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Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 18 (2007) 1257–1263

Synthesis of novel chiral 1,3-aminophenols and application for the enantioselective addition of diethylzinc to aldehydes

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Received 1 May 2007; accepted 22 May 2007

Abstract—Novel chiral 1,3-aminophenols were efficiently synthesized by applying a Friedel–Crafts reaction and optical resolution. The catalytic activity of the aminophenols was studied for the addition of diethylzinc to benzaldehyde. The results showed that (*S*)-**5a** with bulky *tert*-butyl groups on the stereogenic carbon atom and 4,6-positions of phenol favored higher enantioselectivity (94% ee). The same ligand was also used with other aldehydes, to give optically active alcohols in good chemical yields and ee values (up to 99%).

1. Introduction

In recent years, there has been a great deal of interest in the synthesis of chiral ligands which work for catalytic asymmetric carbon–carbon bond formation with high enantioselectivity.[1] The chiral ligands for this purpose mainly include aminoalcohols, with a few examples of aminothiols, amines, diols, disulfides, and diselenides.[2] Aminoalcohols have mostly been used as chiral ligands in the alkylation of aldehydes with dialkylzinc. Although aminophenols are analogous to amino alcohols, they were not used as chiral ligands in asymmetric catalysis until Cardellicchio's work in 1998, in which they gave high enantioselectivities.[3] Since then, interest in their application for the asymmetric catalysis of aminophenols and their derivatives has increased significantly.[4] Herein, we report the synthesis of novel chiral 1,3-aminophenol ligands **4a–b**, **5a–b** and **6a–b** as well as their uses as chiral ligands for the enantioselective addition of diethylzinc to aldehydes.

2. Results and discussion

2.1. Synthesis of optically active 1,3-aminophenols 4a–b, 5a–b and 6a–b

Chiral aminophenols **1a** and **1b** can be prepared from 2-methoxybenzaldehyde and 2-methoxybenzoic acid in five steps, according the literature,[5] in overall yields of 64% and 40%, respectively, with enantiomeric excess exceeding 99%.

The synthesis of aminophenol **3a** starts from commercially available 1-(2-methoxy-5-methylphenyl)-2-phenylethylamine **2a**. The resolution of **2a** was realized by the recrystallization of the D-(−)-tartaric acid salt to obtain (*R*)-**2a** in >99% ee. The deprotection step was performed by treating (*R*)-**2a** with anhydrous $AlBr_3$ in dry toluene at 0 °C for 50 h. After chromatography, (*R*)-**3a** was obtained in 75% yield (Scheme 1).

The synthesis of aminophenol **3b** is very similar to that of **3a** with a modification in the resolution process. As shown in Scheme 2, commercially available amine **2b** was deprotected to afford aminophenol *rac*-**3b** in 78% yield. Subsequently, the optical resolution of *rac*-**3b** was realized by recrystallization of the dehydroabietic acid (DAA)[6] salt to obtain (−)-**3b** in 36% yield in >99% ee.

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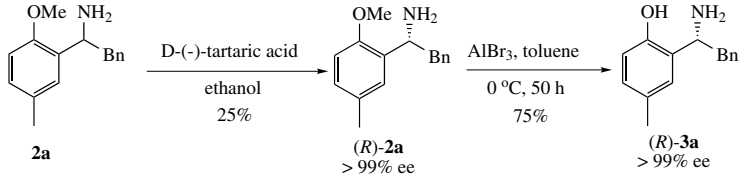
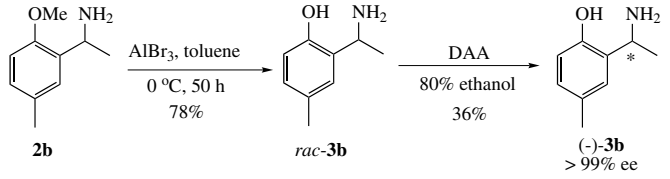
doi:10.1016/j.tetasy.2007.05.027



Scheme 1.



Scheme 2.

Novel chiral 1,3-aminophenols **4a**–**b**, **5a**–**b** and **6a**–**b** were synthesized by Friedel–Crafts alkylation of **1** and **3** with urea and *t*-BuOH in 75% H_2SO_4 at room temperature for 72 h in 13–79% yields in 99% ee after chromatography (Scheme 3).[7]

The structures of (*S*)-**5a** and (*S*)-**5b** were determined by single crystal X-ray diffraction analysis (Figs. 1 and 2).[8,9]

2.2. Catalytic asymmetric addition of diethylzinc to aldehydes

It is well known that the reaction of aldehydes with diethylzinc to give the corresponding *sec*-alcohols takes place in the presence of a catalytic amount of amino alcohols.[2] Excellent chiral inductions including asymmetric amplifications by use of chiral aminoalcohols in this reaction have been reported.[2] This interesting reaction has been widely utilized for the evaluation of chiral ligands. In order to clarify the chiral induction abilities of the present novel 1,3-aminophenols, we first examined the enantioselective addition reaction of diethylzinc to benzaldehyde in the presence of catalytic amounts (10 mol %) of these 1,3-aminophenols (Scheme 4, Table 1).

As shown in Table 1, a high yield and high ee could be achieved by using the chiral aminophenol (*S*)-**5a** with bulky

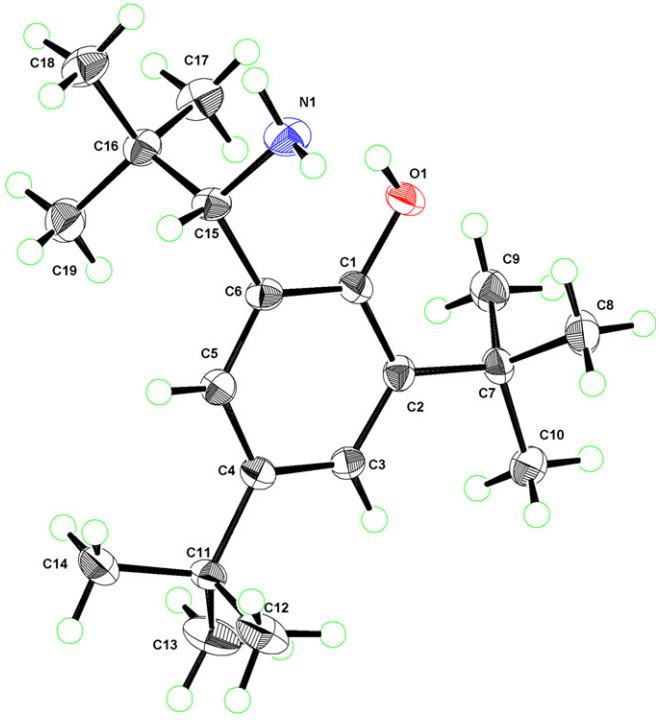
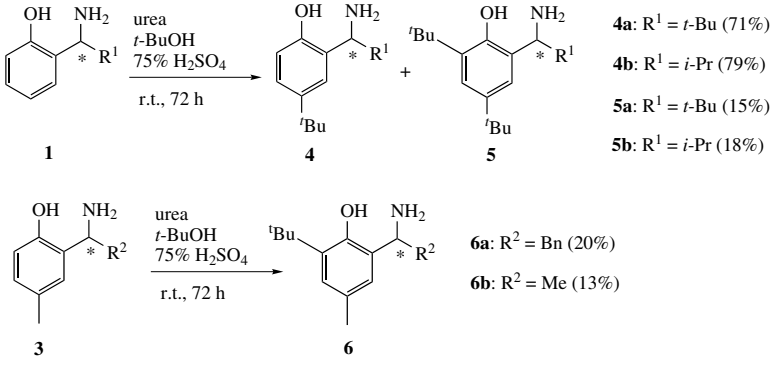


Figure 1. X-ray structure of compound (*S*)-**5a**.

tert-butyl groups on the stereogenic carbon atom and 4,6-positions of phenol (Table 1, entry 4). This result suggests that high stereoselectivity can be achieved by introduction of sterically bulky substituents into the chiral ligand. To our surprise, when using chiral ligand (*S*)-**1a** or (*S*)-**4a** without a *tert*-butyl group at the *ortho*-position of phenol, the opposite enantiomer was obtained (Table 1, entries 1 and 2). These results mean that from the single stereogenic cen-



Scheme 3.

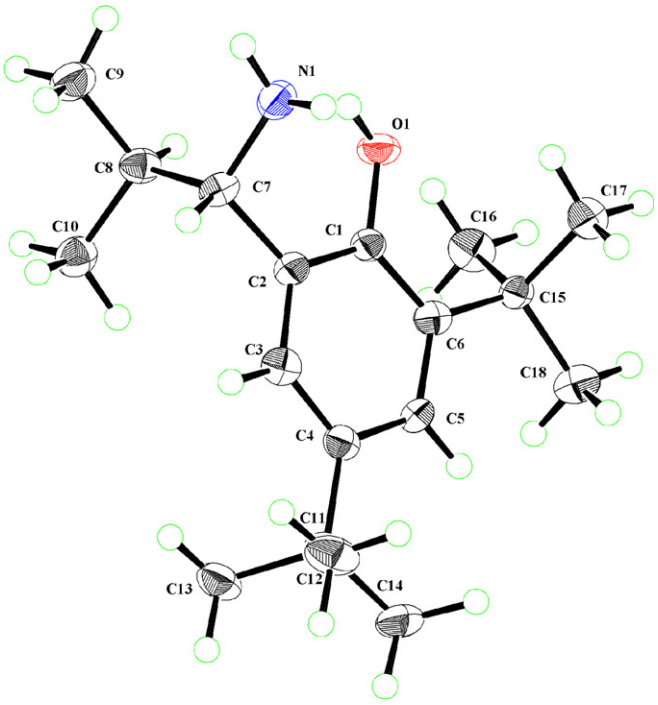
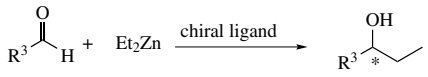


Figure 2. X-ray structure of compound (*S*)-**5b**.



Scheme 4.

Table 1. Enantioselective addition reaction of diethylzinc to benzaldehyde ($R^3 = C_6H_5$) in the presence of 10 mol % chiral 1,3-aminophenol ligands **4a–b**, **5a–b** and **6a–b**

Entry	Ligand	Yield[c] (%)	ee[d] (%)	Configuration[e]
1[a]	(*S*)-**1a**	18	32	(*S*)
2[a]	(*S*)-**4a**	18	14	(*S*)
3[a]	(*S*)-**4b**	19	6	(*R*)
4[b]	(*S*)-**5a**	65	93	(*R*)
5[b]	(*S*)-**5b**	46	66	(*R*)
6[b]	(*R*)-**6a**	36	56	(*S*)
7[b]	(−)-**6b**	40	55	(*S*)

[a] Reaction conditions: toluene, 22 h, rt.
[b] Reaction conditions: toluene/hexane (1:1, v/v), 22 h, −17 °C.
[c] Isolated yields.
[d] Based on HPLC analysis using Chiralcel OB-H.
[e] Determined by comparison of the sign of optical rotation values with those in Ref. 10.

ter of **1a** both enantiomers were obtained in low to high ee values in the case of $R^3 = Ph$. Under these conditions, we also observed the formation of some amounts of imines derived from the condensation of aldehydes and chiral ligands in all cases.

Chiral ligand **5a** was further investigated by varying reaction solvent and temperature (Table 2). The solvent had an important role in the enantioselective process (Table 2, entries 1–3). Toluene or toluene/hexane (1:1, v/v) gave the best results with 62%, 71% yields and 86%, 85% ee, respectively (Table 2, entries 1 and 3). The presence of hexane lowered the ee value of the resulting alcohol (Table 2, entry 2). Therefore, toluene/hexane (1:1, v/v) was selected as the reaction solvent in the following reactions.

The reaction was also studied with several different aldehydes using 10 mol % of (*S*)-**5a** in toluene/hexane (1:1, v/v) at −17 °C (Table 3). Using (*S*)-**5a**, the catalytic diethylzinc addition proceeded in high enantioselectivity toward the aldehyde possessing an electron-withdrawing or electron-donating group at the *para*-position of the aromatic ring (all up to 99% ee, entries 2–6). These results suggested there is no effect of a substituent at the *para*-position on the enantioselectivity. However, an *ortho*-substituent lowered the enantiomeric purity of the product while the effect of a *meta*-substituent was small (entries 7–10). On the other hand, the chemical yield decreases in the order of *para*-, *meta*-, *ortho*-substitution, probably due to the steric hindrance except for *p*-MeO–, and NO_2–benzaldehyde. These two aldehydes remained unreacted after the reaction time, which is contrary to the literature;[1a,f] the reaction is apparently retarded by these functional group but the effect is not clear at present. The reaction was also tested with aliphatic aldehydes (Table 3, entries 11 and 12) and provided the corresponding alcohols with lower yields than the aromatic ones due to lower reactivity. The electronic or steric effect causing large differences in enantiomeric excess (95% ee for decanal and 28% ee for phenylpropanal) should be the subject of further studies. In all cases some amounts of imines derived from condensation of aldehydes and chiral ligands were also formed.

The currently accepted mechanism for the addition of dialkylzinc to aldehydes[12] has been reviewed and applied to the present system. In analogy to that established by Noyori and Yamakawa[12d] for the β-amino alcohols, a six-membered Zn-chelate species is initially formed by the reaction of 1,3-aminophenol (*S*)-**1a** with diethylzinc. This complex coordinates to a new molecule of diethylzinc and aldehydes by the O and Zn atoms, respectively (Fig. 3). Such coordination activates the molecules to cause the enantioselective addition reaction through tricyclic 6/4/4-membered Noyori's *anti* type transition states (Fig. 3). The energy differences between the transition states, which lead to the opposite enantiomers by means of semi-empirical PM5 calculations[13] show that the structure *anti*-(*S*) is more stable, with a small difference of 1.42 kcal/mol. This value supports the experimental result, which shows the (*S*)-1-phenylpropanol with a low enantioselectivity (32% ee) as the major product (Table 1, entry 1). Taking the results into account, we can attempt to provide a rationale for the stereochemical outcome of the reaction with (*S*)-**5a**, as well as of the influence of the substituent present at the *ortho*-position of phenol. From two transition states *anti*-(*S*) and *anti*-(*R*) in (*S*)-**5a** (Fig. 4) we can see that in *anti*-(*R*) the equatorial *tert*-butyl $^tBu^{\#}$ and the ethyl group on zinc ($Et^{\#}$) are on opposite sides, while in *anti*-(*S*) the $^tBu^{\#}$ and $Et^{\#}$ moieties are on the same sides. Therefore, greater destabilization of the *anti*-(*S*) with respect to the *anti*-(*R*) transition state results, giving rise to a greater energy differ-

Table 2. Optimization of the enantioselective addition of diethylzinc to benzaldehyde ($R^3 = C_6H_5$) by chiral ligand **5a**[a]

Entry	Ligand	Reaction conditions	Yield[c] (%)	ee[d] (%)	Configuration[e]
1	(*R*)-**5a**	Toluene, rt	62	86	(*S*)
2	(*R*)-**5a**	Hexane, rt	54	71	(*S*)
3	(*R*)-**5a**	Toluene/hexane (1:1, v/v), rt	71	85	(*S*)
4	(*S*)-**5a**	Toluene/hexane (1:1, v/v), rt	71	85	(*R*)
5	(*S*)-**5a**	Toluene/hexane (1:1, v/v), 0 °C	79	86	(*R*)
6	(*S*)-**5a**	Toluene/hexane (1:1, v/v), −17 °C	65	93	(*R*)
7[b]	(*S*)-**5a**	Toluene/hexane (1:1, v/v), −17 °C	59	92	(*R*)

[a] In the presence of 10 mol % chiral 1,3-aminophenol ligand **5a** for 22 h.
[b] In the presence of 15 mol % chiral 1,3-aminophenol ligand (*S*)-**5a** for 22 h.
[c] Isolated yields.
[d] Based on HPLC analysis using Chiralcel OB-H.
[e] Determined by comparison of the sign of specific rotation values with those in Ref. 10.

Table 3. Enantioselective addition reaction of diethylzinc to aldehydes in the presence of 10 mol % chiral ligand (*S*)-**5a**[a]

Entry	R^3	Yield[b] (%)	ee (%)	Configuration[g]
1	C_6H_5	65	93[c]	(*R*)
2	*p*-ClC_6H_4	89	99[c]	(*R*)
3	*p*-BrC_6H_4	71	99[c]	(*R*)
4	*p*-MeC_6H_4	66	99[c]	(*R*)
5	*p*-$MeOC_6H_4$	29	99[c]	(*R*)
6	*p*-$NO_2C_6H_4$	41	99[c]	(*R*)
7	*m*-ClC_6H_4	64	88[c]	(*R*)
8	*m*-$NO_2C_6H_4$	48	99[d]	n.d.
9	*o*-ClC_6H_4	41	74[c]	(*R*)
10	*o*-MeC_6H_4	38	72[c]	(*R*)
11	$CH_3(CH_2)_8$	18	95[e]	(*R*)
12	$C_6H_5CH_2CH_2$	22	28[f]	(*R*)

[a] Reaction conditions: toluene/hexane (1:1, v/v), 22 h, −17 °C.
[b] Isolated yields.
[c] Determined by HPLC analysis using Chiralcel OB-H.
[d] Determined by HPLC analysis using Chiralcel OD-H.
[e] Determined by HPLC analysis of corresponding benzonate using Chiralcel OJ.
[f] Determined by HPLC analysis using Chiralcel OJ.
[g] Determined by comparison of the sign of the specific rotation values with those in Refs. 10 and 11.

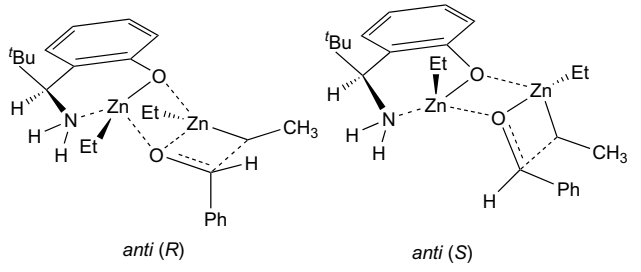


Figure 3.

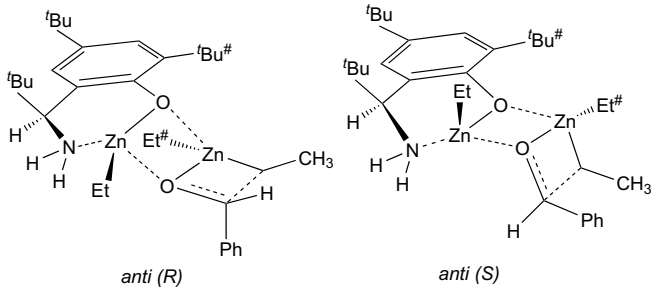


Figure 4.

ence[14] between the two transition states, and leading to the higher enantioselectivity experimentally observed for (*S*)-**5a**.

3. Conclusions

In conclusion, novel chiral 1,3-aminophenols have been synthesized and proven to be good promoters of the addition of diethylzinc to aldehydes. The results obtained clearly show that the enantioselectivity was strongly influenced by the presence of bulky *tert*-butyl groups on the stereogenic carbon atom and 4,6-positions of phenol. Ligand (*S*)-**5a** gave good asymmetric induction not only with aromatic aldehydes (best ee up to 99%) but also with aliphatic aldehydes (best ee 95%). Work is now in progress on the use of these compounds for other enantioselective transformations.

4. Experimental

^{1}H NMR spectra were recorded on a Bruker AC300 or DPX400 MHz in Molecular Analysis and Life Science Cen-

ter (Saitama University). The chemical shifts were reported in ppm downfield from Me_4Si in $CDCl_3$ solution. Coupling constants are given in Hz. IR spectra were recorded on an FT/IR 400. Enantiomeric excess determination was carried out using a set of JASCO LC 900 series with chiral columns. Optical rotations were measured with a JASCO DIP-370 polarimeter. Melting points were determined with a Mitamura Riken Kogyo MEL-TEMP instrument and reported uncorrected. All reagents that were commercially available were purchased at the highest quality and purified by distillation when necessary. Hexane and toluene were distilled and stored on a sodium wire before use.

4.1. Optical resolution of 2a

Racemic **2** (23.6 g, 97.8 mmol) and D-(−)-tartaric acid (14.60 g, 97.3 mmol) were dissolved in ethanol to prepare the diastereomeric salt. After the ethanol was removed, the diastereomeric salt was recrystallized from 80% ethanol 3 times to give the diastereomerically pure less-soluble salt of (*R*)-(−)-**2**·D-(−)-tartaric acid (6.69 g, 19.0 mmol, 39%). $[\alpha]_D^{16} = -71.9$ (*c* 0.5, H_2O). The less-soluble salt was liberated by 6 M aqueous NaOH solution and the aqueous layer extracted with diethyl ether to give enantiomerically pure (*R*)-(−)-**2** (3.97 g, total yield, 25%). $[\alpha]_D^{16} = -21.2$ (*c* 0.5, MeOH). Enantiomeric excess >99% was determined by HPLC analysis (CHIRALCEL OD-H, hexane–*i*-PrOH 80:20, 0.5 ml/min) of the corresponding acetamide derivative at retention time: $t = 12.7$ min.

4.2. 2-((*R*)-1-Amino-2-phenylethyl)-4-methylphenol (*R*)-(−)-3a

A solution of (*R*)-(−)-**2a** (2.40 g, 10 mmol) in dry toluene (50 ml) was added dropwise to $AlBr_3$ (10.40 g, 38.6 mmol) and the yellow solution stirred at 0 °C for 50 h. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (100 ml) at 0 °C and the mixture was extracted with ethyl acetate (15 ml × 4). The organic layer was dried with anhydrous Na_2SO_4 and the solvent removed under reduced pressure. The crude product was purified by column chromatography of silica gel (eluent: ethyl acetate) to give a white solid (*R*)-(−)-**3a** (6.59 g, 29.0 mmol, 75%). Mp: 90–92 °C. $[\alpha]_D^{20} = -48.0$ (*c* 0.5, MeOH). Enantiomeric excess >99% was determined by HPLC analysis (CHIRALCEL OD-H, hexane–*i*-PrOH 80:20, 0.5 ml/min) at retention time $t = 11.9$ min. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 7.30 (m, 5H, ArH), 6.97 (d, $J = 8.0$ Hz, 1H, ArH), 6.78 (d, $J = 8.0$ Hz, 2H, ArH), 4.26 (dd, $J = 4.3$ Hz, $J = 5.9$ Hz, 1H, $CHNH_2$), 3.07 (dd, $J = 4.3$ Hz, $J = 9.1$ Hz, 1H, $ArCH_2$), 2.94 (dd, $J = 3.2$ Hz, $J = 10.2$ Hz, 1H, $ArCH_2$), 2.24 (s, 3H, $ArCH_3$). IR (KBr) 3075, 3030, 1807, 1779, 1638, 1605, 1543, 1445, 1388, 1300, 1261, 1179, 904, 849, 757 cm^{-1}. Anal. as HCl salt. Calcd for $C_{15}H_{18}ClNO$: C, 68.30; H, 6.88; N, 5.31. Found: C, 68.44; H, 7.00; N, 5.21.

4.3. 2-(1-Aminoethyl)-4-methylphenol 3b

This compound was synthesized via the same procedure as **3a**. A pale yellow solid. Yield 78%. Mp: 96–98 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 6.94 (d, 1H, $J = 8.1$ Hz, ArH), 6.75 (m, 2H, ArH), 4.27 (q, 1H, $J = 6.6$ Hz, CH), 2.24 (s, 3H, $ArCH_3$), 1.46 (d, 3H, $J = 6.6$ Hz, CH_3CO). IR (KBr) 2981, 2899, 2492, 2190, 1652, 1612, 1528, 1481, 1267, 821, 792, 626 cm^{-1}. Anal. as HCl salt. Calcd for $C_9H_{14}ClNO$: C, 57.60; H, 7.52; N, 7.46. Found: C, 57.46; H, 7.56; N, 7.36.

4.4. Optical resolution of 3b

Racemic **3b** (1.91 g, 0.013 mol) and DAA (dehydroabietic acid) (3.80 g, 0.013 mol) were dissolved in ethanol. After the ethanol was removed, the diastereomeric salt was recrystallized from 75% ethanol 3 times to yield the less-soluble diastereomerically pure salt of (−)-**3b**·DAA (1.29 g, 23%). $[\alpha]_D^{20} = +31.4$ (*c* 0.5, MeOH). The less-soluble salt (−)-**3b**·DAA (1.13 g, 2.5 mmol) was dissolved in 6 M aqueous HCl solution. Precipitated DAA was separated and 6 M aqueous NaOH solution added to the filtrate till pH 8–9. Precipitated aminophenol was extracted with chloroform and the organic layer dried with anhydrous Na_2SO_4, filtered, and the solvent removed under reduced pressure to give enantiomerically pure (−)-**3b** (0.35 g, total yield, 36%). $[\alpha]_D^{20} = -16.2$ (*c* 0.5, 0.1 M HCl (aq)). Enantiomeric excess >99% ee was determined by HPLC analysis (CHIRALCEL OD-H, hexane–*i*-PrOH 85:15, 0.5 ml/min) of the corresponding acetamide derivative at retention time: $t = 12.5$ min.

4.5. General procedure for the synthesis of chiral 1,3-aminophenols 4a–b, 5a–b, 6a–b

After dissolving urea (2.51 g, 42.0 mmol) in 75% H_2SO_4 (20 ml), the solution was cooled to below 10 °C. *tert*-BuOH (7.92 ml, 84 mmol) was then added in one portion, and the mixture stirred at the same temperature for a further 1 h. Enantiomerically pure (*R*)-**1a** (3.45 g, 21.0 mmol) was added and the mixture stirred at rt for 72 h. At 0 °C, a saturated aqueous solution of Na_2CO_3 was added to make the solution pH 8–9 and the mixture was extracted with ethyl acetate (10 ml × 3). The combined organic layers were dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude mixture was purified by column chromatography of silica gel (eluent: $CHCl_3$) to give a white solid (*R*)-**4a** (3.67 g, 16.6 mmol, 71%) and a white solid (*R*)-**5a** (1.04 g, 3.75 mmol, 15%). In the same way, (*R*)-**4a** was reacted further with urea and *tert*-BuOH in 75% H_2SO_4 to obtain (*R*)-**5a** and recovered (*R*)-**4a**. Using enantiomerically pure (*S*)-**1a**, (*S*)-**4a** and (*S*)-**5a** were synthesized, respectively.

4.5.1. 2-(1-Amino-2,2-dimethylpropyl)-4-*tert*-butylphenol 4a. A white solid. Mp: 99–101 °C. (*S*)-**4a**; $[\alpha]_D^{20} = -6.8$ (*c* 0.326, diethyl ether), (*R*)-**4a**, $[\alpha]_D^{20} = +8.4$ (*c* 0.330, diethyl ether). Enantiomeric excess >99% was determined by HPLC analysis (CHIRALCEL OD-H, hexane–*i*-PrOH 90:10, 0.5 ml/min) at retention time: $t_S = 12.7$ min; $t_R = 13.8$ min. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 7.15 (dd, $J = 8.6$ Hz, $J = 1.4$ Hz, 1H, ArCH), 6.88 (d, $J = 1.3$ Hz, 1H, ArH), 6.74 (d, $J = 8.6$ Hz, 1H, ArH), 3.85 (s, 1H, $(CH_3)_3CHAr$), 1.27 (s, 9H, $(CH_3)_3Ar$), 0.978 (s, 9H, $(CH_3)_3CHAr$). IR (KBr) 3067, 2983, 1598, 1485, 1448, 1386, 1298, 1137, 913, 868 cm^{-1}. Anal. Calcd for $C_{15}H_{25}NO$: C, 76.55; H, 10.71; N, 5.95. Found: C, 76.67; H, 10.85; N, 6.01.

4.5.2. 2-(1-Amino-2-methylpropyl)-4-*tert*-butylphenol 4b. A colorless oil, 79% yield. (*S*)-**4b**; $[\alpha]_D^{20} = -13.9$ (*c* 0.36, $CHCl_3$). Enantiomeric excess >99% was determined by HPLC analysis (CHIRALCEL OD-H, hexane–*i*-PrOH 90:10, 0.5 ml/min) at retention time: $t = 12.8$ min. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 7.15 (dd, $J = 8.5$ Hz, $J = 2.6$ Hz, 1H, ArCH), 6.89 (d, $J = 2.8$ Hz, 1H, ArH), 6.75 (d, $J = 8.5$ Hz, 1H, ArH), 3.83 (d, $J = 7.0$ Hz, 1H, $CHNH_2$), 2.08 (m, 1H, $(CH_3)_2CH$), 1.33 (s, 9H, $(CH_3)_3$) 1.02 (d, $J = 6.6$ Hz, 3H, CH_3), 0.838 (d, $J = 6.6$ Hz, 3H, CH_3). IR (neat) 3379, 3302, 2961, 1588, 1496, 1470, 1387, 1366, 1256, 1175, 825, 754 cm^{-1}. Anal. as HCl salt. Calcd for $C_{14}H_{24}ClNO$: C, 65.23; H, 9.38; N, 5.43. Found: C, 65.34; H, 9.35; N, 5.49.

4.5.3. 2-(1-Amino-2,2-dimethylpropyl)-4,6-di-*tert*-butylphenol 5a. A white solid. Mp: 108–110 °C. (*S*)-**5a**; $[\alpha]_D^{20} = +22.0$ (*c* 0.5, $CH_3COOCH_2CH_3$), (*R*)-**5a**; $[\alpha]_D^{20} = -12.7$ (*c* 1.0, MeOH). Enantiomeric excess >99% was determined by HPLC analysis (CHIRALCEL OJ, hexane–*i*-PrOH 85:15, 0.5 ml/min) at retention time: $t_S = 8.63$ min, $t_R = 13.2$ min. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 7.18 (d, $J = 2.7$ Hz, 1H, ArCH), 6.74 (d, $J = 2.7$ Hz, 1H, ArH), 3.86 (s, 1H, $(CH_3)_3CHAr$), 1.41 (s, 9H, $(CH_3)_3ArOH$), 1.28 (s, 9H, $(CH_3)_3Ar$), 0.965 (s, 9H, $(CH_3)_3CHAr$). IR (KBr) 3485, 2977, 2957, 1693, 1627, 1604, 1454, 1376, 1353, 1331, 1268, 1244, 1151, 969, 958, 794 cm^{-1}. Anal. Calcd for $C_{19}H_{33}NO$: C, 78.29; H, 11.41; N, 4.81. Found: C, 78.41; H, 11.31; N, 4.90.

4.5.4. 2-(1-Amino-2-methylpropyl)-4,6-di-*tert*-butylphenol 5b. A white solid. Mp: 98–100 °C. (*S*)-**5b**; $[\alpha]_D^{20} = +5.8$ (*c* 0.584, diethyl ether). Enantiomeric excess >99% was determined by HPLC analysis (CHIRALCEL OJ, hexane–*i*-PrOH 97:3, 0.5 ml/min) at retention time: $t = 11.1$ min. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 7.18 (d, $J = 2.1$ Hz, 1H, ArCH), 6.76 (d, $J = 2.1$ Hz, 1H, ArH), 3.76 (d, $J = 7.5$ Hz, 1H, $CHNH_2$), 2.07 (m, 1H, $(CH_3)_2CH$), 1.41 (s, 9H, $(CH_3)_3$), 1.28 (s, 9H, $(CH_3)_3$), 1.01 (d, $J = 7.0$ Hz, 3H, CH_3), 0.817 (d, $J = 7.0$ Hz, 3H, CH_3). IR (KBr) 3366, 3295, 2959, 1579, 1477, 1439, 1387, 1362, 1251, 1234, 1159, 981, 882, 823 cm^{-1}. Anal. Calcd for $C_{18}H_{31}NO$: C, 77.92; H, 11.26; N, 5.05. Found: C, 78.09; H, 11.55; N, 5.14.

4.5.5. 2-((*R*)-1-Amino-2-phenylethyl)-6-*tert*-butyl-4-methylphenol (*R*)-(−)-6a. A colorless oil. (*R*)-**6a**; $[\alpha]_D^{20} = -26.1$ (*c* 1.8, $CHCl_3$). Enantiomeric excess >99% was determined by HPLC analysis (CHIRALCEL OJ, hexane–*i*-PrOH 90:10, 0.5 ml/min) at retention time: $t = 16.1$ min. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 7.30 (m, 5H, ArH), 7.00 (d, $J = 2.1$ Hz, 1H, ArCH), 6.71 (d, $J = 2.1$ Hz, 1H, ArH), 4.26 (dd, $J = 4.3$ Hz, $J = 5.9$ Hz, 1H, $CHNH_2$), 3.02 (m, 2H, $ArCH_2$), 2.24 (s, 3H, $ArCH_3$), 1.43 (s, 9H, $(CH_3)_3$). IR (neat) 3080, 3067, 3003, 1805, 1793, 1633, 1600, 1552, 1420, 1395, 1375, 1306, 1223, 1174, 786, 772, 700 cm^{-1}. Anal. as HCl salt. Calcd for $C_{19}H_{26}ClNO$: C, 71.34; H, 8.19; N, 4.38. Found: C, 71.45; H, 8.10; N, 4.26.

4.5.6. (−)-2-(1-Aminoethyl)-6-*tert*-butyl-4-methylphenol 6b. A pale green solid. Mp: 40–42 °C. (−)-**6a**; $[\alpha]_D^{20} = -21.2$ (*c* 0.6, $CHCl_3$). Enantiomeric excess >99% was determined by HPLC analysis (CHIRALCEL OD-H, hexane–*i*-PrOH 90:10, 0.5 ml/min) at retention time: $t = 9.6$ min. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 6.97 (s, 1H, ArCH), 6.66 (s, 1H, ArH), 4.26 (q, $J = 6.6$ Hz, 1H, $CHNH_2$), 2.24 (s, 3H, $ArCH_3$), 1.47 (d, $J = 6.6$ Hz, 3H, CH CH_3), 1.41 (s, 9H, $(CH_3)_3$). IR (KBr) 3004, 1631, 1596, 1467, 1384, 1308, 1260, 1173, 1115, 917, 907, 783 cm^{-1}. Anal. Calcd for $C_{13}H_{21}NO$: C, 75.32; H, 10.21; N, 6.76. Found: C, 75.13; H, 10.32; N, 6.66.

4.6. General procedure for the enantioselective addition of diethylzinc to aldehydes

Diethylzinc (1.0 M solution in hexane, 1.20 mmol) was added to a solution of chiral ligand (0.1 mmol) in anhydrous mixed solvents toluene/hexane (1.5 ml, v/v, 1:1). After 30 min, a solution of aldehyde (1 mmol) in mixed solvents toluene/hexane (2.0 ml, v/v, 1:1) was added dropwise and the resulting mixture stirred for 22 h. The reaction was quenched by 1 M aqueous HCl solution (4 ml) and the product extracted three times with ethyl acetate. The combined organic phase was washed by saturated aqueous solution of NaCl and dried over anhydrous Na_2SO_4. After filtration and evaporation of the solvent, the crude alcohol was purified by TLC of silica gel to give the enantiomer enriched alcohol. The ee values of the alcohols were determined by chiral HPLC analysis.

Acknowledgement

The authors, X.-F.Y. and G.-Y.Z., greatly thank from the Scientific Fund of University of Jinan (B0001) for the financial support.

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8. Crystallographric data for the structure of compound **5a** have been deposited with the Cambridge Crystallographic Data Center as Supplementary Publication No. CCDC 644401. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk]. Crystal data of **5a**: $C_{19}H_{33}N_1O_1$, $M = 291.46$, orthorhombic, space group $C2221$, $a = 13.4310(14)$ Å, $b = 13.7194(14)$ Å, $c = 39.470(4)$ Å, $V = 7272.9(13)$ Å^3, $D = 1.065$ Mg/m^3, $\mu = 0.064$ mm^{-1}, $F(000) = 2592$, $Z = 16$, $R_1 = 0.0578$, $\omega R_2 = 0.1503$. Data collection for the crystal structure determination was carried out on a diffractometer using Mo Kα radiation ($\lambda = 0.71069$ Å) at a temperature of 123(2) K. Of the 25,665 reflections measured in the $1.03 \leqslant \theta \leqslant 27.50°$ range, 8380 reflections were unique and 7471 reflections with $I > 2\sigma(I)$ were used in structure solution and refinement, $R_{int} = 0.1222$, $w = 1/[\sigma^2(F_o^2) + (0.1000P)^2 + 0.0000P]$, where $P = (F_o^2 + 2F_c^2)/3$. The structure was solved by direct method using SHELXL-97. All of the non-hydrogen atoms were refined by Full-matrix least-squares on F^2 using anisotropic displacement parameters.
9. Crystallographic data for the structure of compound **5b** have been deposited with the Cambridge Crystallographic Data Center as Supplementary Publication No. CCDC 644402. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk]. Crystal data of **5b**: $C_{18}H_{31}N_1O_1$, $M = 277.44$, monoclinic, space group $C2$, $a = 27.828(6)$ Å, $b = 5.9272(12)$ Å, $c = 10.734(2)$ Å, $V = 1730(6)$ Å^3, $D = 1.065$ Mg/m^3, $\mu = 0.064$ mm^{-1}, $F(000) = 616$, $Z = 4$, $R_1 = 0.0522$, $\omega R_2 = 0.1114$. Data collection for the crystal structure determination was carried out on a diffractometer using Mo Kα radiation ($\lambda = 0.71069$ Å) at a temperature of 123(2) K. Of the 4801 reflections measured in the $1.50 \leqslant \theta \leqslant 27.50°$ range, 3190 reflections were unique and 2634 reflections with $I > 2\sigma(I)$ were used in structure solution and refinement, $R_{int} = 0.0164$, $w = 1/[\sigma^2(F_o^2) + (0.0285P)^2 + 5.0566P]$, where $P = (F_o^2 + 2F_c^2)/3$. The structure was solved by direct method using SHELXL-97. All of the non-hydrogen atoms were refined by Full-matrix least-squares on F^2 using anisotropic displacement parameters.
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13. Semi-empirical PM5 calculations were performed with the MOPAC 2002 Version 2.5.3 of CAChe Version 7.5.0.85.
14. The transition state *anti-Re*, which is more stable than *anti-Si* of 2.75 kcal/mol by means of semi-empirical PM5 calculations, leads to the alkyl addition of the benzaldehyde to the *Re* face to afford (*R*)-1-phenylpropanol, which is in agreement with the experimental results.