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Novel atropisomeric aminophosphine ligands with a bridge across the 5,5′-position of biphenyl for Rh(I)-catalyzed asymmetric hydrogenation

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ABSTRACT

A new type of atropisomeric bisaminophosphine ligands **2** with a bridge across the 5,5′-position of biphenyl has been developed. The axial chirality of this type of ligands can be retained by macro-ring strain produced from 5,5′-linkage of biphenyl even without 6,6′-substituents on biphenyls. The ligand (*R*)-**2a** showed high catalytic activities and enantioselectivities (up to 95.3% ee and quantitative yields) for Rh(I)-catalyzed asymmetric hydrogenation of a variety of methyl (*Z*)-2-acetamido-3-arylacrylates.

The design and synthesis of chiral phosphine ligands have played a significant role in the development of transition-metal catalyzed asymmetric reactions, and have attracted a great deal of attention from both academia and industry.[1] Since Noyori and co-workers developed the historical axially chiral bisphosphine ligand BINAP in the early 1980s,[2] many bisphosphine ligands supported by an atropisomeric scaffold have been developed and applied successfully in various asymmetric catalytic reactions.[3] It was found that modulation of the steric and electronic properties of atropisomeric scaffold of the ligand could remarkably influence on their efficiency in asymmetric catalytic reactions. Recently, the steric design of the biaryl core has been extensively explored such as BIPHEMP,[4] MeO-BIPHEP,[4] TunePhos,[5] SEGPHOS,[6] SYNPHOS,[7] and DIFLUORPHOS.[8] It was demonstrated that the ligand displaying a narrow dihedral angle of biaryl backbone showed better enantioselectivities in Ru(II)-catalyzed asymmetric hydrogenation of β-keto esters.[9] Quite recently, we developed novel atropisomeric framework **1** (Fig. 1),[10] in which the biphenyl has only two coordinating groups next to the axis, and the axial chirality of the ligand can be retained by steric hindrance of two bulky coordinating groups and macro-ring strain produced from 5,5′-linkage of biphenyls even without 6,6′-substituents. The modulation of the length of the backbone carbon chain could control the conformational flexibility of the metal chelate rings formed with atropisomeric ligands to provide more suitable chiral environment for asymmetric catalysis. In our initial study, we found that the bisoxazolines[10a] and bismethylenephosphines[10b] with atropisomeric framework **1** are provided with stable axial chirality at appropriate temperature, and they can be effectively applied in Pd(II)-catalyzed asymmetric Wacker-type cyclization of 2-allylphenols and Rh(I)-catalyzed asymmetric hydrogenation of dehydroamino acids, respectively.

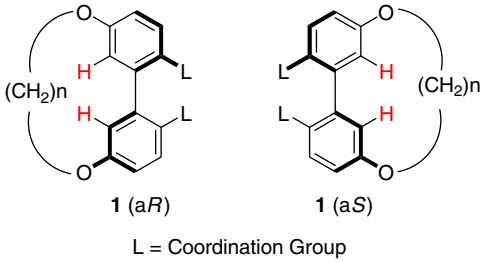

Figure 1. Atropisomeric ligands with a bridge across the 5,5′-positions of biphenyl.

Over the last three decades, most effort on asymmetric hydrogenation has been focused on the use of rhodium and ruthenium catalysts containing chiral phosphine ligands.

Recently, it has been shown that some of the results obtained with chiral phosphinite,[11] phosphite,[12] phosphonite[13] or phosphoramidite[14] ligands can match those obtained by using phosphine ligands. The easily prepared bisaminophosphine ligands were also found to be effective ligands for the rhodium-catalyzed asymmetric hydrogenation.[15] For example, bisaminophosphines (BDPAB) (see Fig. 2) with binaphthyl have effectively been applied in asymmetric hydrogenation of enamides[15c] and dehydroamino

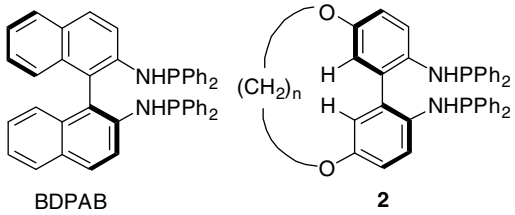

Figure 2. Bisaminophosphine ligands with axial biaryl backbone.

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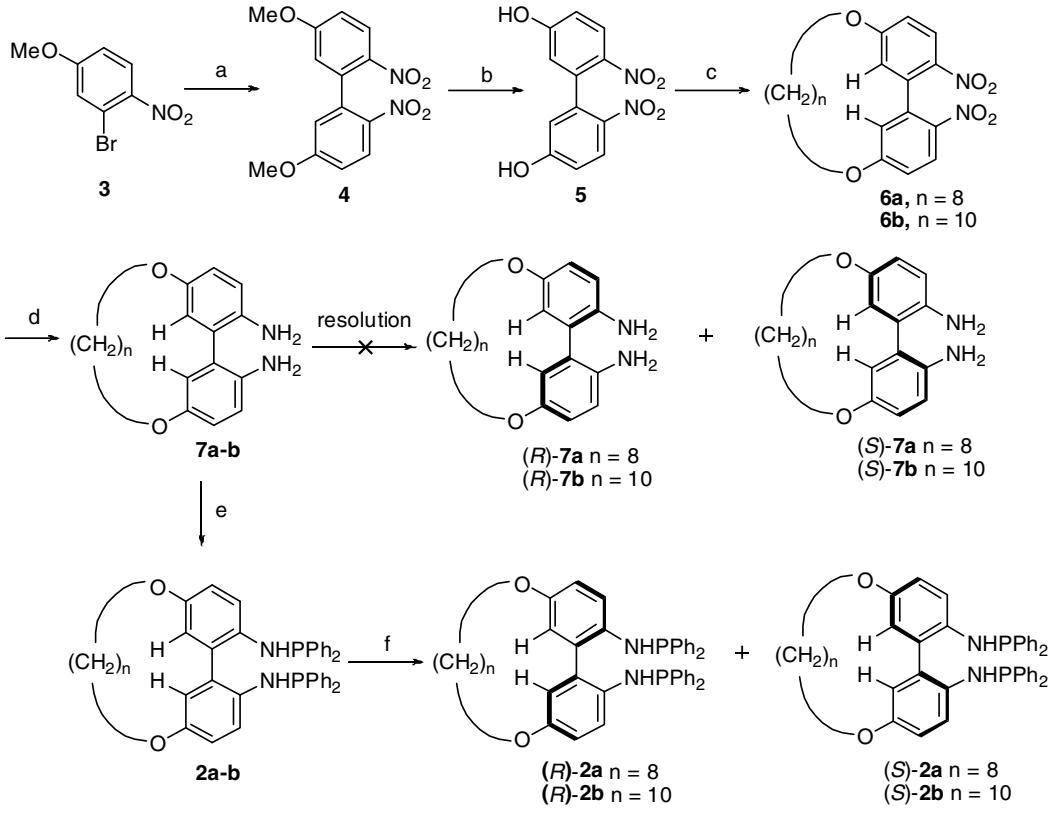
acid derivatives.[15a] However, only a limited number of bisaminophosphines for asymmetric hydrogenation have been investigated.[16] Herein we wish to report novel bisaminophosphine ligands with our atropisomeric framework **1**, 2,2′-bis(diphenylphosphinoamino)-5,5′-(polymethylenedioxy)-1,1′-biphenyls **2** (see Fig. 2), and their application in Rh(I)-catalyzed asymmetric hydrogenation of de- hydroamino acid derivatives.

The optically pure bisaminophosphine ligands **2** were readily prepared from 3-bromo-4-nitroanisole **3**[17] as illustrated in Scheme 1. Ullman coupling of **3** with activated copper powder furnished the biphenyl skeleton **4** in 78% yield. Demethylation of **4** with aluminum chloride and 1-dodecanethiol afforded compound **5** in 79% yield. Cyclization of **5** with 1,8-dibromooctane and 1,10-dibromodecane led to the key intermediates **6a** and **6b** in 58% and 55% yields, respectively. Straightforward reduction of **6a** with Pd/C under 5 atm of hydrogen gave quantitatively biphenyldiamine **7a**. Then, we tried optical resolution of biphenyldiamine **7a** to obtain optically pure diamine compound, however, all attempts in resolution of **7a** failed. The reaction of racemic biphenyldiamine **7a** with chlorodiphenylphosphine in the presence of triethylamine furnished racemic bisaminophosphine **2a** in 81% yield. The optical separation of racemic **2a** by chiral preparative HPLC using a Daicel Chiralcel AD-H column afforded, respectively, enantiomerically pure (>99% ee) (+)-**2a** and (−)-**2a** in 42% yield.[18] In the same way, the optically pure aminophosphine ligand **2b** was prepared from 5,5′-decamethylenedioxy-biphenyl-2,2′-dinitrate (**6b**) in 31% overall yield.[19] The sense of axial chirality of **2a** was determined by the major *Cotton* effects (CE) in the CD spectra. The CD curve of (−)-**2a** displayed negative CE at 237.0 nm. This signed feature is the characteristic of (*R*)-configuration at chiral axis, which was in contrast with the spectra in the literature of axially chiral biphenyl compounds.[20]

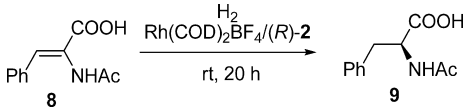
To evaluate the effectiveness of our atropisomeric bisaminophophine ligands **2** in Rh(I)-catalyzed asymmetric hydrogenation, typically, (*Z*)-α-acetamidocinnamic acid (**8**) was used as a model substrate for the hydrogenation. The hydrogenation reaction was catalyzed by 1 mol % of the Rh(I)-(*R*)-**2a** complex generated in situ by mixing $Rh(COD)_2BF_4$ with bisaminophosphine (*R*)-**2a** in methanol at room temperature. It was found that the catalytic efficiency largely depended on the hydrogen pressure. As shown in Table 1, the hydrogenation reaction showed higher catalytic activity with enhancement of the hydrogen pressure (entries 1–4). The enantioselectivity also enhanced with the hydrogen pressure increasing from 1 to 3 atm (from 88.2% to 89.7% ee, entries 1 and 2). However, further raising the hydrogen pressure, the enantioselectivity remarkably decreased (entries 3 and 4). With (*R*)-**2b** as a ligand, which had decamethylenedioxy bridge, the enantioselectivity decreased to 84.1% ee under 3 atm of hydrogen pressure (entry 5). The reaction medium had also effects on the catalytic activity and enantioselectivity in the hydrogenation reaction (entries 6–9). The highest enantioselectivity (89.8% ee) was obtained in THF under 3 atm of hydrogen pressure (entry 7).

Methyl (*Z*)-α-acetamidocinnamate (**10a**) was also used as a substrate for the hydrogenation by mixing $Rh(COD)_2BF_4$ with bisaminophosphine (*R*)-**2a** in methanol at room temperature. It was found that the catalytic efficiency also largely depended on the hydrogen pressure, the ligand structure and a reaction solvent. As shown in Table 2, the reaction results have similar tendencies with hydrogenation of (*Z*)-α-acetamidocinnamic acid (**8**). However, the obviously higher enantioselectivities for the hydrogenations of methyl (*Z*)-α-acetamidocinnamate (**10a**) were observed than those for the hydrogenations of corresponding acid **8** in the same reaction conditions. The highest enantioselectivity (94.4% ee) for the hydrogenation of methyl (*Z*)-α-acetamidocinnamate (**10a**) was



Scheme 1. Reagents and conditions: (a) Cu, 78%; (b) $AlCl_3$, 1-dodecanethiol, CH_2Cl_2, 79%; (c) $Br(CH_2)_nBr$, K_2CO_3, DMF; for **6a**, 58%; for **6b**, 55%; (d) H_2, Pd/C, EtOAc; for **7a**, 100%; for **7b**, 99%; (e) $ClPPh_2$, Et_3N, CH_2Cl_2; for **2a**, 81%; for **2b**, 79%; (f) chiral preparative HPLC, a Daicel Chiralcel AD-H column, for **2a**, 42%; for **2b**, 39%.

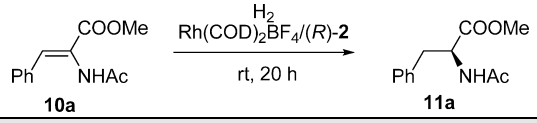
Table 1
Rh(I)-Catalyzed asymmetric hydrogenation of (*Z*)-α-acetamidocinnamic acid using bisaminophosphines (*R*)-**2** as ligands[a]



Entry	Ligand	H_2 press (atm)	Solvent	Conv.[b] (%)	ee[c] (%)
1	**2a**	1	MeOH	75	88.2
2	**2a**	3	MeOH	96	89.7
3	**2a**	5	MeOH	100	81.9
4	**2a**	10	MeOH	100	66.6
5	**2b**	3	MeOH	100	84.1
6	**2a**	3	IPA	100	83.1
7	**2a**	3	THF	100	89.8
8	**2a**	3	CH_2Cl_2	100	89.6
9	**2a**	3	Acetone	91	81.8

[a] All reactions were carried out at room temperature for 20 h. The catalyst was prepared in situ from $Rh(COD)_2BF_4$ and ligand (substrate:Rh:ligand = 100:1:1.1).
[b] Determined by ^1H NMR analysis.
[c] The enantiomeric excesses were determined by chiral HPLC using a Daicel Chiralcel OD-H column. The *S* absolute configurations were assigned by comparison of optical rotations with the literature data.[21]

Table 2
Rh(I)-Catalyzed asymmetric hydrogenation of methyl (*Z*)-α-acetamidocinnamate using bisaminophosphines (*R*)-**2** as ligands[a]



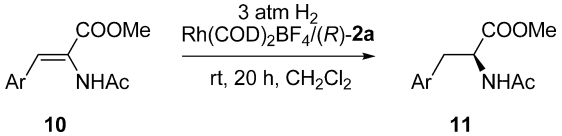
Entry	Ligand	H_2 press (atm)	Solvent	Conv.[b] (%)	ee[c] (%)
1	**2a**	1	MeOH	85	91.4
2	**2a**	3	MeOH	99	92.1
3	**2a**	5	MeOH	100	83.8
4	**2a**	10	MeOH	100	84.3
5	**2b**	3	MeOH	100	87.1
6	**2a**	3	IPA	100	92.4
7	**2a**	3	THF	100	94.1
8	**2a**	3	CH_2Cl_2	100	94.4
9	**2a**	3	Acetone	91.7	84.0

[a] All reactions were carried out at room temperature for 20 h. The catalyst was prepared in situ from $Rh(COD)_2BF_4$ and ligand (substrate:Rh:ligand = 100:1:1.1).
[b] Determined by ^1H NMR analysis.
[c] The enantiomeric excesses were determined by chiral HPLC using a Daicel Chiralcel OD-H column. The *S* absolute configurations were assigned by comparison of optical rotations with the literature data.[21]

obtained using bisaminophosphine (*R*)-**2a** as a chiral ligand in methylene chloride under 3 atm of hydrogen (entry 8). With optimization reaction conditions in hand, we have performed asymmetric hydrogenations of various methyl (*Z*)-2-acetamido-3-arylacrylates **10** catalyzed by Rh(I)-(*R*)- **2a** complex. A variety of substrates **10** can be hydrogenated to produce the corresponding α-amino ester derivatives **11** in quantitative conversions with high enantioselectivities (Table 3). The electronic nature of the phenyl ring of the substrate had a little influence on the enantioselectivity for the reaction. Electron-donating groups, 4-methyl-substituted and 4-methoxy-substituted substrates, **10b** (entry 2, 95.3% ee) and **10c** (entry 3, 95.1% ee), gave better ee values than halogenated substrates (entries 4–6), while substitution at the *ortho* or *meta* position of the phenyl ring of a substrate led to a slightly lower enantioselectivity (entries 7 and 8).

In summary, we have developed a new type of atropisomeric bisaminophosphine ligands **2** with a bridge across the 5,5′-position of biphenyl. It was demonstrated that the axial chirality of this

Table 3
Rh(I)-Catalyzed asymmetric hydrogenation of methyl (*Z*)-α-acetamido-3-arylacrylates using bisaminophosphine (*R*)-**2a** as a ligand[a]



Entry	Substrate	Ar	Conv.[b] (%)	ee[c] (%)
1	**10a**	Ph	100	94.4
2	**10b**	*p*-Me-Ph	100	95.3
3	**10c**	*p*-OMe-Ph	100	95.1
4	**10d**	*p*-Cl-Ph	100	94.3
5	**10e**	*p*-F-Ph	100	93.4
6	**10f**	*p*-Br-Ph	100	92.1
7	**10g**	*o*-Cl-Ph	100	91.3
8	**10h**	*m*-Cl-Ph	100	91.6

[a] All reactions were carried out at room temperature in CH_2Cl_2 for 20 h. The catalyst was prepared in situ from $Rh(COD)_2BF_4$ and ligand (substrate:Rh:ligand = 100:1:1.1).
[b] Determined by ^1H NMR analysis.
[c] The enantiomeric excesses were determined by chiral HPLC using a Daicel Chiralcel OD-H column. The *S* absolute configurations were assigned by comparison of optical rotations with the literature data.[21]

type of ligands can be retained by macro-ring strain produced from 5,5′-linkage of biphenyl. The Rh(I) complex of bisaminophosphine (*R*)-**2a** as a catalyst showed high catalytic activities and enantioselectivities (up to 95.3% ee) for the asymmetric hydrogenation of various methyl (*Z*)-2-acetamido-3-arylacrylates **10**. Further study of development and application of this type of atropisomeric ligands are in progress.

Acknowledgements

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18. *2,2′-Bis(diphenylphosphinoamino)-5,5′-(octamethylenedioxy)-1,1′-biphenyl* (**2a**): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.23 (m, 22H), 6.86 (dd, J = 8.8 Hz, 2.8 Hz, 2H), 6.75 (d, J = 9.2 Hz, 2.8 Hz, 2H), 4.55 (d, J = 6 Hz, 2H), 4.20 (m, 2H), 4.05 (m, 2H), 1.89 (m, 2H), 1.62 (m, 2H), 1.48–1.29 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.33, 137.55, 137.40, 131.34, 131.13, 130.88, 130.67, 128.91, 128.89, 128.54, 128.49, 128.47, 128.43, 119.08, 118.74, 118.55, 116.15, 67.16, 28.32, 27.99, 24.95; ^{31}P NMR ($CDCl_3$, 161 MHz) δ 34.27; HRMS (Micromass LCT) calcd for $C_{44}H_{43}N_2O_2P_2$: 693.2800; found: 693.2808. For (*R*)-**2a**: mp 138–141 °C; $[\alpha]_D^{25}$ −32.8 (*c* 1, $CHCl_3$). For (*S*)-**2a**: mp 138–141 °C; $[\alpha]_D^{25}$ +31.9 (*c* 1, $CHCl_3$).
19. *2,2′-Bis(diphenylphosphinoamino)-5,5′-(decamethylenedioxy)-1,1′-biphenyl* (**2b**): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.25 (m, 22H), 6.87 (dd, J = 8.8 Hz, 2.8 Hz, 2H), 6.73 (d, J = 9.2 Hz, 2.8 Hz, 2H), 4.44 (d, J_{P-H} = 6.4 Hz, 2H), 4.12 (m, 2H), 4.00 (m, 2H), 1.85 (m, 2H), 1.61 (m, 2H), 1.41–1.29 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.44, 137.98, 137.80, 131.14, 130.93, 130.91, 130.71, 128.93, 128.85, 128.52, 128.45, 118.36, 118.07, 117.87, 117.10 68.96, 28.71, 28.65, 28.02, 25.10; ^{31}P NMR ($CDCl_3$, 161 MHz) δ 32.86; HRMS (Micromass LCT) calcd for $C_{46}H_{47}N_2O_2P_2$: 721.3113; found: 721.3152. For (*R*)-**2b**: mp 119–121 °C; $[\alpha]_D^{25}$ −37.5 (*c* 1, $CHCl_3$). For (*S*)-**2b**: mp 119–121 °C; $[\alpha]_D^{25}$ +39.7 (*c* 1, $CHCl_3$).
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