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Syntheses and resolutions of new chiral biphenyl backbones: 2-amino-2′-hydroxy-6,6′-dimethyl-1,1′-biphenyl and 2-amino-2′-hydroxy-4,4′,6,6′-tetramethyl-1,1′-biphenyl

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Abstract—The new chiral backbones (*R*)-(+)- and *S*-(−)-2-amino-2′-hydroxy-6,6′-dimethyl-1,1′-biphenyl and (*R*)-(+)- and (*S*)-(−)-2-amino-2′-hydroxy-4,4′,6,6′- tetramethyl-1,1′-biphenyl were synthesized from *o*-methylaniline and 2,4-dimethyl-aniline respectively in seven steps. A new resolution method was developed to provide homochiral enantiomers (from diastereomeric salts) in reasonably high yields. The absolute configuration of the new biphenyls was confirmed by X-ray structural analysis.

1. Introduction

Asymmetric catalysis is currently one of the most attractive research areas in synthetic chemistry.[1] Within asymmetric catalysis, the discovery of new chiral ligands plays a crucial role in developing new efficient metal-catalyzed asymmetric transformations since the electronic and steric properties of the ligand are usually the decisive factors that can influence the reactivity and enantioselectivity of asymmetric reactions.[2] It is important to explore effective ligands with new chiral backbones for broad application in asymmetric catalysis. In the past decade, 1,1′-binaphthyls with different substituents at the 2,2′-positions, such as MOP[3] and NOBIN[4] have gained much attention. A number of chiral ligands derived from the above backbones have been developed for transition metal-catalyzed asymmetric reactions.[5,6] In contrast to the binaphthyl derivatives, non-C_2 symmetrical biphenyl analogues are relatively unexplored. Herein, we report the syntheses and resolutions of new chiral biphenyl backbones (+)-2-amino-2′-hydroxy-6,6′-dimethyl-1,1′-biphenyl (*R*)-**1a**, (−)-2-amino-2′-hydroxy-6,6′-dimethyl-1,1′-biphenyl (*S*)-**1a** from 2-methylaniline and (+)-2-amino- 2′-hydroxy-4,4′,6,6′-tetramethyl-1,1′-biphenyl (*R*)-**1b**, (−)-2-amino-2′-hydroxy-4,4′,6,6′-tetramethyl-1,1′-biphenyl (*S*)-**1b** from 2,4-dimethyl-aniline in seven steps.

2. Results and discussion

The biphenyl framework has certain unique characteristics, which allow one to make subtle alterations to its geometric, steric, and electronic properties. The substituents at the 6,6′-positions are deemed necessary to warrant sufficient thermal stability to thermal racemization.[7] In this regard, we have designed the new axially chiral biphenyl backbones (*R*)-**1a**, (*S*)-**1a** from 2-methylaniline and (*R*)-**1b**, (*S*)-**1b** from 2,4-dimethyl-aniline (Scheme 1).

2-Methyl-6-nitroaniline **3a** could be synthesized from 2-methylaniline **2a** via nitration and separated from the mixture of **3a** and 2-methyl-4-nitroaniline by steam distillation according to the literature report.[8] However, steam distillation cannot be easily scaled up in the laboratory, because **3a** is a structure which could form an intermolecular hydrogen bond, while 2-methyl-4-nitroaniline is not. We thus developed an effective separation method of **3a** and 2-methyl-4-nitroaniline. When the concentrated HCl solution of the mixture hydrochloric salts of **3a** and 2-methyl-4-nitroaniline was diluted with water, **3a** was precipitated as a solid in 60% yield after recrystallization, while the hydrochloric

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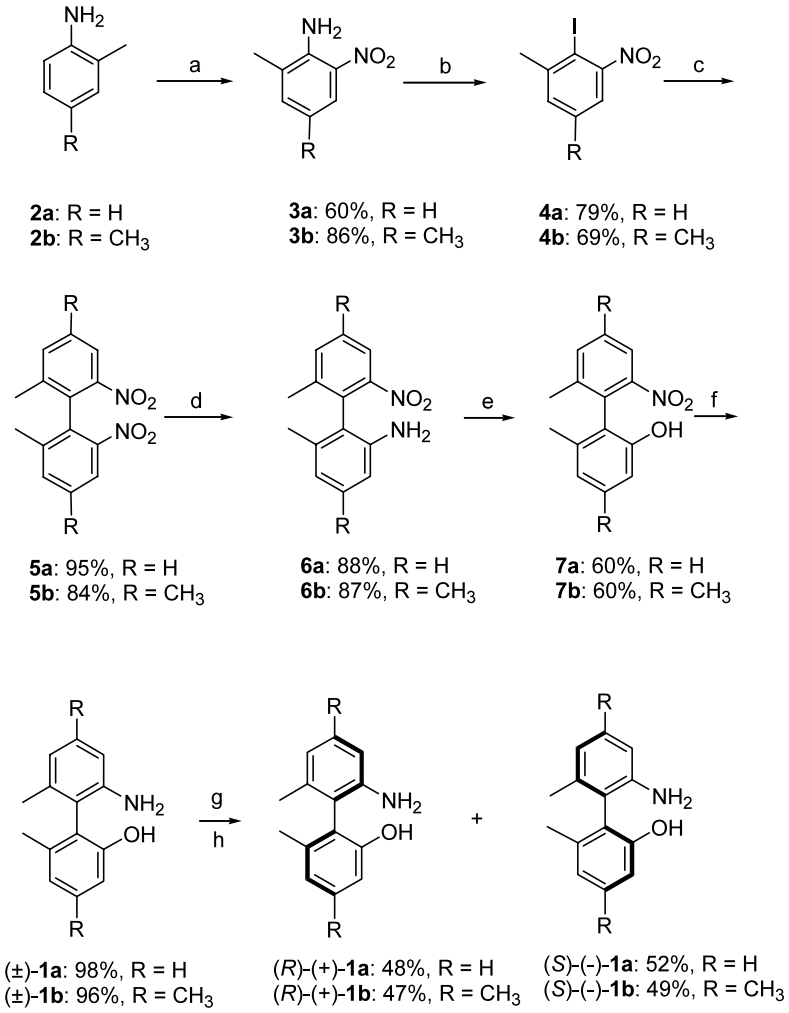
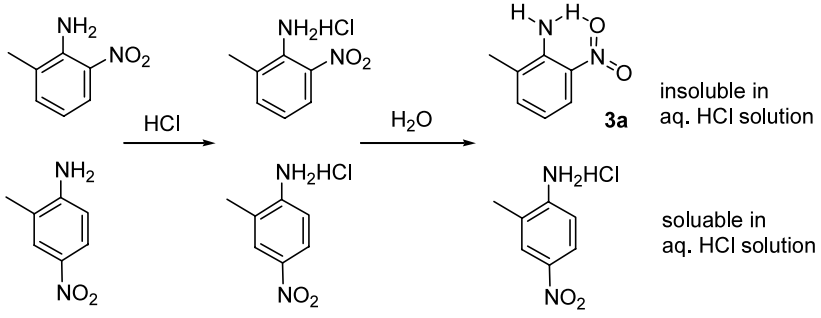
salt of 2-methyl-4-nitroaniline stayed in the dilute HCl solution (Scheme 2).

2,4-Dimethyl-6-nitroaniline **3b** was easily obtained by nitration from 2,4-dimethylaniline **2b**.[9] The yield of the reaction can be increased to 86% (Ref. 9: 75%) by using 96% instead of 65% nitric acid.

Compound **5** was prepared from **3** via diazotation/iodination and Ullmann coupling.[10] Dinitro derivative **5** was converted into nitroamine **6** through selective reduction.[11] Na_2S_2 was found to be superior to Na_2S_x as the reducing agent because it is difficult to remove the residual sulfur in the latter case, which would poison the Pd catalyst in the following step. Moreover,



Scheme 1. *Reagents and conditions*: (a) i. $(CH_3CO)_2O$, HNO_3, ii. HCl; (b) $NaNO_2$, H_2SO_4, KI; (c) DMF, Cu powder, reflux; (d) i. Na_2S_2; ii. HCl; (e) $NaNO_2$, H_2SO_4, H_2O; (f) H_2, Pd/C, EtOH; (g) treatment with (1*S*)-(+)-10-camphorsulfonic acid to form diastereomeric salts; (h) treatment with saturated aqueous $NaHCO_3$ solution to obtain (*R*)-isomer, then treated the residue with ammonia to obtain (*S*)-isomer.



Scheme 2.

the selectivity of the reduction of nitroamine **6** was very good even if excess Na_2S_2 was used. The crude product was purified by using hot aqueous HCl to remove the unreacted **5**, followed by recrystallization. The yield was 60% when one equivalent of reducing agent was used. The yield could be significantly improved to 85% by using two equivalents of the reducing agent and charging with three portions.

With diazotation/hydrolysis, nitroamine **6** was transferred into compound **7**. This transformation was complicated by lot of by-products. The crude hydrolysis product was then dissolved in concentrated NaOH/MeOH aqueous solution, some insoluble impurities were filtered off, and other organic impurities were removed by toluene extraction. The clean aqueous solution was treated with concentrated HCl solution and extracted with toluene. The pure compound **7** can be easily obtained by passing through a short silica-gel column. Compound **7** can be hydrogenated to give racemic **1** in almost quantitative yield.[11] It is of note that the procedures for **1a** and **1b** can be operated in a large scale.

After obtaining sufficient racemic **1**, we tried a number of resolution methods which had been successfully employed in the resolution of NOBIN.[12] The failure of the molecular crystal method[12c] was not expected, because Toda succeeded in using benzylcinchonidium chloride to resolve racemic 2,2′-dihydroxy-1,1′-binaphthyl (BINOL) and 2,2′-dihydroxy-4,4′,6,6′-tetramethyl-1,1′-biphenyl.[13] Ding also used this method to resolve NOBIN.[12c] Recently, Kocovský has successfully used this method to resolve *iso*-NOBIN.[12d] We believed this molecular crystal method would help us obtain both enantiomers. Unfortunately, no precipitate was observed under the same conditions that Toda made 2,2′-dihydroxy-4,4′,6,6′-tetramethyl-1,1′-biphenyl.[13b] Changing the solvent did not give any promising results.

We then tried (1*S*)-(+)-10-camphorsulfonic acid (CSA) as the resolving reagent and toluene/ethanol as the solvent for resolution, a mixture of diastereomeric salts was obtained in a high yield. When we used ammonia to liberate the diastereomeric salt (**1a**–CSA) to recover racemic **1a**, we found that the precipitate was optically active, which was confirmed by HPLC analysis. Considering that two salts may have different reaction rates with a base, we mixed the diastereomeric salts, ammonia and diethyl ether together at room temperature, then checked ether layer by HPLC with a chiral OD-H column. We found that the liberated **1a** in the ether layer had about 10% ee. We then optimized the resolution conditions, by changing the concentration of ammonia, temperature, and reaction time. 48 mg of (–)-**1a** with 39% ee was obtained when 0.20 g of **1a**–CSA was stirred in 11 ml of 1/10 ammonia solution at room temperature for 24 h. When a less basic saturated aqueous $NaHCO_3$ solution was employed, the selectivity was improved. However, the liberation rate in saturated aqueous $NaHCO_3$ solution was much slower. Because of the insolubility of diastereomeric salt in diethyl ether, **1a**–CSA salt was stirred in a saturated aqueous $NaHCO_3$ solution and diethyl ether at 25°C. The ee of **1a** in diethyl ether layer was determined by HPLC analysis. The results of ee versus time were summarized in Figure 1. The major isomer liberated by $NaHCO_3$ was (+)-**1a**.

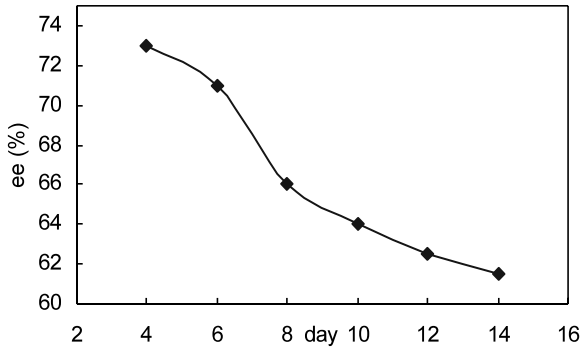
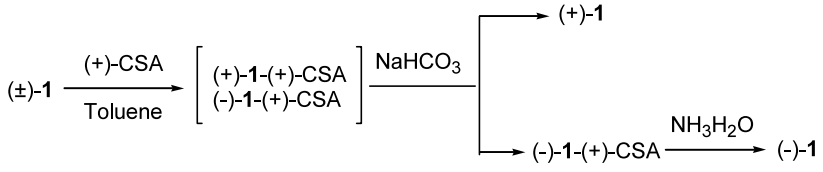


Figure 1. Ee of (*R*)-**1a** versus liberation time in satd aq. $NaHCO_3$ solution.

The actual resolution was carried out in the mixture of diastereomeric salt and saturated aqueous $NaHCO_3$ solution. Experimental data showed half amount of diastereomeric salt of **1a** liberated in 14 days. The first liberated **1a** was extracted with diethyl ether and after evaporation of the solvent, the residue was twice recrystallized with benzene to afford (*R*)-**1a** (>99% ee) in 48–50% yield. The residual $NaHCO_3$ solution was extracted with methylene chloride. After removal of methylene chloride under reduced pressure, and the residue was treated with concentrated ammonia at 50°C overnight. After cooling to room temperature, the mixture was extracted with diethyl ether, followed by the same procedure as described for (*R*)-**1a** to afford (*S*)-**1a** (>99% ee) in 48–52% yield (Scheme 3).

The absolute configuration of (–)-**1a** was confirmed by the X-ray structural analysis of the crystal of the amide arising from (–)-**1a** and (+)-10-camphorsulfonyl chloride.

The resolution procedure for **1b** was almost the same. The liberation time of half amount of diastereomeric salt was about 12 days for *R*-**1b**. The ee's of enan-



Scheme 3.

tiomers of *R*-**1b** and *S*-**1b** were above 99% after two recrystallizations from benzene.

3. Conclusion

We have optimized the process of the preparation of racemic **1a** and **1b** on a practical scale, and developed a novel resolution method of providing the enantiomers, which makes use of the difference of reaction rates of diastereomeric salts ((±)-**1**-CSA) with saturated aqueous $NaHCO_3$ solution. The new homochiral backbones (*R*)-(+)-2-amino-2′-hydroxy-6,6′-dimethyl-1,1′-biphenyl *R*-**1a** and (*S*)-(−)-2-amino-2′-hydroxy-6,6′-dimethyl-1,1′-biphenyl *S*-**1a**, (*R*)-(+)-2-amino-2′-hydroxy-4,4′,6,6′-tetramethyl-1,1′-biphenyl *R*-**1b** and (*S*)-(−)-2-amino-2′-hydroxy-4,4′,6,6′-tetramethyl-1,1′-biphenyl *S*-**1b** can be obtained in reasonable yields.

4. Experimental

4.1. Material and equipment

Melting points (uncorrected) were obtained on a Yazawa micro apparatus. Optical rotations were measured on a JASCO 1200 polarimeter. ^1H, ^{13}C NMR spectra were recorded on a Bruker DRX 400/Mercury-300 using $CDCl_3$ as the solvent with TMS as an internal reference. The FAB-HRMS spectra were measured by Beijing Institute of Chemistry, the Chinese Academy of Sciences. HPLC analysis of ee's of chiral backbones was performed on an Agilent 1100 with a Chiralcel OD-H column at 254 nm. X-Ray structural analysis was carried out in Shanghai Institute of Organic Chemistry, the Chinese Academy of Sciences. 2,4-Dimethylaniline, (1*S*)-CSA and (+)-10-camphorsulfonyl chloride were purchased from Acros. All solvents were treated with standard methods before using,

4.2. 2-Methyl-6-nitroaniline 3a

To a 1500 ml four-necked jacketed flask with a mechanic stirrer, a reflux condenser, a dropping funnel and a thermometer, was charged 650 ml of acetic anhydride. 107g of 2-methylaniline **2a** (1.0 mol) was slowly added through the funnel. After the addition was complete, the mixture was cooled to 12–13°C and stirred until the aniline was totally converted to amide. To the other dropping funnel was added 126 ml of 65% nitric acid (2.0 mol). After the mixture was cooled to the desired temperature, nitric acid was added dropwise to the cold slurry at a rate which the temperature could be controlled between 10–12°C in 1–2 h. After the addition was complete, stirring was kept for another half an hour. The mixture was poured into 3 L of ice-water with stirring. The resulting cream-colored solid was collected by suction, washed with ice water (3×500 ml). The wet product was charged into a 1000 ml round flask, then added 300 ml of concentrated HCl solution and heated to reflux until the solid was completely dissolved, kept the reflux another hour. The mixture was cooled to rt and added water with stirring until no precipitate observed. Compound **3a** was liberated as an orange solid and recrystallized from ethanol to afford 90.5 g (60%) of **3a** as needles: mp 95–96°C (Ref. 8: 94–95°C); ^1H NMR δ 2.23 (s, 3H), 6.12 (br, 2H), 6.62 (t, $J=7.8$ Hz, 1H), 7.26 (d, $J=6.8$ Hz, 1H), 8.02 (d, $J=8.8$ Hz, 1H).

4.3. 2,4-Dimethyl-6-nitroaniline 3b

To a 1000 ml jacketed flask, was added 500 ml of acetic anhydride. Under stirring, 75 g of 2,4-dimethylaniline **2b** (0.6 mol) was slowly added and then cooled to 5–7°C. To the mixture, 50 ml of 96% nitric acid ($d=1.5$, 1.2 mol) was carefully added in a period of 1 h, the temperature was strictly controlled below 7°C during the addition. After the addition was complete, kept stirring for another 10 min. The mixture was poured into 2 L of ice-water with stirring. The yellowish solid was collected by suction, and the wet product was added into a 1000 ml round flask and added 100 ml of 37% HCl solution and 200 ml of EtOH, then heated to reflux for 4 h. Distilled 150 ml of aqueous ethanol, poured the residue into 200 ml of ammonia and 1000 ml of water. The red–brown solid was collected by suction, washed with water (3×500 ml) and dried to afford 86.5 g of **3b** (86%), which could be directly used for next step by TLC. Analysis sample was recrystallized from ethanol to obtain a pale yellow crystal: mp: 69–71°C (Ref. 9: 68–70°C); ^1H NMR δ 2.22 (s, 3H), 2.24 (s, 3H), 6.05 (br. 2H), 7.13 (s, 1H), 7.82 (s, 1H).

4.4. 2-Methyl-6-nitro-iodobenzene 4a

To a 1500 ml four-necked flask, were added 90 g of **3a** (0.59 mol) and 600 ml of glacial acetic acid. The mixture was warmed to form a clear solution, then cooled to 15°C. A pre-cooled solution of 60 g of sodium nitrite (0.95 mol) in 330 ml of cold concentrated sulfuric acid was slowly added in a period of 1 h and stirred for another hour, then heated to 75°C, stirred for 2 h and cooled to 25°C. The mixture was poured into 2500 ml of ice-water with stirring then successively treated with 60 g of urea, aqueous KI solution (140 g/600 ml). After aqueous KI solution was completely added, lots of solid was precipitated, then added solid $NaHSO_3$ until the color of the mixture was obviously changed. The crude product was collected by suction and washed with water (3×200 ml). Recrystallized the wet solid from aqueous ethanol to afford 122 g (79%) of **4a**: mp 66–68°C (Ref. 10: 66–68°C); ^1H NMR δ 2.58 (s, 3H), 7.38 (m, 3H).

4.5. 2,4-Dimethyl-6-nitro-iodobenzene 4b

With the same method of synthesis of **4a**, from 86 g of **3b** (0.52 mol), obtained 113 g of crude product. Recrystallized from petroleum ether to afford 98.6 g of **4b** (69%) as orange crystals: mp 107–108°C (Ref. 9: 106–107°C); ^1H NMR δ 2.34 (s, 3H), 2.52 (s, 3H), 7.25 (s, 2H).

4.6. 2,2′-Dinitro-6,6′-dimethyl-1,1′-biphenyl 5a

To a 1000 ml four-necked flask, were charged 150 ml of dry DMF and 122 g of **4a** (0.46 mol). The resulting solution was heated to 100°C with stirring. About 120 g of fresh copper powder was added gradually. The mixture was heated to reflux for 6 h. Cool to rt. The residual copper powder was filtered off and the wet cake was washed with DMF. DMF was removed under reduced pressure. 400 ml of water was added to the residue to obtain an earth yellow solid. Recrystallized the wet solid from ethanol to afford 59.5 g (95%) of **5a** as pale yellow needles: mp 108–110°C (Ref. 10: 109–110°C); ^{1}H NMR δ 1.98 (s, 3H). 7.46 (t, J=8.0 Hz, 1H), 7.56 (d, J=7.6 Hz, 1H), 7.97 (d, J=8.0 Hz, 1H).

4.7. 2,2′-Dinitro-4,4′,6,6′-tetramethyl-1,1′-biphenyl 5b

With the same method of synthesis of **5a**, from 98.5 g of **4b** (0.36 mol), obtained 45.1g (84%) of **5b** as yellow crystals: mp 136–138°C (Ref. 11: 136–137°C); ^{1}H NMR δ 1.93 (s, 6H), 2.43 (s, 6H), 7.37 (s, 2H), 7.76 (s, 2H).

4.8. 2-Amino-2′-nitro-6,6′-dimethyl-1,1′-biphenyl 6a

40.8 g of **5a** (0.150 mol) was dissolved in 300 ml of boiling ethanol, then an Na_2S_2 solution prepared from 72.0 g of Na_2S $9H_2O$ (0.30 mol) and 9.6 g of sulfur (0.30 mol) in 250 ml of water was added in three portions at a rate of ca. 1.5 ml per minute via a pump. The mixture was kept refluxing for 3 h between the portions. After concentration to about 300 ml and cooling, the precipitate was extracted with toluene (2× 200 ml). Toluene was removed under reduced pressure, the residue was boiled with 350 ml of 2 M HCl solution, filtered off. The water insoluble solid was treated with 60 ml of 2 M HCl solution and filtered off. The combined aqueous filtrates were neutralized with ammonia. The solid was collected by suction and recrystallization with aqueous ethanol to afford 31.9 g (88%) of **6a**: mp: 124–126°C; ^{1}H NMR δ 1.86 (s, 3H), 2.09 (s, 3H), 3.25 (br, 2H), 6.64 (d, J=7.96 Hz, 1H), 6.70 (d, J=7.4 Hz, 1H), 7.09 (t, J=7.74 Hz, 1H), 7.43 (t, J=7.88 Hz, 1H), 7.56 (d, J=7.4 Hz, 1H), 7.73 (d, J=8.0 Hz, 1H); ^{13}C NMR 19.69, 19.46, 113.09, 120.20, 121.19, 121.31, 128.35, 128.78, 131.20, 134.23, 136.18, 140.36, 143.67, 150.72; FAB-HRMS (m/z): $(M+1)^+$ calcd for $C_{14}H_{15}N_2O_2$ 243.1128; found, 243.1125.

4.9. 2-Amino-2′-nitro-4,4′,6,6′-tetramethyl-1,1′-biphenyl 6b

With the same method as for the synthesis of **6a**, from 65.4 g of **5b** (0.218 mol), obtained 51.3 g (87%) of **6b** as orange crystals: mp 122–123°C (Ref. 11: 117–118°C); ^{1}H NMR δ 1.82 (s, 3H), 2.05 (s, 3H), 2.25 (s, 3H), 2.43 (s, 3H), 3.30 (br, 2H), 6.45 (s, 1H), 6.51 (s, 1H), 7.36 (s, 1H), 7.51 (s, 1H).

4.10. 2-Hydroxy-2′-nitro-6,6′-dimethyl-1,1′-biphenyl 7a

To a suspension of 42.0 g of **6a** (0.17 mol) and 12 ml of 37% HCl solution and 88 ml of EtOH, was added 16.3 g of $NaNO_2$ (0.24 mol) in 20 ml water, kept the mixture temperature below 0°C in an ice bath. When the addition was complete, the mixture was stirred for another hour at 0°C. The resulting dark red diazonium-salt solution was added dropwise to a boiling mixture of 600 ml of 15% of H_2SO_4 and 250 ml of toluene. When gaseous N_2 was no longer given off, the mixture was cooled to rt. Toluene layer was separated, the aqueous layer was extracted with toluene (3×200 ml). After evaporation of toluene under reduced pressure, the residue was treated with 75 ml of 40% NaOH and 25 ml of MeOH, then filtered off. The filtrate was extracted with toluene (3×20 ml). The aqueous layer was acidified with concentrated HCl. The resulting precipitate was extracted with toluene (5×50 ml). The combined toluene solutions were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by a silica gel column (petroleum ether/EtOAc: 30/1) and recrystallized from methylene chloride/petroleum ether to afford 26 g of **7a** (60%): mp 82–84°C; ^{1}H NMR δ 1.90 (s, 3H), 2.06 (s, 3H), 4.71 (br, 1H), 6.74 (d, J=8.0 Hz, 1H), 6.85 (d, J=7.6 Hz, 1H), 7.16 (t, J=8.0 Hz, 1H), 7.43 (t, J=7.8 Hz, 1H), 7.55 (d, J=7.6 Hz, 1H), 7.75 (d, J=8.0 Hz, 1H); ^{13}C NMR 19.52, 19.73, 113.23, 121.50, 122.55, 128.66, 129.23, 129.78, 134.36, 137.07, 140.44, 150.72, 152.32; FAB-HRMS (m/z): $(M+1)^+$ calcd for $C_{14}H_{14}NO_3$ 244.0968; found, 244.0966.

4.11. 2-Hydroxy-2′-nitro-4,4′,6,6′-tetramethyl-1,1′-biphenyl 7b

With the same method as for the synthesis of **7a**, from 30.0g of **6b** (0.11 mol), obtained 18.0 g (60%) of **7b** as pale yellow crystals: mp 127–128°C; ^{1}H NMR δ 1.88 (s, 3H), 2.02 (s, 3H), 2.29 (s, 3H), 2.43 (s, 3H), 4.44 (br. 2H), 6.60 (s, 1H), 6.67 (s, 1H), 7.35 (s, 1H), 7.53 (s, 1H); ^{13}C NMR 19.72, 19.94, 21.19, 21.46, 114.12, 119.72, 121.96, 123.64, 126.77, 129.23, 135.11, 137.07, 139.23, 139.41, 140.58, 152.30, 152.62; FAB-HRMS (m/z): $(M+1)^+$ calcd for $C_{16}H_{18}NO_3$ 272.1281; found, 272.1284.

4.12. (±)-2-Amino-2′-hydroxy-6,6′-dimethyl-1,1′-biphenyl (±)-1a

22.0 g of racemic **1a** was obtained via catalytic hydrogenation of 26.0 g (98%, recrystallized with EtOH) of **7a** (0.21 mol) over 10% Pd/C in ethanol according to the literature report.[11] Mp 162–164°C; ^{1}H NMR δ 1.94 (s, 3H), 2.01 (s, 3H), 3.46 (br, 2H), 4.93 (br, 1H), 6.64 (d, J=7.92 Hz, 1H), 6.73 (d, J=7.52 Hz, 1H), 6.89–6.85 (m, 2H), 7.11 (t, J=7.78 Hz, 1H), 7.22 (t, J=7.84 Hz, 1H); ^{13}C NMR 19.31, 19.65, 112.79, 112.93, 118.60, 120.27, 122.25, 122.72, 129.05, 129.36, 138.23, 138.77, 145.02, 153.08; FAB-HRMS (m/z): $(M+1)^+$ calcd for $C_{14}H_{16}NO$ 214.1226; found, 214.1228. HPLC analysis condition for (±)-**1a**: Chiralcel OD-H, 80/20 hexanes/*i*-PrOH, 0.7 ml/min, 25°C, retention time: $t_R(S)$=8.15 min; $t_R(R)$=11.03 min.

4.13. (±)-2-Amino-2′-hydroxy-4,4′,6,6′-tetramethyl-1,1′-biphenyl (±)-1b

With the same procedure, from 3.60 g of **7b** (13.3 mmol), obtained 3.07 g (96%) of (*RS*)-**1b** as white crystals: mp 178–180°C; ^{1}H NMR δ 1.92 (s, 3H), 1.98 (s, 3H), 2.23 (s, 3H), 2.32 (s, 3H), 3.43 (br, 2H), 4.78 (s, 1H), 6.49 (s, 1H), 6.57 (s, 1H), 6.70 (s, 1H), 6.71 (s, 1H); ^{13}C NMR 19.56, 19.90, 21.56, 113.45, 113.84, 115.82, 119.96, 121.60, 123.41, 138.34, 139.01, 139.20, 139.41, 145.40, 153.29; FAB-HRMS (*m*/*z*): $(M+1)^+$ calcd for $C_{16}H_{20}NO$ 242.1539; found, 242.1532. HPLC condition for (±)-**1b**: Chiralcel OD-H, 80/20 hexanes/*i*-PrOH, 0.7 ml/min, 25°C, retention time: $t_R(S)=6.64$ min; $t_R(R)=8.99$ min.

4.14. Diastereomeric salt of 1a–CSA

To a 250 ml of flask, 5.01 g of racemic **1a** (23.5 mmol), 5.90 g of CSA (25.4 mmol) and 80 ml of toluene were added. The mixture was stirred at 90°C, the white precipitate appeared after half an hour, and stirring was continued overnight. The mixture was cooled down to rt, filtered off, the solid washed with toluene (2×20 ml), and dried to afford 9.90 g (94%) of white solid as the diastereomeric salt.

4.14.1. (*R*)-(+)-1a. To a 1000 ml flask, 9.90 g of diastereomeric salt and 500 ml of saturated aqueous $NaHCO_3$ solution were added. The solution was stirred for 14 days at 25°C. The mixture was transferred into a 1000 ml separation funnel. The liberated **1a** was extracted with diethyl ether (3×80 ml). The combined ether layers were washed with 50 ml of water, dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to afford 2.35 g of reddish solid (61.5% ee by HPLC analysis). Recrystallization twice from benzene (80 ml) to afford 1.20 g (48%) of white solid as *R*-(+)-**1a**, mp: 192–194°C; $[\alpha]_D^{24}$ 73.8 (*c* 0.5, $CHCl_3$), >99% ee ($t_R(R)=11.02$ min).

4.14.2. (*S*)-(−)-1a. The residual aqueous $NaHCO_3$ layer was then extracted with methylene chloride (3×80 ml). Combined methylene chloride layers and evaporated the solvent, added 80 ml of concentrated ammonia to the residue. Heated up to 50°C and stirred overnight, then cooled to rt. The mixture was extracted with diethyl ether (3×80 ml). The combined ether layers were washed with 50 ml of water, dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to afford 2.40 g of reddish solid (66.5% ee). Recrystallization twice from benzene to afford 1.30 g (52%) of white solid as *S*-(−)-**1a**, mp: 192–194°C; $[\alpha]_D^{24}$ −74.7 (*c* 0.5, $CHCl_3$), >99% ee ($t_R(S)=8.17$ min).

4.15. (−)-(*S*)-2-((*D*)-10-Camphorsulfonyl amido)-2′-hydroxy-6,6′-dimethyl-1,1′-diphenyl

To a solution of 0.20 g of (−)-**1a** (0.94 mmol) and 0.282 g of *D*-(+)-10-camphor sulfonyl chloride (1.12 mmol) in 20 ml of methylene chloride, was added 0.5 ml of triethylamine via syringe. The solution was stirred at 10°C for 3 h, then diluted with 10 ml of 5% HCl solution. The mixture was extracted with diethyl ether (2×10 ml). The combined organic layers were washed with brine (10 ml), dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel to afford 0.38 g of amide (94.7%). The analysis sample was recrystallized from hexanes. Mp: 102–104°C. $[\alpha]_D^{12}$ −14.5 (*c* 0.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 0.73 (s, 3H), 0.91 (s, 3H), 1.34–1.38 (m, 1H), 1.48–1.53 (m, 1H), 1.85–1.90 (m, 2H), 1.92–1.97 (m, 4H), 2.04 (t, $J=4.4$ Hz, 1H), 2.11 (s, 3H), 2.17–2.21 (m, 1H), 2.28–2.35 (m, 1H), 2.57 (d, $J=14.8$ Hz, 1H), 3.27 (d, $J=14.8$ Hz), 4.38 (br, 2H), 6.68–6.78 (m, 2H), 7.07–7.12 (m, 1H), 7.26–7.35 (m, 3H); ^{13}C NMR 19.41, 19.50, 19.90, 24.75, 26.83, 42.35, 42.65, 47.84, 48.20, 57.59, 113.90, 121.05, 122.12, 128.81, 128.94, 129.01, 130.25, 137.81, 140.03, 142.80, 147.26, 213.67. X-Ray structural analysis, see Fig. 2.

4.16. Diastereomeric salt of 1b–CSA

To a 250 ml of flask, were added 5.00 g of racemic **1b** (20.7 mmol), 5.30 g of CSA (22.8 mmol) and 80 ml of toluene. The mixture was stirred at 95°C overnight, cooled down to rt, as the white precipitate collected by suction, washed with toluene (2×20 ml) and dried to afford 9.25 g (94%) of white solid as the diastereomeric salt **1b**–CSA.

4.16.1. (*R*)-(+)-1b. To a 1000 ml flask, were added 9.25 g of **1b**–CSA and 500 ml of saturated aqueous $NaHCO_3$ solution. The solution was stirred for 12 days at 25°C. The mixture was transferred into a 1000 ml separation funnel. The liberated **1b** was extracted with diethyl ether (3×100 ml). The combined ether layers were washed with 50 ml of water, dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to afford 2.32 g of yellowish solid (61.9% ee). Recrystallization twice from benzene to afford 1.18 g (47%) of white solid as (*R*)-(+)-**1b**, mp: 210–212°C; $[\alpha]_D^{24}$ 59.5 (*c* 0.5, $CHCl_3$), >99% ee ($t_R(R)=8.99$ min).

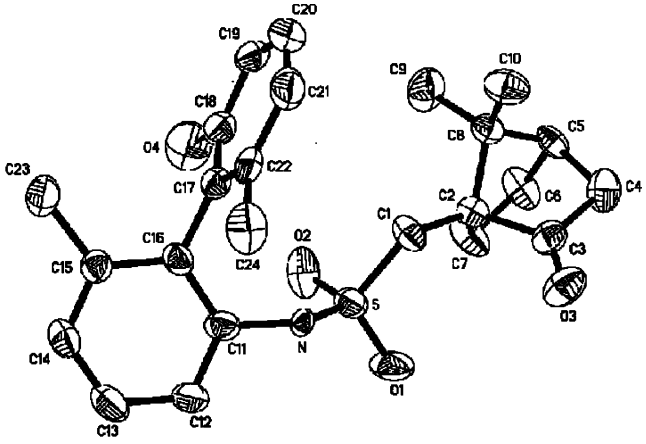


Figure 2. X-Ray structural analysis of 2-(*D*-(+)-10-camphorsulfonyl amido)-2′-hydroxy-6,6′-dimethyl-1,1′-diphenyl (hydrogen atoms omitted).

4.16.2. (*S*)-(−)-1b. The residual aqueous $NaHCO_3$ layer was then extracted with methylene chloride (3×80 ml). After evaporation of the solvent and addition of 250 ml of concentrated ammonia to the residue, it was heated to 50°C and stirred overnight, then cooled to rt. The mixture was extracted with methylene chloride (3×80 ml). The combined organic layers were washed with 50 ml of water, dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure afforded 2.26 g of yellowish solid (67.7% ee). Recrystallization twice from benzene afforded 1.23 g (49%) of white solid as (*S*)-(−)-**1b**, mp: 210–212°C; $[\alpha]_D^{24}$ −58.7 (*c* 0.5, $CHCl_3$), >99% ee ($t_R(S) = 6.60$ min).

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