A Novel Axially Chiral Phosphine-Oxazoline Ligand with an Axis-Unfixed Biphenyl Backbone: Preparation, Complexation, and Application in an Asymmetric Catalytic Reaction

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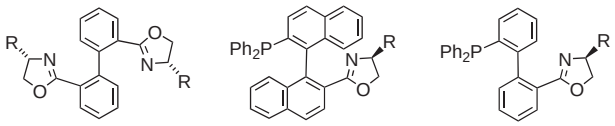
Abstract: A novel chiral phosphine-oxazoline ligand **3** with an axis-unfixed biphenyl backbone was prepared. This ligand existed as a mixture of two diastereomers in equilibrium in solution. However, when it was coordinated with palladium(II), only one of the two kinds of possible diastereomer complexes with different axial chirality was formed. When this axis-unfixed chiral ligand was used, up to 90% ee was attained for the palladium-catalyzed asymmetric allylic alkylation.

Key words: *P*,*N*-ligands, chiral biaryl ligands, oxazoline ligands, axial chirality, palladium-catalyzed allylic alkylation

Chiral oxazoline ligands derived from readily available amino acids have found widespread use in metal-catalyzed asymmetric reactions, and extensive efforts have been devoted to the preparation of their efficient structural derivatives.[1] As it is well known that axially chiral biaryl catalysts exhibit excellent chirality transfer properties in asymmetric synthesis, a number of oxazoline containing axially chiral biaryl ligands have been developed.[2] These enantiomerically stable biaryls require at least three *ortho*-substituents to avoid the racemization due to the rotation around the internal bond of the biaryls. Most of these chiral axis-fixed biaryl ligands finally need process of resolution and only one of the two diastereomers shows excellent catalytic activities and enantioselectivities for most cases. Different from these ligands with an axis-fixed biaryl backbone, a novel kind of chiral oxazoline ligands with an axis-unfixed biaryl backbone such as ligand **1** was developed by us; it exists as a mixture of two diastereomers in equilibrium in solution.[3] When this ligand was coordinated to Cu(I), only one of the two possible diastereomeric complexes was formed and showed excellent enantioselectivities in metal-catalyzed asymmetric reactions. On the other hand, we had also developed a novel chiral phosphino-oxazoline ligand **2** with an axis-fixed binaphthyl backbone.[4] These chiral *P*,*N*-ligands were successfully employed in the palladium-catalyzed allylic alkylation and showed excellent enantioselectivities. Taking into account of the advantages of chiral *P*,*N*-chelating binaphthyl ligand **2** and axis-unfixed biphenyl ligand **1** (Figure 1) with high usage efficiency and unnecessary resolution process, we designed a novel chiral phosphine-oxazoline ligand **3** with an axis-unfixed biphenyl backbone. We report here the synthesis and complexation of **3**, and its application in the palladium-catalyzed allylic alkylation of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate.



1 **2** **3**

a: R = *i*-Pr; **b**: R = *t*-Bu

Figure 1

Compound **3** was synthesized as shown in Scheme 1. 2,2′-Biphenol as starting material was treated with trifluoromethanesulfonic anhydride (Tf_2O) to give triflate **4**. Then the palladium-catalyzed insertion reaction of **4** with diphenylphosphine oxide was carried out to afford compound **5**. Furthermore, in the presence of methanol, the palladium-catalyzed insertion reaction of **5** with CO gave monocarboxylic acid ester **6**. In the presence of a catalytic amount of sodium hydride, the reaction of **6** with amino alcohol afforded amide compound **7**. Then, **7** was treated with methanesulfonyl chloride in the presence of triethylamine to give chiral monooxazoline compound **8**. Finally, the reduction of **8** with trichlorosilane afforded the novel chiral ligand **3**.[5] Each of the derivatives **3a** and **3b** were obtained in 33% overall yield after six steps.

The behavior of ligand **3** in solution was then investigated. As expected, two diastereomers were observed in solution for each ligand by ^1H NMR in CD_2Cl_2, existing in an equilibrium due to the rotation around the internal bond of the biphenyl backbone (Scheme 2). It was also found that the bulkiness of the substituents on the oxazoline ring had little effect on the ratio of the two diastereomers for the two derivatives **3a** and **3b** as shown in Table 1. The complexation behavior of ligands **3a** and **3b** to palladium(II) using complex $[Pd(\eta^3\text{-}1,3\text{-diphenylallyl})Cl]_2$ in solution was then examined. As expected, both of the two ligands gave only one of the two possible diastereomer complexes **9a**,**b** with different axial chirality in CD_2Cl_2, respectively, according to their ^1H NMR and ^{31}P NMR spectra like ligand **1** (Scheme 2 and Table 1).[6]

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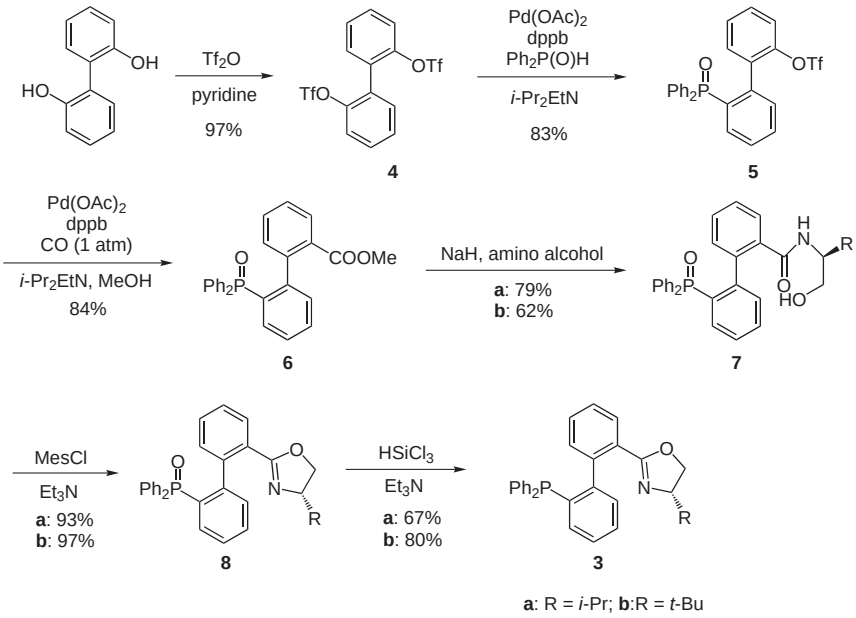
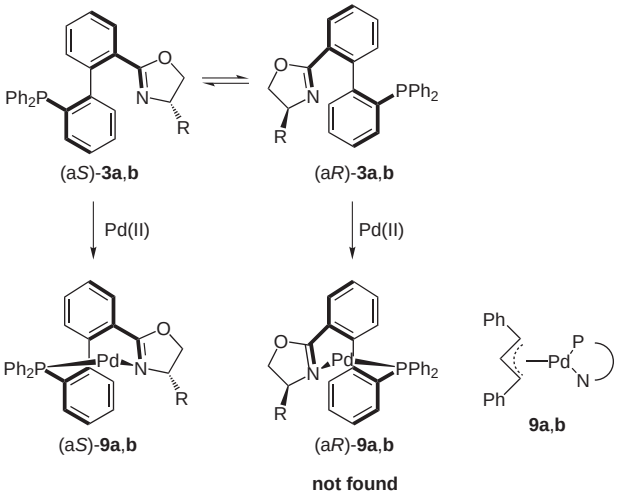


Scheme 1

Then, the absolute configuration of the axial chirality of complex **9** was investigated. It was reported that the absolute configuration of 2,2′-bridged biphenyl compounds could be determined by their CD spectrum, that is negative Cotton effect at 250 nm corresponding to *S*-configuration of axial chirality and vice versa.[7,8] This result encourages us to test our complex **9** which has a similar 2,2′-bridged eight-membered ring biphenyl backbone. As a result, both **9a** and **9b** showed a negative Cotton effect at 250 nm. This suggests that complex **9** has an *S* configuration in its axial chirality (Scheme 2).



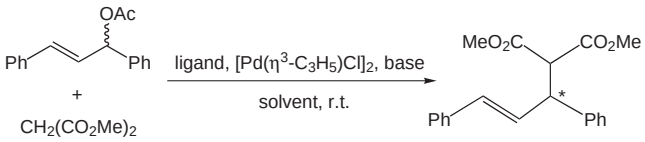
Scheme 2

Table 1 Diastereomeric Ratio of Ligands and Complexes

Ligand or complex	Axial major:axial minor[a]
3a (R = *i*-Pr)	52:48
3b (R = *t*-Bu)	54:46
9a (R = *i*-Pr)	100:0
9b (R = *t*-Bu)	100:0

[a] Determined by ^{1}H NMR and ^{31}P NMR in CD_2Cl_2 at 24 °C.

Palladium-catalyzed asymmetric allylic alkylation as an important asymmetric reaction has been investigated using various chiral oxazoline ligands.[9] We also carried out this model reaction using 1,3-diphenyl-2-propenyl acetate as a typical substrate to compare the ability of the new chiral phosphine-oxazoline ligand **3** with that of ligand **2** bearing an axis-fixed biaryl backbone (Scheme 3). The results are summarized in Table 2. Using bis(trimethylsilyl)acetamide (BSA) and a small amount of KOAc as the base, both of **3a** and **3b** gave high chemical yields and high enantiomeric excesses for the *S*-configured product. Particularly, when **3b** was used, the highest enantioselectivity of 90% ee for *S*-configured product was obtained. This result indicates that axis-unfixed ligand **3** can afford the similar enantioselectivity and reactivity to axis-fixed biaryl ligand **2**. The fact that *S*-configured product was obtained with ligand **3** also suggests that the complex **9** has an *S* configuration (Scheme 2) because in the case of ligand **2**, the *S*-axial chirality afforded *S*-configured product and vice versa (Table 2).[4]



Scheme 3

Table 2 Palladium-Catalyzed Allylic Alkylation of 1,3-Diphenyl-2-propenyl Acetate[a]

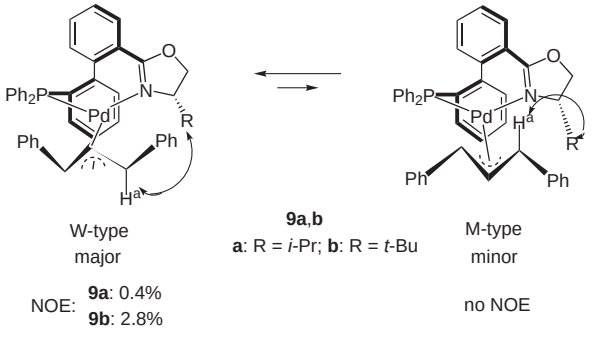
Ligand	Solvent	Base	Yield (%)	ee, %[b] (config)[c]
3a	THF	BSA–KOAc	96	83 (*S*)
	CH_2Cl_2	BSA–KOAc	89	82 (*S*)
3b	THF	BSA–KOAc	97	88 (*S*)
	CH_2Cl_2	BSA–KOAc	96	90 (*S*)
(a*S*)-**2a**[4]	THF	BSA–KOAc	93	85 (*S*)
(a*R*)-**2a**[4]	THF	BSA–KOAc	91	90 (*R*)

[a] Conducted at r.t. with 1,3-diphenyl-2-propenyl acetate (1 mmol), dimethylmalonate (3 mmol), BSA (3 mmol), and KOAc (20 μmol) in 3 mL of solvent under argon in the presence of the catalyst which was prepared from ligand (30 mmol) and $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (13 μmol) in 1 mL solvent for 1 h before use. All of the reactions finished within 1 h.

[b] Determined by HPLC (Chiralcel OD).

[c] Determined by comparing the sign of its optical rotation with literature data.

Finally, the stability and reactivity of reaction intermediates (*S*)-**9** were examined. For both (*S*)-**9a** and (*S*)-**9b**, two diastereomeric intermediates with W- and M-type were observed in their ^{1}H NMR and ^{31}P NMR spectrum in the ratio of 54:46 and 58:42, respectively (Scheme 4). The major was assigned as W-type by NOE observation between the proton of the substituent on oxazoline and H^a, and the minor was assigned as M-type by observing no NOE (Scheme 4). For the asymmetric alkylation, it is known that, because the *trans* effect directs nucleophilic attack to the allylic terminus *trans* to phosphorus atom,[10] the W-type intermediate leads to the product of *R* configuration, and the M-type one leads to the product of *S* configuration.[11] In the present case, with both **9a** and **9b**, the *S*-configured product was obtained. This result shows that the minor M-type diastereomer has much more reactivity than the major W-type one, due to the position *trans* to the phosphorus atom becoming more cationic, caused by the steric repulsion between the substituent on oxazoline ring and phenyl group.



Scheme 4

In conclusion, we have developed a novel chiral phosphine-oxazoline ligand **3** with an axis-unfixed biphenyl backbone existing as a mixture of two diastereomers in equilibrium in solution. It was found that when this compound coordinated to palladium(II), only one of the two possible kinds of diastereomer complexes with different axial chirality was formed. With this compound as a chiral ligand, up to 90% ee was attained for the palladium-catalyzed asymmetric allylic alkylation.

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(5) Compound **3a**: ^{1}H NMR (400 MHz, $CDCl_3$; major/minor = 57:43 in $CDCl_3$): δ = 7.89 (dd, *J* = 1.5, 7.7 Hz, 1 H), 7.88 (dd, *J* = 1.5, 7.7 Hz, 1 H), 7.38–7.07 (m, 32 H), 6.89 (br d, *J* = 7.7 Hz, 1 H), 4.09 (dd, *J* = 8.4, 9.5 Hz, 1 H), 4.01 (dd, *J* = 6.6, 8.1 Hz, 1 H), 3.90–3.80 (m, 3 H), 3.69 (t, *J* = 8.4 Hz, 1 H), 1.71–1.62 (m, 1 H), 1.61–1.52 (m, 1 H), 0.84 (d, *J* = 7.0 Hz, 3 H), 0.80 (d, *J* = 7.0 Hz, 3 H), 0.84 (d, *J* = 6.9 Hz, 3 H). ^{31}P NMR ($CDCl_3$, PPh_3 = –6.0 ppm): δ = –14.8 (major), –15.0 (minor). HRMS (EI): *m/z* calcd for $C_{30}H_{28}NOP$: 449.1910; found: 449.1905. Anal. Calcd for $C_{31}H_{30}NOP$: C, 80.16; H, 6.28; N, 3.12. Found: C, 79.78; H, 5.89; N, 3.11. $[\alpha]_D^{25}$ = –54.2 (*c* 0.48, $CHCl_3$).
Compound **3b**: ^{1}H NMR (400 MHz, $CDCl_3$, major/minor = 53:47 in $CDCl_3$): δ = 7.89 (dd, *J* = 1.1, 7.7 Hz, 1 H), 7.88 (dd, *J* = 1.1, 7.7 Hz, 1 H), 7.39–7.07 (m, 32 H), 6.88 (br d, *J* = 8.1 Hz, 1 H), 6.83 (br d, *J* = 8.1 Hz, 1 H), 4.06–3.93 (m, 3 H), 3.89–3.75 (m, 3 H), 0.81 (s, 9 H), 0.73 (s, 9 H).

^{31}P NMR ($CDCl_3$, PPh_3 = –6.0 ppm): δ = –14.9 (major), –15.0 (minor). HRMS (EI): *m/z* calcd for $C_{31}H_{30}NOP$: 463.2067; found: 463.2064. Anal. Calcd for $C_{31}H_{30}NOP$: C, 80.32; H, 6.52; N, 3.02. Found: C, 80.03; H, 6.62; N, 2.87. $[\alpha]_D^{25}$ –28.7 (*c* 0.52, $CHCl_3$).

(6) Complex **9** is formed with only one kind of axial chirality, but exists as a mixture of two diastereomers with W- and M-type.
Compound **9a**: ^{1}H NMR (400 MHz, CD_2Cl_2, major/minor = 54:46 in CD_2Cl_2): δ = 7.86–6.53 (m, 56 H), 5.91 (br d, *J* = 8.0 Hz, 1 H), 5.88 (br d, *J* = 7.6 Hz, 1 H), 5.80–5.68 (m, 2 H), 4.94 (d, *J* = 10.9 Hz, 1 H), 4.85 (d, *J* = 12.3 Hz, 1 H), 3.97–3.80 (m, 4 H), 3.34 (t, *J* = 9.4 Hz, 1 H), 2.48–2.38 (m, 1 H), 1.86–1.77 (m, 1 H), 1.50–1.40 (m, 1 H), 0.71 (d, *J* = 6.9 Hz, 3 H), 0.51 (d, *J* = 6.9 Hz, 3 H), 0.38 (d, *J* = 6.9 Hz, 3 H), 0.08 (d, *J* = 6.9 Hz, 3 H). ^{31}P NMR (CD_2Cl_2, PPh_3 = –6.0 ppm): δ = 28.8 (minor), 24.8 (major).
Compound **9b**: ^{1}H NMR (400 MHz, CD_2Cl_2, major/minor = 58:42 in CD_2Cl_2): δ = 7.87–6.58 (m, 55 H), 6.54 (dd, *J* = 11.2, 13.1 Hz, 1 H), 5.93–5.83 (m, 3 H), 5.53 (t, *J* = 10.9 Hz, 1 H), 4.94 (d, *J* = 11.2 Hz, 1 H), 4.80 (d, *J* = 12.3 Hz, 1 H), 4.03–3.96 (m, 2 H), 3.87 (dd, *J* = 9.1, 10.5 Hz, 1 H), 3.68 (dd, *J* = 5.4, 10.5 Hz, 1 H), 3.09 (t, *J* = 9.4 Hz, 1 H), 2.23 (br s, 1 H), 0.64 (s, 9 H), 0.43 (s, 9 H). ^{31}P NMR (CD_2Cl_2, PPh_3 = –6.0 ppm): δ = 29.1 (minor), 25.2 (major).

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