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Synthesis, resolution, and applications of 3-amino-2,2-dimethyl-1,3-diphenylpropan-1-ol, a conformationally restricted 1,3-aminoalcohol

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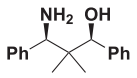
ABSTRACT

Efficient synthetic routes to both *syn* and *anti* diastereomers of a conformationally restricted 1,3-aminoalcohol were devised. Resolution of the aminoalcohols was accomplished through diastereomeric salt with *R*-(−)-*O*-acetyl mandelic acid. These aminoalcohols were examined as ligands for two standard reactions, namely, enantioselective addition of Et_2Zn to aldehydes and reduction of prochiral ketones with BH_3.

1. Introduction

Aminoalcohols and their derivatives are useful chiral ligands and auxiliaries for a variety of enantioselective reactions.[1] A wide variety of aminoalcohols, mostly 1,2-aminoalcohols have been reported in the literature,[1c,2] whereas only a few examples for the use of chiral 1,3-aminoalcohols are known.[3,4] Conformational rigidity is one of the desired features for stereoselective organic reactions. 1,3-Disubstituted acyclic chiral molecules are therefore unlikely to prove useful ligand/auxiliary. With the exception of the ones derived from camphor,[4a,f,i,j] most 1,3-aminoalcohols posses flexible backbone and provide poor enantioselectivity.[4b,c,g,h,k,l] We conceived the structure **1** and **2**, which could be obtained through a straightforward protocol.[5]



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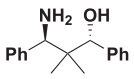

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2. Results and discussion

These molecules would offer particular advantage for selectivity due to conformational rigidity induced by two methyl groups at beta position. Synthesis of the *syn* aminoalcohol (**1**) is depicted in Scheme 1.

First and the crucial step of the scheme is an Aldol–Tishchenko[6] reaction between isobutyrophenone and benzaldehyde in the presence of LiO^tBu. The resulting γ-hydroxybenzoate **3** was treated with thionyl chloride to obtain the *anti* chlorobenzoate **4** with retention of configuration. Compound **4** was then converted to azidobenzoate **5** by treatment with sodium azide in DMF with an inversion of the configuration. The resulting *syn* azidobenzoate **5** was first hydrolyzed to azidoalcohol **6**, followed by hydrogenation to obtain *syn*-1,3-amino alcohol **1** in overall 45% yield. A same strategy was applied for the preparation of *anti*-1,3-aminoalcohol **2**, as shown in Scheme 2.

The required *syn* hydroxylbenzoate **8**, which is the key intermediate for further transformation, was prepared from the *meso* 1,3-diol **7**.[7] 1,3-Diketone[8] was reduced using $LiBH_4/TiCl_4$ to obtain 1,3-diol in 92:8 *syn*/*anti* ratio. The mixture was converted to pure *syn* hydroxybenzoate **8** by treatment with 1 equiv of PhCOCl followed by crystallization. Treatment of **8** with $SOCl_2$ formed chlorobenzoate **9** (in 80% yield) with retention of configuration. The *anti* azidobenzoate **10** was obtained by reaction of the compound **9** with sodium azide. Hydrolysis of **10** followed by hydrogenation provided the corresponding *anti*-1,3-aminoalcohol **2** in overall 33% yield.

3. Resolution

The resolution of amines/aminoalcohols through diastereomeric salts with homochiral carboxylic/sulfonic acids is a standard

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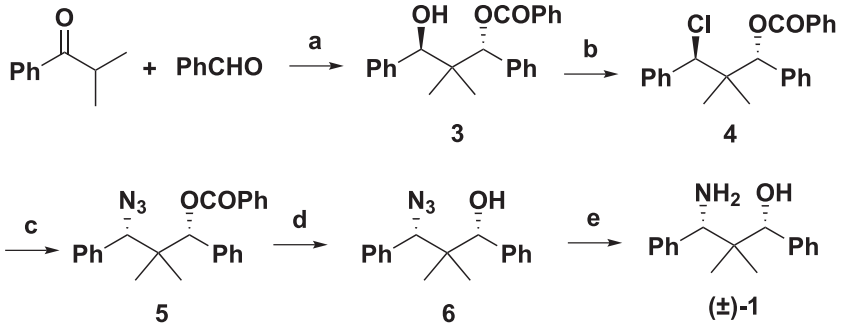
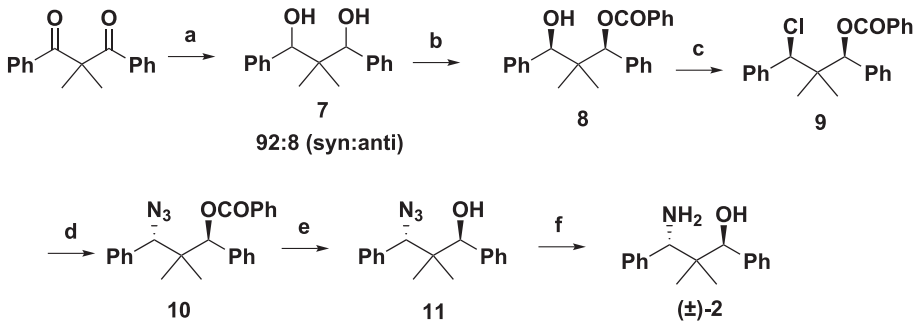
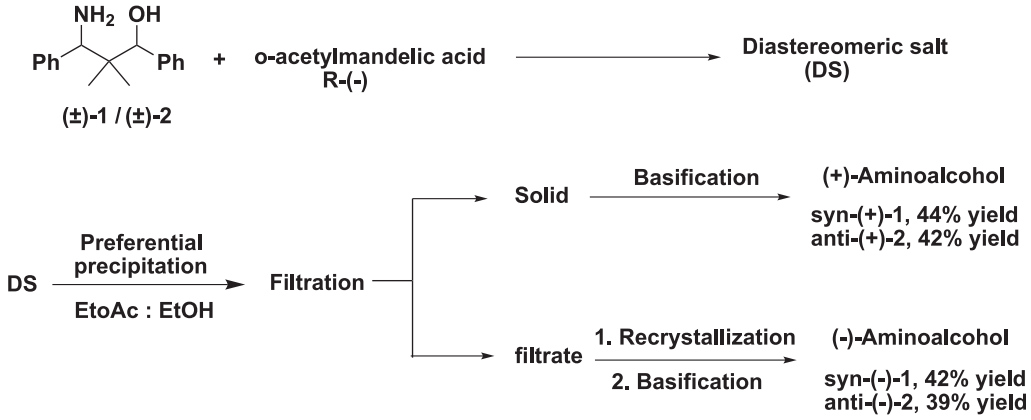


Scheme 1. Synthesis of compound **1**. Reagents and conditions: (a) LiO^{t}Bu, THF, 0 °C to rt, 74%; (b) $SOCl_2$, CH_2Cl_2, rt, 83%; (c) NaN_3, DMF, reflux, 83%; (d) KOH, MeOH; (e) H_2-Pd/C, MeOH, 90% (over two steps).



Scheme 2. Synthesis of compound **2**. Reagents and conditions: (a) $LiBH_4$, $TiCl_4$, 82%; (b) BzCl, Pyridine, CH_2Cl_2, rt, 71%; (c) $SOCl_2$, CH_2Cl_2, rt, 80%; (d) NaN_3, DMF, reflux, 78%; (e) KOH, MeOH; (f) H_2-Pd/C, MeOH, 90% (over two steps).

procedure. We examined various mono- as well as dibasic acids for the resolution of **1** and **2**. Unfortunately we could not separate the diastereomeric salts prepared from almost all commonly used chiral acids.[9] Either the resulting salts were not solid or did not crystallize with resolution. Finally the resolution could be accomplished through preferential precipitation of one of the salts obtained from *R*-(−)-*O*-acetyl mandelic acid. Unlike the regular method of crystallization which needs to be repeated at least twice to obtain complete separation of the mixture, this unusual procedure provides very high degree of separation in single step. The mixture of diastereomeric salts was prepared by dissolving the acid and the aminoalcohol in methanol, and evaporating to dryness to obtain a powdery mass. Crystallization of the residue from a mixture of EtOH/EtOAc did not result in the resolution. We then examined the possibility of preferential precipitation from a mixture of the solvents. Indeed, excellent separation of the two diastereomers was obtained when the diastereomeric mixture of salt was stirred with a combination of EtOH/EtOAc (~15:85). The precipitated solid after basification with aqueous ammonia gave the enantiopure (+)-**1** while (−)-**1** was recovered from the filtrate. The same protocol was also applied for the resolution of **2** (Scheme 3).



Scheme 3. Resolution of aminoalcohols.

Optical purity of all the four stereoisomers of 3-amino-2,2-dimethyl-1,3-diphenylpropan-1-ol was determined by chiral HPLC and found to be more than 99%. The absolute configuration was established by anomalous dispersion effects in X-ray diffraction measurements on the crystal of the hydrobromide salts. The ORTEP diagram for compound (−)-1 and (−)-2 are shown in Figure 1.[10]

A standard test for the stereodifferentiating efficacy of an aminoalcohol, is in its performance during the addition of diethylzinc to aldehyde[2,11,12] and oxazaborolidine-catalyzed reduction of ketone.[1d,13] We first examined the methyl derivatives of **1** and **2** as ligands for the addition of Et_2Zn. The derivatives **12**–**15** were obtained by judicious methylation as shown in Scheme 4.

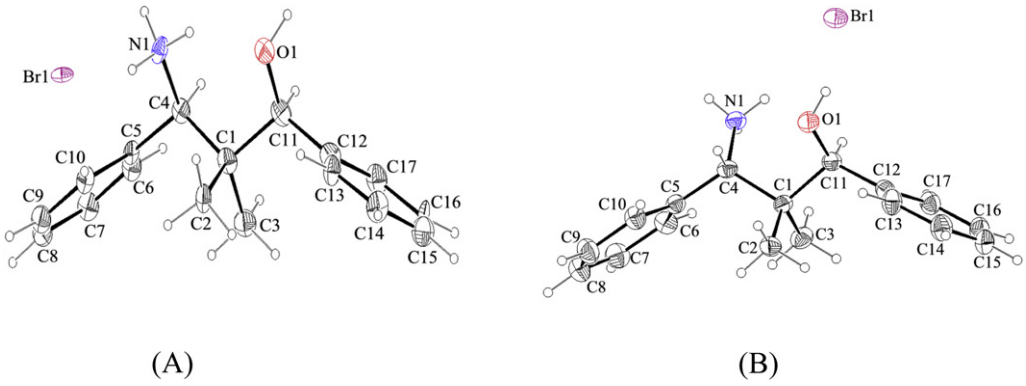
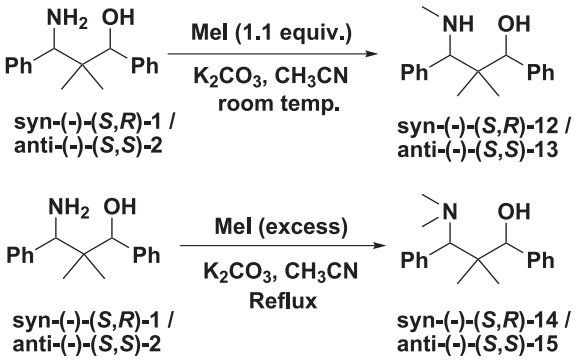


Figure 1. ORTEPs (A) and (B) of (−)-**1** and (−)-**2**, respectively, show the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% and 30% probability level for (−)-**1** and (−)-**2**, respectively and H atoms are shown as small spheres of arbitrary radii.

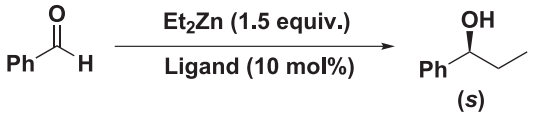


Scheme 4. Synthesis of ligands **12**–**15**.

4. Enantioselective addition of Et_2Zn to aldehydes

The test reaction involving Et_2Zn and benzaldehyde was carried out in toluene–hexane using 10 mol % of the ligand. The results are summarized in Table 1.

Table 1
Enantioselective addition of Et_2Zn to benzaldehyde



Entry	Ligand	Time (h)	Yield[a] (%)	er[b]
1	(−)-**12**	4	69	92:8
2	(−)-**13**	4	70	70:30
3	(−)-**14**	1	90	97:3
4	(−)-**15**	2	80	80:20
5[c]	(−)-**14**	2	86	97:3

[a] Isolated yield.
[b] Determined by chiral HPLC analysis.
[c] Reaction carried out at 0 °C.

As expected, better enantioselectivity was realized with dimethyl derivative than the monomethyl derivative. The highest degree of enantioselectivity (97:3 er) was observed with *syn N,N,*-dimethyl aminoalcohol (−)-**14** (entry 3). Unexpectedly, the corresponding *anti* derivative provided only moderate yield and moderate enantioselectivity. In the case of the ligand (−)-**14**, the reaction was complete within 1 h at room temperature with 100% conversion. It was found that lowering the temperature decreased the reaction rate, but yield and enantioselectivity were comparable (entries 3 and 5). The 6/4/4 tricyclic transition structure explains the observed enantioselectivity (Fig. 2).[14]

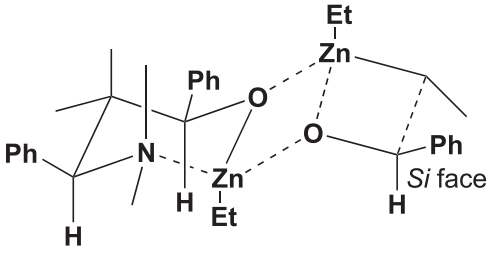


Figure 2. Transition state involving *syn*-(−)-**14**.

Several aromatic and aliphatic aldehydes were also examined for the reaction with ligand **14** (Table 2). High level of enantioselection were observed in all the cases. The sterically hindered α-napthaldehyde (entry 4) was alkylated with 97:3 er. Even the less reactive cyclohexanecarboxaldehyde (entry 6), was alkylated with excellent enantioselectivity and yield (96:4 er, 90% yield). However hydrocinnamaldehyde an aliphatic aldehyde (entry 7), provided moderate enantioselectivity although with excellent yield (88:12 er, 90% yield).

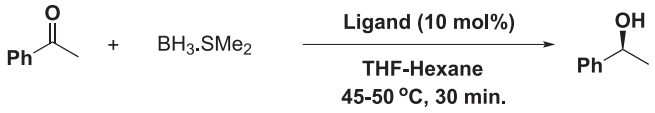
Table 2
Enantioselective addition of Et_2Zn to aldehydes catalyzed by (−)-14[a]

Entry	Aldehyde	Time (h)	Yield (%)	er	Configuration
1	*o*-Tolualdehyde	1.5	87	96:4[b]	s
2	*p*-Tolualdehyde	1.5	88	95:5[b]	s
3	*p*-Chlorobenzaldehyde	1	86	95:5[c]	s
4	α-Naphthaldehyde	2	88	97:3[b]	s
5	β-Naphthaldehyde	2	89	98:2[b]	s
6	Cyclohexanecarboxaldehyde	3	84	96:4[c]	s
7	Hydrocinnamaldehyde	2	90	88:12[b]	s

[a] All the reaction were conducted at room temperature using 10 mol % ligand and 1.5 equiv Et_2Zn.
[b] Determined by chiral HPLC analysis.
[c] Determined by chiral GC analysis.

5. Reduction of acetophenone

We also evaluated aminoalcohols (−)-**1**, (−)-**2**, (−)-**12**, and (−)-**13** as chiral ligands for the enantioselective reduction of acetophenone with borane. The oxazaborinane catalyst was prepared by treating the aminoalcohol with borane according to the procedure published by our group earlier.[13i] Baring aminoalcohol **1** (er 80:20), the results with other derivatives were disappointing (Scheme 5). However we do believe that optimization of the ligand-structure would provide better selectivities. It is obvious from the present work that one can access a wide range of 1,3-aminoalcohols by varying the substituents on aryl group as well as at the C2 position.



Scheme 5. Enantioselective reduction of acetophenone.

6. Conclusion

In conclusion, we have prepared and resolved all the stereoisomers of 3-amino-2,2-dimethyl-1,3-diphenylpropan-1-ol. The synthesis was accomplished in good yields using commercially available starting materials. Two typical model reactions were examined for the application in asymmetric catalysis. It was found that *syn*-1,3-amino alcohol provides good stereoselectivity for the addition of diethylzinc to aldehydes and only moderate enantioselectivity for reduction of ketone with borane. Other applications of these conformationally restricted 1,3-aminoalcohols are under investigation. We are optimistic that these molecules would prove to be valuable new additions in the repertoire of synthetic chemists.

7. Experimental section

7.1. General

All the solvents and reagents were purified and dried according to procedures given in D. D. Perrin's *purification of Laboratory Chemicals*.[15] Diethylzinc was purchased from Aldrich. All the aldehydes were freshly distilled prior to use. The reactions were monitored by TLC using silica gel 60 F_{254} precoated plates, and the products were purified by Column chromatography on silica gel (100–200 or 230–400 mesh). Melting points were recorded on Yamaco micro melting point apparatus and are uncorrected. Optical rotations were measured on Bellimheam+Standley ADP220 digital polarimeter. ^{1}H NMR spectra were recorded at 200 MHz with TMS as the internal standard. ^{13}C NMR spectra were recorded at 50 MHz with CDCl3 (δ=77) as the reference. Microanalytical data were obtained using a Carlo–Erba CHNS-0 EA 1108 elemental analyzer. Enantiomeric excess was determined using chiral columns on HPLC.

*7.1.1. anti-(±)-3-Hydroxy-2,2-dimethyl-1,3-diphenylpropyl benzoate (**3**).* A cooled solution of anhydrous *tert*-butanol (1.9 mL, 20 mmol) in 10 mL anhydrous THF was treated with ^{n}BuLi (20 mmol, 15.4 mL, 1.3 M solution in cyclohexane) followed by isobutyrophenone (3 mL, 20 mmol). The mixture was allowed to stir for 10 min. Benzaldehyde (5.1 mL, 50 mmol) dissolved in anhydrous THF (25 mL) was then added dropwise over a period of 30 min. The mixture was allowed to stir at room temperature for 16 h. The reaction mixture was quenched by the addition of 1 N HCl (30 mL) and product was extracted with ethyl acetate (100 mL×2). Combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (200–400 mesh) using ethyl acetate/petroleum ether as the eluent to obtain **3** as a white solid (5.3 g, 74%), >99:1 dr (by ^{1}H NMR), mp 138–139 °C; [Found: C, 80.13; H, 6.56. $C_{24}H_{24}O_3$ requires C, 79.97; H, 6.71%]; R_f (10% EtOAc/PE) 0.32; ν_{max} ($CHCl_3$): 3610, 1720 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) 7.26–8.17 (m, 15H), 6.37 (s, 1H), 4.76 (s, 1H), 2.16 (s, 1H), 0.87 (s, 3H), 0.81 (s, 3H); ^{13}C NMR (50.32 MHz, $CDCl_3$) 166.0, 141.1, 137.9, 133.2, 130.2, 129.7, 128.5, 128.2, 128.1, 127.8, 127.5, 127.3, 80.0, 76.9, 42.9, 19.2, 17.8.

*7.1.2. anti-(±)-3-Chloro-2,3-dimethyl-1,3-diphenylpropyl benzoate (**4**).* Compound **3** (7.2 g, 20 mmol) was dissolved in anhydrous CH_2Cl_2 (40 mL) and treated dropwise with thionyl chloride (2.9 mL, 40 mmol). The reaction was monitored by the evolution of gas (HCl and SO_2). After stirring for 24 h at room temperature, CH_2Cl_2 and excess thionyl chloride were evaporated under rotavapour. The residue was dissolved in CH_2Cl_2 (50 mL), washed with water, sodium bicarbonate, and brine. The solution was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by filtration column through a short column of silica gel (100–200 mesh) followed by crystallization from ethyl acetate/petroleum ether (1:9) to obtain **4** as a white solid (6.3 g, 83%), >99:1 dr (by ^{1}H NMR). Mp 167–168 °C; [Found: C, 75.99; H, 6.30. $C_{24}H_{23}ClO_2$ requires C, 76.08; H, 6.12%]; R_f (10% EtOAc/PE) 0.54; ν_{max} ($CHCl_3$): 3018, 1722, 1452 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) 7.29–8.17 (m, 15H), 6.33 (s, 1H), 5.25 (s, 1H), 0.97 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (50.32 MHz, $CDCl_3$) 164.9, 138.5, 137.7, 133.1, 130.2, 129.5, 129.3, 128.5, 128.0, 127.8, 79.8, 69.1, 43.7, 19.9, 18.4.

*7.1.3. syn-(±)-3-Azido-2,3-dimethyl-1,3-diphenylpropyl benzoate (**5**).* A mixture of chlorobenzoate **4** (7.58 g, 20 mmol), sodium azide (5.85 g, 90 mmol), and DMF (90 mL) was stirred under reflux for 3 days. The reaction mixture was cooled to room temperature, poured into 300 mL of ice water, and extracted with ether (200 mL×3). Combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (200–400 mesh) using ethyl acetate/petroleum ether as the eluent followed by crystallization to obtain **5** as a white solid (6.4 g, 83%), >99:1 dr (by ^{1}H NMR). Mp 145–146 °C; [Found: C, 74.48; H, 5.77; N, 10.61. $C_{24}H_{23}N_3O_2$ requires C, 74.78; H, 6.01; N, 10.90%]; R_f (10% EtOAc/PE) 0.54; ν_{max} ($CHCl_3$): 3018, 2104, 1720 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) 7.22–8.12 (m, 15H), 5.81 (s, 1H), 4.45 (s, 1H), 1.20 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (50.32 MHz, $CDCl_3$) 165.0, 137.4, 135.9, 133.1, 130.3, 129.5, 128.8, 128.5, 128.3, 128.0, 127.8, 79.8, 71.7, 42.8, 19.3, 19.1.

*7.1.4. syn-(±)-3-Azido-2,3-dimethyl-1,3-diphenylpropan-1-ol (**6**).* A mixture of **5** (7.7 g, 20 mmol) and KOH (3.36 g, 60 mmol) was stirred in methanol (80 mL) for 16 h at room temperature. Methanol was then removed on a rotary evaporator. Water was added and the reaction mixture was extracted with ether (30 mL×3). Combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (200–400 mesh) using ethyl acetate/petroleum ether as the eluent followed by crystallization from ethyl acetate/petroleum ether (1:9) to obtain **6** as a white solid (5.1 g, 90%), >99:1 dr (by ^{1}H NMR). Mp 145–146 °C; [Found: C, 72.34; H, 6.96; N, 15.29. $C_{17}H_{19}N_3O$ requires C, 72.57; H, 6.81; N, 14.94%]; R_f (10% EtOAc/PE) 0.42; ν_{max} ($CHCl_3$): 3608, 3018, 2104 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) 7.26–7.40 (m, 10H), 4.71 (s, 1H), 4.40 (s, 1H), 1.85 (s, 1H), 1.09 (s, 3H), 0.61 (s, 3H); ^{13}C NMR (50.32 MHz, $CDCl_3$) 141.2, 136.9, 128.9, 128.0, 127.9, 127.7, 127.6, 78.2, 72.7, 43.1, 19.1, 17.7.

*7.1.5. syn-(±)-3-Amino-2,3-dimethyl-1,3-diphenylpropan-1-ol (**1**).* A solution of **6** (2.81 g, 10 mmol) in methanol (25 mL) was hydrogenated at room temperature and at 50 psi pressure using 10% Pd/C (300 mg) for 1 h. Usual work-up provided (±)-3-amino-2,3-dimethyl-1,3-diphenylpropan-1-ol (**1**) as a white solid (2.56 g, ~100%), >99:1 dr (by ^{1}H NMR). Mp 168–170 °C; [Found: C, 79.95; H, 8.28; N, 5.27. $C_{17}H_{21}NO$ requires C, 79.96; H, 8.29; N, 5.49%]; R_f (40% MeOH/EtOAc) 0.45; ν_{max} ($CHCl_3$): 3388, 3018, 1215 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) 7.23–7.38 (m, 10H), 4.84 (s, 1H), 4.02 (s, 1H), 0.94 (s, 3H), 0.39 (s, 3H); ^{13}C NMR (50.32 MHz, $CDCl_3$) 143.5, 141.6, 128.4, 128.0, 127.5, 127.3, 127.2, 127.0, 84.9, 66.2, 41.1, 24.8, 11.8.

*7.1.5.1. Resolution of (±)-(**1**).* The aminoalcohol **1** (2.56 g, 10 mmol) and *R*-(−)- *O*-acetyl mandelic acid (1.94 g, 10 mmol) were dissolved in methanol (20 mL). The resulting clear solution was evaporated to dryness under reduced pressure. The salt was dissolved in minimum amount of hot ethanol (5 mL) and diluted with ethyl acetate (30 mL). The resulting solution was stirred at room

temperature for 1 h, to obtain one of the diastereomeric salts as white precipitate. The mixture was filtered to obtain solid salt (2 g, 44%), mp 196–197 °C, $[\alpha]_D^{26}$ −66 (*c*=1, MeOH). The second isomer of the salt was isolated from mother liquor by evaporation followed by recrystallization from ethanol: ethyl acetate (1:9), (1.9 g, 42%), mp 160–161 °C, $[\alpha]_D$ −42 (*c* 1, MeOH). Basification of the salts was carried out using aqueous NH_3 to provide the corresponding optically pure aminoalcohols. (+)-**1** Isomer of aminoalcohol was obtained from the precipitated salt while (−)-**1** isomer was isolated from the salt left in the filtrate.

(1*R*,3*S*)-(+)-**1**; 44% yield, mp 169–171 °C, $[\alpha]_D^{26}$ +42 (*c* 1, $CHCl_3$), >99:1 er (Kromasil-5-Amycoat column, 2-propanol/PE/TFA).

(1*S*,3*R*)-(−)-**1**; 42% yield, mp 170–171 °C, $[\alpha]_D^{26}$ −42 (*c* 1, $CHCl_3$), >99:1 er (Kromasil-5-Amycoat column, 2-propanol/PE/TFA).

*7.1.6. syn-(±)-3-Hydroxy-2,2-dimethyl-1,3-diphenylpropyl benzoate (**8**).* The diol **7** (as a mixture of *syn*/*anti* in 92:8, 6.4 g, 25 mmol) was dissolved in anhydrous CH_2Cl_2 (75 mL). To the stirred solution, pyridine (2 mL, 25 mmol) followed by benzoyl chloride (2.9 mL, 25 mmol) were added dropwise. It was then stirred for 16 h at room temperature. The reaction mixture was diluted with CH_2Cl_2 (100 mL) and washed with 1 N HCl, water, $NaHCO_3$, water, and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by 'flash chromatography' on silica gel (200–400 mesh) using ethyl acetate/petroleum ether as the eluent followed by crystallization from ethyl acetate/petroleum ether (1:9) to obtain **8** as a white solid (6.4 g, 71%), >99:1 dr (by ^1H NMR), mp 151–153 °C; [Found: C, 80.26; H, 6.38. $C_{24}H_{24}O_3$ requires C, 79.97; H, 6.71%]; R_f (10% EtOAc/PE) 0.32; ν_{max} ($CHCl_3$): 3610, 1720 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 7.26–8.11 (m, 15H), 6.10 (s, 1H), 4.49 (s, 1H), 2.00 (s, 1H), 1.19 (s, 3H), 0.84 (s, 3H); ^{13}C NMR (50.32 MHz, $CDCl_3$) 165.3, 141.2, 138.1, 132.9, 130.6, 129.6, 128.4, 127.9, 127.8, 127.8, 127.7, 127.7, 127.6, 80.3, 77.8, 43.1, 19.2, 18.0.

*7.1.7. syn-(±)-3-Chloro-2,3-dimethyl-1,3-diphenylpropyl benzoate (**9**).* The same procedure was followed as described for the compound **4**.

Yield 80%, >99:1 dr, mp 136–137 °C; [Found: C, 75.76; H, 6.33. $C_{24}H_{23}ClO_2$ requires C, 76.08; H, 6.12%]; R_f (10% EtOAc/PE) 0.54; ν_{max} ($CHCl_3$): 3018, 1722, 1452 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 7.27–8.12 (m, 15H), 5.91 (s, 1H), 4.84 (s, 1H), 1.35 (s, 3H), 0.95 (s, 3H); ^{13}C NMR (50.32 MHz, $CDCl_3$) 165.0, 138.0, 137.4, 133.2, 130.3, 129.0, 128.5, 128.2, 128.1, 128.0, 127.9, 127.8, 79.9, 69.7, 44.4, 19.8, 19.4.

*7.1.8. anti-(±)-3-Azido-2,3-dimethyl-1,3-diphenylpropyl benzoate (**10**).* The same procedure was followed as described for the compound **5**.

Yield 78%, >99:1 dr, mp 154–155 °C; [Found: C, 75.06; H, 5.76; N, 10.75. $C_{24}H_{23}N_3O_2$ requires C, 74.78; H, 6.01; N, 10.90%]; R_f (10% EtOAc/PE) 0.54; ν_{max} ($CHCl_3$): 3018, 2104, 1720 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 7.26–8.18 (m, 15H), 6.2 (s, 1H), 4.82 (s, 1H), 0.90 (s, 3H), 0.78 (s, 3H); ^{13}C NMR (50.32 MHz, $CDCl_3$) 165.1, 137.7, 136.6, 133.1, 130.3, 129.6, 129.0, 128.5, 128.1, 128.1, 128.0, 127.9, 79.4, 71.3, 42.2, 19.3, 18.5.

*7.1.9. anti-(±)-3-Azido-2,3-dimethyl-1,3-diphenylpropan-1-ol (**11**).* The same procedure was followed as described for the compound **6**.

Yield 90%, >99:1 dr, mp 135–136 °C; [Found: C, 72.63; H, 6.80; N, 15.20. $C_{17}H_{19}N_3O$ requires C, 72.57; H, 6.81; N, 14.94%]; R_f (10% EtOAc/PE) 0.42; ν_{max} ($CHCl_3$): 3608, 3018, 2104 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 7.26–7.38 (m, 10H), 4.97 (s, 1H, −OH), 4.88 (s, 1H), 1.92 (s, 1H), 0.72 (s, 3H), 0.68 (s, 3H); ^{13}C NMR (50.32 MHz, $CDCl_3$) 141.4, 137.0, 129.0, 128.0, 128.0, 127.9, 127.6, 127.4, 78.0, 71.7, 42.2, 19.3, 18.9.

*7.1.10. anti-(±)-3-Amino-2,3-dimethyl-1,3-diphenylpropan-1-ol (**2**).* The same procedure was followed as described for the compound **1**.

Yield ~100%, with >99:1 dr, mp 137–139 °C; [Found: 79.84; H, 8.18; N, 5.33. $C_{17}H_{21}NO$ requires C, 79.96; H, 8.29; N, 5.49%]; R_f (40% MeOH/EtOAc) 0.45; ν_{max} ($CHCl_3$): 3388, 3018, 1215 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 7.24–7.42 (m, 10H), 4.65 (s, 1H), 4.04 (s, 1H), 1.00 (s, 3H), 0.67 (s, 3H); ^{13}C NMR (50.32 MHz, $CDCl_3$) 141.7, 141.1, 128.2, 128.1, 127.6, 127.2, 126.8, 79.5, 65.9, 40.0, 23.6, 20.7.

*7.1.10.1. Resolution of (±)-(**2**).* The same procedure was followed as described for the resolution of (±)-**1**.

Precipitated salt 42% yield, mp 175–177 °C, $[\alpha]_D^{26}$ −60 (*c* 1, MeOH).

Salt from filtrate 39% yield, mp 160–162 °C, $[\alpha]_D^{26}$ −44 (*c* 1, MeOH).

Basification was carried out as described for above.

(1*R*,3*R*)-(+)-2; 42% yield, mp 142–143 °C, $[\alpha]_D^{26}$ +40 (*c* 1, $CHCl_3$), >99:1 er (Kromasil-5-Amycoat column, 2-propanol/PE/TFA).

(1*S*,3*S*)-(-)-2; 42% yield, mp 141–142 °C, $[\alpha]_D^{26}$ −40 (*c* 1, $CHCl_3$), >99:1 er (Kromasil-5-Amycoat column, 2-propanol/PE/TFA).

7.2. General procedure for the preparation of *N*-methyl -1,3-aminoalcohol

A suspension of **1** (1.28 g, 5 mmol), K_2CO_3 (1.04 g, 7.5 mmol), methyl iodide (0.78 g, 5.5 mmol) in acetonitrile (20 mL) was stirred at room temperature for 16 h. The reaction mixture was filtered and concentrated under reduced pressure. The residue was purified by 'flash chromatography' on silica gel (200–400 mesh) using ethyl acetate/petroleum ether as the eluent followed by crystallization from toluene.

*7.2.1. (1S,3R)-2,2-Dimethyl-3-(methylamino)-1,3-diphenylpropan-1-ol, (−)-**12**.* Yield 75%, mp 118–120 °C; [Found: C, 79.93; H, 8.44; N, 5.23. $C_{18}H_{23}NO$ requires C, 80.26; H, 8.61; N, 5.20%]; R_f (20% EtOAc/PE) 0.2; $[\alpha]_D^{26}$ −80 (*c* 1, $CHCl_3$); ν_{max} ($CHCl_3$): 3019, 1454 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 7.20–7.39 (m, 10H), 4.82 (s, 1H), 3.63 (s, 1H), 2.27 (s, 3H), 0.90 (s, 3H), 0.36 (s, 3H); ^{13}C NMR (50.32 MHz, $CDCl_3$) 142.2, 133.0, 131.2, 128.0, 127.6, 127.5, 127.4, 126.8, 84.0, 73.9, 43.6, 42.0, 26.1, 23.9.

*7.2.2. (1S,3S)-2,2-Dimethyl-3-(methylamino)-1,3-diphenylpropan-1-ol, (−)-**13**.* Yield 73%, mp 132–134 °C; [Found: C, 80.36; H, 8.77; N, 4.91. $C_{18}H_{23}NO$ requires C, 80.26; H, 8.61; N, 5.20%]; R_f (20% EtOAc/PE) 0.2; $[\alpha]_D^{26}$ −30 (*c* 1, $CHCl_3$). ν_{max} ($CHCl_3$): 3000, 1495 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 7.18–7.32 (m, 10H), 4.57 (*s*, 1H), 3.55 (s, 1H), 2.25 (s, 3H), 0.99 (s, 3H), 0.70 (s, 3H); ^{13}C NMR (50.32 MHz, $CDCl_3$) 141.5, 138.5, 128.4, 128.2, 127.5, 127.3, 127.1, 85.0, 75.4, 41.0, 34.0, 24.9, 12.4.

7.3. General procedure for the preparation of *N,N*-dimethyl -1,3-aminoalcohol

A suspension of **1** (1.28 g, 5 mmol), K_2CO_3 (2.08 g, 15 mmol), methyl iodide (1.78 g, 12.5 mmol) in acetonitrile (25 mL) was stirred under reflux temperature for 16 h. The product was isolated and purified as described above.

*7.3.1. (1S,3R)-2,2-Dimethyl-3-(dimethylamino)-1,3-diphenylpropan-1-ol, (−)-**14**.* Yield 76%, mp 106–107 °C; [Found: C, 80.63; H, 9.15; N, 4.84. $C_{19}H_{25}NO$ requires C, 80.52; H, 8.89; N, 4.94%]; R_f (20% EtOAc/PE) 0.24; $[\alpha]_D$ −42 (*c* 1, $CHCl_3$); ν_{max} ($CHCl_3$): 3016, 1465 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 7.26–7.39 (m, 10H), 4.80 (s, 1H), 3.75 (s, 1H), 2.35 (s, 6H), 1.27 (s, 3H), 0.37 (s, 3H); ^{13}C NMR (50.32 MHz, $CDCl_3$) 141.1, 133.0, 131.1, 128.5, 127.9, 127.7, 127.2, 127.0, 85.8, 81.1, 43.7, 42.1, 25.5, 15.3.

*7.3.2. (1S,3S)-2,2-Dimethyl-3-(dimethylamino)-1,3-diphenylpropan-1-ol, (−)-**15**.* Yield 75%, mp 116–118 °C; [Found: C, 80.35; H, 9.00; N, 4.76. $C_{19}H_{25}NO$ requires C, 80.52; H, 8.89; N, 4.94%]; R_f (20% EtOAc/PE) 0.24; $[\alpha]_D$ −102 (*c* 1, $CHCl_3$); ν_{max} ($CHCl_3$): 3000, 1451 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 7.14–7.43 (m, 10H), 4.67 (s,

1H), 3.56 (s, 1H), 2.35 (s, 3H), 1.57 (s, 3H), 0.48 (s, 3H);^{13}C NMR (50.32 MHz, $CDCl_3$) 141.1, 133.1, 131.1, 128.5, 127.8, 127.6, 127.1, 127.0, 86.1, 81.1, 43.7, 42.0, 26.4, 15.2.

7.4. General procedure for the enantioselective addition of Et_2Zn to aldehydes

The addition of Et_2Zn to PhCHO in the presence of (−)-**14** was carried out as described elsewhere[4i] to obtain (*S*)-(−)-1-phenyl-1-propanol, 87% yield; $[\alpha]_D$ −46.70 (*c* 5.1, $CHCl_3$) [lit.[16] $[\alpha]_D$ −45.45 (*c* 5.15, $CHCl_3$)].

7.5. General procedure for the enantioselective reduction of acetophenone

The reduction of acetophenone with $BH_3.SMe_2$ mediated by (−)-**1** was carried out as described elsewhere.[13i] to obtain (*S*)-(−)-L-phenyl ethanol; 86% yield; $[\alpha]_D$ −26.6 (*c* 3.3, MeOH) [lit.[13i] $[\alpha]_D$ +44.12 (*c* 3.0, MeOH)].

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2010.05.001.

References and notes

1. (a) *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; Seyden-Penne, J., Ed.; John Wiley & Sons: New York, NY, 1995; (b) Blaser, H. U. *Chem. Rev.* **1992**, *92*, 935–952; (c) Ager, D.; Prakash, I.; Schaad, D. *Chem. Rev.* **1996**, *96*, 835–875; (d) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551–5553.
2. Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757–824.
3. Lait, S. M.; Rankic, D. A.; Keay, B. A. *Chem. Rev.* **2007**, *107*, 767–796.
4. (a) Oppolzer, W.; Radinov, R. N. *Tetrahedron Lett.* **1988**, *29*, 5645–5648; (b) Cicchi, S.; Crea, S.; Goti, A.; Brandi, A. *Tetrahedron: Asymmetry* **1997**, *8*, 293–301; (c) Genov, M.; Kostova, K.; Dimitrov, V. *Tetrahedron: Asymmetry* **1997**, *8*, 1869–1876; (d) Cho, B. T.; Kim, N. *Tetrahedron Lett.* **1994**, *35*, 4115–4118; (e) Hulst, R.; Heres, H.; Fitzpatrick, K.; Peper, N.; Kellogg, R. M. *Tetrahedron: Asymmetry* **1996**, *7*, 2755–2760; (f) Xingshu, L.; Chi-hung, Y.; Albert, S. C. C.; Teng-Kuei, Y. *Tetrahedron: Asymmetry* **1999**, *10*, 759–763; (g) Panev, S.; Linden, A.; Dimitrov, V. *Tetrahedron: Asymmetry* **2001**, *12*, 1313–1321; (h) Dimitrov, V.; Dobrikov, G.; Genov, M. *Tetrahedron: Asymmetry* **2001**, *12*, 1323–1329; (i) Costa, V. E. U.; Oliveira, L. F. *Tetrahedron: Asymmetry* **2004**, *15*, 2583–2590; (j) Aoyama, T.; Yoshiyuki, H. *Synthesis* **2005**, 583–587; (k) Martins, J. E. D.; Clarissa, M. M. *Tetrahedron: Asymmetry* **2006**, *17*, 1817–1823; (l) Martinez, A. G.; Enrique, T. V. *Tetrahedron: Asymmetry* **2007**, *18*, 742–749.
5. Although different molecules, similar structures have been obtained as diastereomeric mixtures: Barluenga, J.; Jardon, J.; Gotor, V. *J. Chem. Res., Synop.* **1986**, 464.
6. (a) Paul, M. B.; Jared, T. S.; Woerpel, K. A. *J. Org. Chem.* **1997**, *62*, 5674–5675; (b) Cheryl, M. M.; Matthew, O. D.; Shih-Yuan, L.; Morken, J. P. *Org. Lett.* **1999**, *1*, 1427–1429; (c) Abu-Hasanayn, F.; Streitwieser, A. *J. Org. Chem.* **1998**, *63*, 2954–2960.
7. Maier, G.; Roth, V.; Schmitt, R. K. *Chem. Ber.* **1985**, *118*, 704–721.
8. For the preparation of 1,3-dikekone, see: Bhowmick, K. C.; Prasad, K. R. K.; Joshi, N. N. *Tetrahedron: Asymmetry* **2002**, *13*, 851–855.
9. Jacques, J.; Collet, A.; Wilen, S. H. *Enantiomers, Racemates, and Resolution*; Wiley: New York, NY, 1981.
10. The crystallographic data of compound (−)- **1** and (−)- 2 has been deposited with the Cambridge Crystallographic Data Center as deposition No. CCDC 765748 & 765749. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 union Road, Cambridge CB2 1EZ, UK [fax: +44 (1223) 336033; e-mail: deposit@ccdc.cam.ac.uk].
11. Oguni, N.; Omi, T. *Tetrahedron Lett.* **1984**, *25*, 2823–2824.
12. (a) Noyori, R.; Suga, S.; Kawai, K.; Okada, S.; Kitamura, M.; Oguni, N.; Hayashi, M.; Kaneko, T.; Matsuda, Y. *J. Organomet. Chem.* **1990**, *382*, 19–37; (b) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49–69; (c) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833–856; (d) Prasad, K. R. K.; Joshi, N. N. *J. Org. Chem.* **1997**, *62*, 3770–3771.
13. (a) Itsuno, S.; Nakano, M.; Miyazaki, K.; Masuda, H.; Ito, K.; Hirao, A.; Nakahama, S. *J. Chem. Soc., Perkin Trans. I* **1985**, 2039–2044; (b) Nishizawa, M.; Noyori, R. In *Comprehensive organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 8, p 139; (c) Bruner, H.; Zettlmeier, W. *Handbook of Enantioselective Catalysis*; VCH: Weinheim, 1993; (d) Singh, V. K. *Synthesis* **1992**, 605–617; (e) Wallabum, S.; Martens, J. *Tetrahedron: Asymmetry* **1992**, *3*, 1475–1504; (f) Deloux, L.; Srebnik, M. *Chem. Rev.* **1993**, *93*, 763–784; (g) Corey, E. J.; Azimioara, M.; Sarshar, S. *Tetrahedron Lett.* **1992**, *33*, 3429–3430; (h) Jones, D. K.; Liotta, D. C.; Shinkai, J.; Mathre, D. J. *J. Org. Chem.* **1993**, *58*, 799–801; (i) Prasad, K. R. K.; Joshi, N. N. *Tetrahedron: Asymmetry* **1996**, *7*, 3147–3152.
14. Panda, M.; Puay-Wah, P.; Kozlowski, M. C. *J. Org. Chem.* **2003**, *68*, 564–571.
15. Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*; Pergamon: Oxford, New York, NY, 1966.
16. Pickard, R. H; Kenyon, J. *J. Chem. Soc.* **1914**, 1115–1131.