Synthesis of Novel Chiral Biphenylamine Ligand 6,6′-Dimethoxy-2,2′-diaminobiphenyl

CHEN, Yi-Xin*,[a](陈亿新) LI, Yue-Ming[b](李月明) LAM, Kim-Hung[b](林剑虹)
CHAN, Albers S. C.*,[b](陈新滋)
[a]*Department of Chemistry, Guangzhou University, Guangzhou, Guangdong 510405, China*
[b]*Open Laboratory of Chirotechnology and Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hung Hom, Kowloon, Hong Kong, China*

A new chiral ligand 6,6′-dimethoxy-2,2′-diaminobiphenyl was successfully prepared from 3-nitrophenol via iodination, Ullmann coupling, and reduction. The resolving reagent (2*R*, 3*R*)- or (2*S*,3*S*)-2,3-di(phenylaminocarbonyl) tartaric acid was prepared from commercially available tartaric acid in large scale and was used to resolve the racemic 6,6′-dimethoxy-2,2′-diaminobiphenyl. The chiral 6,6′- dimethoxy-2,2′-diaminobiphenyl obtained was proved to be enantiomerically pure.

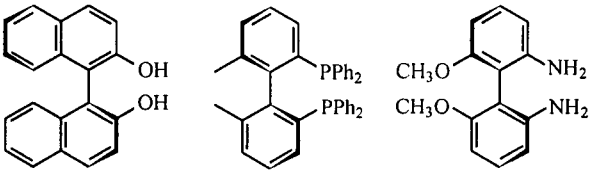
Keyword 6, 6′-Dimethoxy-2, 2′-diaminobiphenyl, chiral, synthesis, resolution

Introduction

The C_2-symmetric biaryl compounds bearing diphosphine or diol functionalities such as BINAP, BINOL and their analogues have shown to be highly effective ligands for catalytic asymmetric reactions.[1] The success of the binaphthyl family chiral ligands such as BINAP, and BINOL originates from the putatively highly skewed and relatively rigid structure when forming complexes with transition metals. Furthermore, a molecule with C_2-symmetric axis may reduce the possibility of competing diastereomeric transition states. To this end, a large number of chiral ligands bearing C_2-symmetry have been prepared and used for asymmetric synthesis of optically active compounds.[2]

2,2′-Dihydroxy-1,1′-binaphthyl [BINOL, **1**] has been widely used as a chiral ligand in stoichiometric as well as catalytic asymmetric reactions,[3] and a variety of methods have been reported for the preparation of enantiomerically pure binaphthyl ligands.[4] Chiral axial biphenyl derivatives, in contrast to their binaphthyl counterparts, have attracted yet much less attention. The optically active diphosphine [BIPHEMP, **2**] bearing biphenyl moiety was reported to be effective in asymmetric catalysis.[5] Recently, we reported the synthesis of an enantiomerically pure mannitiol derivative [DIMOP][6] and biquinoline derivative [BIQOL].[7] Herein, we report the synthesis of a new, enantiomerically pure biphenyl derivative 6,6′-dimethoxy-2,2′-diamino biphenyl (**3**) (Scheme 1).

Scheme 1



1 **2** **3**

Biphenyl ligands also have their own uniqueness: since the biphenyl group is relatively less rigid as compared with its binaphthyl counterpart, such structure may offer a special feature by forming a more flexible transition state which will allow the optimal orientation of sub-

* E-mail: y.xin.chen@163.net
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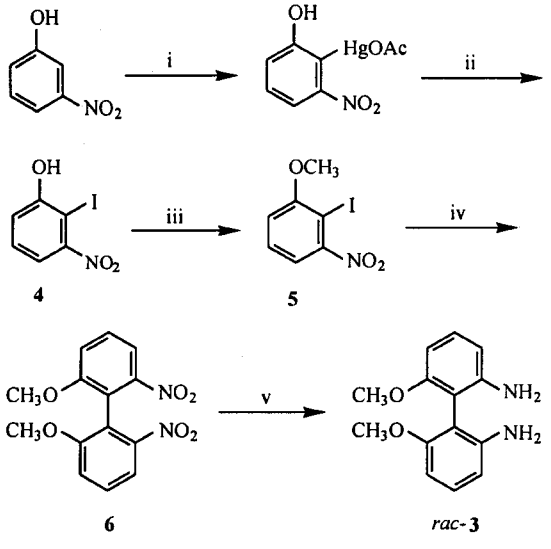
strates on the catalyst and thus enhances the rate and stereoselectivity of the reaction.[8] In addition, the phenyl group may be easily functionalized to obtain chiral ligands with variable geometries, steric hindrance and electronic properties. For instance, bridging the 6,6′-position, through a 7- or 8-membered ring would hold the dihedral angle within a limited range, thus restricting torsional mobility and introducing additional rigidity.[9] Taking these advantages into consideration, we designed a new chiral amino biphenyl ligand for a series of asymmetric catalytic reactions.

Results and discussion

Synthesis of racemic 6, 6′-*dimethoxy*-2, 2′-*diaminobiphenyl*

The first synthesis of the optically active biphenyl derivatives (BIPHEMP, **2**) via the resolution of diphosphine was developed by Otsuka,[10] and Roberts and Wild.[11] In this study we intended to improve the synthesis of enantiomerically pure diaminobiphenyl compound **3**. The racemic biphenyldiamine can be easily prepared from 3-nitrophenol. 2-Iodo-3-nitrophenol (**4**) was prepared through mercuration of 3-nitrophenol followed by replacement of the acetoxymercuric group with iodine. Racemic 6,6′-dimethoxy- 2,2′-diaminobiphenyl (**3**) was then synthesized by Ullmann coupling of 2-iodo-3-nitroanisol (**5**) (obtained according to Scheme 2) followed by catalytic reduction of the nitro groups. These steps complete the synthesis of racemic **3** in high yields.

Scheme 2



i, $Hg(OAc)_2/H_2O$, 100℃, 30 min. 99% yield; ii, 10% KI, 10% KI·K_2, 1 h, 96% yield; iii, CH_3I, acetone/K_2CO_3, reflux, 48 h, 92% yield; iv, Cu, DMF, 140℃, 4 h, 78.3% yield; v, 200 psi H_2, 10% Pd/C, 2 h, 99% yield.

Synthesis of 2,3-*di*(*phenylaminocarbonyl*)*tartaric acid* (*resolving reagent*)

The resolving reagent **9** was prepared from commercially available tartaric acid in good overall yield (Scheme 3). Refluxing a benzene solution of (*S*,*S*)- or (*R*,*R*)-tartaric acid with benzyl alcohol in the presence of *p*-toluenesulfonic acid afforded dibenzyl tartrate **7** in high yield. Dibenzyl-2, 3-di(phenylaminocarbonyl) tartrate **8** was then obtained by isocyanation of **7** with phenyl isocyanate using triethylamine as catalyst. After refluxing the reaction mixture in benzene for 48 h, the crude product was collected and recrystallized from ethyl acetate/hexane to give the product in 76% yield. The resolving reagent (*S*,*S*)- or (*R*,*R*)-**9** was finally obtained in 99% yield via hydrogenolysis of **8** using 10% Pd/C and 200 psi of hydrogen for 3 h. This procedure is simple and easy for large scale preparation (Scheme 3).

Resolution of 6,6′-*dimethoxy*-2,2′-*diaminobiphenyl*

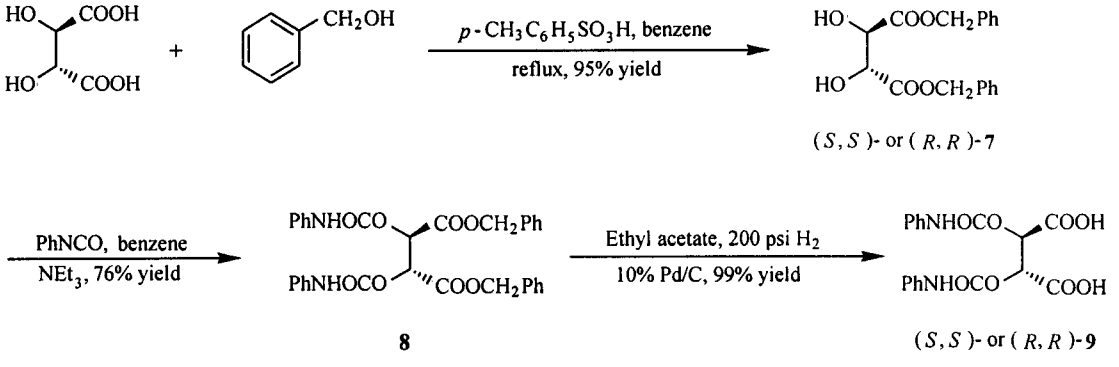
Although the racemic analogous of diphenyl derivatives were first prepared by Baker in 1958,[12] it was only until 1996 that the direct resolution of the diphosphine bearing biphenyl moiety was successfully achieved by Cereghetti.[13] The resolving reagent (*S*,*S*)- or (*R*,*R*)-2,3-di(phenylaminocarbonyl) tartaric acid (**9**) has recently been developed for the resolution of racemic diphosphine oxides.[14] Using this resolving reagent, an exceptionally efficient resolution of our racemic diamine bearing biphenyl moiety was obtained. The resolution procedure is illustrated in Scheme 4.

The resolution of *rac*.-**3** with resolving reagent **9** is remarkably efficient and highly selective. Firstly, the less soluble (*S*)-**3**/(*S*,*S*)-**9** was crystallized in 82% yield from ethyl acetate. To achieve high optical purities, it was proved necessary to repeatedly recrystallize the tartatic acid derivative (1∶1 salts of diamine **3** and resolving reagent **9** to ^1H NMR measurements). A sam-

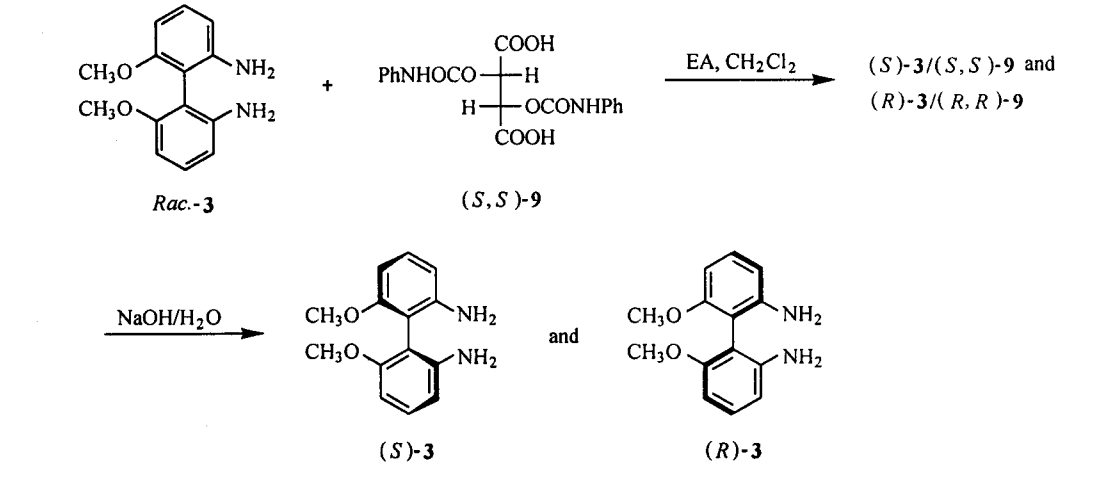
ple of (*S*)-**3**/(*S*,*S*)-**9** (1∶1) showed $[\alpha]_D^{20} = +49.8$ (*C* = 1, CH_2Cl_2). The more soluble (*R*)-**3**/(*S*, *S*)-**9** associate crystallized rather sluggishly from the mother liquid. The optically active diamine (*S*)- or (*R*)-**3** was liberated from the corresponding (*S*)-**3**/(*S*, *S*)-**9** or (*R*)-**3**/(*R*, *R*)-**9** associate quantitatively by treatment with diluted NaOH. Optical purities of the resolved diamines **3** were checked by HPLC analysis with a CHIRALCEL OD column. The enantiomeric excess of (*S*)-**3** was found to be 99.0%, $[\alpha]_D^{20} = -32.9$ (*C* = 1, $CHCl_3$). The resolution of *rac*.-**3** could also be achieved via CHIRALCHL OD preparative column eluted with a mixture of hexane and isopropanol, but only on a limited scale.

In conclusion, we have designed and synthesized a novel chiral diamino biphenyl ligand, and have successfully resolved the compound in its (*R*)- and (*S*)-form. The application of this novel chiral ligand in asymmetric catalytic reactions is in good process, and the results will be reported elsewhere in due course.

Scheme 3



Scheme 4



Experimental

General procedure

All reactions were carried out under inert atmosphere, and the commercial reagents were used as received without further purification. All solvents used were dried with standard and published methods and distilled before use. NMR spectra were recorded on a Bruker Dpx-400 spectrometer. Mass analyses were performed by a Model Mat 95 ST. Optical rotations were measured on a Perkin-Elmer Model 341 polarimeter. Melting points were determined using an Electrothermal 9100 apparatus in capillaries sealed under nitrogen. GLC and HPLC analyses were performed using a Hewlett-Packard Model HP5890 series II GC and a Waters 600E.

2-Iodo-3-nitrophenol (**4**)

Compound **4** was prepared according to the method of Wawzonek, *et al.*[15] with our modification. Yield: 96%, mp: 121—123℃.

2-Iodo-3-nitoranisol (**5**)

A dried 500 mL flask with a magnetic stirring bar was charged with 2-iodo-3-nitro-phenol (**4**) (16 g, 0.06 mol), iodomethane (25.4 g, 0.2 mol), anhydrous K_2CO_3 (9.6 g) and 300 mL of dried acetone. The mixture was refluxed for 48 h with stirring. The solvent was evaporated under reduced pressure and the reaction mixture was poured into 150 mL of water, and then extracted with ethyl acetate (30 mL × 2). The combined organic layer was washed with 10% NaOH and brine, and dried with anhydrous $MgSO_4$. The solvent was then evaporated *in vacuo*. The crude product was recrystallized with petroleum ether (90—130℃) to afford **5** as a bright yellow needle crystal (15.4 g, 92.2% of theoretical yield). Mp: 121—122℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.95 (s, 3H), 6.98 (d, J = 8.24 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 7.44—7.40 (m, 1H).

6,6′-Dimethoxy-2,2′-dinitrobiphenyl (**6**)

A mixture of 2-iodo-3-nitroanisol (**5**, 14 g, 0.05 mol) and activated copper bronze (9.5 g, 0.15 mol), 50 mL of dimethylformamide was stirried at 140℃ for 4 h under nitrogen atmosphere. The cooled mixture was poured into 500 mL of water and filtered. The solid was extracted with three 100 mL portions of boiling ethanol. The ethanol was evaporated *in vacuo* to dryness. The crude product was recrystallized with hot ethanol to give a yellow needle crystal **6** (5.9 g, 78% of theoretical yield). Mp: 117—119°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.72 (s, 6H), 7.18 (d, J = 8.3 Hz, 2H), 7.52—7.48 (m, 2H), 7.74 (d, J = 8.24 Hz, 2H). MS m/z: 304.

Racemic 6,6′-dimethoxy-2, 2′-diaminobiphenyl (*rac.*-**3**)

A 50 mL autoclave equipped with a magnetic stirring bar was charged with 6,6′- dimethoxy-2, 2′-dinitrobiphenyl (**6**, 500 mg, 1.6 mmol), palladium-charcoal (50 mg, 10% Pd) and 20 mL of dimethylformamide. The autoclave was closed and filled with 200 psi of H_2. The solution was stirred for 5 h at ambient temperature. After releasing the hydrogen gas and removing the solid catalyst by filtration, the filtrate was poured into 150 mL of water followed by extraction with dichloromethane (20 mL × 3). The combined extracts were dried with anhydrous Na_2SO_4 and then concentrated using a rotary evaporator to give 386 mg (98.9%) of crude product. The crude product was purified by crystallization with diethyl ether (50 mL) to give 369 mg of crystalline solid **3** (94.2% of theoretical yield). Mp: 79—84C℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.71 (s, 6H), 6.47—6.44 (m, 4H), 7.14 (d, J = 7.49 Hz, 2H). MS m/z: 244.9 (M^+).

Resolving reagent: (*S*,*S*)-*2,3-di*(*phenylaminocarbonyl*)*tartaric acid* [(*S*,*S*)-**9**]

(*S*,*S*)-*Dibenzyl tartrate* [(*S*,*S*)-**7**] (*S*,*S*)-Tartaric acid (15.0 g, 0.10 mol) was dissolved in 200 mL of benzene and benzylalcohol (43.2 g, 0.40 mol), *p*-toluenesulfonic acid (100 mg) was then added to the solution. The mixture was refluxed for 72 h using water separator to remove the thus formed water. After removing the solvent with a rotary evaporator, 150 mL of water was added and the aqueous layer was extracted with ethyl acetate (100 mL × 3). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated and the crude product was recrystallized with diethyl ether to afford (*S*, *S*)-**7** as a white crystal (31 g, 93.9% of theoretical yield). Mp: 52—53.7℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.58 (s, 2H), 5.24 (dd, J = 12.01, 12.15 Hz, 4H), 7.33—7.23 (m, 10H).

(*S*,*S*)-*1,4-Dibenzyl-2,3-di*(*phenylaminocarbonyl*) *tartrate* [(*S*, *S*)-**8**] A 250 mL two-necked, round-bottomed flask was charged with dibenzyl tartrate (**7**) (14 g, 0.04 mol), phenylisocyanate (21 g, 0.16 mol) and a few drops of triethylamine in 100 mL of toluene. The mixture was refluxed for 24 h with a magnetic stirrer followed by removal of toluene and excess phenylisocyanate under reduced pressure. The residue was recrystallized from ethyl acetate and hexane (4:6) to afford a white crystal, (*S*, *S*)-**8** (19 g, 83.7% of

theoretical yield). Mp: 147—149.7℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.05 (d, J = 12.08 Hz, 2H), 5.27 (d, J = 11.95 Hz, 2H), 5.86 (s, 2H), 6.92—6.89 (m, 2H), 7.06—7.16 (m, 14H), 7.29 (d, J = 4.1 Hz, 4H).

(S,S)-2,3-Di(phenylaminocarbonyl) tartaric acid [(*S,S*)-**9**] A solution of (*S,S*)- dibenzyl-2,3-di (phenylaminocarbonyl) tartrate (**8**, 4 g, 0.007 mol) in 20 mL of ethyl acetate and 20 mg of palladium activated carbon (10% Pd) catalyst were added to a 50 mL autoclave equipped with a magnetic stirrer. 300 psi of H_2 was filled and the mixture was stirred at ambient temperature for 3 h. The mixture was then filtered to remove the solid catalyst. Evaporation of ethyl acetate under reduced pressure afforded the crude product which was purified by crystallization with ethyl acetate and hexane (7 :3) to give 2.3 g of white crystals of (*S,S*)-**9** (85.2% of theoretical yield). Mp: 188.3—190.9℃. $[\alpha]_D^{20}$ = −70.8 (*C* = 1, MeOH). ^{1}H NMR (400 MHz, acetone) δ: 5.81 (s, 2H), 7.13—7.09 (m, 1H), 7.39—7.35 (m, 3H), 7.65—7.64 (m, 6H).

Resolution of 6,6′-dimethoxy-2,2′-diaminobiphenyl (**3**)

A sufficiently dry 100 mL round-bottom flask fitted with a magnetic stirring bar was charged with (*S,S*)-2, 3-di(phenylaminocarbonyl) tartaric acid (**9**, 3.88 g, 0.01 mol) and 30 mL of ethyl acetate. The mixture was heated to nearly boiling and was added dropwise a solution of racemic-**3** (2.44 g, 0.01mol) in 5 mL of ethyl acetate and 5 mL of dichloromethane. The mixture was allowed to cool to room temperature and to stand for 24 h for slow crystallization of the less soluble associate (*S*)-**3**/(*S,S*)-**9**. The resulting solid was filtered and then was recrystallized with 50 mL of ethyl acetate to give white crystals of associate (*S*)-**3**/(*S,S*)-**9** (1 : 1) (2.13 g, 83% yield). Mp: 157—160.2℃, $[\alpha]_D^{20}$ = +49.8 (*C* = 1, CH_2Cl_2). ^{1}H NMR (CD_3CN) δ: 3.68 (s, 6H), 5.75 (s, 2H), 6.44—6.49 (m, 4H), 7.13—7.16 (m, 4H), 7.36—7.39 (m, 4H), 7.48 (d, J = 8.02 Hz, 4H). Next, associate of (*S*)-**3**/(*S,S*)-**9** was decomposed by treatment with diluted NaOH, and the aqueous layer was extracted with CH_2Cl_2 (10 mL × 2). The combined organic layer was washed with water and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure to afford the product (*S*)-**3** as a viscous liquid which was solidified in a refrigerator (0.91 g). $[\alpha]_D^{20}$ = −32.9 (*C* = 1, $CHCl_3$). The enantiomeric excess of (*S*)-**3** was found to be over 99% by HPLC analysis with a chiral OD column [eluent, 10% 2-propanol in hexane, flow rate = 1.0 mL/min]. ^{1}H NMR (THF-d_8) δ: 3.74 (s, 6H), 6.46—6.53 (m, 4H), 7.16—7.19 (m, 2H). MS *m/z*: 244.9 (M^+). Anal. Calcd. for $C_{14}H_{16}N_2O_2$: C 68.83, H 6.60, N 11.47. Found: C 68.76, H 6.51, N 11.51.

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