C–H Activation

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Construction of Axial Chirality by Rhodium-Catalyzed Asymmetric Dehydrogenative Heck Coupling of Biaryl Compounds with Alkenes**

*Jun Zheng and Shu-Li You**

Abstract: *Enantioselective construction of axially chiral biaryls by direct C–H bond functionalization reactions has been realized. Novel axially chiral biaryls were synthesized by the direct C–H bond olefination of biaryl compounds, using a chiral [Cp*Rh^{III}] catalyst, in good to excellent yields and enantioselectivities. The obtained axially chiral biaryls were found as suitable ligands for rhodium-catalyzed asymmetric conjugate additions.*

Axially chiral biaryl units are often found in natural products[1] as well as biologically active molecules and serve as privileged scaffolds for chiral auxiliaries, ligands, and catalysts in asymmetric synthesis.[2] Owing to these facts, the synthesis of axially chiral biaryls has been the subject of intensive research. Many elegant methods for the atroposelective construction of axially biaryls are available including asymmetric Suzuki–Miyaura couplings,[3] desymmetrization of prochiral biaryl compounds,[4] atroposelective cleavage of the biaryl lactones,[5] asymmetric oxidative homocouplings,[6] and asymmetric aryl formations by [2+2+2] cycloaddition reactions.[7] Despite these advances, the construction of enantioenriched biaryls by direct C–H bond functionalization of achiral biaryl compounds is much less explored, but an efficient strategy. To the best of our knowledge, there are only a handful of examples reported about the synthesis of axially chiral compounds through direct asymmetric C–H bond functionalization.[8] In 2000, Murai and co-workers reported the atroposelective C–H activation/alkylation of naphthyl pyridines and naphthyl isoquinolines using the rhodium(I) catalyst ligated by a chiral ferrocenyl phosphine ligand, which gave the coupling product in 37% yield and 49% *ee* as the best result.[9] Later, Yamaguchi, Itami, and co-workers elegantly demonstrated that a catalytic amount of $Pd(OAc)_2$ in combination with a chiral bisoxazoline ligand and TEMPO as the oxidant could catalyze asymmetric synthesis of heterobiaryls, although the products were obtained in moderate yields and *ee* values.[10] The same group recently improved the asymmetric coupling to synthesize hindered heterobiaryls by utilizing a Pd^{II}/sulfoxide/oxazoline complex and Fe/phthalocyanine open to air.[11] More recently, the group of Colobert succeeded in developing palladium(II)-catalyzed atroposelective C–H olefination of biphenyls by employing enantiopure *p*-tolyl sulfoxide as the directing group.[12] Nevertheless, the facile construction of axially chiral biaryls by direct catalytic C–H bond functionalization remains challenging.[13] A major obstacle might be the fact that the formation of the five-membered cyclometalated species during the C–H activation process requires the coplanarity of the two sterically hindered arenes, which raises the energetic barrier of the reaction (Figure 1).[14]

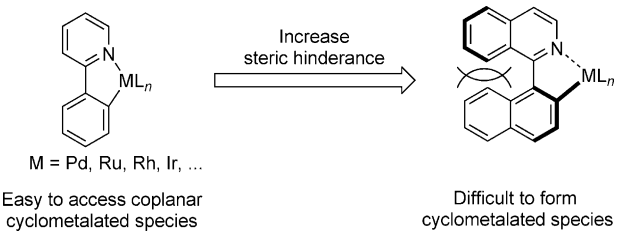

Figure 1. Challenge in accessing five-membered cyclometalated species for axially chiral scaffold.

In 2012, Ward, Rovis and co-workers successfully synthesized a biotinylated [Cp*Rh^{III}] complex and used it along with streptavidin for asymmetric C–H bond functionalization reactions.[15] Almost at the same time, Cramer et al. introduced a series of novel C_2-symmetric chiral Cp ligands.[16a,b] Their rhodium complexes were found to be highly efficient catalysts for enabling various asymmetric C–H bond functionalization reactions for forming central chirality.[16] Recently, Hou and co-workers reported half-sandwich scandium dialkyl complexes, bearing chiral Cp ligands, which catalyzed the enantioselective C–H bond addition of pyridines to alkenes.[17] Inspired by these pioneering works, we decided to explore the construction of axially chiral biaryls by using the Cramer catalyst. Herein, we describe the first synthesis of axially chiral biaryls through a rhodium-catalyzed C–H activation/dehydrogenative alkenylation reaction.

The dehydrogenative coupling of 1-(naphthalene-1-yl)benzo[*h*]isoquinoline (**1a**) with 2-vinylnaphthalene (**2a**) was initially chosen as a model reaction (Table 1). In the presence of 5 mol% of the catalyst **K1** and 5 mol% $(BzO)_2$, several conventional solvents were tested. While various solvents were suitable for the oxidative olefination reaction,

[*] J. Zheng, Prof. Dr. S.-L. You
State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences
345 Lingling Lu, Shanghai 200032 (China)
E-mail: slyou@sioc.ac.cn
Homepage: http://shuliyou.sioc.ac.cn/
Prof. Dr. S.-L. You
Collaborative Innovation Center of Chemical Science and Engineering (Tianjin)

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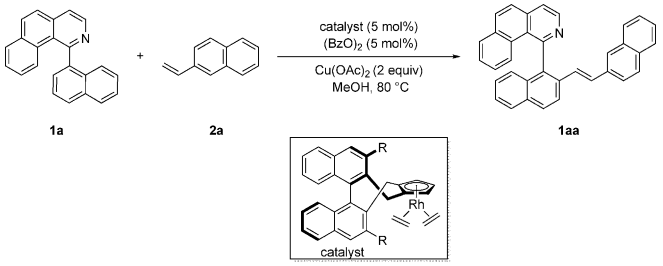
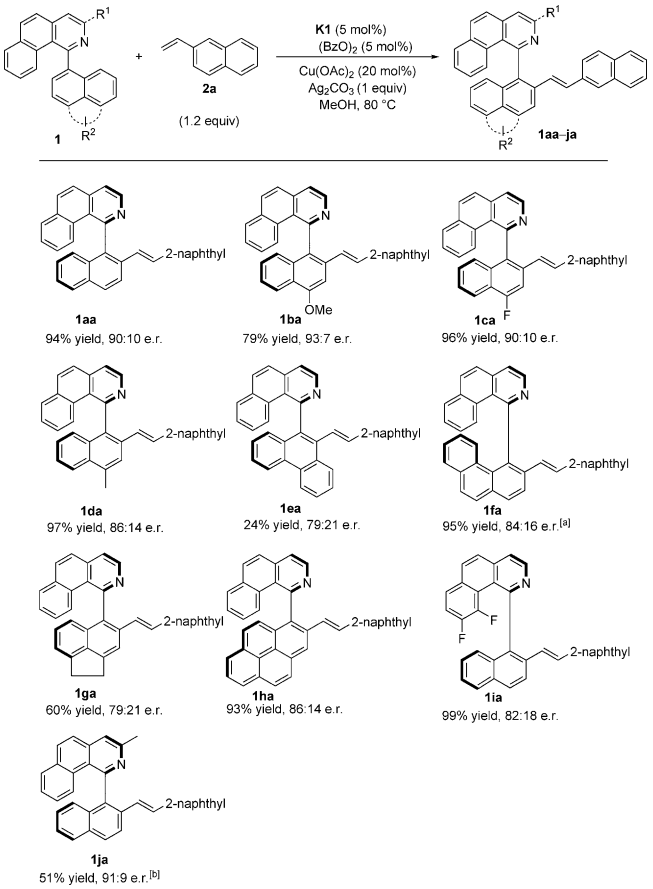
Table 1: Catalyst screening for the enantioselective oxidative Heck coupling reaction.[a]



Entry	Catalyst	Yield [%][b]	e.r.[c]
1	**K1** (R = OMe)	99	86:14
2	**K2** (R = H)	58	71:29
3	**K3** (R = O*i*Pr)	99	86:14
4	**K4** (R = Ph)	26	82:18
5	**K5** (R = OTIPS)	87	83:17
6	**K6** (R = OTBDPS)	64	77:23
7[d]	**K1** (R = OMe)	94	90:10

[a] Unless otherwise noted, all reactions were carried out under the following conditions: **1a** (0.1 mmol), **2a** (0.3 mmol), **K** (5 μmol), $(BzO)_2$ (5 μmol), $Cu(OAc)_2$ (0.2 mmol), 1 mL MeOH, 80 °C. [b] Yield of isolated product. [c] Determined by HPLC analysis using a chiral stationary phase. [d] **2a** (0.12 mmol), $Cu(OAc)_2$ (0.02 mmol), Ag_2CO_3 (0.1 mmol) and 0.5 mL MeOH were used. TBDPS = *tert*-butyldiphenylsilyl, TIPS = triisopropylsilyl, Bz = benzoyl.

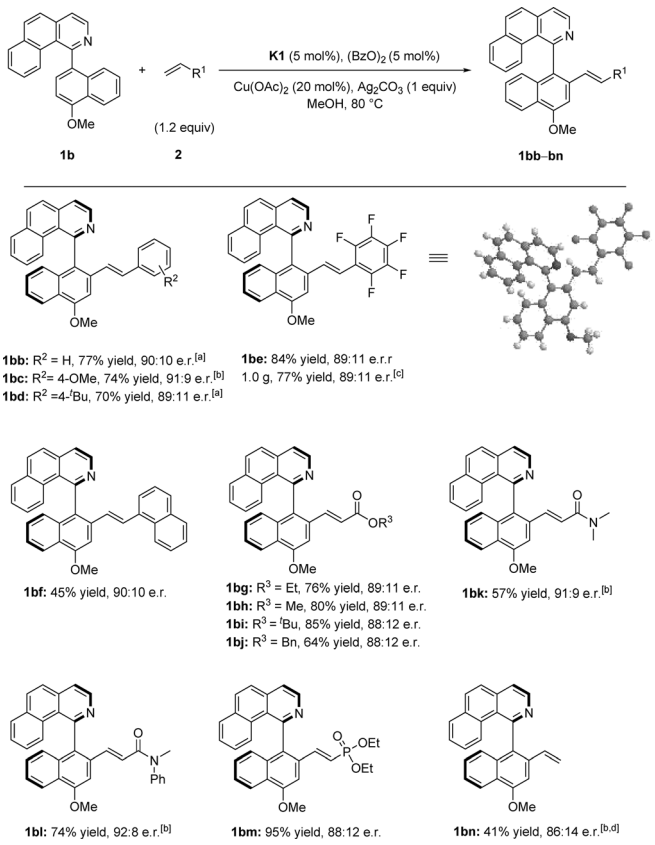


Scheme 1. Rhodium-catalyzed enantioselective alkenylation of biaryls with 2-vinylnaphthalene (**2a**). Reaction conditions: **1** (0.1 mmol), **2a** (0.12 mmol), **K1** (5 μmol), $(BzO)_2$ (5 μmol), $Cu(OAc)_2$ (0.02 mmol), Ag_2CO_3 (0.1 mmol), 0.5 mL MeOH, 80 °C. Yields of isolated products. E.r. is determined by HPLC. [a] At 120 °C. [b] 10 mol% **K1** was used.

methanol was found the optimal choice as it provided the desired product **1aa** in 99% yield and a promising enantiomeric ratio of 86:14 (entry 1; for detailed studies, see the Supporting Information). Different chiral Cp/rhodium complexes (**K2**–**K6**) were further investigated (entries 2–6). The enantioselectivity was almost maintained when the methoxy substituents at the 3,3′-position of the binaphthyl scaffold of the catalyst were replaced by isopropoxy groups (O*i*Pr; **K3**). However, the more bulky substituents, such as a phenyl (Ph; **K4**) or triisopropylsilyloxy (OTIPS; **K5**) group, resulted in diminished reactivities and enantioselectivities. We next examined the influence of oxidants on the enantioselectivity of the reaction. Most silver salts could effectively promote the reaction, whereas other oxidants, such as $PhI(OAc)_2$ and oxone, drastically decreased the yields (for detailed studies, see the Supporting Information). Finally, the combination of Ag_2CO_3 (1.0 equiv) and $Cu(OAc)_2$ (20 mol%) was found optimal and gave **1aa** in 94% yield and 90:10 e.r. (entry 7).

With the optimized reaction conditions in hand, we next investigated the scope of the biaryl substrates for this direct C–H olefination process (Scheme 1). A variety of biaryls worked well with 2-vinylnaphthalene (**2a**), thus generating the desired alkenylated products in moderate to excellent yields and enantioselectivities. Either electron-donating (**1b**, **1d**, **1g**, **1h**) or electron-withdrawing (**1c**) groups were introduced onto the naphthalene ring without affecting the enantioselectivity significantly (up to 97% yield and 93:7 e.r.). However, substrate **1e** bearing sterically more hindered substituents on the naphthalene ring only gave a 24% yield and 79:21 e.r. Rotational restriction between the corresponding atropisomers of **1f** required a higher temperature to ensure the fast interconversion of the atropisomers. The benzo[*h*]isoquinoline **1i**, bearing electron-withdrawing substituents, was also tolerated and delivered the desired product **1ia** in 99% yield with 82:18 e.r. Finally, the installation of a methyl group *ortho* to the nitrogen atom, as in **1j**, resulted in a drastic decrease in reactivity.

Next the generality of olefins was tested with **1b** as the biaryl partner (Scheme 2). The reaction with styrene and 4-substituted styrenes (**2b**, **2d**) proceeded in good yields and enantioselectivities, in the presence of 2 equivalents of Ag_2CO_3. Meanwhile, reaction with 2,3,4,5,6-pentafluorostyrene (**2e**) provided satisfactory results (84% yield, 89:11 e.r.). Notably, the gram-scale reaction between **1b** and **2e** proceeded smoothly without affecting the reaction outcome. However, the reaction with sterically hindered 1-vinylnaphthalene (**2f**) proceeded with low reactivity. The coupling product was obtained in 45% yield and 90:10 e.r. Moreover, the reaction conditions could tolerate acrylates bearing ethyl, methyl, *tert*-butyl, and benzyl esters. The corresponding products were obtained in good yields and enantioselectivities (64–85% yields, 88:12 to 89:11 e.r.). This asymmetric transformation was also suitable for vinyl phosphonate ester (**2m**) and acrylamides (**2k, 2l**) with 10 mol% rhodium catalyst.



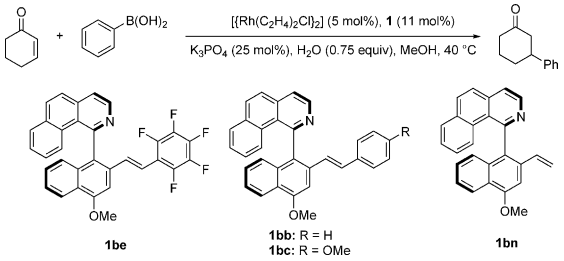
Scheme 2. Rhodium-catalyzed enantioselective construction of axially chiral biaryls with varied olefins. Reaction conditions: **1b** (0.1 mmol), **2** (0.12 mmol), **K1** (5 μmol), $(BzO)_2$ (5 μmol), $Cu(OAc)_2$ (0.02 mmol), Ag_2CO_3 (0.1 mmol), 0.5 mL MeOH, 80 °C. Yields of isolated products. E.r. is determined by HPLC. [a] 3 equiv olefin, 2 equiv Ag_2CO_3 were used. [b] 10 mol% **K1** was used. [c] 2.5 mmol **1b**, 3 mmol **2e** and 5 mL MeOH were used. [d] 5 atm ethylene was used.

Notably, ethylene was also tested and the desired product was obtained with 86:14 e.r.

The absolute configuration of product **1be** was assigned as a*S* by X-ray analysis of a single crystal from an enantiopure sample (for details, see the Supporting Information).[18] Interestingly, a phenomenon of self-disproportionation of enantiomers (SDE) was observed for **1be**.[19] The enantiopure **1be** could be obtained by silica gel column chromatography of an enantioenriched sample. During chromatography of the enantioenriched **1be**, the first fraction was almost enantiopure (99.5:0.5 e.r.), and the last fraction was essentially racemic. The reason for this SDE phenomenon might be the formation of tight intermolecular π–π stacking interactions, which were found in the racemic sample of **1be** by crystal X-ray analysis, but not observed in the enantiomerically pure sample of **1be** (for details, see the Supporting Information).[18] This difference resulted in a much better solubility of enantiopure sample than that of the racemic one.

To demonstrate the utility of the products, we explored their suitability as chiral ligands. To test these products as N/olefin ligands,[20] rhodium-catalyzed conjugate addition of phenylboronic acid to cyclohexenone was chosen as a model reaction. The reaction with **1be** (99.5:0.5 e.r.) proceeded

Table 2: Rhodium-catalyzed conjugate addition of phenylboronic acid to cyclohexenone.



Entry	**1** (e.r.)	Yield [%][a]	e.r.[b]
1	**1be** (99.5:0.5)	77	84:16
2	**1be** (89:11)	74	76:24
3	**1bb** (90:10)	81	41:59
4	**1bc** (90:10)	79	38:62
5	**1bn** (87:13)	25	55:45

[a] Yield of isolated product. [b] Determined by HPLC analysis on a chiral stationary phase.

smoothly to afford the addition product in 77% yield with 84:16 e.r. (Table 2, entry 1). With **1be** (89:11 e.r.) as the ligand, the addition product was obtained in 74% yield and 76:24 e.r. (entry 2), thus indicating there is no nonlinear effect in this reaction. Several other enantioenriched ligands (**1bb**, **1bc**, **1bn**) were also tested. However, none of them provided superior results (entries 3–5).

In conclusion, we have developed an asymmetric rhodium/(III)-catalyzed direct alkenylation of biaryl derivatives with olefins. Axially chiral biaryls were synthesized in excellent yields with good enantioselective control for a broad range of substrates. The axially chiral biaryl products have been demonstrated as suitable ligands in rhodium-catalyzed conjugate addition reaction. For the first time chiral Cp rhodium complexes have found application in oxidative coupling reactions, thus providing a facile enantioselective synthesis of axially chiral biaryls through a C–H activation process. Further investigations into the mechanism, applications of these axially chiral biaryls, and the development of more efficient catalytic systems are currently under investigation in our laboratory.

Experimental Section

A flame-dried sealed tube was cooled to room temperature and filled with argon. **K1** (5 μmol, 2.8 mg) and $(BzO)_2$ (5 μmol, 1.2 mg) were added to this tube. MeOH was then added and the mixture was stirred at room temperature. After 30 min, the biaryl compound **1** (0.1 mmol), **2** (0.12 mmol), $Cu(OAc)_2$ (0.02 mmol, 3.6 mg), and Ag_2CO_3 (0.1 mmol, 27.6 mg) were added and the reaction mixture was kept at 80 °C for 24 h. After the reaction mixture was cooled to room temperature, saturated $NaHCO_3$ solution (5 mL) and CH_2Cl_2 (5 mL) were added. The organic layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic extracts were washed with brine (3 mL) and dried over Na_2SO_4. The solvent was removed in vacuo. The residue was purified

by column chromatography on silica gel (petroleum ether/acetone = 20:1).

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