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Tetrahedron Letters
Tetrahedron Letters 48 (2007) 4083–4086

Atropisomeric bisoxazoline ligands with a bridge across the 5,5′-position of biphenyl for asymmetric catalysis

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Received 28 February 2007; revised 3 April 2007; accepted 4 April 2007
Available online 11 April 2007

Abstract—A new family of atropisomeric bisoxazoline 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 by 5,5′-linkage of biphenyls even without 6,6′-substituents on biphenyls. The Pd(II)-**2d** complex as catalyst showed high catalytic activity and enantioselectivity for asymmetric Wacker-type cyclization of allylphenols.

The design and synthesis of effective chiral ligands have played a significant role in advancement of asymmetric catalysis, and have attracted a great deal of attention from both academia and industry. Thousands of chiral ligands have been developed and applied in various catalytic asymmetric reactions to produce enantiomerically pure compounds.[1] Among them, atropisomeric biaryl ligands, such as BINAP,[2] BINOL,[3] and boxax,[4] have been explored as effective templates for many transition metal-catalyzed asymmetric reactions.[5] Atropisomerism results from restricted rotation around biaryl axis produced by *ortho*-substituents. Generally, enantiomerically stable biaryls require at least three *ortho*-substituents to prevent racemization.[6] Therefore, for all of the reported bidendate atropisomeric biphenyl ligands, there is at least one steric hindered group at 6- or 6′-position on biphenyls for the sake of stable axial chirality. In contrast to traditional atropisomeric biaryl ligands, we introduce a novel atropisomeric framework **1** (Fig. 1), in which the biphenyls have only two coordinating groups next to the axis. The axial chirality of biphenyls is expected to be retained by macro-ring strain produced by 5,5′-linkage of biphenyls. We hypothesize that compounds **1** with more bulky coordinating groups may lead to more stable axial chirality, and the length of backbone carbon chain can control the conformational flexibility of atropisomeric ligands to provide more suitable chiral environment for asymmetric catalysis.

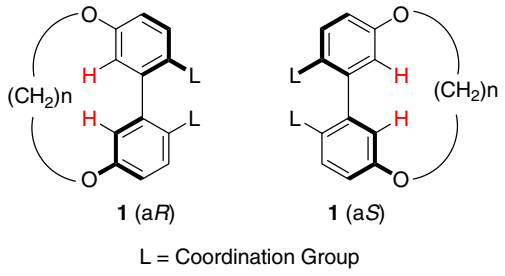

Figure 1. Atropisomeric bisoxazoline ligands with a bridge across the 5,5′-position of biphenyl.

On the other hand, C_2-symmetric bisoxazoline ligands with an axially chiral biaryl backbone as an effective ligand family have been successfully used in some important asymmetric reactions due to their synergistic asymmetric induction by combination of the central chirality of oxazoline rings and the axial chirality of backbone.[7] Moreover, the two atropdiastereomers of the ligands can be easily separated by introducing optically active oxazoline moieties. Thus, we report herein the synthesis of a new family of atropisomeric bisoxazoline ligands with a bridge across the 5,5′-position of biphenyl, 2,2′-bisoxazolinyl-5,5′-(polymethylenedioxy)biphenyls **2**, the evaluation of their stability of axial configurations, and their application in Pd(II)-catalyzed Wacker-type cyclization.

Our synthetic approach to diastereomeric pure (*S*,a*R*)- and (*S*,a*S*)-**2** is depicted in Scheme 1. Ullman coupling

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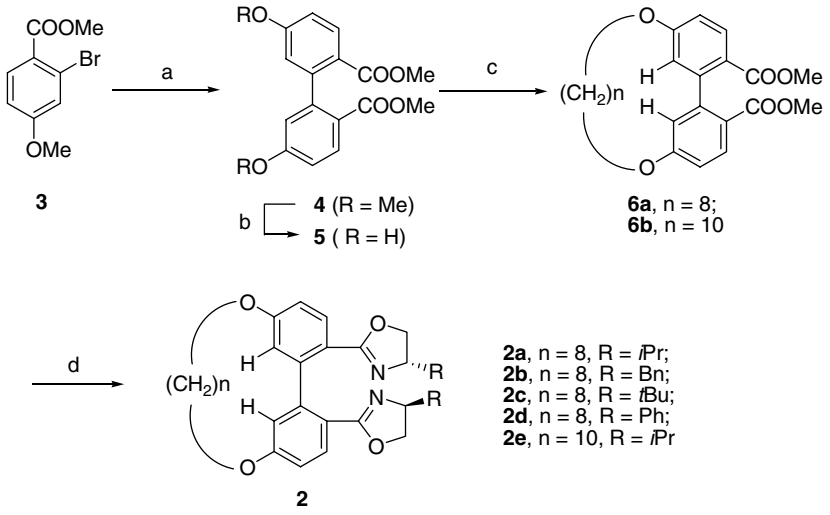
doi:10.1016/j.tetlet.2007.04.007

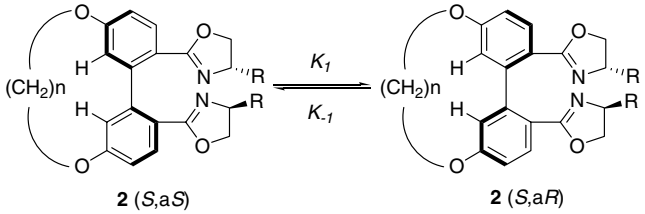


Scheme 1. Reagents and conditions: (a) Cu; (b) (i) $AlCl_3$, 1-dodecanethiol, CH_2Cl_2; (ii) $SOCl_2$, MeOH; (c) $Br(CH_2)_nBr$, K_2CO_3, DMF; (d) (i) amino alcohol, K_2CO_3, MeOH; (ii) MsCl, Et_3N, CH_2Cl_2.

of methyl 2-bromo-4-methoxybenzoate (**3**)[8] with activated copper powder furnished biphenyl skeleton **4** in 61% yield. Demethylation of **4** with aluminum chloride and 1-dodecanethiol afforded a mixture of the corresponding diphenol diester **5**, diphenol monoacid and diphenol diacid. This mixture was further converted to diphenol diester **5** by esterification with $SOCl_2$ and methanol in 81% yield from **4**. Cyclization of **5** with 1,8-dibromooctane and 1,10-dibromodecane led to the key intermediates **6a** and **6b** in 41% and 39% yields, respectively. Direct treatment of **6a** with (*S*)-valinol gave the amides as a mixture of diastereomeric isomers,[9] which were subjected to the oxazoline ring formation by treatment with methanesulfonyl chloride in the presence of triethylamine to give **2a** in 45% yield from **6a**.[10] These diastereomeric isomers were conveniently separated by column chromatography. In the same way, bisoxazolines **2b–e** were prepared in 35–44% yields from **6a** or **6b**. For **2c**, derived from (*S*)-*t*-leucinol, only one diastereomer was obtained in 35% yield after oxazoline ring formation. The sense of axial chirality of **2a** was determined by the major *Cotton* effects (CE) in the CD spectra. The CD curve of one of the two diastereomers of **2a** displayed two negative CE at 328.6 nm and 271.4 nm. This signed feature is the characteristic of (*S*)-configuration at chiral axis, which was in contrast with the spectra in the literature of axially chiral biphenyl compounds.[11] The axial configurations of **2b–e** were assigned by comparison of their chemical shifts of aryl proton in ^1H NMR spectrum with that of **2a**.

To evaluate the stability of axial configuration of bisoxazoline ligands **2**, two pairs of atropdiastereomers (*S*,a*S*)-**2a** and (*S*,a*R*)-**2a**, (*S*,a*S*)-**2e** and (*S*,a*R*)-**2e** were dissolved in various deuterated organic solvents (chloroform-*d*, acetone-d_6, methanol-d_4 and DMSO-d_6) respectively, and stirred at room temperature for 48 h. As a result, no interconversions of the two atropdiastereomers were found in any solvent system by determination of ^1H NMR spectrum. Even the temperature at 60 °C, the ligands still maintained stable axial configuration without any racemization of axial chirality. However, when the temperature was increased to 100 °C, the ligands underwent racemization in DMSO-d_6 (Table 1). It was found that the bulkiness of substituents on the oxazoline ring and the length of backbone carbon chains had a remarkable influence on the stability of axial configuration for bisoxazoline **2**. For ligand **2a** with octamethylenedioxy bridge, the free energy barrier to axial torsion is 129.9 kJ mol^{-1} and the half-life periods is 18.3 h at 100 °C, which were determined by ^1H NMR spectrum[12] (entry 1). When the substituents on the oxazoline rings changed into more bulky *tert*-butyl groups, the half-life periods markedly increased to 49.1 h (entry 2). For bisoxazoline **2e**, in which the ligand backbone bears longer decamethylenedioxy ring, the half-life periods obviously decreased to 4.9 h, which gave $\Delta G^{\ddagger} = 126.8$ kJ mol^{-1}(entry 3). Thus, it can be concluded that the ligands with more bulky coordination groups and more suitable backbone polymethylenedioxy ring provide more stable axial chirality, as we have hypothesized above.

Table 1. Free energy barriers and rates of racemization for atropisomeric bisoxazolines **2** in DMSO-d_6 at 373 K[a]

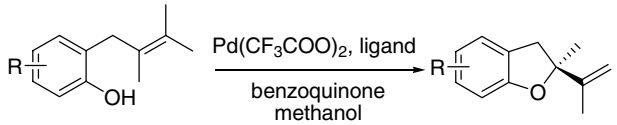


Entry	Ligand	K_1 (h^{-1})	K_{-1} (h^{-1})	$\Delta G^{\ddagger}$ (kJ mol^{-1})	$t_{1/2}$ (h)
1	**2a**	1.81×10^{-2}	1.98×10^{-2}	129.9	18.3
2	**2c**	6.03×10^{-3}	8.09×10^{-3}	133.3	49.1
3	**2e**	4.86×10^{-2}	9.44×10^{-2}	126.8	4.9

[a] Determined by ^1H NMR spectrum analysis.

Pd(II)-catalyzed intramolecular Wacker-type cyclizations have emerged as a versatile strategy in the construction of a range of heterocycles.[13] However, asymmetric oxidative cyclizations with chiral Pd(II)-complexes have received relatively little attention. Although Hayashi and Uozumi have made an important breakthrough on the Pd(II)-catalyzed enantioselective Wacker-type cyclization of 2-allylphenols with chiral bisoxazoline ligands based on binaphthyl backbone (boxax),[14] only a few ligands have been successfully applied in this type of cyclization.[15] To evaluate effectiveness of our atropisomeric bisoxazoline ligands **2** in Wacker-type cyclization, typically, 2-(2,3-dimethyl-2-butenyl)phenol (**7a**) was used as a model substrate for the oxidative cyclization. The reactions were catalyzed by 10 mol % of the Pd(II)-**2** complexes generated in situ by mixing $Pd(OCOCF_3)_2$ with bisoxazolines **2** in the presence of *p*-benzoquinone as reoxidant in methanol at 60 °C (Table 2). It was found that the catalytic efficiency largely depended on the axial configuration. Thus, the palladium complex with (*S*,a*R*)-**2a** showed remarkably higher catalytic activity and enantioselectivity than that with corresponding diastereomer (*S*,a*S*)-**2a** in the cyclization (entries 1 and 2). Changing the substituents on the oxazoline rings of ligands had a little influence on the enantioselectivity, and the highest selectivity (85% ee) was obtained with phenyl-substituted **2d** as the ligand (entries 4 and 5). When the reactions were carried out at 35 °C for 3 d, the enantioselectivities had a little increase, but the isolated yields were remarkably low (entries 3 and 6). With (*S*,a*R*)-**2e**, which had decamethylenedioxy bridge, the enantioselectivity decreased to 79% ee (entry 7). A series of *o*-allylphenols can be cyclized to the corresponding 2,3-dihydrobenzofurans **8** using Pd(II)-**2d** as a catalyst. As exemplified by the substrates with methyl group in 4-, 5- and 6-positions of *o*-allylphenol (entries 8–10), the enantioselectivity was affected slightly by the steric properties of these substrates, but the yield for 6-methyl-2-allylphenol **7d** was correspondingly low in the same reaction conditions. For other substituted *o*-allylphenols **7e**–**h**, the enantioselectivities were delicately affected by the steric and electronic properties of the substrates (entries 11–14). For 2-(2,3-dimethyl-2-butenyl)-1-naphthol (**7i**), the cyclization gave the corresponding dihydronaphtho[1,2-*b*]furan **8i** with good isolated yield and high enantioselectivity (93% ee, entry 15).

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



7 **8**

Entry	Ligand	Substrate	R	Yield[b] (%)	ee[c] (%)
1	(*S*,a*S*)-**2a**	**7a**	H	8	6
2	(*S*,a*R*)-**2a**	**7a**	H	87	83
3[d]	(*S*,a*R*)-**2a**	**7a**	H	39	84
4	(*S*,a*R*)-**2b**	**7a**	H	85	75
5	(*S*,a*R*)-**2d**	**7a**	H	82	85
6[d]	(*S*,a*R*)-**2d**	**7a**	H	45	87
7	(*S*,a*R*)-**2e**	**7a**	H	86	79
8	(*S*,a*R*)-**2d**	**7b**	4-Me	74	88
9	(*S*,a*R*)-**2d**	**7c**	5-Me	81	89
10	(*S*,a*R*)-**2d**	**7d**	6-Me	41	91
11	(*S*,a*R*)-**2d**	**7e**	4-OMe	73	86
12	(*S*,a*R*)-**2d**	**7f**	6-OMe	55	85
13	(*S*,a*R*)-**2d**	**7g**	4-F	80	86
14	(*S*,a*R*)-**2d**	**7h**	4-Ph	62	87
15	(*S*,a*R*)-**2d**	**7i**	1-Naphthol	53	93

[a] All reactions were catalyzed by 10 mol % of the Pd(II)-**2** complex generated in situ by mixing $Pd(OCOCF_3)_2$ with bisoxazolines **2** (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 or HPLC.

[d] The reaction was carried out at 35 °C for 3 days.

In summary, we have developed a new family of atropisomeric bisoxazoline ligands **2** with a bridge across the 5,5′-position of biphenyl. It was demonstrated that the axial chirality of this type of ligands can be retained by macro-ring strain produced from 5,5′-linkage of biphenyls even without 6,6′-substituents. The Pd(II)-**2d** complex as catalyst showed high catalytic activity and enantioselectivity in Wacker-type cyclization of allylphenols **7**. Further studies will focus on the development and application of this class of atropisomeric ligands.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (grant nos. 20572070 and 20502015), the Ministry of Education of China (EYTP and SRFDP).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.04.007.

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