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Highly enantioselective Pd(II)-catalyzed Wacker-type cyclization of 2-allylphenols by use of bisoxazoline ligands with axis-unfixed biphenyl backbone

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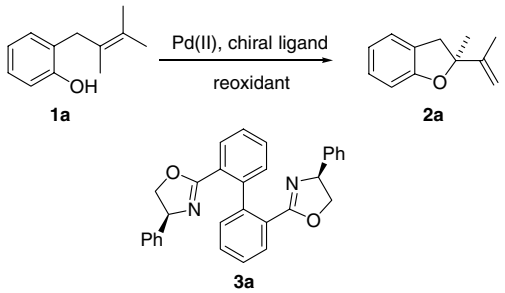
Abstract—A series of axis-unfixed bisoxazoline ligands with different steric and electronic properties has been synthesized. Due to the different steric interactions, the ligands afforded only one of the two possible diastereomeric Pd(II)-complexes upon metal coordination. The palladium complex (*S*,a*S*)-**8c** showed excellent catalytic activities and enantioselectivities in Wacker-type cyclization of allylphenols with up to 98% ee.

Pd(II)-catalyzed intramolecular Wacker-type cyclizations have emerged as a versatile strategy in the construction of a range of heterocycles.[1] However, in striking contrast to the well-defined Pd(0)-catalyzed asymmetric reactions,[2] asymmetric oxidative cyclizations with Pd(II)-complexes have received relatively little attention. Previous attempts at asymmetric version of this oxidative cyclizations were reported by Hosokawa and Murahashi,[3] nevertheless, the Wacker-type cyclization of 2-allylphenols by use of a chiral π-allylpalladium complex afforded dihydrobenzofurans with only 29% ee. Recently, Hayashi and co-workers reported an important breakthrough on the Pd(II)-catalyzed enantioselective Wacker-type cyclization of 2-allylphenols with chiral bisoxazoline ligands based on binaphthyl backbone (boxax).[4,5] In the cyclization of **1a**, 96% ee was obtained in the presence of *p*-benzoquinone in methanol by using boxax.[4a] Sasai and co-workers reported asymmetric oxidative tandom cyclization of alkenyl alcohols with spiro bisoxazoline ligands (SPRIXs) which gave a bicyclic product with a high enantiomeric excess (up to 95%).[6] Enantioselective aerobic cyclization was also reported with Pd(II)/sparteine as a catalyst system, however, the enantioselectivities are not sufficiently high.[7]

Recently, we reported C_2-symmetric bisoxazoline ligands **3a** bearing an axis-unfixed biphenyl backbone.[8] These ligands exist as an equilibrium mixture of diastereomers in solution as a result of the rotation around axis of biphenyl backbone, but only one of the two possible diastereomers was observed on complexation of ligands **3a** with copper(I) salts. In view of atom economy, traditional axis-fixed oxazoline ligands[9] require inconvenient diastereomeric separation in their synthetic processes, and generally, only one diastereomeric pure form of the ligands works effectively in catalytic asymmetric reactions due to their configurational matching–mismatching effect. Whereas the axial flexible ligands can afford completely a single diastereomeric metal catalyst on complexing process without any ligand wasting caused by configurational mismatching. Therefore, herein we report the development of highly enantioselective Pd(II)-catalyzed Wacker-type cyclization of 2-allylphenols with our axial flexible bisoxazoline **3** as chiral ligands.



1a **2a** **3a**

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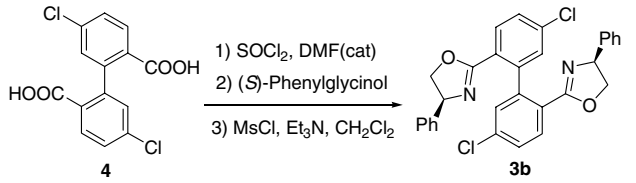
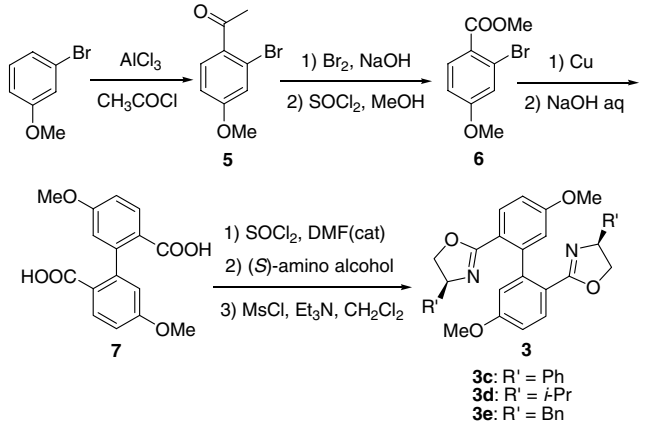
In order to evaluate the influence of steric and electronic properties of ligands on the enantioselective transformation, a series of axis-unfixed oxazoline ligands **3b–e** has been synthesized. Bisoxazoline ligand, 2,2′-bis[(4′*S*)-isopropyl oxazolin-2′-yl]-5,5′-dichloro-1,1′-biphenyl (**3b**)[10] was synthesized in three steps in 63% overall yield starting from 5,5′-dichloro-1,1′-biphenyl-2,2′-dicarboxylic acid (**4**)[8c] according to the well-known procedures of oxazoline ring formation[11] (Scheme 1). 5,5′-Dimethoxylated bisoxazolines **3c–e** were synthesized starting from 3-bromoanisole as depicted in Scheme 2. Friedel–Crafts acylation of 3-bromoanisole gave acylated compound **5** in 59% yield.[12] Bromoform reaction of compound **5**, followed by esterification of carboxylic acid in methanol, afforded 2-bromo-4-methoxybenzoate (**6**) in 87% yield.[13] Ullman coupling of compound **6** with activated copper powder followed by hydrolysis furnished biphenyl skeleton **7** in 58% yield. Diacid **7** was subjected to oxazoline ring formation as the same way for synthesis of **3b** to afford 5,5′-dimethoxylated bisoxazoline **3c–e**[14] in 54%, 50%, and 60% overall yields, respectively. The two diastereomers of axis-unfixed bisoxazolines **3** can be observed in solution at room temperature by ^{1}H NMR spectroscopy. Due to the different steric interactions, one diastereomer dominated over the other one. Thus, the ratios of the two diastereomers of **3** were within 1.3:1 to 2.5:1 by examination of ^{1}H NMR spectroscopy (Table 1). It was also shown that the two diastereomers of all ligands **3** are in equilibrium in solution because the ratios changed as the temperature was varied.

To evaluate the coordinating behavior of axis-unfixed bisoxazolines **3**, the reactions of **3** with 1 equiv of $PdCl_2$ in acetonitrile-d_3 at 16 °C were monitored by ^{1}H NMR spectroscopy. As expected, all of the resultant solutions

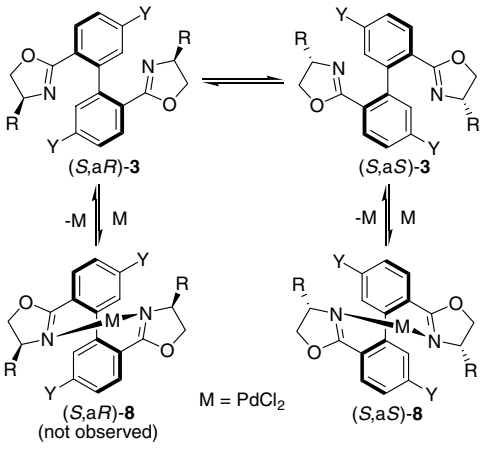


Scheme 1.



Scheme 2.

Table 1. The complexation behavior of ligands **3**



	a	b	c	d	e
(*S*,a*R*)-**3**: (*S*,a*S*)-**3**[a]	1:1.4	1:1.4	1:2.2	1:2.5	1:1.3
(*S*,a*R*)-**8**: (*S*,a*S*)-**8**[a]	0:100	0:100	0:100	0:100	0:100

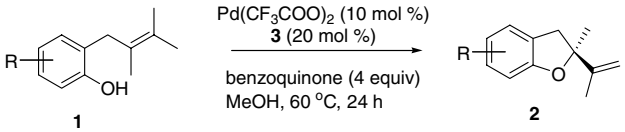
[a] The ratios of the two diastereomers of **3** and **8** were determined by ^{1}H NMR (400 MHz) in CD_3CN at 16 °C.

afforded only one set of peaks in ^{1}H NMR spectroscopy.[15] This observation obviously suggested that only one diastereomer quantitatively formed through the coordinating process of ligands **3** with palladium ion (Table 1). The axial configurations of the obtained complexes **8** were assigned as *S* by comparison with our previous report on this type of metal complexes.[8]

With the complexation behavior in hand, the Pd(II)-complexes of axis-unfixed bisoxazoline ligands **3** were used in Pd(II)-catalyzed intramolecular Wacker-type cyclization. Typically, 2-(2,3-dimethyl-2-butenyl)phenol (**1a**) was used as a model substrate for the oxidative cyclization. The reactions were catalyzed by 10 mol % of the Pd(II)–**3** complexes generated in situ by mixing $Pd(CF_3COO)_2$ with bisoxazolines **3** in a 1:2 molar ratio in the presence of *p*-benzoquinone as reoxidant in methanol at 60 °C. It was found that the catalytic efficiencies in the cyclization reaction largely depended on the electronic properties of the 5 and 5′-substituents of the ligand as well as bulkiness of substituents on the oxazoline rings. As shown in Table 2, with the standard axis-unfixed bisoxazoline **3a** as ligand, allylphenol **1a** was cyclized with 92% ee in high isolated yield (entry 1). However, the catalytic activity and enantioselectivity in the cyclization were markedly decreased with 5,5′-dichlorinated bisoxazoline **3b** as ligand (entry 2). Whereas using ligand **3c**, which has electronic donating methoxy groups in ligand backbone, the reactivity and enantioselectivity were dramatically improved (entry 3). However, when the substituents on the oxazoline rings of ligands changed to isopropyl or benzyl groups (**3d** or **3e**), the cyclization afforded product **2a** with remarkably lower enantioselectivity (entries 4–5).

The generality of the chelation-induced axially chiral Pd-catalyst, **3c**–$Pd(CF_3COO)_2$, has been successfully demonstrated through the Wacker-type cyclization of a series of *o*-allylphenols **1b–h** and *o*-allylnaphthols **1i**,

Table 2. Pd(II)-catalyzed asymmetric Wacker-type cyclization of **1**[a]



1 2

Entry	Ligand	Substrate	R	Yield[b] (%)	ee[c] (%)
1	**3a**	**1a**	H	86	92
2	**3b**	**1a**	H	67	84
3	**3c**	**1a**	H	92	94
4	**3d**	**1a**	H	81	53
5	**3e**	**1a**	H	89	80
6	**3c**	**1b**	4-Me	92	90
7	**3c**	**1c**	5-Me	83	93
8	**3c**	**1d**	6-Me	74	98
9	**3c**	**1e**	4-OMe	80	90
10	**3c**	**1f**	6-OMe	79	98
11	**3c**	**1g**	4-F	65	94
12	**3c**	**1h**	4-Ph	73	91[d]
13	**3c**	**1i**	1-Naphthol	75	92[e]

[a] All reactions were catalyzed by 10 mol % of the Pd(II)–**3** complex generated in situ by mixing $Pd(CF_3COO)_2$ with bisoxazolines **3** (Pd/ligand 1:2) in the presence of 4 equiv of *p*-benzoquinone in methanol at 60 °C for 24 h.

[b] Isolated yield by column chromatography.

[c] The enantiomeric excesses were determined by chiral GC on a CP-Chirasil-Dex CB column. The absolute configurations were determined by comparing the sign of the optical rotation with that reported in Ref. 4

[d] The enantiomeric excess was determined by HPLC on a Chiracel OD-H column.

[e] The enantiomeric excess was determined by HPLC on a Chirapak AD-H column.

providing corresponding chiral 2,3-dihydrobenzofurans **2b–h** and dihydronaphtho[1,2-*b*]furan **1i** with excellent enantioselectivities (90–98% ee). As exemplified by the substrates with methyl groups in 4-, 5- and 6-positions of allylphenol, the steric properties of the substrates certainly affected the reactivity and enantioselectivity. Thus, the Wacker-type cyclization of sterically more hindered 6-methyl-2-allylphenol **1d** showed significantly higher enantioselectivity than that of **1b** and **1c**, but the isolated yield of **2d** was lower than that of **2b** and **2c** (entries 6–8). Similar trends in enantioselecitivity were observed in the cyclization of 4- and 6-methoxylate substrates, **1e** and **1f** (entries 9–10). The cyclization of **1g** and **1h** with fluoro and phenyl group at the 4-position of 2-allylphenol, respectively, also afforded good yields and excellent enantioselectivities (entries 11–12). Furthermore, for 2-(2,3-dimethyl-2-butenyl)-1-naphthol (**1i**), the cyclization gave the corresponding dihydronaphtho[1,2-*b*]furan **2i** with good isolated yield and high enantioselectivity (92% ee, entry 13).

In summary, a series of axis-unfixed bisoxazoline ligands **3** with different steric and electronic properties was synthesized. These ligands were proven to exist as a mixture of two diastereomers in equilibrium in solution. Significantly, upon coordination with a Pd(II) ion, ligands **3** afforded only one of the two possible diastereomeric Pd(II)-complexes. In their application in Wacker-type cyclization of allylphenols, pronounced effects of the electronic and steric properties of the ligand on enantioselectivity have been observed, and excellent catalytic activities and enantioselectivities with up to 98% ee were obtained by using Pd(II)–**3c** complex as catalyst.

Acknowledgment

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10. Compound **3b**: $[\alpha]_D^{25}$ −144.76 (*c* 1.20, $CHCl_3$); ^1H NMR (400 M, $CDCl_3$) major: δ 7.91 (d, $J = 8.0$ Hz, 2H, ArH), 7.20–7.45 (m, 10H, ArH), 7.12–7.18 (m, 4H, ArH), 5.15–5.25 (m, 2H, NCH), 4.43–4.53 (m, 2H, OCH_2), 3.92 (t, $J = 8.0$ Hz, 2H, OCH_2); minor: δ 7.95 (d, $J = 8.4$ Hz, 2H, ArH), 7.20–7.45 (m, 10H, ArH), 7.03–7.08 (m, 4H, ArH), 5.15–5.25 (m, 2H, NCH), 4.43–4.53 (m, 2H, OCH_2), 3.98 (t, $J = 8.4$ Hz, 2H, OCH_2); ^{13}C NMR (100 M, $CDCl_3$) δ 70.0, 70.1, 74.6, 75.3, 126.5, 126.7, 127.4, 127.6, 127.7,

128.0, 128.7, 128.8, 130.1, 130.2, 131.2, 136.6, 141.8, 142.1, 164.8, 162.1; HRMS (Micromass LCT) Calcd. for $C_{30}H_{22}N_2O_2Cl_2$: 512.1058. Found: 512.1075.

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14. Compound **3c**: $[\alpha]_D^{25}$ −187.48 (*c* 0.88, $CHCl_3$); ^1H NMR (400 M, $CDCl_3$) major: δ 7.91 (d, $J = 8.4$ Hz, 2H, ArH), 7.15–7.35 (m, 10H, ArH), 7.08–7.13 (m, 2H, ArH), 6.90–6.96 (m, 2H, ArH), 5.15–5.24 (m, 2H, NCH), 4.48 (dd, $J = 10.0$, 8.8 Hz, 2H, OCH_2), 3.89 (t, $J = 8.0$ Hz, 2H, OCH_2), 3.85 (s, 6H, OCH_3); minor: δ 7.95 (d, $J = 8.4$ Hz, 2H, ArH), 7.15–7.35 (m, 10H, ArH), 6.90–6.96 (m, 2H, ArH), 6.80 (d, $J = 2.0$ Hz, 2H, ArH), 5.15–5.24 (m, 2H, NCH), 4.42 (dd, $J = 10.0$, 8.8 Hz, 2H, OCH_2), 3.98 (t, $J = 8.0$ Hz, 2H, OCH_2), 3.82 (s, 6H, OCH_3); ^{13}C NMR (100 M, $CDCl_3$) δ 55.5, 69.8, 69.9, 74.5, 75.2, 112.9, 115.5, 120.4, 126.7, 126.8, 127.3, 127.5, 128.5, 128.7, 131.5, 142.8, 142.9, 143.2, 143.9, 161.1, 166.0; HRMS (Micromass LCT) Calcd. for $C_{32}H_{29}N_2O_4$: 505.2127. Found: 505.2135. Compound **3d**: $[\alpha]_D^{25}$ −92.31 (*c* 1.75, $CHCl_3$); ^1H NMR (400 M, $CDCl_3$) major: δ 7.74 (d, $J = 8.8$ Hz, 2H, ArH), 6.82–6.86 (m, 2H, ArH), 6.79 (br, 2H, ArH), 4.05 (t, $J = 8.0$ Hz, 2H, OCH_2), 3.65–3.85 (m, 10H, OCH_2, OCH_3 and NCH), 1.50–1.70 (m, 2H, CH), 0.65–0.82 (m, 12H, CH); minor: δ 7.79 (d, $J = 8.8$ Hz, 2H, ArH), 6.82–6.86 (m, 2H, ArH), 6.70 (br, 2H, ArH), 4.04 (t, $J = 12.0$ Hz, 2H, OCH_2), 3.65–3.85 (m, 10H, OCH_2, OCH_3 and NCH), 1.50–1.70 (m, 2H, CH), 0.65–0.82 (m, 12H, CH); ^{13}C NMR (100 M, $CDCl_3$) δ 18.1, 18.4, 18.9, 19.0, 32.6, 32.9, 55.3, 70.2, 72.4, 72.5, 112.6, 112.8, 115.0, 115.4, 120.0, 120.5, 130.9, 131.1, 143.1, 143.5, 160.4, 160.6, 163.7, 164.0; HRMS (Micromass LCT) Calcd. for $C_{26}H_{32}N_2O_4$: 436.2362. Found: 436.2358. Compound **3e**: $[\alpha]_D^{25}$ −147.86 (*c* 1.71, $CHCl_3$); ^1H NMR (400 M, $CDCl_3$) major: δ 7.74 (d, $J = 8.4$ Hz, 2H, ArH), 7.06–7.30 (m, 10H, ArH), 6.90 (d, $J = 2.8$ Hz, 2H, ArH), 6.85–6.89 (m, 2H, ArH), 4.26–4.38 (m, 2H, NCH), 4.05 (t, $J = 8.8$ Hz, 2H, OCH_2), 3.86 (s, 6H, OCH_3), 3.70–3.90 (m, 2H, OCH_2), 2.98 (dd, $J = 4.8$, 13.6 Hz, 2H, CH_2), 2.51–2.60 (m, 2H, CH_2); minor: δ 7.82 (d, $J = 8.4$ Hz, 2H, ArH), 7.06–7.30 (m, 10H, ArH), 6.85–6.89 (m, 2H, ArH), 6.78 (d, $J = 2.8$ Hz, 2H, ArH), 4.26–4.38 (m, 2H, NCH), 3.97 (t, $J = 8.8$ Hz, 2H, OCH_2), 3.81 (s, 6H, OCH_3), 3.70–3.90 (m, 2H, OCH_2), 3.07 (dd, $J = 4.8$, 13.6 Hz, 2H, CH_2), 2.51–2.60 (m, 2H, CH_2); ^{13}C NMR (100 M, $CDCl_3$) δ 41.7, 41.8, 55.6, 68.1, 72.1, 112.7, 113.0, 115.5, 115.8, 126.4, 126.5, 128.6, 128.7, 129.3, 129.5, 131.1, 131.5, 138.6, 143.5, 161.1, 164.6; HRMS (Micromass LCT) Calcd. for $C_{34}H_{33}N_2O_4$: 533.2440. Found: 533.2434.
15. Compound (*S*,a*S*)-**8a**: ^1H NMR (400 M, CD_3CN): δ 9.11 (dd, $J = 1.6$, 7.2 Hz, 2H, ArH), 8.25 (dd, $J = 1.2$, 7.6 Hz, 2H, ArH), 7.50–7.90 (m, 14H, ArH), 5.44 (t, $J = 10.8$ Hz, 2H, NCH), 4.81 (dd, $J = 8.8$, 9.6 Hz, 2H, OCH_2), 3.81 (dd, $J = 8.8$, 11.2 Hz, 2H, OCH_2). Compound (*S*,a*S*)-**8b**: ^1H NMR (400 M, CD_3CN): δ 9.04 (d, $J = 8.4$ Hz, 2H, ArH), 8.43 (d, $J = 2.0$ Hz, 2H, ArH), 7.50–7.70 (m, 12H, ArH), 5.45 (t, $J = 11.2$ Hz, 2H, NCH), 4.85 (dd, $J = 8.8$, 9.6 Hz, 2H, OCH_2), 3.94 (t, $J = 8.4$ Hz, 2H, OCH_2). Compound (*S*,a*S*)-**8c**: ^1H NMR (400 M, CD_3CN): δ 9.06 (d, $J = 8.4$ Hz, 2H, ArH), 7.75 (d, $J = 2.8$ Hz, 2H, ArH), 7.51–7.64 (m, 10H, ArH), 7.35 (dd, $J = 2.8$, 8.8 Hz, 2H, ArH), 5.39 (t, $J = 11.2$ Hz, 2H, NCH), 4.78 (t, $J = 9.2$ Hz, 2H, OCH_2), 4.02 (s, 6H, OCH_3), 3.85 (dd, $J = 9.2$, 11.2 Hz, 2H, OCH_2). Compound (*S*,a*S*)-**8d**: ^1H NMR (400 M, CD_3CN): δ 9.02 (d, $J = 8.8$ Hz, 2H, ArH), 7.68 (d, $J = 2.4$ Hz, 2H, ArH), 7.43 (dd, $J = 2.4$, 8.8 Hz, 2H, ArH), 4.56 (m, 2H, NCH), 4.25 (dd, $J = 9.6$, 11.2 Hz, 2H, OCH_2), 4.03 (s, 6H, OCH_3), 3.84 (t, $J = 9.2$, 11.2 Hz, 2H, OCH_2), 1.24 (d, $J = 6.4$ Hz, 6H, CH_3), 1.11–1.25 (m, 2H, CH), 0.51 (d, $J = 6.4$ Hz, 6H, CH_3). Compound (*S*,a*S*)-**8e**: ^1H NMR (400 M, CD_3CN): δ 9.01 (d, $J = 8.8$ Hz, 2H, ArH), 7.56 (d, $J = 2.4$ Hz, 2H, ArH), 7.27–7.40 (m, 12H, ArH), 4.47–4.56 (m, 2H, NCH), 4.38 (dd, $J = 4.4$, 13.6 Hz, 2H, OCH_2), 4.30 (t, $J = 9.2$ Hz, 2H, OCH_2), 4.00 (s, 6H, OCH_3), 3.64 (dd, $J = 8.8$, 10.4 Hz, 2H, $PhCH_2$), 2.88 (dd, $J = 10.0$, 14.0 Hz, 2H, $PhCH_2$).