-phenyl-1-propanol **19**, was isolated by extraction and purified by column chromatography over silica gel and the ee was determined by HPLC analysis using a chiral stationary phase. In general, the chiral ligands **15a–d** possessing a di-*n*-alkylhydroxymethyl group produced (*R*)-**19** as the major enantiomer, whereas the chiral ligands **15e–g** and **18**, having a diarylhydroxymethyl group, induced (*S*)-**19** preferentially. This finding is of interest in the mechanistic consideration. In addition to the low enantioselectivity, the reaction time was significantly longer, the yield of the product was moderate, and benzyl alcohol was formed as the result of reduction by Et_2Zn. All these aspects indicated that the β-*secondary* amino alcohols **15a–g** and **18** were not the efficient ligands. In particular, the diminished enantioselectivity induced by **18** compared to **13a–b** suggested that the 3-indolylmethyl group interfered with the functioning of the amino alcohol moiety. Because of the acidity of indole (pK_a 21.0 in DMSO),[12] a plausible zinc amide[10d,13] might be formed through deprotonation of the indole moiety in **18** and competed for catalysis via multi-component complexation.[14] The less steric demand of the *N*-methyl group might be another factor for the inefficiency of the chiral ligands **15a–g** in stereochemical control.

The effect of the *n*-alkyl chain length on enantioselectivity was observed in the chiral ligands **15a–d** possessing a di-*n*-alkylhydroxymethyl group. As shown in Fig. 3, the % ee of (*R*)-**19** varied regularly with the length of the *n*-alkyl chain to form a 'zigzag' curve. The peaks were found for the chain length of odd number carbon. A maximum value of 44.9% ee was obtained with the *n*-propyl group. A similar phenomenon was noted in the chiral oxazolidine-catalyzed addition of Et_2Zn to PhCHO.[10d] One can assume that this effect originates from the van der Waals interaction and reflects the conformational preference of the *n*-alkyl chain. The effect of the *N*-*n*-alkyl group in (1*S*,2*R*)-*N*,*N*-di-*n*-alkylnorephedrines[15a] and the polymer-supported (1*S*,2*R*)-*N*-*n*-alkylnorephedrines[15b]

Table 1
Addition of Et_2Zn to PhCHO promoted by chiral amino alcohols **15a–g**, **18**, **20a–d** and **21**[a]



entry	L*	t (h)	19 (%)[b]	ee (%)[c]	confgn[c,d]
1	**15a**	96	83	31.0	*R*
2	**15b**	48	59	7.1	*R*
3	**15c**	96	55	44.9	*R*
4	**15d**	96	50	35.8	*R*
5	**15e**	90	68	26.9	*S*
6	**15f**	48	64	27.9	*S*
7	**15g**	88	64	30.3	*S*
8	**18**	61	54	44.3	*S*
9	**20a**	52	50	36.7	*S*
10	**20b**	96	51	13.5	*R*
11	**20c**	69	51	29.6	*R*
12	**20d**	92	48	57.9	*R*
13	**21**	96	70	87.5	*R*

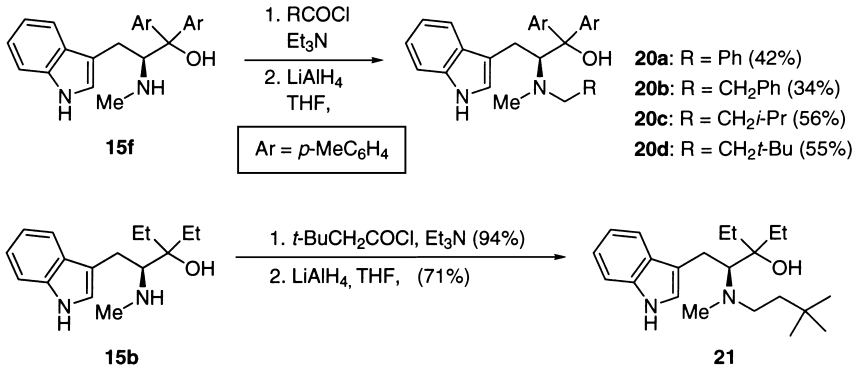
[a]Reaction was carried out in dry PhMe-hexanes (2:1) at 20 °C. Benzyl alcohol was formed as the byproduct and PhCHO was remained in most of the reactions. [b]Isolated yield of alcohol **19**. [c]Determined by HPLC over a Chiralcel OD column eluted with hexane–2-propanol (97.5:2.5) at 1 mL/min using UV detector at 254 nm; t_R = 14.9 min for (*R*)-**19** and t_R = 16.9 min for (*S*)-**19**. [d]Assigned according to the sign of optical rotation and t_R of the HPLC analysis.

was examined, and the carbon number of the *n*-alkyl group for inducing the maximum % ee differed with the catalyst type and the substrate structure.

2.2. Tertiary *amino alcohols*

Next, we turned our attention to the synthesis of alcohols bearing a *tertiary* amino group. Because of the enhanced Lewis basicity of *tertiary* amines compared with the corresponding *secondary* ones, many known chiral ligands such as **4**, **6**, **7**, **8b**, **9**, **11b** and **14a**,**b** given in Fig. 2 are *tertiary* amines and contain either a ring structure or two identical alkyl groups. As the result of less accessibility and complication in a complex formation, *tertiary* amines having three different substituents are seldom used in chiral ligands. Several *tertiary* amines having an *N*-methyl group were synthesized from ephedrine and pseudoephedrine.[8d,16] High enantioselectivity in catalyzing Et_2Zn addition toward aldehydes was observed for these β-amino alcohols. We prepared the *tertiary* amines **20a–d** and **21** as shown in Scheme 2. Selective acylation of **15f** with various RCOCl in the presence of Et_3N gave the amides which were reduced to the *tertiary* amines **20a–d** by $LiAlH_4$ in refluxing THF in 34–56% yield. Similarly, the crystalline β-*tertiary* amino alcohol **21** was prepared in 67% overall yield from **15b**.

Addition of Et_2Zn toward PhCHO was carried out using 10 mol% chiral ligand **20a–d** and **21**, respectively. The results are listed in Table 1, entries 9–13. It is interesting to note that chiral ligand **20a** still induced (*S*)-**19**, whereas **20b–d** produced the antipodal enantiomer. In addition,



Scheme 2.

the % ee of (*R*)-**19** increased with increasing bulkiness of the *N*-alkyl group in the following order: **20b** ($PhCH_2CH_2$) < **20c** (*i*-$PrCH_2CH_2$) < **20d** (*t*-$BuCH_2CH_2$). A plot of the % ee against the bulkiness of the *N*-alkyl group in **15f** and **20a–d** gave the '√' shaped curve (Fig. 3). The ligand **20d** containing the *N*-2-*t*-butylethyl group produced (*R*)-**19** in 57.9% ee. This is a much better result compared to the ligand **14a** (22% ee) shown in Fig. 2. Introduction of this 'magic' 2-*t*-butylethyl group into **15b** to form ligand **21** significantly improved the asymmetric induction from 7.1 to 87.5% ee for (*R*)-**19**. Chiral ligand **21** features some unique functional groups: a diethylhydroxymethyl group, a 3-indolylmethyl group, and an *N*-2-*t*-butylethyl group. It is readily synthesized from (*S*)-abrine **1b** in four steps and in 41% overall yield. Compound **21** is a crystalline compound and is easy for purification and handling.

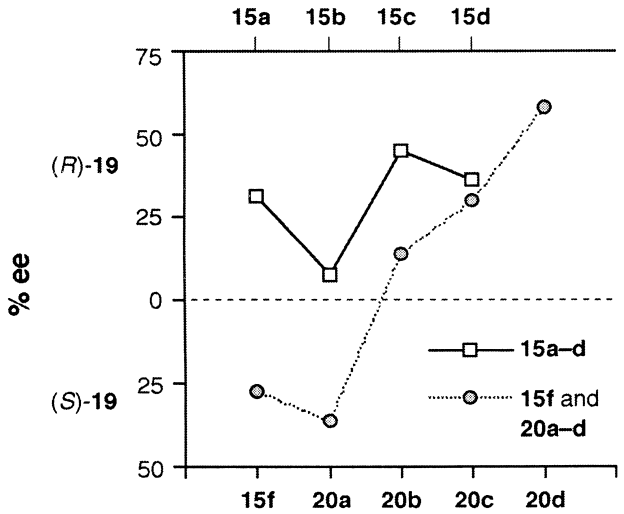


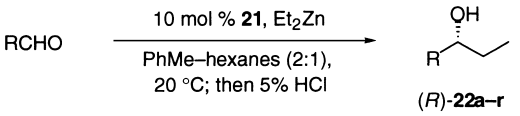
Figure 3. Effects of the alkyl group(s) in chiral ligands **15a–d,f** and **20a–d** on the rotation sign and the ee of **19** formed via the ligand-promoted addition of Et_2Zn toward PhCHO in PhMe:hexanes (2:1) at 20°C

2.3. Catalysis of *21* in Et_2Zn addition toward aldehydes

With the ligand **21** in hand, we examined a number of aldehydes for the enantioselective ethylation with Et_2Zn (Table 2). In general, high enantioselectivity of >93% ee was obtained for

naphthaldehydes and *p*-, and *m*-substituted benzaldehydes, except for *o*-bromobenzaldehyde and *p*-dimethylaminobenzaldehyde. The former aldehyde may be affected by the bulky *ortho* bromine atom. For the latter substrate, the basic dimethylamino group in the substrate and the product (*R*)-**22g** may contribute to some minor catalytic pathways. It then reduces the overall enantioselectivity. This argument is supported by the observation that (*R*)-1-phenyl-1-propanol (*R*)-**19** underwent autoinduction in the addition of Et_2Zn toward benzaldehyde in the presence of a catalytic amount of achiral amine.[14a] Low enantioselectivity (40% ee) was observed previously for *p*-dimethylaminobenzaldehyde catalyzed by an axially chiral pyridylphenol and was explained by the electronic effect of the *para* substituent.[17a] We tried to make the Hammett plots of log[(*R*)-**22**/(*S*)-**22**)] versus substituent constants σ_p^+, σ_p, or σ_I for *p*-Me_2N, *p*-MeO, *p*-Me, *p*-Cl, *p*-Br, and

Table 2
Addition of Et_2Zn to RCHO promoted by **21**[a]



(*R*)-**22a–r**

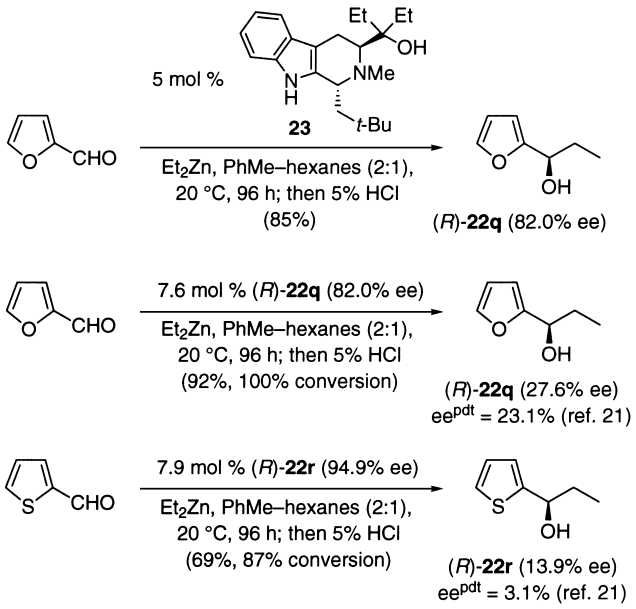
entry	R	*t* (h)	yield (%)[b]	ee (%)[c]
1	Ph	96	(*R*)-**19**: 70	87.5
2	*p*-ClC_6H_4	96	(*R*)-**22a**: 99	96.9
3	*m*-ClC_6H_4	117	(*R*)-**22b**: 92	97.0
4	*p*-BrC_6H_4	117	(*R*)-**22c**: 93	95.7
5	*o*-BrC_6H_4	117	(*R*)-**22d**: 82	85.1
6	*p*-MeC_6H_4	96	(*R*)-**22e**: 90	95.7[d]
7	*p*-$MeOC_6H_4$	96	(*R*)-**22f**: 90	95.8
8	*p*-$Me_2NC_6H_4$	116	(*R*)-**22g**: 94	80.0
9	3,5-$Cl_2C_6H_4$	116	(*R*)-**22h**: 94	94.9[d]
10	3,5-$(MeO)_2C_6H_4$	116	(*R*)-**22i**: 93	94.1
11	1-Naph	116	(*R*)-**22j**: 90	93.5
12	2-Naph	96	(*R*)-**22k**: 99	96.1
13	*trans*-PhCH=CH	48	(*R*)-**22l**: 100	81.3
14	*c*-Hexyl	40	(*R*)-**22m**: 65	94.8[d]
15	2-Py	116	(*R*)-**22n**: 41	5.4
16	3-Py	116	(*R*)-**22o**: 81	24.3
17	4-Py	116	(*R*)-**22p**: 79	7.5
18	2-Furyl	96	(*R*)-**22q**: 72	78.0[d]
19	2-Thienyl	96	(*R*)-**22r**: 84	94.9[d]

[a]Reaction was carried out in dry PhMe–hexanes (2:1) at 20 °C. [b]Isolated yield of pure product. The *R* configuration was assigned according to the sign of optical rotation. [c]Determined by HPLC over a chiral column, see Experimental Section for analyzing conditions. [d]Determined for the corresponding benzoate.

p-H,[18] respectively. But the linearity of the plots is very poor. The data suggested that the stereochemistry of the ethylation catalyzed by chiral ligand **21** is not only determined by the electronic effect.[17b]

A high enantioselectivity (94.8% ee) was obtained for (*R*)-**22m** formed from a saturated aldehyde, cyclohexanecarboxaldehyde. *trans*-Cinnamaldehyde gave a reasonably high ee of 81.3% for (*R*)-**22l**. The heterocyclic aromatic aldehydes, 2-furaldehyde and 2-thiophenecarboxaldehyde provided (*R*)-**22q** (78.0% ee) and (*R*)-**22r** (94.9% ee) in good to excellent enantioselectivity. However, pyridinecarboxaldehydes were the poorest substrates of the ethylation reaction giving 5.4 to 24.3% ee.[19a] The results are interpreted by the competitive side catalytic cycle involving the basic heteroatom. In fact, autocatalysis of the nitrogen-containing aromatic aldehydes was investigated extensively by the Soai's group.[19b–i] For example, 3-pyridinecarboxaldehyde was converted into (–)-1-(3-pyridyl)-1-propanol (*S*)-**22o** of 14% ee in the presence of 20 mol% of (*S*)-**22o** possessing 56% ee.[19b] In general, the ee of the product is much lower than the ee of the initially used promoter, except for the cases where the ee of the product is high (or higher than the ee of the initial catalyst) using a bulky *i*-Pr_2Zn.[19b–i] Because of the proximity of the nitrogen atom to the reacting center, 2-pyridinecarboxaldehyde failed to give chiral 1-(2-pyridyl)-1-propanol in the chiral ligand-catalyzed ethylation.[20] Another possibility is worthy of mentioning. Because of the bulkiness of the *tertiary* amino group in **21**, complexation of the nitrogen atom with metal species is rather weak and can be easily replaced by other Lewis bases. This argument agrees well with the enhanced ee in (*R*)-**22n**,**q**,**r** according to the diminished Lewis basicity of the heteroatoms: pyridine > furan > thiophene. Therefore, in the presence of a stronger Lewis base, the chiral ligand **21** cannot function properly and gives a low ee of the product.

We examined the autocatalysis of (*R*)-**22q** and (*R*)-**22r** shown in Scheme 3. Compound (*R*)-**22q** with 82.0% ee was obtained from the ethylation of 2-furaldehyde in 85% yield in the presence of the chiral ligand **23**, previously synthesized by us from (*S*)-abrine (**1b**).[10c] Using this chiral alcohol



Scheme 3.

(*R*)-**22q** (82.0% ee) as the promoter (7.6 mol%), the addition of Et_2Zn to 2-furaldehyde in PhMe:hexanes (2:1) completed within 96 h and (*R*)-**22q** was isolated in 92% yield and in 27.6% ee.[21] Similarly, addition of Et_2Zn to 2-thiophenecarboxaldehyde in the presence of 7.9 mol% (*R*)-**22r** (94.9% ee) afforded (*R*)-**22r** (13.9% ee)[21] in 69% yield with 87% conversion of the aldehyde. The newly formed product ee induced by (*R*)-**22q** (82.0% ee) and (*R*)-**22r** (94.9% ee) is calculated to be 23.1 and 3.1% ee, respectively.[21] It is evident that (*R*)-1-(2′-furyl)-1-propanol (*R*)-**22q** is a much more efficient promoter than (*R*)-1-(2′-thienyl)-1-propanol (*R*)-**22r** in terms of reactivity and asymmetric autocatalysis. As a result of the autocatalysis by (*R*)-**22q**, a relatively low enantioselectivity (78.0% ee) was obtained for the chiral ligand **21** promoted ethylation of 2-furaldehyde.

2.4. Transition state consideration

Noyori and co-workers investigated the chirality amplification phenomenon in the chiral β-amino alcohol promoted alkylation of aldehydes with dialkylzincs and demonstrated the existence of an equilibrium among monomeric and dimeric Zn–ligand complexes.[22] Recently, they confirmed that the alkylation occurs through the monomeric alkylzinc aminoalkoxide as the catalytic species.[23] In the product-forming transition state (TS), a dinuclear Zn complex with the chiral ligand and the aldehyde substrate was proposed.[24a] Based on the molecular orbital calculations at the restricted Hartree–Fock (RHF) level, the 5/4/4–fused tricyclic transition states were established and the alkyl migration was predicted to take place with retention of configuration.[24a,25–27] Among the two possible stereoisomeric μ-O TS', the *anti*-TS is 2.9 kcal/mol much more stable than the *syn*-TS.[24a] These results have recently been reproduced by Houk and Goldfuss in the PM3 and ONIOM(RHF/LanL2DZ:UFF) TS models.[24b,c] For the fenchone derivatives, the μ-O *syn*-TS may dominate compared to the μ-O *anti*-TS depending on the nature of the donor group.[24c]

According to these theoretical studies, we use the *anti*-TS(*R*) and *syn*-TS(*S*) **I** and **II** to explain the stereochemistry induced by the chiral ligands **15a–g**, **18**, **20b–d**, and **21** (Fig. 4).[28] Because of the *gem* disubstituents at the hydroxymethyl group, the chirality at the carbon bearing the 3-indolylmethyl group controls the stereochemical course of the alkylation. In both TS' **I** and **II**, the 3-indolylmethyl group points away from the Zn_2O_2 ring to minimize the steric interaction. For the *anti*-TS(*R*) **I**, there may be a repulsive intereaction among the $\mathbf{X^1}$ and the passive ethyl group Et_p. The two substituents on the nitrogen atom should be arranged with R_L being opposite to the 3-indolylmethyl group. In the case of β-*tertiary* amino alcohols **20b–d** and **21**, the bulky groups [3-indolylmethyl, *N*-CH_2CH_2X (X = Ph, *i*-Pr, *t*-Bu), and Zn_a-Et] on the five-membered chelate align with each other in the 1,2-*trans* relationship. The ethyl group Et_T is transferred from the *re*-face of the aldehyde to form the *R* enantiomer. The electron-rich diethylhydroxymethyl group in **21** should increase the Lewis basicity of the alkoxide and enhances the rigidity of the five-membered chelate. It gives a higher preference for the *anti*-TS(*R*) **I** and results in a better stereochemical control. This accounts for the excellent performance of the chiral ligand **21** described above, as well as the remarkably improved enantioselectivity of **14b** over **14a** (Fig. 2). It has been known that the β-*secondary* amino alcohols **13a–c** induced the *S* alcohols,[9o,p] and a zinc monoalkoxide was proposed as the catalytic species.[9o] We suggest the *syn*-TS(*S*) **II** for the asymmetric induction of **15e–g** and **18**. With R_S being H, steric repulsion between R_S and the transferring ethyl group Et_T is less demanding. Thus, TS **II** becomes much more stable than **I** and the *S* product is formed predominantly.[24c] A similar TS of the type **II** can be proposed for the catalysis of **13a–c**.

The higher ee observed for **13a–c** compared to **18** may be rationalized by considering the possible catalysis of an indole zinc amide of **18**.[10d] For the ligands **15a–d**, a reversal in asymmetric induction was observed. It may result from the preference of *anti*-TS(*R*) **I** over *syn*-TS(*S*) **II** where the steric repulsion between $\mathbf{X^2}$ (alkyl) and Et_T causes destabilization. It seems reasonable that the electronic effect of the alkoxide should enhance the rigidity of the five-membered chelate and bring the $\mathbf{X^2}$ (alkyl) closer to Et_T in *syn*-TS(*S*) **II**. Moreover, an alkyl group may have a larger 'effective size' than an aryl group. Thus, both electronic and steric effects of the dialkylhydroxymethyl group in the β-*secondary* amino alcohols **15a–d** destabilizes the *syn*-TS(*S*) **II**. However, it must be mentioned that the energy difference between *anti*-TS(*R*) **I** and *syn*-TS(*S*) **II** may be within 3 kcal/mol according to reported calculations.[24] It is not surprising to see the preference for the TS switched over with a minor modification on the catalyst structure.

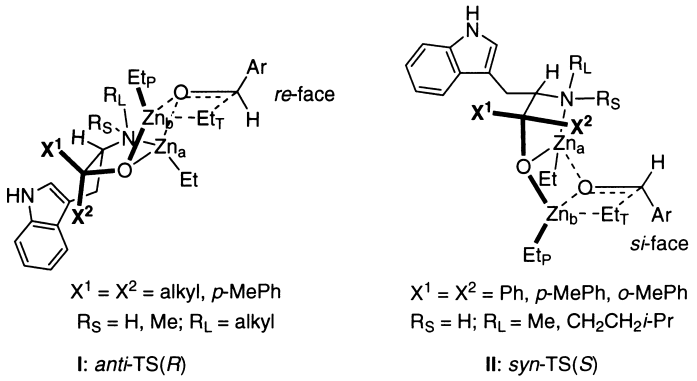


Figure 4. 5/4/4-Fused tricyclic transition states for chiral ligand-promoted ethylation of aldehydes

3. Conclusion

We have synthesized a novel series of chiral β-amino alcohols **15a–g**, **20a–d**, and **21** from the alkaloid, (*S*)-abrine, isolated from the red beans of *Abrus precatorius* L. Enantioselective ethylation of aldehydes with Et_2Zn was investigated in the presence of a catalytic amount of the chiral β-amino alcohols and the effects of the ligand structures on the enantioselectivity were examined. As a result of our efforts, a chiral ligand **21** was discovered. This promoted the ethylation of a number of naphthaldehydes, *p*- and *m*-substituted benzaldehydes, cyclohexanecarboxaldehyde, and 2-thiophenecarboxaldehyde in $>93\%$ ee. An *anti* 5/4/4–fused tricyclic TS **I** was proposed to rationalize the asymmetric induction. Unlike the known cyclic β-amino alcohols, such as the pyrrolidine derivatives **10–12**, and β-amino alcohols attached to a ring skeleton, such as the camphor derivatives **4** and **5**, acyclic β-amino alcohols are relatively flexible for positioning the *N*-alkyl groups in the aminoalkoxide–zinc chelate. Particularly, unsymmetrical *tertiary* amines can form two possible chelates and reduce the stereochemical control in the TS. The success of the chiral ligand **21** relies on the larger steric difference among the *N*-methyl and the *N*-2-*t*-butylethyl groups. In combination with the electron-rich diethylhydroxylmethyl group, a well-defined and rigid TS **I** operates for the **21**-promoted ethylation. The 3-indolylmethyl group does not seem to be absolutely necessary and other bulky arylmethyl substituents should act in a similar manner.[9p]

We believe that the results described above are very helpful in a novel chiral ligand design for enantioselective catalysis. The current study provides another good example for the use of natural products as a source of chiral ligands.

4. Experimental

4.1. General methods

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ (300, 400, or 500 MHz for ^{1}H and 75, 100, or 125 MHz for ^{13}C, respectively) with $CHCl_3$ as the internal reference. IR spectra were taken on a FT-IR spectrophotometer. Mass spectra (MS) were measured by CI or FAB method. Both high resolution mass spectra (HRMS, measured by EI or FAB method) and elemental analysis were performed by Kunming Institute of Botany, The Chinese Academy of Sciences. All reactions were carried out under a nitrogen atmosphere and monitored by thin-layer chromatography on 0.25 mm E. Merck silica gel plates (60 F-254) using UV light, or 7% ethanolic phosphomolybdic acid and heating as the visualizing methods. E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials. (*S*)-Abrine was isolated from the extract of the seeds of *Abrus precatorius* collected in the Yunnan Province of China.[5] Et_2Zn (1.0 M in hexanes) and other reagents were obtained commercially and used as received. Room temperature is around 20°C.

4.2. (S)-Abrine methyl ester **1c**

To methanol (20 mL) in a 250 mL round-bottomed flask cooled to –20––15°C was added dropwise $SOCl_2$ (1.0 mL). After stirring for 15 min, (*S*)-abrine **1b** (1.50 g, 6.88 mmol) was added followed by stirring at room temperature for 48 h. The reaction mixture was condensed under reduced pressure, water was added to the residue, and the aqueous solution was adjusted to pH 9–10 using saturated aqueous Na_2CO_3. The resultant aqueous solution was extracted with CH_2Cl_2 (3×40 mL), and the organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtrated, and condensed under reduced pressure to give **1c** (1.52 g, 95%): pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.88 (br s, 1H), 7.65 (d, J=7.7 Hz, 1H), 7.30 (d, J=8.1 Hz, 1H), 7.28–7.13 (m, 2H), 6.97 (s, 1H), 3.71 (s, 3H), 3.64 (t, J=6.9 Hz, 1H), 3.26 (dd, J=14.4, 5.8 Hz, 1H), 3.17 (dd, J=14.4, 7.2 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.0, 136.2, 127.2, 123.0, 121.7, 119.1, 118.4, 111.2, 110.4, 63.7, 51.6, 34.6, 29.0; HRMS (+EI) calcd for $C_{13}H_{16}N_2O_2$ (M^+): 232.1212; found: 232.1195.

4.3. Synthesis of secondary amino alcohols from **1c**; general procedure

To a solution of **1c** (1.00 g, 4.3 mmol) in dry THF (20 mL) cooled in an ice–water bath (ca. 0°C) was added a THF solution of RMgBr or ArMgBr (6 mol equiv.) followed by stirring at room temperature for 15 h. The reaction mixture was quenched by saturated aqueous NH_4Cl and extracted with EtOAc (3×50 mL). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 5% MeOH–CH_2Cl_2) to give the alcohols.

*4.3.1. 3-(3′-Indolyl)-1,1-dimethyl-(2*S*)-(*N*-methylamino)-1-propanol* ***15a***

Prepared from **1c** in 78% yield; pale yellow foam; $[\alpha]_D^{20}$ –48.2 ($c=1.05$, MeOH); IR (KBr) 3332, 3224 (br), 1457, 1359, 1171 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.03 (br s, 1H), 7.54 (d, $J=7.44$ Hz, 1H), 7.32 (d, $J=8.12$ Hz, 1H), 7.14 (t, $J=7.08$ Hz, 1H), 7.06 (t, $J=7.56$ Hz, 1H), 7.03 (s, 1H), 3.28 (br s, 2H), 3.02 (d, $J=12.48$ Hz, 1H), 2.70–2.61 (m, 2H), 2.11 (s, 3H), 1.33 (s, 3H), 1.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.5, 127.2, 122.4, 121.8, 119.0, 118.4, 112.7, 111.3, 72.0, 68.9, 37.0, 27.5, 26.8, 23.8; MS (+FAB) m/z (relative intensity) 233 (M+H$^+$, 100); HRMS (+FAB) calcd for $C_{14}H_{21}N_2O$ (M+H$^+$): 233.1654; found: 233.1664.

*4.3.2. 1,1-Diethyl-3-(3′-indolyl)-(2*S*)-(*N*-methylamino)-1-propanol* ***15b***

Prepared from **1c** in 64% yield; pale yellow foam; $[\alpha]_D^{20}$ –51.9 ($c=2.24$, $CHCl_3$); IR (KBr) 3420 (br), 1460, 1360, 1110 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (br s, 1H), 7.64 (d, $J=7.8$ Hz, 1H), 7.38 (d, $J=8.1$ Hz, 1H), 7.24–7.12 (m, 2H), 7.04 (d, $J=2.1$ Hz, 1H), 3.07 (dd, $J=10.8$, 3.6 Hz, 1H), 2.80 (dd, $J=14.1$, 3.6 Hz, 1H), 2.65 (dd, $J=14.7$, 10.8 Hz, 1H), 2.11 (s, 3H), 1.74–1.51 (m, 4H), 1.00 (t, $J=7.5$ Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.5, 127.6, 122.2, 122.1, 119.4, 118.7, 113.8, 111.3, 74.9, 65.0, 38.2, 28.7, 27.0, 26.6, 8.0, 7.9; MS (+CI) m/z (relative intensity) 261 (M+H$^+$, 100); HRMS (+FAB) calcd for $C_{16}H_{25}N_2O$ (M+H$^+$) 261.1967; found: 261.1977; anal. calcd for $C_{16}H_{24}N_2O$: C, 73.81; H, 9.29; N, 10.76; found: C, 73.85; H, 9.37; N, 10.48.

*4.3.3. 3-(3′-Indolyl)-(2*S*)-(*N*-methylamino)-1,1-di-*n*-propyl-1-propanol* ***15c***

Prepared from **1c** in 60% yield; pale yellow foam; $[\alpha]_D^{20}$ –13.0 ($c=1.02$, MeOH); IR (KBr) 3264 (br), 1459, 1436, 1354 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (br s, 1H), 7.56 (d, $J=7.88$ Hz, 1H), 7.39 (d, $J=8.12$ Hz, 1H), 7.20–7.13 (m, 2H), 7.11 (t, $J=7.05$ Hz, 1H), 3.56 (br s, 2H), 3.09 (dd, $J=14.77$, 2.76 Hz, 1H), 2.94 (dd, $J=10.86$, 3.16 Hz, 1H), 2.80 (dd, $J=14.72$, 11.02 Hz, 1H), 2.10 (s, 3H), 1.75–1.40 (m, 8H), 0.98 (t, $J=7.06$ Hz, 3H), 0.96 (t, $J=7.06$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.6, 127.0, 123.2, 121.8, 119.1, 118.2, 111.5 (×2), 75.0, 66.4, 39.3, 37.3, 37.1, 29.6, 25.8, 16.6, 14.7, 14.6; MS (+FAB) m/z (relative intensity) 289 (M+H$^+$, 57); HRMS (+FAB) calcd for $C_{18}H_{29}N_2O$ (M+H$^+$): 289.2280; found: 289.2194.

*4.3.4. 1,1-Di-*n*-butyl-3-(3′-indolyl)-(2*S*)-(*N*-methylamino)-1-propanol* ***15d***

Prepared from **1c** in 63% yield; pale yellow foam; $[\alpha]_D^{20}$ –11.7 ($c=0.32$, MeOH); IR (KBr) 3467, 3415, 3309 (br), 1458 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (br s, 1H), 7.62 (d, $J=7.70$ Hz, 1H), 7.37 (d, $J=8.10$ Hz, 1H), 7.21 (t, $J=7.00$ Hz, 1H), 7.14 (t, $J=7.05$ Hz, 1H), 7.06 (d, $J=1.95$ Hz, 1H), 3.06 (ddd, $J=14.63$, 3.61, 0.92 Hz, 1H), 2.79 (dd, $J=10.68$, 3.64 Hz, 1H), 2.66 (dd, $J=14.64$, 10.70 Hz, 1H), 2.11 (s, 3H), 1.70–1.25 (m, 12H), 0.95 (t, $J=7.23$ Hz, 3H), 0.92 (t, $J=7.17$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.5, 127.6, 122.3, 122.2, 119.4, 118.7, 113.8, 111.3, 74.8, 65,8, 38.2, 36.9, 35.0, 26.7, 25.8, 25.75, 23.7, 23.5, 14.2 (×2); MS (+FAB) m/z (relative intensity) 317 (M+H$^+$, 100); HRMS (+FAB) calcd for $C_{20}H_{33}N_2O$ (M+H$^+$): 317.2593; found: 317.2539.

*4.3.5. 3-(3′-Indolyl)-(2*S*)-(*N*-methylamino)-1,1-diphenyl-1-propanol* ***15e***

Prepared from **1c** in 52% yield; pale yellow foam; $[\alpha]_D^{20}$ –14.5 ($c=2.11$, $CHCl_3$); IR (KBr) 3395 (br), 1450 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (br s, 1H), 7.79–7.70 (m, 4H), 7.61 (d, $J=7.5$ Hz, 1H), 7.38–7.13 (m, 9H), 6.99 (d, $J=1.8$ Hz, 1H), 3.98 (dd, $J=10.8$, 3.0 Hz, 1H), 3.30–2.55 (br s, 2H), 2.92 (dd, $J=15.3$, 2.4 Hz, 1H), 2.63 (dd, $J=15.3$, 10.8 Hz, 1H), 1.83 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.9, 145.3, 136.5, 128.2, 128.1, 127.5, 126.5, 126.4, 125.9, 125.6, 122.4, 122.2,

119.5, 118.9, 113.2, 111.3, 77.8, 66.4, 37.1, 27.1; MS (+CI) *m/z* (relative intensity) 357 ($M+H^+$, 100); HRMS (+FAB) calcd for $C_{24}H_{25}N_2O$ ($M+H^+$): 357.1967; found: 357.1908; anal. calcd for $C_{24}H_{24}N_2O$: C, 80.87; H, 6.79; N, 7.86; found: C, 80.75; H, 6.96; N, 7.77.

*4.3.6. 3-(3′-Indolyl)-(2*S*)-(*N*-methylamino)-1,1-di(4″-methylphenyl)-1-propanol* ***15f***

Prepared from **1c** in 59% yield; pale yellow foam; $[\alpha]_D^{20}$ –12.5 ($c=1.94$, $CHCl_3$); IR (KBr) 3400 (br), 1450 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.10 (br s, 1H), 7.67–7.59 (m, 5H), 7.34 (d, $J=8.1$ Hz, 1H), 7.24–7.12 (m, 6H), 6.97 (d, $J=1.5$ Hz, 1H), 3.94 (dd, $J=10.5$, 2.7 Hz, 1H), 3.60–2.50 (br s, 2H), 2.95 (dd, $J=15.3$, 2.1 Hz, 1H), 2.62 (dd, $J=15.3$, 10.8 Hz, 1H), 2.32 (s, 3H), 2.31 (s, 3H), 1.85 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.1, 142.6, 136.5, 135.9, 135.8, 128.9, 128.8, 127.5, 125.8, 125.5, 122.4, 122.1, 119.4, 118.9, 113.4, 111.2, 77.8, 66.4, 37.2, 27.2, 20.9, 20.8; MS (+CI) *m/z* (relative intensity) 385 ($M+H^+$, 100); HRMS (+FAB) calcd for $C_{26}H_{29}N_2O$ ($M+H^+$): 385.2280; found: 385.2242; anal. calcd for $C_{26}H_{28}N_2O$: C, 81.21; H, 7.34; N, 7.29; found: C, 81.50; H, 7.43; N, 7.01.

*4.3.7. 3-(3′-Indolyl)-(2*S*)-(*N*-methylamino)-1,1-di(2″-methylphenyl)-1-propanol* ***15g***

Prepared from **1c** in 50% yield; pale yellow foam; $[\alpha]_D^{20}$ –45.6 ($c=2.27$, $CHCl_3$); IR (KBr) 3398 (br), 1452 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.01 (br s, 1H), 7.81 (br d, $J=6.0$ Hz, 1H), 7.68 (dd, $J=7.7$, 1.8 Hz, 1H), 7.57 (d, $J=7.7$ Hz, 1H), 7.35 (dd, $J=7.0$, 1.0 Hz, 1H), 7.25–7.10 (m, 7H), 7.05 (d, $J=7.4$ Hz, 1H), 6.82 (d, $J=1.8$ Hz, 1H), 4.06 (dd, $J=9.6$, 3.3 Hz, 1H), 3.05 (dd, $J=15.6$, 3.0 Hz, 1H), 2.62 (dd, $J=15.3$, 9.6 Hz, 1H), 2.22 (s, 3H), 2.16 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.4, 142.1, 138.8, 136.4, 132.8, 132.2, 128.4, 127.5, 127.3, 127.0, 126.8, 124.8, 124.5, 122.1, 122.0, 119.4, 118.7, 113.7, 111.2, 81.0, 64.0, 36.5, 28.1, 22.4, 22.0; MS (+CI) *m/z* (relative intensity) 385 ($M+H^+$, 100); HRMS (+FAB) calcd for $C_{26}H_{29}N_2O$ ($M+H^+$): 385.2280; found: 385.2253; anal. calcd for $C_{26}H_{28}N_2O$: C, 81.21; H, 7.29; N, 7.29; found: C, 81.57; H, 7.50; N, 6.98.

*4.4. (2*S*)-Amino-3-(3′-indolyl)-1,1-diphenyl-1-propanol* ***17***

To a solution of L-tryptophan methyl ester hydrochloride (**16**, 1.05 g, 3.93 mmol) in dry THF (20 mL) cooled in an ice–water bath (ca. 0°C) was added a solution of PhMgCl (15.0 mL, 2.0 M in THF, 30.0 mmol) followed by stirring at room temperatue for 19 h. The reaction mixture was quenched by saturated aqueous NH_4Cl and extracted with Et_2O (3×30 mL). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, MeOH:CH_2Cl_2:hexane = 1:10:10) to give **17** (852 mg, 60%): pale yellow foam; ^1H NMR (300 MHz, $CDCl_3$) δ 8.05 (br s, 1H), 7.67 (t, $J=8.7$ Hz, 4H), 7.52 (d, $J=7.5$ Hz, 1H), 7.45–7.15 (m, 9H), 7.03 (d, $J=1.8$ Hz, 1H), 4.30 (dd, $J=10.2$, 3.0 Hz, 1H), 2.75 (dd, $J=14.7$, 2.7 Hz, 1H), 2.66 (dd, $J=14.4$, 10.5 Hz, 1H), 2.10–1.40 (br s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.1, 144.5, 136.6, 128.5, 128.3, 127.3, 126.7, 126.6, 125.8, 125.4, 122.6, 122.2, 119.4, 118.9, 113.4, 111.3, 78.5, 56.4, 26.3.

*4.5. 3-(3′-Indolyl)-(2*S*)-(isovalerylamino)-1,1-diphenyl-1-propanol*

To a solution of **17** (340 mg, 0.99 mmol) in dry THF (5 mL) cooled in an ice–water bath was added Et_3N (0.18 mL, 1.29 mmol) and isovaleryl chloride (0.14 mL, 1.15 mmol) followed by stirring at room temperature for 6 h. The precipitate was filtered off through Celite with rinsing

by Et_2O (3×20 mL). The combined organic layer was washed with brine, dried over anydrous $MgSO_4$, filtered, and condensed under reduced pressure. The residue was purified by flash column chromatography (silica gel, 25% EtOAc–hexane) to give the amide of **17** (295 mg, 69%): pale yellow foam; IR (KBr) 3410, 3320 (br), 1640, 1450 cm^{-1}; ^1H NMR (300 MHz, CD_3CN) δ 8.87 (br s, 1H), 7.56–7.51 (m, 2H), 7.43–7.38 (m, 2H), 7.25–7.14 (m, 2H), 7.09–7.00 (m, 4H), 6.96–6.88 (m, 2H), 6.84 (d, $J=2.4$ Hz, 1H), 6.79 (ddd, $J=8.1$, 6.9, 1.2 Hz, 1H), 6.40 (d, $J=8.8$ Hz, 1H), 5.57 (br s, 1H), 4.73 (ddd, $J=11.9$, 8.7, 2.1 Hz, 1H), 2.91 (dd, $J=14.7$, 11.1 Hz, 1H), 2.57 (ddd, $J=14.7$, 2.1, 0.6 Hz, 1H), 11.55–1.41 (m, 3H), 0.35 (d, $J=6.6$ Hz, 3H), 0.29 (d, $J=6.0$ Hz, 3H); ^{13}C NMR (75 MHz, CD_3CN) δ 172.9, 147.0, 146.3, 136.4, 128.3, 127.7, 126.6, 126.3, 125.8, 125.6, 123.1, 121.1, 118.6, 118.3, 112.3, 111.2, 80.5, 58.8, 45.2, 25.6, 24.4, 21.4, 21.2; MS (+CI) *m/z* (relative intensity) 427 ($M+H^+$, 8), 409 (M^+-H_2O, 11), 280 (100); HRMS (+FAB) calcd for $C_{28}H_{31}N_2O_2$ ($M+H^+$): 427.2386; found: 427.2470; anal. calcd for $C_{28}H_{30}N_2O_2$: C, 78.84; H, 7.09; N, 6.57; found: C, 78.59; H, 7.42; N, 6.30.

4.6. 3-(3′-Indolyl)-(2S)-(3″-methylbutylamino)-1,1-diphenyl-1-propanol **18**

To a suspension of $LiAlH_4$ (76 mg, 2.00 mmol) in dry THF (10 mL) cooled in an ice–water bath (ca. 0°C) was added a solution of the amide obtained above from **17** (200 mg, 0.47 mmol) in dry THF (5 mL). The resultant mixture was then heated at refluxing temperature for 43 h. After cooled to ca. 0°C in an ice–water bath, the reaction mixture was quenched by 5% aqueous NaOH (4 mL) and filtered through Celite with rinsing by EtOAc. The filtrate was extracted with EtOAc (3×20 mL), and the combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and condensed in vacuo. The residue was purified by flash column chromatography (silica gel, 20% EtOAc–hexane) to give **18** (109 mg, 56%): pale yellow foam; $[\alpha]_D^{20}$ –23.4 ($c=2.18$, $CHCl_3$); IR (KBr) 3420 (br), 1450, 1350 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.01 (br s, 1H), 7.78 (t, $J=8.1$ Hz, 4H), 7.65 (d, $J=7.5$ Hz, 1H), 7.40–7.17 (m, 9H), 6.95 (d, $J=1.5$ Hz, 1H), 5.60–5.05 (br s, 2H), 4.04 (dd, $J=10.8$, 2.7 Hz, 1H), 2.95 (dd, $J=15.3$, 2.7 Hz, 1H), 2.56 (dd, $J=15.3$, 11.1 Hz, 1H), 1.98 (dt, $J=11.4$, 6.9 Hz, 1H), 1.85 (dt, $J=11.4$, 6.9 Hz, 1H), 1.10 (sept., $J=6.6$ Hz, 1H), 0.90–0.75 (m, 2H), 0.53 (d, $J=6.6$ Hz, 3H), 0.43 (d, $J=6.6$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.2, 145.5, 136.6, 128.1, 128.0, 127.5, 126.4, 126.3, 126.0, 125.7, 122.2, 122.1, 119.4, 118.9, 113.5, 111.2, 77.6, 64.5, 47.7, 39.2, 27.4, 25.1, 22.3, 22.0; MS (+CI) *m/z* (relative intensity) 413 ($M+H^+$, 100); HRMS (+FAB) calcd for $C_{28}H_{33}N_2O$ ($M+H^+$): 413.2593; found: 413.2506; anal. calcd for $C_{28}H_{32}N_2O$: C, 81.51; H, 7.82; N, 6.79; found: C, 81.41; H, 7.98; N, 6.66.

4.7. Synthesis of amides of **15b** and **15f**; general procedure

To a solution of **15b** or **15f** (3.03 mmol) in dry THF (30 mL) cooled in an ice–water bath was added Et_3N (0.50 mL, 3.59 mmol) and the acyl chloride (3.60 mmol) followed by stirring at room temperature for 17 h. The precipitate was filtered off through Celite with rinsing by Et_2O (3×30 mL). The combined organic layer was washed with brine, dried over anydrous $MgSO_4$, filtered, and condensed under reduced pressure. The residue was purified by flash column chromatography (silica gel, EtOAc:hexane:CH_2Cl_2 = 1:3:3) to give the amide.

4.7.1. 1,1-Diethyl-3-(3′-indolyl)-(2S)-(N-methyl-N-3″,3″-dimethylbutyrylamino)-1-propanol

Prepared from **15b** in 94% yield; pale yellow foam; IR (KBr) 3250 (br), 1600, 1450, 1355 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.26 (br s, 1H), 7.56 (d, $J=7.8$ Hz, 1H), 7.37 (d, $J=7.8$ Hz, 1H),

7.19 (t, $J=7.2$ Hz, 1H), 7.11 (t, $J=7.2$ Hz, 1H), 6.95 (s, 1H), 6.42 (s, 1H), 3.64 (dd, $J=14.7$, 12.0 Hz, 1H), 3.34 (dd, $J=12.0$, 3.0 Hz, 1H), 3.08 (dd, $J=14.7$, 2.4 Hz, 1H), 2.41 (s, 3H), 2.19 (d, $J=14.4$ Hz, 1H), 2.01 (d, $J=14.7$ Hz, 1H), 1.90–1.30 (m, 3H), 1.05 (s, 9H), 1.00 (t, $J=7.5$ Hz, 3H), 0.90 (t, $J=7.5$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.6, 136.4, 127.5, 122.8, 121.9, 119.3, 118.4, 113.6, 111.4, 75.8, 73.8, 46.7, 43.0, 31.6, 30.1, 28.4, 27.9, 21.0, 8.8, 7.8; MS (+CI) *m/z* (relative intensity) 359 ($M+H^+$, 1), 156 (100); HRMS (+FAB) calcd for $C_{22}H_{35}N_2O_2$ ($M+H^+$): 359.2699; found: 359.2735; anal. calcd for $C_{22}H_{34}N_2O_2$: C, 73.70; H, 9.56; N, 7.81; found: C, 73.50; H, 9.70; N, 7.58.

*4.7.2. (2*S*)-(*N*-Benzoyl-*N*-methylamino)-3-(3′-indolyl)-1,1-di(4″-methylphenyl)-1-propanol*

Prepared from **15f** in 60% yield; pale yellow foam; IR (KBr) 3420 (br), 1600, 1450, 1360 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36 (br s, 1H), 8.14 (s, 1H), 7.80 (d, $J=8.1$ Hz, 2H), 7.64–7.01 (m, 14H), 6.77 (d, $J=6.9$ Hz, 2H), 4.56 (dd, $J=11.7$, 2.4 Hz, 1H), 4.04 (dd, $J=15.0$, 12.3 Hz, 1H), 3.16 (dd, $J=14.7$, 2.1 Hz, 1H), 2.40 (s, 3H), 2.29 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7, 144.0, 142.5, 136.4, 136.3, 135.9, 129.3, 129.1, 128.4, 128.2, 127.4, 126.0, 125.7, 125.3, 122.9, 122.0, 119.4, 118.7, 113.2, 111.4, 79.9, 74.4, 44.3, 21.8, 20.9, 20.8; MS (+CI) *m/z* (relative intensity) 489 ($M+H^+$, 100); HRMS (+FAB) calcd for $C_{33}H_{33}N_2O_2$ ($M+H^+$): 489.2542; found: 489.2565; anal. calcd for $C_{33}H_{32}N_2O_2$: C, 81.12; H, 6.60; N, 5.73; found: C, 80.80; H, 6.83; N, 5.41.

*4.7.3. 3-(3′-Indolyl)-(2*S*)-(*N*-methyl-*N*-phenylacetylamino)-1,1-di(4″-methylphenyl)-1-propanol*

Prepared from **15f** in 96% yield; pale yellow foam; IR (KBr) 3390 (br), 1600, 1450, 1350 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (br s, 1H), 8.08 (s, 1H), 7.73 (d, $J=8.1$ Hz, 2H), 7.46–7.01 (m, 13H), 6.76 (s, 1H), 6.75 (d, $J=6.6$ Hz, 2H), 4.38 (d, $J=9.6$ Hz, 1H), 3.78 (dd, $J=14.7$, 12.0 Hz, 1H), 3.44 and 3.33 (AB q, $J=15.0$ Hz, 2H), 3.01 (d, $J=14.7$ Hz, 1H), 2.36 (s, 3H), 2.30 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 144.4, 143.0, 136.2, 135.6, 133.0, 129.0, 128.5, 128.4, 127.4, 126.5, 125.6, 125.2, 122.5, 121.9, 119.4, 118.6, 113.6, 111.3, 79.6, 76.7, 43.1, 42.5, 21.7, 20.9; MS (+CI) *m/z* (relative intensity) 503 ($M+H^+$, 100); HRMS (+FAB) calcd for $C_{34}H_{35}N_2O_2$ ($M+H^+$): 503.2699; found: 503.2703; anal. calcd for $C_{34}H_{34}N_2O_2$: C, 81.24; H, 6.82; N, 5.57; found, C, 81.01; H, 6.99; N, 5.26.

*4.7.4. 3-(3′-Indolyl)-(2*S*)-(*N*-isovaleryl-*N*-methylamino)-1,1-di(4″-methylphenyl)-1-propanol*

Prepared from **15f** in 83% yield; pale yellow foam; IR (KBr) 3420 (br), 1610, 1450 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (br s, 1H), 8.23 (s, 1H), 7.73 (d, $J=8.1$ Hz, 2H), 7.44–7.10 (m, 8H), 7.03 (d, $J=8.1$ Hz, 2H), 6.92 (d, $J=1.8$ Hz, 1H), 4.36 (dd, $J=11.7$, 2.4 Hz, 1H), 3.78 (dd, $J=15.0$, 11.7 Hz, 1H), 3.00 (dd, $J=15.0$, 2.1 Hz, 1H), 2.36 (s, 3H), 2.27 (s, 3H), 2.24 (s, 3H), 1.89–1.77 (m, 3H), 0.81 (d, $J=6.0$ Hz, 3H), 0.67 (d, $J=6.0$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.9, 144.5, 143.1, 136.2, 135.6, 129.0, 128.3, 125.6, 125.3, 122.4, 121.9, 119.4, 118.7, 114.0, 111.2, 79.7, 76.6, 43.9, 42.9, 25.2, 22.5, 22.3, 21.7, 20.9, 20.8; MS (+CI) *m/z* (relative intensity) 469 ($M+H^+$, 100); HRMS (+FAB) calcd for $C_{31}H_{37}N_2O_2$ ($M+H^+$): 469.2855; found: 469.2832; anal. calcd for $C_{31}H_{36}N_2O_2$: C, 79.45; H, 7.74; N, 5.98; found: C, 79.11; H, 7.99; N, 5.67.

*4.7.5. 3-(3′-Indolyl)-(2*S*)-(*N*-methyl-*N*-3″,3″-dimethylbutyrylamino)-1,1-di(4‴-methylphenyl)-1-propanol*

Prepared from **15f** in 85% yield; pale yellow foam; IR (KBr) 3300 (br), 1610, 1450, 1370 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 (br s, 1H), 8.20 (s, 1H), 7.73 (d, $J=8.1$ Hz, 2H), 7.46–7.10 (m,

8H), 7.02 (d, $J=8.1$ Hz, 2H), 6.92 (d, $J=2.1$ Hz, 1H), 4.39 (dd, $J=11.7$, 2.7 Hz, 1H), 3.80 (dd, $J=15.0$, 11.7 Hz, 1H), 2.97 (dd, $J=14.7$, 2.4 Hz, 1H), 2.35 (s, 3H), 2.29 (s, 3H), 2.22 (s, 3H), 1.97 and 1.85 (AB q, $J=14.1$ Hz, 2H), 0.75 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.5, 144.6, 143.2, 136.1, 135.6, 129.0, 128.4, 127.4, 125.5, 125.3, 122.5, 121.9, 119.4, 118.7, 113.9, 111.2, 79.6, 76.6, 46.7, 43.8, 31.4, 29.6, 21.4, 20.9, 20.8; MS (+CI) *m/z* (relative intensity) 483 ($M+H^+$, 100); HRMS (+FAB) calcd for $C_{32}H_{39}N_2O_2$ ($M+H^+$): 483.3012; found: 483.3044; anal. calcd for $C_{32}H_{38}N_2O_2$: C, 79.63; H, 7.94; N, 5.80; found: C, 79.35; H, 8.10; N, 5.56.

4.8. *Synthesis of* tertiary *amino alcohols by $LiAlH_4$ reduction of amides; general procedure*

To a suspension of $LiAlH_4$ (217 mg, 5.72 mmol) in dry THF (10 mL) cooled in an ice–water bath (ca. 0°C) was added a solution of the amide obtained above from **15b** or **15f** (2.79 mmol) in dry THF (20 mL). The resultant mixture was then heated at refluxing temperature for 12 h. After cooled to ca. 0°C in an ice–water bath, the reaction mixture was quenched by 5% aqueous NaOH (4 mL) and filtered through Celite with rinsing by EtOAc. The filtrate was extracted with EtOAc (3×20 mL), and the combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and condensed in vacuo. The residue was purified by flash column chromatography (silica gel, MeOH:CH_2Cl_2:hexane = 1:8:16) to give the product.

4.8.1. *(2S)-(*N-*Benzyl*-N-*methylamino)-3-(3′-indolyl)-1,1-di(4″-methylphenyl)-1-propanol* ***20a***

Prepared from the corresponding amide in 70% yield; pale yellow foam; $[\alpha]_D^{20}$ –10.2 ($c=2.10$, $CHCl_3$); IR (KBr) 3410 (br), 1450, 1340 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (br s, 1H), 7.59–7.49 (m, 5H), 7.36 (d, $J=8.1$ Hz, 1H), 7.23–7.17 (m, 9H), 7.04–6.99 (m, 3H), 4.23 (dd, $J=9.3$, 4.5 Hz, 1H), 3.52 (d, $J=13.2$ Hz, 1H), 3.30 (d, $J=13.2$ Hz, 1H), 3.24–3.21 (m, 2H), 2.38 (s, 3H), 2.37 (s, 3H), 1.98 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.1, 141.2, 139.4, 136.7, 136.4, 136.2, 128.7, 128.6, 128.5, 128.3, 128.2, 128.0, 127.4, 127.2, 126.9, 122.5, 122.0, 119.3, 119.1, 114.3, 111.2, 78.5, 72.0, 61.5, 38.3, 23.6, 21.0; MS (+CI) *m/z* (relative intensity) 475 ($M+H^+$, 100); HRMS (+FAB) calcd for $C_{33}H_{35}N_2O$ ($M+H^+$: 475.2749; found: 475.2785; anal. calcd for $C_{33}H_{34}N_2O$: C, 83.51; H, 7.22; N, 5.90; found: C, 83.60; H, 7.29; N, 5.69.

4.8.2. *3-(3′-Indolyl)-(2S)-(*N-*methyl*-N-*2″-phenylethylamino)-1,1-di(4‴-methylphenyl)-1-propanol* ***20b***

Prepared from the corresponding amide in 35% yield; pale yellow foam; $[\alpha]_D^{20}$ +37.6 ($c=1.20$, $CHCl_3$); IR (KBr) 3420 (br), 1500, 1450, 1350 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (br s, 1H), 7.51–7.46 (m, 5H), 7.35 (d, $J=8.1$ Hz, 1H), 7.22–7.11 (m, 9H), 6.95 (s, 1H), 6.86 (d, $J=6.9$ Hz, 2H), 4.06 (br s, 1H), 3.11 (d, $J=7.2$ Hz, 2H), 2.65–2.25 (m, 4H), 2.41 (s, 3H), 2.35 (s, 3H), 2.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.0, 141.0, 139.7, 136.8, 136.4, 136.3, 128.8, 128.7, 128.3, 128.1, 127.6, 127.2, 126.0, 122.4, 122.0, 119.4, 119.1, 114.4, 111.2, 78.2, 73.0, 58.1, 39.7, 35.4, 23.5, 21.0; MS (+CI) *m/z* (relative intensity) 489 ($M+H^+$, 42), 211 (100); HRMS (+FAB) calcd for $C_{34}H_{37}N_2O$ ($M+H^+$): 489.2906; found: 489.2972; anal. calcd for $C_{34}H_{36}N_2O$: C, 83.57; H, 7.43; N, 5.73; found: C, 83.40; H, 7.45; N, 5.51.

4.8.3. *3-(3′-Indolyl)-(2S)-(*N-*methyl*-N-*3″-methylbutylamino)-1,1-di(4‴-methylphenyl)-1-propanol* ***20c***

Prepared from the corresponding amide in 67% yield; pale yellow foam; $[\alpha]_D^{20}$ +40.0 ($c=1.03$, $CHCl_3$); IR (KBr) 3380 (br), 1450, 1350 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (br s, 1H),

7.56–7.49 (m, 5H), 7.32–7.11 (m, 7H), 6.96 (d, $J=1.8$ Hz, 1H), 4.06 (dd, $J=10.8$, 3.3 Hz, 1H), 3.18 (dd, $J=15.3$, 2.7 Hz, 1H), 3.09 (dd, $J=15.3$, 11.1 Hz, 1H), 2.40 (s, 3H), 2.37 (s, 3H), 2.35–2.05 (m, 2H), 2.02 (s, 3H), 1.33–1.25 (m, 2H), 1.20–1.05 (m, 1H), 0.70 (d, $J=6.3$ Hz, 3H), 0.69 (d, $J=6.6$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.1, 141.3, 136.7, 136.3, 136.1, 129.1, 128.7, 128.2, 128.1, 127.6, 127.2, 126.4, 122.4, 121.9, 119.2, 119.1, 114.3, 111.1, 77.7, 72.3, 55.0, 39.2, 37.8, 26.0, 23.5, 22.8, 22.3, 21.0; MS (+CI) m/z (relative intensity) 455 ($M+H^+$, 11), 211 (100); HRMS (+FAB) calcd for $C_{31}H_{39}N_2O$ ($M+H^+$): 455.3062; found: 455.3115; anal. calcd for $C_{31}H_{38}N_2O$: C, 81.89; H, 8.42; N, 6.16; found: C, 81.93; H, 8.53; N, 5.93.

*4.8.4. 3-(3′-Indolyl)-(2S)-(*N*-methyl-*N*-3″,3″-dimethylbutylamino)-1,1-di(4‴-methylphenyl)-1-propanol* ***20d***

Prepared from the corresponding amide in 65% yield; pale yellow foam; $[\alpha]_D^{20}$ +48.4 ($c=1.39$, $CHCl_3$); IR (KBr) 3310 (br), 1470, 1370 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (br s, 1H), 7.57–7.50 (m, 5H), 7.33 (d, $J=8.1$ Hz, 1H), 7.21–7.08 (m, 6H), 6.96 (d, $J=1.8$ Hz, 1H), 6.60–6.05 (br s, 1H), 4.08 (dd, $J=10.5$, 3.0 Hz, 1H), 3.21–3.06 (m, 2H), 2.40 (s, 3H), 2.37 (s, 3H), 2.33–2.07 (m, 2H), 2.04 (s, 3H), 1.34–1.06 (m, 2H), 0.69 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.2, 141.3, 136.7, 136.4, 136.1, 128.7, 128.2, 128.1, 127.6, 127.3, 122.4, 121.9, 119.2, 119.1, 114.4, 111.1, 77.6, 72.1, 52.0, 42.3, 40.0, 29.3, 23.6, 21.0; MS (+CI) m/z (relative intensity) 469 ($M+H^+$, 8), 211 (100); HRMS (+FAB) calcd for $C_{32}H_{41}N_2O$ ($M+H^+$): 469.3219; found: 469.3242; anal. calcd for $C_{32}H_{40}N_2O$: C, 82.01; H, 8.60; N, 5.98; found: C, 81.82; H, 8.77; N, 5.77.

*4.8.5. 1,1-Diethyl-3-(3′-indolyl)-(2*S*)-(*N*-methyl-*N*-3″,3″-dimethylbutylamino)-1-propanol* ***21***

Prepared from the corresponding amide in 71% yield; colorless solid; mp 122–123.5°C (EtOAc–hexane); $[\alpha]_D^{20}$ –17.8 ($c=2.29$, $CHCl_3$); IR (KBr) 3240 (br), 1440, 1350 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 and 8.15 (br s, 1H), 7.65 (d, $J=7.8$ Hz, 1H), 7.37 (d, $J=7.8$ Hz, 1H), 7.26–7.11 (m, 2H), 7.03 (d, $J=1.8$ Hz, 1H), 4.68 (br s, 1H), 3.29 (br d, $J=10.2$ Hz, 1H), 3.13 (dd, $J=15.0$, 10.8 Hz, 1H), 2.86 (dd, $J=15.0$, 3.3 Hz, 1H), 2.55–2.28 (m, 2H), 2.34 (s, 3H), 1.90–1.78 (m, 1H), 1.68–1.49 (m, 2H), 1.47–1.14 (m, 3H), 1.00 (t, $J=7.2$ Hz, 3H), 0.98 (t, $J=7.5$ Hz, 3H), 0.74 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.4, 127.3, 122.4, 121.9, 119.2, 118.8, 114.7, 111.2, 73.8, 67.4, 42.6, 29.5, 29.3, 28.8, 28.1, 21.4, 8.0; MS (+CI) m/z (relative intensity) 345 ($M+H^+$, 100); HRMS (+FAB) calcd for $C_{22}H_{37}N_2O$ ($M+H^+$): 345.2906; found: 345.2906; anal. calcd for $C_{22}H_{36}N_2O$: C, 76.69; H, 10.53; N, 8.13; found: C, 76.63; H, 10.91; N, 8.08.

4.9. The chiral ligand-promoted addition of Et_2Zn to aldehydes; general procedure

To a solution of the chiral ligand **21** (0.18 mmol) in dry PhMe (8 mL) under a nitrogen atmosphere cooled in an ice–water bath (ca. 0°C) was added a solution of Et_2Zn (4 mL, 1 M in hexanes) via a syringe. After stirring for 10 min, freshly distilled benzaldehyde (0.20 mL, 1.80 mmol) was added into the mixture via another syringe. The resultant mixture was allowed to warm up to room temperature and stirred for 96 h at the same temperature. The reaction mixture was cooled in an ice–water bath and quenched by 5% HCl aqueous solution. The mixture was extracted with Et_2O (3×20 mL), washed with brine, dried over anhydrous $MgSO_4$, and condensed under reduced pressure. The residue was purified by flash column chromatography (silica gel, 10% EtOAc in hexane) to give (*R*)-**19** in 70% yield. For other chiral ligands, the reaction time, yield, and enantiomeric excess are summarized in Tables 1 and 2.

4.10. General conditions for HPLC analysis of chiral alcohols

Method A: Chiralcel OD column eluted with hexane:2-propanol (97.5:2.5) at 1.0 mL/min using UV detector at 254 nm.

Method B: Chiralcel OD column eluted with hexane:2-propanol (96:4) at 0.5 mL/min using UV detector at 254 nm.

Method C: Chiralcel OD column eluted with hexane:2-propanol (97:3) at 0.5 mL/min using UV detector at 254 nm.

Method D: Chiralcel OD column eluted with hexane:2-propanol (85:15) at 0.5 mL/min using UV detector at 254 nm.

Method E: Chiralcel OD column eluted with hexane:2-propanol (95:5) at 1.0 mL/min using UV detector at 254 nm.

Method F: Chiralcel OD column eluted with hexane:2-propanol (90:10) at 0.5 mL/min using UV detector at 254 nm.

Method G: two Chiralcel OD columns eluted with hexane:2-propanol (96:4) at 0.6 mL/min using UV detector at 254 nm.

Method H: two Chiralpak AD columns eluted with hexane:2-propanol (99.6:0.4) at 1.0 mL/min using UV detector at 230 nm.

Method I: two Chiralpak AD columns eluted with hexane:2-propanol (98:2) at 1.0 mL/min using UV detector at 230 nm.

Method J: Chiralcel OD column eluted with hexane:2-propanol (99.8:0.2) at 1.0 mL/min using UV detector at 230 nm.

Method K: Chiralpak AD column eluted with hexane:2-propanol (98:2) at 1.0 mL/min using UV detector at 230 nm.

4.10.1. (R)-1-Phenyl-1-Propanol (R)-**19**

$[\alpha]_D^{20}$ +42.9 ($c = 3.58$, $CHCl_3$) {lit.[29] $[\alpha]_D$ +45.6 ($CHCl_3$)}; 87.5% ee by HPLC analysis using Method A: $t_R = 14.9$ min for (*R*)-**19** and $t_R = 16.9$ min for (*S*)-**19**.

4.10.2. (R)-1-(4′-Chlorophenyl)-1-propanol (R)-**22a**

$[\alpha]_D^{20}$ +26.4 ($c = 5.27$, PhH) {lit.[30] (*S*)-**22a**, $[\alpha]_D^{22}$ –28.2 ($c = 5.01$, PhH), 100% ee}; 96.9% ee by HPLC analysis using Method A: $t_R = 11.7$ min for (*R*)-**22a** and $t_R = 10.9$ min for (*S*)-**22a**.

4.10.3. (R)-1-(3′-Chlorophenyl)-1-propanol (R)-**22b**

$[\alpha]_D^{20}$ +26.6 ($c = 2.36$, PhH) {lit.[16a] (*R*)-**22b**, $[\alpha]_D$ +24.2 (PhH), 78% ee}; 97.0% ee by HPLC analysis using Method B: $t_R = 14.6$ min for (*R*)-**22b** and $t_R = 14.0$ min for (*S*)-**22b**.

4.10.4. (R)-1-(4′-Bromophenyl)-1-propanol (R)-**22c**

$[\alpha]_D^{20}$ +16.5 ($c = 1.07$, PhH) {lit.[31] (*R*)-**22c**, $[\alpha]_D^{20}$ +13.33 ($c = 1.0$, PhH), 76% ee}; 95.7% ee by HPLC analysis using Method B: $t_R = 15.5$ min for (*R*)-**22c** and $t_R = 14.8$ min for (*S*)-**22c**.

4.10.5. (R)-1-(2′-Bromophenyl)-1-propanol (R)-**22d**

$[\alpha]_D^{20}$ +54.2 ($c = 2.46$, PhH) {lit.[32] (*R*)-**22d**, $[\alpha]_D$ +52.4 ($c = 1.3$, PhH), >99% ee}; 85.1% ee by HPLC analysis using Method G: $t_R = 22.4$ min for (*R*)-**22d** and $t_R = 23.5$ min for (*S*)-**22d**.

*4.10.6. (*R*)-1-(4′-Methylphenyl)-1-propanol (*R*)-**22e***

$[\alpha]_D^{20}$ +39.3 ($c=3.65$, PhH) {lit.[33] (*S*)-**22e**, $[\alpha]_D^{25}$ –39.3 ($c=5.0$, PhH), 91% ee}; 95.7% ee by HPLC analysis of the corresponding benzoate using Method K: $t_R=6.9$ min for (*R*)-**22e** and $t_R=9.5$ min for (*S*)-**22e**.

*4.10.7. (*R*)-1-(4′-Methoxyphenyl)-1-propanol (*R*)-**22f***

$[\alpha]_D^{20}$ +35.4 ($c=4.84$, PhH) {lit.[33] (*S*)-**22f**, $[\alpha]_D^{25}$ –34.6 ($c=5.0$, PhH), 90% ee}; 95.8% ee by HPLC analysis using Method A: $t_R=16.5$ min for (*R*)-**22f** and $t_R=19.3$ min for (*S*)-**22f**.

*4.10.8. (*R*)-1-(4′-Dimethylaminophenyl)-1-propanol (*R*)-**22g***

$[\alpha]_D^{20}$ +31.3 ($c=2.22$, PhH) {lit.[34] (*S*)-**22g**, $[\alpha]_D$ –45.85 ($c=5.0$, $CHCl_3$),[35] 14% ee}; 80.0% ee by HPLC analysis using Method E: $t_R=11.6$ min for (*R*)-**22g** and $t_R=14.1$ min for (*S*)-**22g**.

*4.10.9. (*R*)-1-(3′,5′-Dichlorophenyl)-1-propanol (*R*)-**22h***

$[\alpha]_D^{20}$ +28.8 ($c=2.21$, $CHCl_3$);[36] 94.9% ee by HPLC analysis of the corresponding benzoate using the Method J: $t_R=11.4$ min for (*R*)-**22h** and $t_R=12.6$ min for (*S*)-**22h**.

*4.10.10. (*R*)-1-(3′,5′-Dimethoxyphenyl)-1-propanol (*R*)-**22i***

$[\alpha]_D^{20}$ +19.4 ($c=2.46$, $CHCl_3$) {lit.[37] (*R*)-**22i**, $[\alpha]_D^{23}$ +24.1 ($c=0.6$, $CHCl_3$), 75% ee}; 94.1% ee by HPLC analysis using Method C: $t_R=21.2$ min for (*R*)-**22i** and $t_R=32.0$ min for (*S*)-**22i**.

*4.10.11. (*R*)-1-(1′-Naphthyl)-1-propanol (*R*)-**22j***

$[\alpha]_D^{20}$ +52.6 ($c=2.55$, $CHCl_3$) {lit.[37] (*R*)-**22j**, $[\alpha]_D^{23}$ +45.5 ($c=0.8$, $CHCl_3$), 74% ee}; 93.5% ee by HPLC analysis using Method D: $t_R=19.4$ min for (*R*)-**22j** and $t_R=12.4$ min for (*S*)-**22j**.

*4.10.12. (*R*)-1-(2′-Naphthyl)-1-propanol (*R*)-**22k***

$[\alpha]_D^{20}$ +27.5 ($c=3.80$, PhH) {lit.[30] (*S*)-**22k**, $[\alpha]_D^{22}$ –26.6 ($c=3.35$, PhH), 97% ee}; 96.1% ee by HPLC analysis using Method F: $t_R=18.8$ min for (*R*)-**22k** and $t_R=17.7$ min for (*S*)-**22k**.

*4.10.13. (*R*)–(*E*)-1-Phenyl-1-penten-3-ol (*R*)-**22l***

$[\alpha]_D^{20}$ +5.2 ($c=1.91$, $CHCl_3$) {lit.[38] (*S*)-**22l**, $[\alpha]_D^{22}$ –6.6 ($c=3.2$, $CHCl_3$), 75% ee}; 81.3% ee by HPLC analysis using Method E: $t_R=11.9$ min for (*R*)-**22l** and $t_R=20.0$ min for (*S*)-**22l**.

*4.10.14. (*R*)-1-Cyclohexyl-1-propanol (*R*)-**22m***

$[\alpha]_D^{20}$ +6.35 ($c=3.00$, $CHCl_3$) {lit.[39a] (*R*)-**22m**, $[\alpha]_D^{20}$ +8.1 ($CHCl_3$), 100% ee; lit.[39b] (*S*)-**22m**, $[\alpha]_D^{24}$ –6.39 ($c=1.05$, $CHCl_3$), 97% ee}; 94.8% ee by HPLC analysis of the corresponding benzoate using Method H: $t_R=15.9$ min for (*R*)-**22m** and $t_R=18.4$ min for (*S*)-**22m**.

*4.10.15. (*R*)-1-(2′-Pyridyl)-1-propanol (*R*)-**22n***

$[\alpha]_D^{20}$ +5.7 ($c=2.25$, MeOH) {lit.[40] (*R*)-**22n**, $[\alpha]_D^{25}$ +38.0 ($c=1.68$, MeOH), 52.1% ee}; 5.4% ee by HPLC analysis using Method E: $t_R=7.5$ min for (*R*)-**22n** and $t_R=8.0$ min for (*S*)-**22n**.

*4.10.16. (*R*)-1-(3′-Pyridyl)-1-propanol (*R*)-**22o***

$[\alpha]_D^{20}$ +9.1 ($c=2.16$, MeOH) {lit.[20] $[\alpha]_D^{28}$ –41.4 ($c=2.1$, MeOH), 88% ee};[41] 24.3% ee by HPLC analysis using Method E: $t_R=21.1$ min for (*R*)-**22o** and $t_R=20.0$ min for (*S*)-**22o**.

*4.10.17. (*R*)-1-(4′-Pyridyl)-1-propanol (*R*)-**22p***

$[\alpha]_D^{20}$ +2.6 ($c=2.34$, MeOH) {lit.[20] $[\alpha]_D^{29}$ –41.1 ($c=2.0$, MeOH), 83% ee};[41] 7.5% ee by HPLC analysis using Method C: $t_R=26.8$ min for (*R*)-**22p** and $t_R=25.2$ min for (*S*)-**22p**.

*4.10.18. (*R*)-1-(2′-Furyl)-1-propanol (*R*)-**22q***

$[\alpha]_D^{20}$ +14.3 ($c=2.20$, $CHCl_3$) {lit.[42a] (*R*)-**22q**, $[\alpha]_D^{25}$ +12.6 ($c=2.09$, $CHCl_3$), 95% ee; lit.[42b] (*S*)-**22q**, $[\alpha]_{578}^{22}$ –17.9 ($c=1.75$, $CHCl_3$), 91% ee;}; 78.0% ee by HPLC analysis of the corresponding benzoate using Method I: $t_R=10.4$ min for (*R*)-**22q** and $t_R=11.6$ min for (*S*)-**22q**.

*4.10.19. (*R*)-1-(2′-Thienyl)-1-propanol (*R*)-**22r***

$[\alpha]_D^{20}$ +25.3 ($c=2.24$, $CHCl_3$) {lit.[43a] (*R*)-**22r**, $[\alpha]_D^{25}$ +25.9 ($c=2.1$, $CHCl_3$); lit.[43b] (*S*)-**22**, $[\alpha]_D^{25}$ –25.3 ($c=1.6$, $CHCl_3$), >99% ee}; 94.9% ee by HPLC analysis of the corresponding benzoate using Method I: $t_R=12.1$ min for (*R*)-**22r** and $t_R=15.4$ min for (*S*)-**22r**.

*4.11. Autocatalysis of (*R*)-1-(2′-furyl)-1-propanol (*R*)-**22q***

To a solution of the chiral alcohol (*R*)-**22q** (82.0% ee, 19.2 mg, 0.152 mmol) in dry PhMe (8 mL) under a nitrogen atmosphere cooled in an ice–water bath (ca. 0°C) was added a solution of Et_2Zn (4 mL, 1 M in hexanes) via a syringe. After stirring for 10 min, 2-furaldehyde (165.5 μL, 2.00 mmol) was added into the mixture via another syringe. The resultant mixture was allowed to warm up to room temperature and stirred for 96 h at the same temperature. The reaction mixture was cooled in an ice–water bath and quenched by 5% HCl aqueous solution. The mixture was extracted with ethyl ether (3×20 mL), washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, and condensed under reduced pressure. The residue was purified by flash column chromatography (silica gel, MeOH:EtOAc:hexane=1:10:50) to give (*R*)-**22q** (250.0 mg, 92% yield): $[\alpha]_D^{20}$ +5.45 ($c=2.40$, $CHCl_3$); 27.6% ee by HPLC analysis of the corresponding benzoate using Method I. The ee of the newly formed product was calculated to be 23.1% ee.[21]

*4.12. Autocatalysis of (*R*)-1-(2′-thienyl)-1-propanol (*R*)-**22r***

To a solution of the chiral alcohol (*R*)-**22r** (94.9% ee, 22.4 mg, 0.158 mmol) in dry PhMe (8 mL) under a nitrogen atmosphere cooled in an ice–water bath (ca. 0°C) was added a solution of Et_2Zn (4 mL, 1 M in hexanes) via a syringe. After stirring for 10 min, 2-thiophenecarboxaldehyde (187 μL, 2.00 mmol) was added into the mixture via another syringe. The resultant mixture was allowed to warm up to room temperature and stirred for 96 h at the same temperature. The reaction mixture was cooled in an ice–water bath and quenched by 5% HCl aqueous solution. The mixture was extracted with ethyl ether (3×20 mL), washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, and condensed under reduced pressure. The residue was purified by flash column chromatography (silica gel, MeOH:EtOAc:hexane=1:10:50) to give 2-thiophenecarboxaldehyde (30.0 mg, 13% recovery) and (*R*)-**22r** (191.0 mg, 68% yield): $[\alpha]_D^{20}$ +3.51 ($c=2.56$, $CHCl_3$); 13.9% ee by HPLC analysis of the corresponding benzoate using Method I. The ee of the newly formed product was calculated to be 3.1%.[21]

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References

1. For the anticancer alkaloid, Taxol®, see: (a) Nicolaou, K. C.; Dai, W.-M.; Guy, R. K. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 15. (b) *Taxane Anticancer Agents, Basic Science and Current Status*, ACS Symposium Series 583; Georg, G. I.; Chen, T. T.; Ojima, I.; Vyas, D. M., Eds.; American Chemical Society: Washington, DC, 1995.
2. For the anticancer alkaloid, camptothecin, see: Wall, M. E.; Wani, M. C. In *Cancer Chemotherapeutic Agents*; Foye, W. O., Ed.; ACS: Washington, DC, 1995; pp. 293–310.
3. (a) *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH Publishers: New York, 1993. (b) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley & Sons: New York, 1994. (c) *Enantioselective Synthesis*; Gladysz, J. A.; Michl, J., Eds.; *Chem. Rev.* 1992; Vol. 92, No. 5. (d) Seyden-Penne, J. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; John Wiley & Sons: New York, 1995. (e) *Advances in Catalytic Processes*; Doyle, M. P., Ed.; JAI Press: Greenwich, 1995. (f) *Handbook of Enantioselective Catalysis*; Brunner, H.; Zettlmeier, W., Eds.; VCH Publishers: New York, 1993; Vols. 1–2.
4. Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH Publishers: New York, 1993; pp. 227–272.
5. *Dictionary of Organic Compounds*, 5th ed.; Buckingham, J., Ed.; Chapman and Hall: New York, 1982; p. 4084.
6. For chiral indole-containing ligands for catalytic enantioselective reactions, see: (a) Nakagawa, M.; Nakao, H.; Watanabe, K. *Chem. Lett.* **1985**, 391. (b) Nitta, H.; Yu, D.; Kudo, M.; Mori, A.; Inoue, S. *J. Am. Chem. Soc.* **1992**, *114*, 7969. (c) Corey, E. J.; Loh, T.-P. *J. Am. Chem. Soc.* **1991**, *113*, 8966. (d) Corey, E. J.; Loh, T.; Roper, T. D.; Aziminoara, M. C.; Noe, M. C. *J. Am. Chem. Soc.* **1992**, *114*, 8290. (e) Corey, E. J.; Loh, T.-P. *Tetrahedron Lett.* **1993**, *34*, 3979. (f) Corey, E. J.; Cywin, C. L.; Roper, T. D. *Tetrahedron Lett.* **1992**, *33*, 6907. (g) Kinugasa, M.; Harada, T.; Oku, A. *J. Org. Chem.* **1996**, *61*, 6772.
7. For (*S*)-Abrine–Cu(II)-catalyzed Diels–Alder reaction, see: (a) Otto, S.; Boccaletti, G.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1998**, *120*, 4238. (b) Otto, S.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1999**, *121*, 67988.
8. (a) Oguni, N.; Omi, T. *Tetrahedron Lett.* **1984**, *25*, 2823. (b) Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc.* **1986**, *108*, 6071. For reviews, see: (c) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49. (d) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833. (e) Ref. 3b, pp. 255–297. (f) Oguni, N. *Kikan Kagaku Sosetsu* **1993**, *19*, 143.
9. For selected chiral β-amino alcohols for enantioselective addition of Et_2Zn to aldehydes for **4**, see: Ref. 8b and (a) Noyori, R.; Suga, S.; Kawai, K.; Okada, S.; Kitamura, M.; Oguni, N.; Hayashi, M.; Kaneko, T.; Matsuda, Y. *J. Organomet. Chem.* **1990**, *382*, 19. For **5**, see: (b) Tanaka, K.; Ushio, H.; Suzuki, H. *J. Chem. Soc., Chem. Commun.* **1989**, 1700. For **6**, see: Ref. 8b and (c) Hayashi, M.; Kaneko, T.; Oguni, N. *J. Chem. Soc., Perkin Trans. 1* **1991**, 25. For **7** and **11b**, see: (d) Soai, K.; Ookawa, A.; Ogawa, K.; Kaba, T. *J. Chem. Soc., Chem. Commun.* **1987**, 4678. (e) Soai, K.; Ookawa, A.; Kaba, T.; Ogawa, K. *J. Am. Chem. Soc.* **1987**, *109*, 7111. (f) Niwa, S.; Soai, K. *J. Chem. Soc., Perkin Trans. 1* **1990**, 25. For **8a**,**b**, see: (g) Peper, V.; Martens, J. *Chem. Ber.* **1996**, *129*, 691. For **9**, see: (h) Soai, K.; Niwa, S.; Yamada, Y.; Inoue, H. *Tetrahedron Lett.* **1987**, *28*, 4841. (i) Soai, K.; Yokoyama, S.; Ebihara, K.; Hayasaka, T. *J. Chem. Soc., Chem. Commun.* **1987**, 1690. For **10**, see: (j) Corey, E. J.; Yuen, P.; Hannon, F. J.; Wierda, D. A. *J. Org. Chem.* **1990**, *55*, 784. For analogues of **11b**, see: (k) Yang, X.; Shen, J.; Da, C.; Wang, R.; Choi, M. C. K.; Yang, L.; Wong, K.-Y. *Tetrahedron: Asymmetry* **1999**, *10*, 133. For **11a** and **12**, see: (l) Wallbaum, S.; Martens, J. *Tetrahedron: Asymmetry* **1993**, *4*, 637. For *gem*-dialkyl analogues of **12**, see: (m) Wilken, J.; Kossenjans, M.; Gröger, H.; Martens, J. *Tetrahedron: Asymmetry* **1997**, *8*, 2007. For **13a**,**b** and **14a**, see: (o) Soai, K.; Watanabe, M.; Yamamoto, A.; Yamashita, T. *J. Mol. Catal.* **1991**, *64* L27. For **13c** and **14b**, see: (p) Beliczey, J.; Giffels, G.; Kragl, U.; Wandrey, C. *Tetrahedron: Asymmetry* **1997**, *8*, 1529. For other chiral amines possessing a diphenylhydroxymethyl or dialkylhydroxymethyl group, see: (q) Solà, L.; Reddy, K. S.; Vidal-Ferran, A.; Moyano, A.; Pericàs, M. A.; Riera, A.; Alvarez-Larena, A.; Piniella, J.-F. *J. Org. Chem.* **1998**, *63*, 7078. (r) Guijarro, D.; Pinho, P.; Andersson, P. G. *J. Org. Chem.* **1998**, *63*, 2530. (s) Kossenjans, M.; Pennemann, H.; Martens, J.; Juanes, O.; Rodríguez-Ubis, J. C.; Brunet, E. *Tetrahedron: Asymmetry* **1998**, *9*, 4123. (t) Liu, G.; Ellman, J. A. *J. Org. Chem.* **1995**, *60*, 7712.
10. (a) Dai, W.-M.; Zhu, H. J.; Hao, X.-J. *Tetrahedron: Asymmetry* **1995**, *6*, 1857. (b) Dai, W.-M.; Zhu, H. J.; Hao, X.-J. *Tetrahedron: Asymmetry* **1996**, *7*, 1245. (c) Dai, W.-M.; Zhu, H. J.; Hao, X.-J. *Tetrahedron Lett.* **1996**, *37*, 5971. (d) Zhu, H.-J.; Zhao, B.-T.; Dai, W.-M.; Zhou, J.; Hao, X.-J. *Tetrahedron: Asymmetry* **1998**, *9*, 2879.
11. (a) Braun, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 519. (b) For an early study on the chiral ligands containing the dialkylhydroxymethyl group in enantioselective addition of RLi to aldehydes, see: Mukaiyama, T.; Soai, K.; Sato, T.; Shimizu, H.; Suzuki, K. *J. Am. Chem. Soc.* **1979**, *101*, 1455.
12. Bordwell, F. G.; Drucker, G. E.; Fried, H. E. *J. Org. Chem.* **1981**, *46*, 632.

13. For zinc amides of *secondary* amines, see: (a) Chelucci, G.; Falorni, M.; Giacomelli, G. *Tetrahedron: Asymmetry* **1990**, *1*, 843. (b) Chelucci, G.; Conti, S.; Falorni, M.; Giacomelli, G. *Tetrahderon* **1991**, *47*, 8251. (c) Prasad, K. R. K.; Joshi, N. N. *J. Org. Chem.* **1997**, *62*, 3770. (d) Asami, M.; Inoue, S. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 1687. (e) Asami, M.; Watanabe, H.; Honda, K.; Inoue, S. *Tetrahedron: Asymmetry* **1998**, *9*, 4165. For reports against the formation of zinc amides from *secondary* amines and Et_2Zn, see: (f) Tanaka, K.; Oshio, H.; Suzuki, H. *J. Chem. Soc., Chem. Commun.* **1989**, 1700. (g) Pini, D.; Mastantuono, A.; Uccello-Barretta, G.; Iuliano, A.; Salvadori, P. *Tetrahedron* **1993**, *49*, 9613.
14. For an amine–alcohol two-component combination as the promoter in Et_2Zn addition to aldehydes, see: (a) Li, S.; Jiang, Y.; Mi, A.; Yang, G. *J. Chem. Soc., Perkin Trans. 1* **1993**, 885. Also, see: (b) Ding, K.; Ishii, A.; Mikami, K. *Angew. Chem., Int. Ed.* **1999**, *38*, 497.
15. (a) Soai, K.; Yokoyama, S.; Hayasaka, T. *J. Org. Chem.* **1991**, *56*, 4264. (b) Soai, K.; Niwa, S.; Watanabe, M. *J. Chem. Soc., Perkin Trans. 1* **1989**, 109.
16. For *tertiary* amines of ephedrine and pseudoephedrine, see: Ref. 15b and (a) Chaloner, P. A.; Perera, S. A. R. *Tetrahedron Lett.* **1987**, *28*, 3013. (b) Chaloner, P. A.; Longadianon, E. *Tetrahedron Lett.* **1990**, *31*, 5185. (c) Corey, E. J.; Hannon, F. J. *Tetrahedron Lett.* **1987**, *28*, 5233 and 5237. (d) Muchov, G.; Vannonoorenberghe, Y.; Buono, G. *Tetrahedron Lett.* **1987**, *28*, 6163. (e) Soai, K.; Nishi, M.; Ito, Y. *Chem. Lett.* **1987**, 2405. (f) Soai, K.; Niwa, S.; Watanabe, M. *J. Org. Chem.* **1988**, *55*, 927. (g) Watanabe, M.; Araki, S.; Butsugan, Y.; Uemura, M. *Chem. Express* **1990**, *5*, 761.
17. (a) Zhang, H.; Xue, F.; Mak, T. C. W.; Chan, K. S. *J. Org. Chem.* **1996**, *61*, 8002. (b) Suggestion for dependence of ee on the basicity of the functional group in the aromatic aldehyde was mentioned in the ethylation catalyzed by the chiral hydroxy sulfamide–modified titanium(IV) species; see Ref. 34.
18. The Hammett constants σ_p^+, σ_p, and σ_I are taken from the book by: Exner, O. *Correlation Analysis of Chemical Data*; Plenum Press: New York, 1988.
19. Addition of Et_2Zn to 3-pyridinecarboxaldehyde using *N*,*N*-dibutylnorphedrine with 74% ee was reported: (a) Soai, K.; Hori, H.; Niwa, S. *Heterocycles* **1989**, *29*, 2065. For autocatalysis in dialkylzincs addition to pyridinecarboxaldehydes, see: (b) Soai, K.; Niwa, S.; Hori, H. *J. Chem. Soc., Chem. Commun.* **1990**, 982. (c) Shibata, T.; Morioka, H.; Tanji, S.; Hayase, T.; Kodaka, Y.; Soai, K. *Tetrahedron Lett.* **1996**, *37*, 8783. To quinolinecarboxaldehydes, see: (d) Shibata, T.; Choji, K.; Morioka, H.; Hayase, T.; Soai, K. *Chem. Commun.* **1996**, 751. (e) Shibata, T.; Choji, K.; Hayase, T.; Aizu, Y.; Soai, K. *Chem. Commun.* **1996**, 1235. To pyrimidinecarboxaldehydes, see: (f) Soai, K.; Shibata, T.; Morioka, H.; Choji, K. *Nature* **1995**, *378*, 767. (g) Shibata, T.; Morioka, H.; Hayase, T.; Choji, K.; Soai, K. *J. Am. Chem. Soc.* **1996**, *118*, 471. (h) Shibata, T.; Hayase, T.; Yamamoto, J.; Soai, K. *Tetrahedron: Asymmetry* **1997**, *8*, 1717. (i) Shibata, T.; Yonekubo, S.; Soai, K. *Angew. Chem., Int. Ed.* **1999**, *38*, 659. Also, see: Alberts, A. H.; Wynberg, H. *J. Am. Chem. Soc.* **1989**, *111*, 7265.
20. Ishizaki, M.; Hoshino, O. *Chem. Lett.* **1994**, 1337.
21. These are the ee values of the total amount of the initially used promoter and the forming product. The ee of the newly formed product (ee^{pdt}) in the reaction is calculated according to the following formula: for *R*-enantiomer being the major product, $ee^{pdt} = [(W_R^{pdt} - W_S^{pdt})/(W_R^{pdt} + W_S^{pdt})] \times 100\%$, where $W_R^{pdt} = W_R^{iso} - W_R^{init}$ and $W_S^{pdt} = W_S^{iso} - W_S^{init}$. W_R^{init} and W_S^{init} are the weights of the initially used *R*- and *S*-enantiomers in the reaction as the promoter, W_R^{iso} and W_S^{iso} are the total weights of the *R*- and *S*-enantiomers isolated from the reaction, and W_R^{pdt} and W_S^{pdt} are the calculated weights of the newly formed *R*- and *S*-enantiomers in the reaction, respectively.
22. (a) Kitamura, M.; Suga, S.; Niwa, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 4832. (b) Kitamura, M.; Yamakawa, M.; Oka, H.; Suga, S.; Noyori, R. *Chem. Eur. J.* **1996**, *2*, 1173. (c) Kitamura, M.; Suga, S.; Oka, H.; Noyori, R. *J. Am. Chem. Soc.* **1998**, *120*, 9800. Also see: Oguni, N.; Matsuda, Y.; Kaneko, T. *J. Am. Chem. Soc.* **1988**, *110*, 7877.
23. Kitamura, M.; Oka, H.; Noyori, R. *Tetrahedron* **1999**, *55*, 3605.
24. For computational modelings on TS, see: (a) Yamakawa, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 6327. (b) Goldfuss, B.; Houk, K. N. *J. Org. Chem.* **1998**, *63*, 8998. (c) Goldfuss, B.; Steigelmann, M.; Khan, S. I.; Houk, K. N. *J. Org. Chem.* **2000**, *65*, 77.
25. For the original proposals of the reaction mechanism, see: (a) Itsuno, S.; Fréchet, J. M. J. *J. Org. Chem.* **1987**, *52*, 4140. (b) Evans, D. A. *Science* **1988**, *240*, 420. (c) Corey, E. J.; Hannon, F. J. *Tetrahedron Lett.* **1987**, *28*, 5233 and 5237. (d) Corey, E. J.; Yuen, P.-W.; Hannon, F. J.; Wierda, D. A. *J. Org. Chem.* **1990**, *55*, 784. (e) Kitamura, M.; Okada, S.; Suga, S.; Noyori, R. *J. Am. Chem. Soc.* **1989**, *111*, 4028.
26. For the related 4/4-fused bicyclic structure in the reaction of trimethylaluminum with benzophenone, see: (a) Jeffery, E. A.; Mole, T.; Saunders, J. K. *Aust. J. Chem.* **1968**, *21*, 649. (b) Jeffery, E. A.; Mole, T. *Aust. J. Chem.*

1970, *23*, 715. For theoretical studies on reaction of MeLi with aldehydes in vaccum and in solution, see: (c) Kaufmann, E.; Schleyer, P. von R.; Houk, K. N.; Wu, Y.-D. *J. Am. Chem. Soc.* **1985**, *107*, 5560. (d) Nakamura, M.; Nakamura, E.; Koga, N.; Morokuma, K. *J. Am. Chem. Soc.* **1993**, *115*, 11016.
27. (a) Matteson, D. S. *Organomet. Chem. Rev. Sect. A* **1969**, 4, 263. (b) Matteson, D. S. *Organometallics Reaction Mechanism on the Nontransition Elements*; Academic: New York, 1974; pp. 146–147.
28. For similar 5/4/4-fused tricyclic TS′, see: Vidal-Ferran, A.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron Lett.* **1997**, *38*, 8773.
29. Soai, K.; Watanabe, M. *Tetrahedron: Asymmetry* **1991**, *2*, 97.
30. Watanabe, M.; Araki, S.; Butsugan, Y.; Uemura, M. *J. Org. Chem.* **1991**, *56*, 2218.
31. Chaloner, P. A.; Perena, S. A. R. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2731.
32. Nakano, H.; Kumagai, N.; Matsuzaki, H.; Kabuto, C.; Hongo, H. *Tetrahedron: Asymmetry* **1997**, *8*, 1391.
33. Ishizaki, M.; Fujita, K.; Shimamoto, M.; Hoshino, O. *Tetrahedron: Asymmetry* **1994**, *5*, 411.
34. Ramón, D. J.; Yus, M. *Tetrahedron: Asymmetry* **1997**, *8*, 2479.
35. The specific rotation value of –45.85 for 14% ee of (*S*)-**22g** does not seem to be correct.
36. The absolute configuration of (+)-**22h** was assigned by comparison with the specific rotation data of (*R*)-**22b**.
37. Williams, D. R.; Fromhold, M. G. *Synlett* **1997**, 523.
38. Sato, T.; Gotoh, Y.; Wakabayashi, Y.; Fujisawa, T. *Tetrahedron Lett.* **1983**, *24*, 4123.
39. (a) Burrows, E. P.; Welch, F. J.; Mosher, H. S. *J. Am. Chem. Soc.* **1960**, *82*, 880. (b) Asami, M.; Watanabe, H.; Honda, K.; Inoue, S. *Tetrahedron: Asymmetry* **1998**, *9*, 4165.
40. Ohno, A.; Nakai, J.; Nakamura, K. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 3482.
41. The absolute configurations of (–)-**22o**,**p** were not assigned in Ref. 20. By comparison of the longer retention times on the Chiralcel OD column with the reported data for 2-methyl-1-(3′-pyridyl)-1-propanol (Ref. 19b), the absolute configuration of (+)-**22o**,**p** is assigned as *R*.
42. (a) Kametani, T.; Tsubuki, M.; Tatsuzaki, Y.; Honda, T. *J. Chem. Soc., Perkin Trans. 1* **1990**, 639. (b) Oeveren, A. V.; Menge, W.; Feringa, B. L. *Tetrahedron Lett.* **1989**, *30*, 6427.
43. (a) Fujiwara, M.; Mori, K. *Agric. Biol. Chem.* **1986**, *50*, 2925. (b) Kang, S.-K.; Jeon, J.-H.; Yamaguchi, T.; Kim, J.-S.; Ko, B.-S. *Tetrahedron: Asymmetry* **1995**, *6*, 2139.