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To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201701281

Link to VoR: http://dx.doi.org/10.1002/adsc.201701281

10.1002/adsc.201701281

FULL PAPER

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

An *Atropos* Chiral Biphenyl Bisphosphine Ligand Bearing Only 2,2'-Substituents and Its Application in Rh-Catalyzed Asymmetric Hydrogenation

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Received: ((will be filled in by the editorial staff))

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Abstract. An *atropos* chiral biphenyl bisphosphine ligand bearing only 2,2'-substituents was rationally designed and easily synthesized utilizing a bulky chiral *t*-butylmethylphosphino block. Computational results showed a large difference in the free energies between the two diastereomers (7.8 kcal/mol) and attainable rotational energy barriers from one diastereomer to another (27.7 kcal/mol and reverse 19.9 kcal/mol). This ligand avoids the time-consuming optical resolution generally needed for the preparation of axially chiral ligands and shows high reactivity and enantioselectivity in Rh-catalyzed asymmetric hydrogenations.

Keywords: *Atropos*; Biphenyl; Bisphosphine ligand; Rh-catalyzed; Asymmetric hydrogenation

Introduction

Chiral ligands play a key role in defining the efficiency and applicability of metal-catalyzed asymmetric reactions.[1] The biaryl group, particularly the biphenyl group, is undoubtedly the most widely used backbone for the construction of versatile axially chiral ligands. Generally, these types of ligands, e.g. BINAP, BINOL, BIPHEP and SegPhos, require at least three substituents at the 2,2'- and 6,6'-positions to create a chiral biphenyl axis possessing an adequate rotational energy barrier.[2] In order to minimize the torsion angle imposed by the steric repulsion between the substituents at the 2,2'- and 6,6'-positions, we previously designed and synthesized a new type of chiral biphenyl ligand (such as 5,5'-BridgePhos shown in Figure 1) without substituents at the 6,6'-positions.[3] The rotational energy barrier in these ligands is alternatively produced by introduction of bridged substituents at the 5,5'-positions. However, the *atropos* property of the aforementioned ligands requires an indispensable resolution of the enantiomers.

Since 1997, we have developed a series of *tropos* ligands bearing an unfixed biphenyl axis with only two chiral 2,2'-substituents (Figure 1). Due to the chiral substituents at the 2,2'-positions, the bis(oxazoline) ligand BiphBOX showed an unequal diastereoisomeric ratio (29:71) according to NMR spectra. Interestingly, only one of these two reversal diastereoisomers was able to form a stable complex with Cu or Pd, thus no resolution step for the axial chirality is needed.[4] This phenomenon can be explained by the large differences in coordinating energy barriers (dynamics) and free energies (thermodynamics) between the two diastereomeric complexes. Subsequently, the biphenyl phosphine-oxazoline ligands BiphPHOX and their Pd- and Ir-complexes were also developed by us using the same strategy and showed high efficiency in asymmetric catalysis.[5] The preparation of these ligands has an obvious synthetic advantage over the preparation of the binaphthyl phosphine-oxazoline ligand, which requires separation of the diastereoisomers before coordination with Pd.[6] In 2015, Trapp and coworkers developed a new biphenyl bisphosphine ligand 3,3'-Biphep with C-stereogenic (*S*-

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configuration) substituents at the 3,3'-positions (Figure 1).[7] This ligand also exhibits an *atropos*-to-*tropos* property but only when its Rh-complex is heated at high temperature (70 °C) for a certain period of time (300 min). At room temperature, a 61:39 diastereoisomeric mixture was detected and completely retained after coordination with Rh. We considered that the rotational energy barrier was markedly increased by the 3,3'-substituents and the relatively fixed biphenyl axis reduced the epimerization rate of the biphenyl axis so that the rotation rate was much slower than the coordination rate at room temperature. Therefore, to use bisphosphine ligands with strong coordinating ability in dynamic kinetic way is difficult, especially at low temperature. Nevertheless, since the chiral 3,3'-substituents are remote from the chiral biphenyl axis and active metal center, bulky groups are always demanded in order to obtain satisfactory stereocontrol.

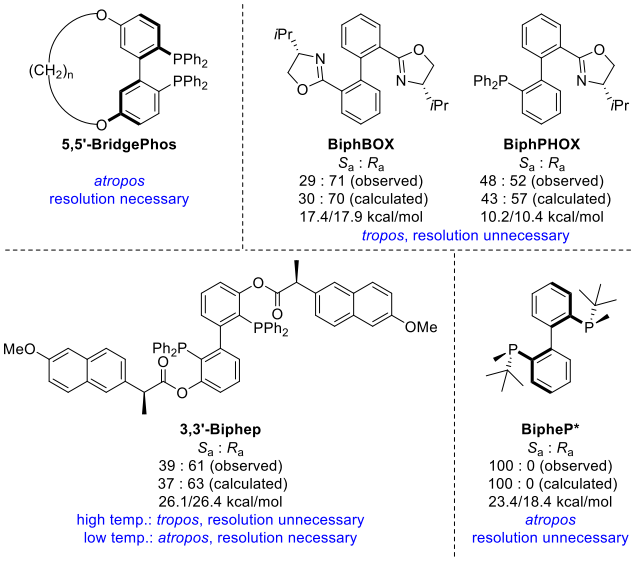
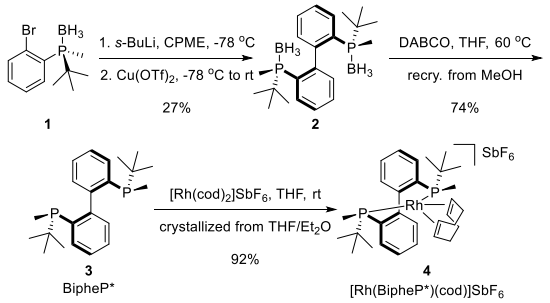


Figure 1. Design of Ligand BipheP*.

To overcome these problems, we proposed to introduce bulky chiral 2,2'-substituents exclusively on the biphenyl skeleton to increase the rotational energy barrier and to provide a more well-defined chiral environment. Furthermore, the presence of suitable chiral groups at the 2,2'-positions will also increase the free energy difference between the two diastereoisomers and make it possible to obtain the ligand, as a single enantiomer, without requiring a resolution step. In continuation of our research concerning P-stereogenic ligands bearing a *tert*-butylmethylphosphino group,[8] we designed a new ligand named BipheP* with the aid of theoretical calculations (Figure 1). The calculated results obtained using a theoretical method of B3LYP/6311G+(d,p) showed a great difference in the free energies between the two diastereomers (5.0 kcal/mol) and considerable rotational energy barriers that must be overcome to convert from one diastereomer to the other (23.4 kcal/mol and reverse 18.4 kcal/mol). These results indicate that a ligand possessing a chiral axis could be produced due to the presence of the P-stereogenic (*R*-configuration depicted) *tert*-butylmethylphosphino group and a single diastereoisomer could be obtained without the need for further resolution. This finding represents the first synthesis of an *atropos* chiral biphenyl ligand bearing only 2,2'-substituents and would bring inspiration for the design of new axially chiral ligands and organocatalysts.

Results and Discussion

The preparation of the ligand BipheP* required only a few simple steps (Scheme 1). The starting material (*R*)-2-bromophenyl(*tert*-butyl)(methyl)phosphane-borane (**1**) could be easily synthesized from (*S*)-*tert*-butylmethylphosphane-borane and 1,2-dibromobenzene according to a literature procedure.[8c,d] Compound **1** was then treated with *s*-BuLi and transformed to (R_P,R_P)-2,2'-bis(boranoto(*tert*-butyl)(methyl)phosphino)biphenyl (**2**) via a Cu-promoted homocoupling in a relatively low yield of 27% due to the formation of a debrominated byproduct. Judging from the ^{31}P NMR spectrum, only one of the two diastereoisomers was obtained. The borane protecting group was easily removed by the reaction with DABCO and the free ligand (R_P,R_P)-2,2'-bis((*tert*-butyl)(methyl)phosphino)biphenyl (**3**, BipheP*) was obtained by recrystallization from methanol. It is worth to mention that this ligand is an air-stable crystalline solid. The rhodium complex **4** [Rh(BipheP*)(cod)]SbF_6 was crystallized from THF/Et_2O after coordination with [Rh(cod)$_2$]SbF_6 in THF.



Scheme 1. Synthesis of Ligand BipheP* and Its Rh Complex.

^{31}P NMR experiments carried out at different temperatures showed presence of a single diastereomer of **3**; no dynamic effects were detected in the temperature range from -50 to 25 °C (Figure 2). The more detailed computation (wB97XD/6311G+(d,p)/SMD(methanol)) showed that the R_P,R_P,S_a-isomer is thermodynamically favoured for 7.8 kcal/mol (Figure 3). In the same fashion, the ^{31}P NMR and calculated results of the

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rhodium complex **4** also indicated a single R_P,R_P,S_a-isomer with an energy difference of 9.7 kcal/mol ((wB97XD/631G(d,p)/SMD(methanol)), Figure 4 and Figure 5), hence that the axial chirality of the biphenyl backbone did not change during the coordination process. Unfortunately, attempts to obtain good crystals of either **3** or **4** for X-ray analysis were unsuccessful.

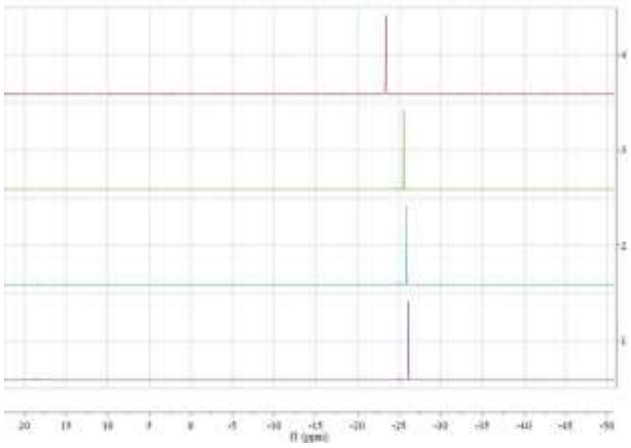

Figure 2. The ^{31}P NMR of Compound **3** (2-1: 223 K; 2-2: 233 K; 2-3: 250 K; 2-4: 298 K).

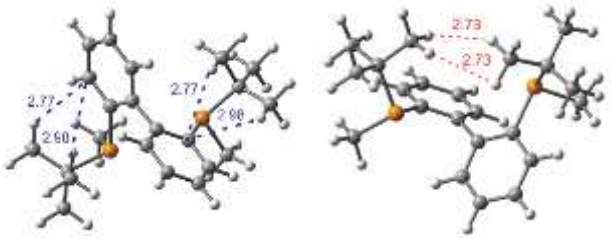

Figure 3. Computed Structure of **3** (Left: R_P,R_P,S_a-isomer, 0.0 kcal/mol. Right: R_P,R_P,R_a-isomer, 7.8 kcal/mol).

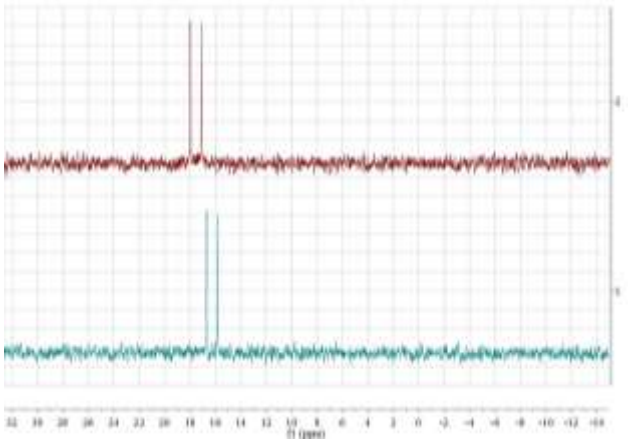

Figure 4. The ^{31}P NMR of Compound **4** (4-1: 223 K; 4-2: 298 K).

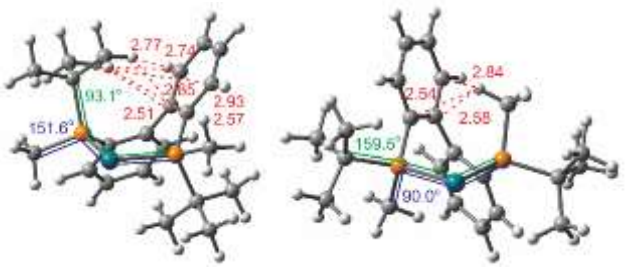

Figure 5. Computed Structure of **4** (Left: R_P,R_P,S_a-isomer, 0.0 kcal/mol. Right: R_P,R_P,R_a-isomer, 9.7 kcal/mol. Coordinated COD is not shown for clarity).

To get insight into the reasons of the significant difference in the stabilities of two conformations of **3**, we have scanned the changes of the relative energy and molecular structure during the rotation around the internal bond of the biphenyl backbone (Figure 6). The energy scan (wB97XD/631G(d,p)/SMD(methanol)) demonstrated the presence of two conformations separated by significant activation barrier (the full scan contains another relatively unstable minimum that was not accounted in the further analysis). Despite the relatively small size of a molecule of **3,** a significant number of interatomic distances in the range of 2-3 Å is detected in either of the conformations. To find the crucial intramolecular interactions characteristic for each conformation and making it a minimum in energy, we considered that a stabilizing intramolecular interaction must be conserved even when the configuration is removed from the minimum one by changing the dihedral angle. We have found four such interatomic distances (corresponding to the C-H…π interactions) for the R_P,R_P,S_a-isomer, and only two C-H…H-C interactions of that kind for another diastereomer. From the Figure 6 (down) one can see that these interatomic distances are keeping the same value in a wide range of the dihedral angles that is a clear indication of their attractive character. We concluded therefore that R_P,R_P,S_a-conformation is stabilized by C-H…π interactions of a *tert*-butyl group and corresponding phenyl ring, since they overcome in number the attractive C-H…H-C interactions in the other diastereomer. Apparently, essentially the same intramolecular interactions affect the structure of the Rh complex **4**. As a result, a strong difference in the dihedral angled P-Rh—P-C for the methyl and *tert*-butyl groups is observed, thus making the methyl groups quasi-equatorial substituents that is usually not observed in other Rh complexes of this kind (Figure 5, left).

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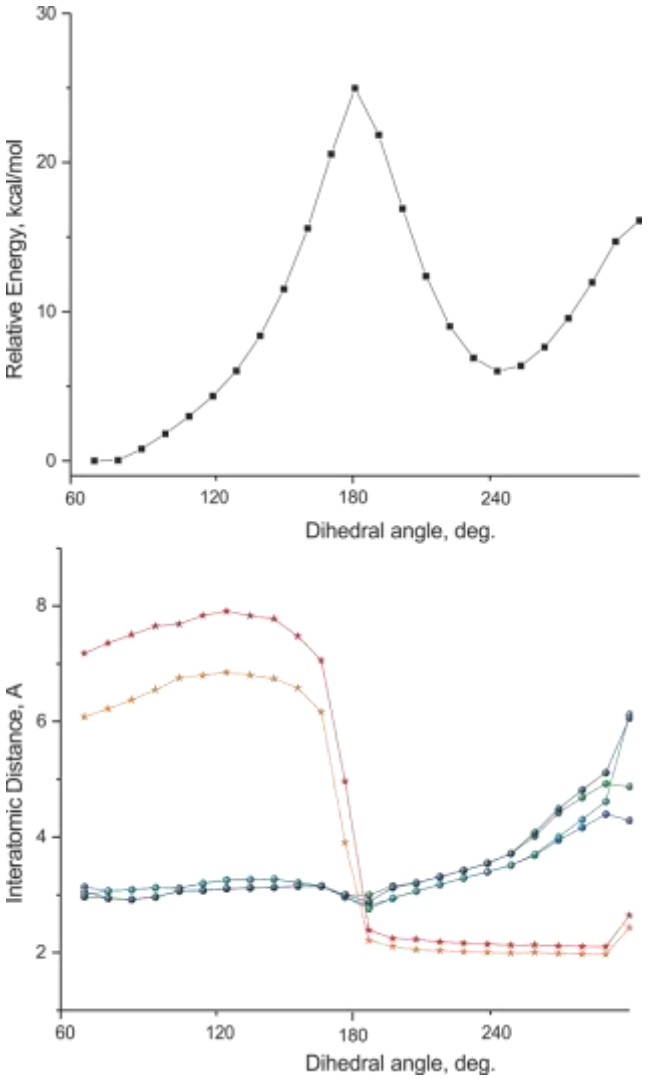
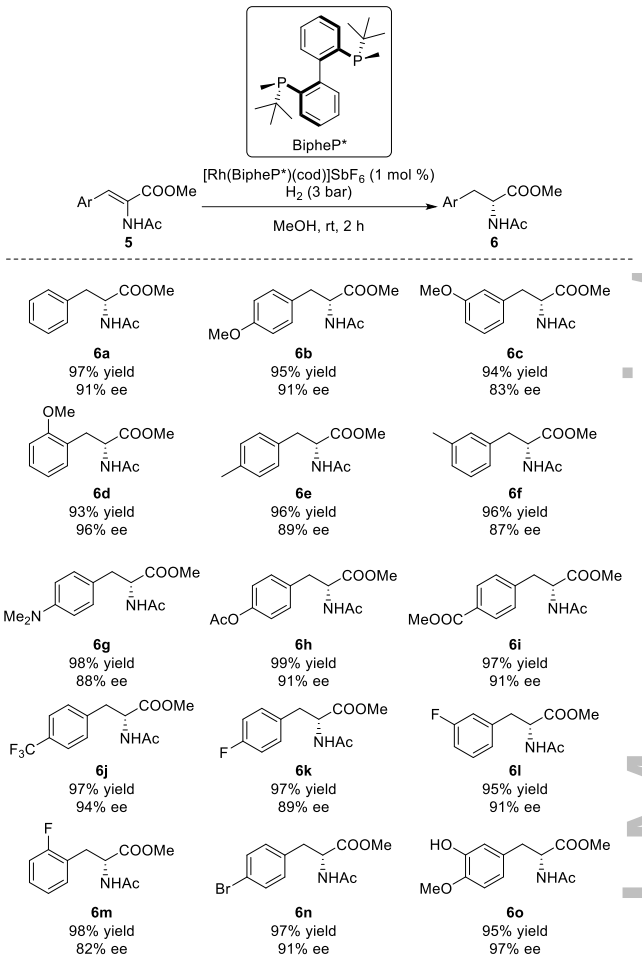


Figure 6. Up: section plot of the computed energy scan of the rotation around the C-C single bond in the biphenyl unit. Down: spheres, changes of interatomic distances H…C shown in the Figure 3 (left); stars, changes of interatomic distances H…H shown in the Figure 3 (right).

To test the activity and enantioselectivity of this rhodium complex, methyl (*Z*)-2-acetamido-3-arylacrylates were chosen as prochiral substrates and their asymmetric hydrogenations were performed under standard reaction conditions.[9] Firstly, solvent screening showed that polar protic solvents are better than less polar solvents (see Supporting Information for details). Catalyst [Rh((*R*P,*R*P,*S*a)-BipheP*)(cod)]SbF_6 in MeOH solvent provides promising enantioselectivity for the hydrogenation of **5a** (91% ee). Then, various substrates bearing different substituents on the phenyl ring were tested and high enantioselectivities were obtained (82-97% ee) (Scheme 2). The *para*-substituted substrates, such as **5b**, **5e**, **5g-k**, and **5n**, gave their corresponding products with approximately 90% ees. For substrates bearing electron-donating methoxy groups, *ortho*-substituted **5d** gave a better enantioselectivity than *meta*-substituted **5c**, while the electron-withdrawing fluoro group showed an opposite trend (**5l** and **5m**). To our delight, the *meta*,*para*-disubstituted substrate **5o** gave its corresponding product with the highest enantioselectivity of 97% ee. When the S/C was increased to 4000, the hydrogenation of **5a** was completed within 8 hours and with 86% ee.



Scheme 2. Substrate Scope. Conditions: **5** (0.2 mmol), [Rh(BiPheP*)(cod)]SbF_6 (1 mol %), H_2 (3 bar), MeOH (2 mL), rt, 2 h; Isolated yields were obtained after chromatography; The ee values were determined by HPLC.

Conclusion

In conclusion, we have prepared the first example of *atropos* chiral biphenyl bisphosphine ligands bearing only two chiral groups at 2,2'-positons. Both the theoretical calculations and experimental data verify that only one axial isomer exists. Its Rh-complex showed high activity and enantioselectivity in the asymmetric hydrogenation of α-dehydroamino acid esters (up to 97% ee and 4000 S/C). Other catalytic asymmetric reactions using BipheP* are currently being developed in our laboratory and similar ligands utilizing the same tactic are being prepared.

Experimental Section

General information

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All air- and moisture-sensitive manipulations were carried out with standard Schlenk techniques under nitrogen. All hydrogenation reactions were performed in autoclave under an atmosphere of hydrogen. Solvents were dried and distilled by standard procedures. All commercially available reagents were used as received. ^{1}H, ^{13}C, ^{31}P NMR spectra were obtained using a Varian MERCURY plus-400 spectrometer with an internal standard. Melting points were measured with SGW X-4 micro melting point apparatus. Enantioselectivities were determined by high performance liquid chromatography (HPLC) using Daicel CHIRALPAK AD-H or OD-H columns with hexane/*i*PrOH as eluent. Optical rotations were measured on a Rudolph Research Analytical Autopol VI automatic polarimeter using a 50 mm path-length cell at 589 nm. High Resolution Mass Spectrometry (HRMS) analysis was carried out using an electrospray spectrometer Waters Micromass Q-TOF Premier Mass Spectrometer.

Preparation of ligand and its Rh-complex

(*R*)-2-Bromophenyl(*tert*-butyl)(methyl)phosphane-borane (1):[8c,d] *n*-BuLi (8.5 mL, 1.3 M in hexane, 11 mmol, 1.1 eq) was added dropwise into a solution of borano (*S*)-*tert*-butyl(methyl)phosphane (1.17 g, 10 mmol) in THF (10 mL) at -78 °C under the atmosphere of nitrogen. The solution was stirred for 1 hour followed by the slow addition of a solution of 1,2-dibromobenzene (3.54 g, 15 mmol, 1.5 eq) in THF (5 mL). The temperature was gradually elevated up to 0 °C. The reaction was stirred for 6 hours and quenched with water. The mixture was extracted with EtOAc and then the combined organic phases were dried over Na_2SO_4 and filtered. The solvent was evaporated and the residue was purified by column chromatography on silica gel using petroleum ether/EtOAc (10:1) as the eluent. The product was recrystallized from hexane to give white needles (1.54 g, 56% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (ddd, J = 12.8, 7.8, 1.8 Hz, 1H), 7.63 (ddd, J = 7.9, 2.4, 1.3 Hz, 1H), 7.39 (tt, J = 7.7, 1.4 Hz, 1H), 7.34-7.28 (m, 1H), 1.90 (d, J = 10.0 Hz, 3H), 1.19 (d, J = 14.4 Hz, 9H), 1.04-0.37 (br m, 3H). ^{31}P NMR (162 MHz, $CDCl_3$) δ 39.01 (dd, J = 119.0, 52.5 Hz).

(R_P,R_P)-2,2'-Bis(boranoto(*tert*-butyl)(methyl)phosphino)biphenyl (2): To a solution of compound **1** (0.82 g, 3.0 mmol) in cyclopentyl methyl ether (CPME) (10 mL) was added *s*-BuLi (3.2 mL of 1 M hexane solution, 3.2 mmol) under nitrogen at -78 °C. The reaction was stirred for 45 min before $Cu(OTf)_2$ (1.63 g, 4.5 mmol) was added and the temperature was gradually elevated to room temperature. The reaction was quenched with ammonium hydroxide after the starting material was expended. The mixture was extracted with ethyl acetate twice. The combined organic phases were dried over Na_2SO_4. TLC check and ^{31}P NMR analysis indicate that only one of the two diastereoisomers was obtained in the reaction. The volatiles were evaporated and the residue was purified by chromatography on silica gel using petrol ether/ethyl acetate (50:1) as the eluent to give compound **2** as a white powder (157 mg, 27% yield). Mp 152-153 °C. $[\alpha]^{25}_D$ +72.6 (*c* 0.50, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59-7.52 (m, 2H), 7.48-7.37 (m, 4H), 7.25-7.20 (m, 2H), 1.67 (d, J = 9.2 Hz, 6H), 1.07 (d, J = 13.4 Hz, 18H), 0.36--0.61 (m, 6H). ^{31}P NMR (162 MHz, $CDCl_3$) δ 25.46 (br s). ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.84 (d, J = 16.1 Hz), 133.66 (s), 132.82 (d, J = 8.8 Hz), 129.43 (s), 127.85 (d, J = 45.9 Hz), 127.19 (d, J = 6.3 Hz), 30.73 (d, J = 32.2 Hz), 26.64 (s), 9.12 (d, J = 39.0 Hz). HR-MS (ESI) m/z calculated for $C_{22}H_{39}B_2P_2$ $[M\text{-}BH_3+H]^+$ 373.2380, found 373.2387.

(R_P,R_P,S_a)-2,2'-Bis((*tert*-butyl)(methyl)phosphino)biphenyl (3): A solution of compound **2** (151.6 mg, 0.39 mmol) and DABCO (133.1 mg. 1.19 mmol) were heated to reflux temperature in THF under nitrogen for 3 h. The solvent was removed under reduced pressure and the residue was extracted with degassed hexane (5 mL × 3). The combined solution was removed under reduced pressure and the residue was recrystallized in hot degassed MeOH to give compound **3** as a white solid (104.5 mg, 74% yield). Mp 106-109 °C. $[\alpha]^{25}_D$ +48.6 (*c* 0.53, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (t, J = 3.6 Hz, 2H), 7.34 (dd, J = 5.6, 3.3 Hz, 4H), 7.18-7.14 (m, 2H), 1.26 (t, J = 2.4 Hz, 6H), 0.74 (t, J = 6.0 Hz, 18H). ^{31}P NMR (162 MHz, $CDCl_3$) δ -23.39 (s). At 223 K, δ -26.11 (s). A slight amount of partially oxidation product was detected at 18.70 (d, P(O)) and -25.10 (d, P). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.49 (s), 137.56 (s), 131.31 (s), 130.98 (s), 128.15 (s), 126.34 (s), 29.81 (d, J = 24.8 Hz), 27.63 (t, J = 7.5 Hz), 5.86 (t, J = 9.5 Hz). HR-MS (ESI) m/z calculated for $C_{22}H_{33}P_2$ $[M+H]^+$ 359.2052, found 359.2056.

((R_P,R_P,S_a)-2,2'-Bis((*tert*-butyl)(methyl)phosphino)biphenyl)(1,5-cyclooctadiene)rhodium(I) hexafluoroantimonate ([Rh(3)(cod)]SbF$_6$, 4): A solution of compound **3** (68.7 mg, 0.19 mmol) in THF (0.5 mL) was added dropwise to a solution of $[Rh(cod)_2]SbF_6$ (96.7 mg, 0.17 mmol) in THF (0.5 mL) under nitrogen. The solution was stirred for 40 min under room temperature and then for 20 min under 0 °C. The solution was concentrated under reduced pressure to 0.5 mL followed by the addition of diethyl ether (about 5 mL). The precipitated solid was collected via filtration and washed with a small amount of diethyl ether to give compound **4** as an orange solid (142.0 mg, 92% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (t, J = 7.4 Hz, 2H), 7.51 (t, J = 7.9 Hz, 2H), 7.45 (t, J = 7.4 Hz, 2H), 7.20 (d, J = 7.3 Hz, 2H), 5.38 (br s, 2H), 4.73 (br s, 2H), 2.47 (br s, 4H), 2.24 (br s, 4H), 1.62 (d, J = 4.7 Hz, 6H), 0.84 (d, J = 13.9 Hz, 18H). ^{31}P NMR (162 MHz, $CDCl_3$) δ 17.54 (d, J = 140.5 Hz). ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.54 (t, J = 7.1 Hz), 135.87 (t, J = 3.5 Hz), 131.67 (s), 130.95 (s), 129.32 (t, J = 2.9 Hz), 128.80 (s), 101.55-101.22 (m), 91.56 (dd, J = 12.5, 6.3 Hz), 37.27-36.93 (m), 33.68 (s), 29.85-29.57 (m), 28.36 (s), 7.00-6.65 (m). HR-MS (ESI) m/z calculated for $C_{30}H_{44}P_2Rh$ $[M\text{-}SbF_6]^+$ 569.1968, found 569.1997.

General procedure for asymmetric hydrogenation

Substrate (0.2 mmol), rhodium catalyst (0.002 mmol), and a magnetic stir bar were charged in a hydrogenation bottle and autoclave. The system was evacuated and filled with hydrogen. After repeating this operation three times,

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degassed solvent (2 mL) was added and the vessel was filled with hydrogen (3 bar). Vigorous stirring was continued for 2 hours. The reaction mixture was evaporated under reduced pressure and the residue was passed through a short column of silica gel. The solvent was removed under reduced pressure and the product was dried in vacuum. The enantiomeric excess was determined by HPLC.

Acknowledgements

This work was partially supported by the National Natural Science Foundation of China (Nos. 21232004, 21572131 and 21620102003), Shanghai Municipal Education Commission (No. 201701070002E00030) and Science and Technology Commission of Shanghai Municipality (No. 15JC1402200). We thank the Instrumental Analysis Center and the High Performance Computing Center of Shanghai Jiao Tong University.

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10.1002/adsc.201701281

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An *Atropos* Chiral Biphenyl Bisphosphine Ligand Bearing Only 2,2'-Substituents and Its Application in Rh-Catalyzed Asymmetric Hydrogenation

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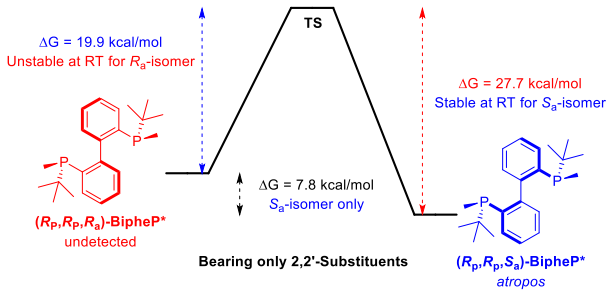

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