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Enantioselective Synthesis of Biaryl Atropisomers via Pd-Catalyzed C–H Olefination using Chiral Spiro Phosphoric Acid Ligands

Jun Luo,[a] Tao Zhang,[b] Lei Wang,[a] Gang Liao,[a] Qi-Jun Yao,[a] Yong-Jie Wu,[a] Bei-Bei Zhan,[a] Yu Lan,*[b] Xu-Feng Lin,*[a] and Bing-Feng Shi*[a]

Abstract: The discovery of proper ligands to simultaneously modulate the reactivity and effectively control the stereoselectivity is a central topic in the field of enantioselective C-H activation. Herein, we reported the synthesis of axially chiral biaryls via Pd-catalyzed atroposelective C-H olefination. A novel chiral spiro phosphoric acid, STRIP, was identified as a superior ligand for this transformation. A broad range of axially chiral quinoline derivatives were synthesized in good yields with excellent enantioselectivities (up to 98% ee). Density functional theory was used to gain a theoretical understanding of the enantioselectivities in this reaction.

Biaryl atropisomers, especially those containing *N*-heteroarenes, are prevalent in bioactive active compounds, pharmaceuticals, and also play an important role in asymmetric synthesis.[1] For example, the quinoline-based biaryls has been identified as a HIV integrase inhibitor with special biological activity.[2] QUINAP,[3a] one of the most useful chiral *P,N*-ligands, has widely applications in asymmetric catalysis (Figure 1a).[3] The development of efficient methods for the asymmetric construction of axially chiral biaryls has been a long pursuing goal in organic synthesis.[4] Recently, transition metal-catalyzed directed asymmetric *ortho*-C-H functionalization to lock a preformed biaryl axis has emerged as a promising synthetic tool and several elegant strategies have been developed,[5-13] including: 1) chiral auxiliary-directed diastereoselective C-H functionalization, which have been well investigated by Wencel-Delord and Colobert,[6] and Yang;[10a] 2) chiral Cp^{x}Rh(III)-catalyzed atroposelective C-H functionalization, with innovative contributions by the groups of You;[7a,c,8] 3) catalytic asymmetric C-H functionalization cooperatively catalyzed by transition metals and chiral ligands.[7b,9,10b,11] Ideally, the final category of reactions is more appealing but inherently more challenging for two main reasons. First, competitive background reaction and racemization under typically elevated reaction temperatures for C-H activation might lead to significant erosion of enantioselectivity. Second, the identification of appropriate chiral ligands that can simultaneously modulate the reactivity and effectively control the atroposelectivity is extremely difficult.[5c]

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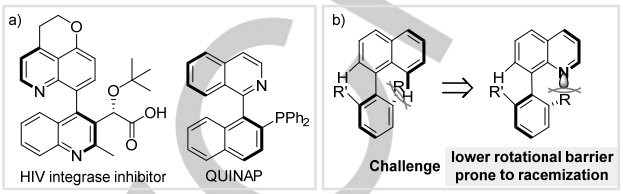
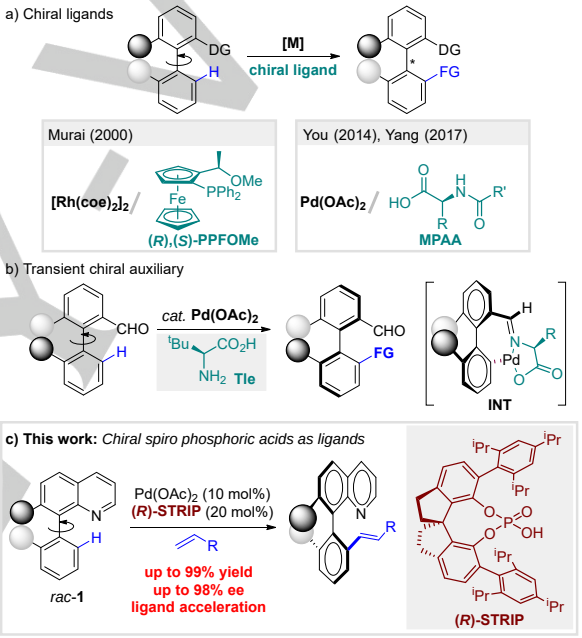


Figure 1. Importance of Quinoline-Derived Biaryls and Synthetic Challenge.



Scheme 1. Synthesis of Axially Chiral Biaryls via Directed, Asymmetric C–H Functionalization Using Catalytic Chiral Ligands.

Therefore, the discovery of proper ligands has been a central topic in this field, though with limited success.[7b,9,10b,11] In 2000, the Murai group reported the enantioselective C-H alkylation of biaryls catalyzed by $[Rh(coe)_2]_2$ and a chiral ferrocenyl phosphine ligand [(*R*),(*S*)-PPFOMe], albeit only one example with low enantioselectivity (Scheme 1a, up to 49% ee) was reported.[9] The major breakthrough was made by You (Scheme 1a). In 2014, they achieved the atroposelective C-H iodination catalyzed by $Pd(OAc)_2$ and mono-protected amino acid (MPAA),[7b] a catalytic system first reported by Yu and co-workers[14] and later was recognized as a privileged catalytic system for enantioselective C-H activation.[5] This catalytic system was further applied to phosphine oxide directed atroposelective C-H functionalization by Yang.[5j,10b] Inspired by Yu's innovative work,[15] our group reported the high enantioselective synthesis of axially chiral biaryls via C-H functionalization of biaryl aldehydes using catalytic $Pd(OAc)_2$ and *tert*-leucine (up to >99% ee).[11] In this system, *tert*-leucine acted as a catalytic, transient chiral auxiliary rather than a chiral ligand (Scheme 1b, **INT**).[15,16] This protocol relies on the use of

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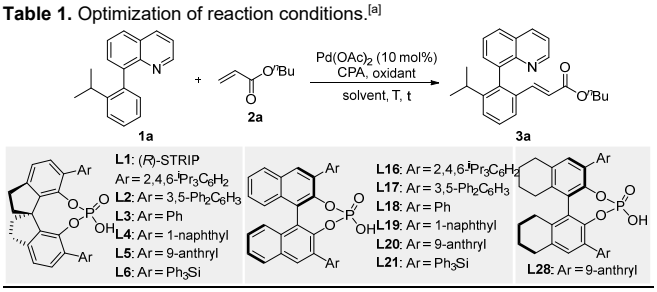
aldehyde as DG, thereby is incompatible with quinoline-derived atropoisomers. Notably, the synthesis of quinoline-derived atropoisomers itself is much more challenging than their naphthalene analogues, because the lower conformational stability resulted from much less steric hindrance of nitrogen lone pair and therefore prone to racemization (Figure 1b).[7,17] Herein, we reported the use of spiro phosphoric acids (SPAs) as chiral anionic ligands to enable the Pd-catalyzed atroposelective C-H olefination to prepare axially chiral quinoline-derived biaryls. A novel chiral spiro phosphoric acid, STRIP, was identified as a superior ligand in atroposelective C-H activation for the first time.

Table 1. Optimization of reaction conditions.[a]



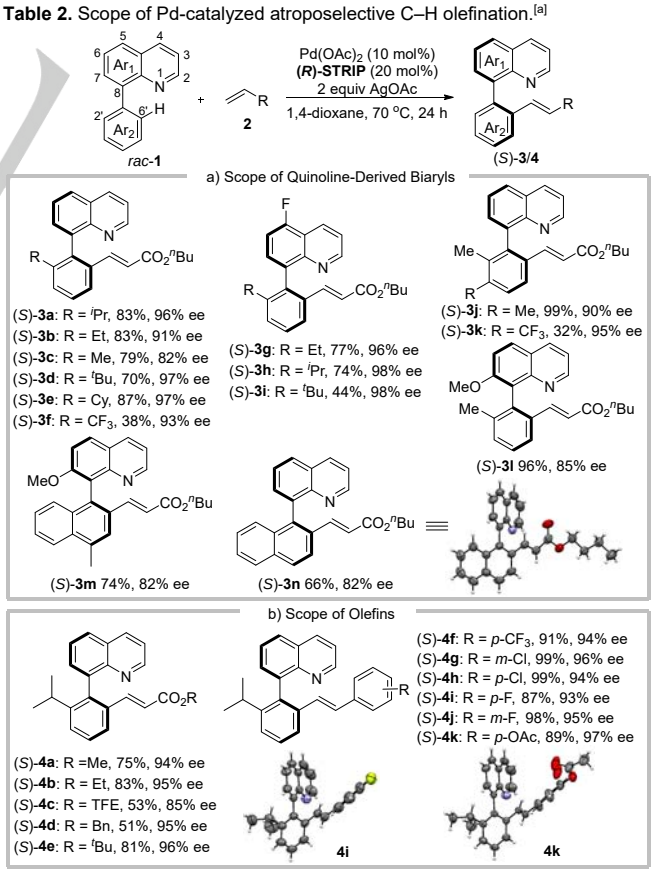
Entry	Solvent	Oxidant	CPA	T (°C)	t [h]	Yield (%)[b]	ee (%)[c]
1	DCE	BQ	**L1**	40	20	30	93
2	DCE	BQ	**L2**	40	20	15	43
3	DCE	BQ	**L3**	40	20	17	-23
4	DCE	BQ	**L4**	40	20	18	40
5	DCE	BQ	**L5**	40	20	10	77
6	DCE	BQ	**L6**	40	20	23	60
7	DCE	BQ	**L16**	40	20	23	-86
8	DCE	BQ	**L17**	40	20	10	-40
9	DCE	BQ	**L18**	40	20	24	-13
10	DCE	BQ	**L19**	40	20	24	-28
11	DCE	BQ	**L20**	40	20	18	-40
12	DCE	BQ	**L21**	40	20	34	-42
13	DCE	BQ	**L28**	40	20	16	-47
14	1,4-dioxane	BQ	**L1**	40	20	8	99
15	1,4-dioxane	BQ	**L1**	60	60	13	97
16	1,4-dioxane	AgOAc	**L1**	80	24	93	93
17	1,4-dioxane	AgOAc	**L1**	70	24	90 (83)[d]	96
18[e]	1,4-dioxane	AgOAc	**L1**	70	24	87	94
19	1,4-dioxane	$AdCO_2Ag$	**L1**	70	24	89	92
20	1,4-dioxane	Ag_2CO_3	**L1**	70	24	45	98

[a] Reaction conditions: **1a** (0.05 mmol), **2a** (0.1 mmol), $Pd(OAc)_2$ (10 mol%), CPA (20 mol%), BQ (1.0 equiv)/AgOAc (2.0 equiv), solvent (0.5 mL) under air. [b] Determined by ^1H NMR using dibromomethane as the internal standard. [c] The ee value was determined by HPLC. [d] Isolated yield. [e] **L1** (10 mol%). BQ = 1,4-benzoquinone, DCE = 1,2-dichloroethane.

Considering that most Pd-catalyzed C-H activation is proposed to occur through a carboxylate-assisted concerted metalation-deprotonation (CMD) mechanism, in which the presence of carboxylic acid might enhance the reactivity.[18] Therefore, the use of chiral carboxylate or related anionic ligands to enable the Pd(II)-catalyzed enantioselective C-H activation has been realized.[5,14,20] The Yu group pioneeringly reported the Pd(II)-catalyzed enantioselective C-H functionalization using bidentate MPAA ligands,[5,14] which was later adopted to the biaryl systems by You and Yang.[7b,10b] Unfortunately, extensive screening of various MPAA ligands only led to poor enantioselectivity (<3% ee). These results stimulated us to explore new types of ligands that could significantly accelerate the reaction to outcompete the quinoline-directed background reaction. Recently, chiral phosphoric acids (CPAs), a class of strong Brønsted acids,[19] has been recognized as a novel type of monodentate chiral ligands in enantioselective C-H activation to create point chirality.[20,21] In particular, CPA ligands are compatible with strongly coordinating directing groups,[20a,c,d,e] though have never been shown to be effective in the creation of axial chirality.

We then set out to test the effect of CPA ligands (Table 1). Three kinds of CPAs containing different skeletons, namely SPAs,[22] BINOL-derived phosphoric acids,[19] and H8-BINOL-derived phosphoric acids, have been investigated. Generally, SPAs showed better stereocontrol than the analogous counterparts (entries 1-6 *vs* entries 7-12 and 13). We rationalized that the narrow well-defined channel of SPAs could provide more rigid chiral pocket than their BINOL-derived counterparts, thereby leading to better steric interaction with the substrates.[22] Gratefully, (*R*)-STRIP **L1** gave high enantioselectivity at 30% yield (entry 1, 93% ee). The use of 1,4-dioxane as solvent led to better enantocontrol (entry 14, 99%), but with dramatically reduced yield (8%). Thus, we further tested the influence of oxidants and temperature to increase the reactivity and maintain the stereoselecitvity. A significant enhancement on the reactivity was observed, when AgOAc was used as oxidant at 70 °C (entry 17, 83% isolated yield, 96% ee). Attempts to increase the enantioselectivity by lowering reaction temperature with prolonged reaction time, led to erosion of ee (see Table S1), presumably due to the racemization under the reaction conditions. Reducing the loading of **L1** to 10 mol% gave slightly lower ee (entry 18, 94%). Other silver carboxylates led to lower yield or ee (entries 19-20 and Table S2).

Table 2. Scope of Pd-catalyzed atroposelective C–H olefination.[a]



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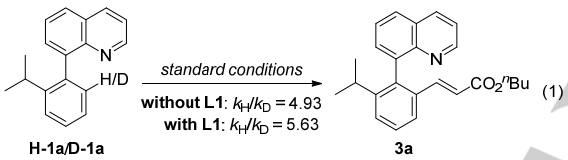
[a] Reaction conditions: **1** (0.1 mmol), **2** (0.2 mmol), $Pd(OAc)_2$ (0.01 mmol), CPA (0.02 mmol), AgOAc (0.2 mmol) in 1.4-dioxane (1 mL) at 70 °C for 24 h under air. Isolated yield.

With the optimal conditions in hand, we set out to explore the scope of this transformation (Table 2). In general, a range of quinoline-derived biaryls with different substituents were amenable to this strategy. The reaction is sensitive to steric hindrance in the 2'-position and with the increasing bulk from Me to ^{t}Bu, the enantioselectivities were improved (**3c**, R = Me, 82% ee; **3b**, R = Et, 91% ee; **3a**, R = ^{i}Pr, 96% ee; **3d**, R = ^{t}Bu, 97% ee). Substrates bearing electron-deficient substituents were generally less reactive than electron-rich ones (**3f**, 2'-CF_3, 38% yield *vs* **3a-3e**, 2'-alkyl, 70-87% yield; **3k**, 3'-CF_3, 32% *vs* **3j**, 3'-Me, 99% yield); while the enantioselectivity were independent on the electronic effect. The generality of olefins was also investigated (Table 2b). Various acrylates were compatible with this reaction, giving the desired products in good yields and enantioselectivities (**4a-4e**). This atroposelective olefination was also suitable for styrenes with various substituents (**4f-4k**). Halogens (F, Cl) on the aryl ring proceeded smoothly to afford the desired products in high yields (87-99%) with high enantioselectivity (**4g-4j**, 93-97% ee). The absolute configuration of products **3n**, **4i** and **4k** was determined as S_a by X-ray crystallographic analysis and those of the others were assigned by analogy.[23]



A number of experiments were conducted to shed light into the mechanism. First, on the basis of initial rate kinetics, the KIE values of 4.93 (without **L1**) and 5.63 (with **L1**) was obtained respectively (eq 1), indicating that the cleavage of C-H bond is the turnover-limiting step. The dependence of isotope effect on **L1** also suggests a unique ligand effect. This was supported by a significant ligand acceleration, where initial rate with **L1** was faster than ligandless conditions (Figure S3, k_{rel} 4.39). Next, a linear correlation between the ee value of **3a** and **L1** was observed (Figure S4), indicating that a single SPA ligand is involved in the stereodetermining step.[15]

To better illustrate the origin of enantioselectivity in C-H olefination, we briefly investigated this new system with the density functional theory (DFT) method M11-L (see supporting information for details). Both of acetate and phosphate are considered as either counterion or base for concerted metalation-deprotonation (CMD). The computational results showed that in the presence of chiral phosphate as counterion to stabilize Pd, acetate plays as base to conduct CMD type C-H activation. [24,25]

As shown in Figure 2, two possible CMD type transition states **Spinol-ts-*S*** and **Spinol-ts-*R*** are located in the C-H bond cleavage step. The *S*-configuration product could afford through transition state **Spinol-ts-*S*** with an energy barrier of 17.5 kcal/mol. Alternatively, the *R*-configuration product would be formed through transition state **Spinol-ts-*R*** with an energy barrier of 20.5 kcal/mol, the relative free energy of which is 3.0 kcal/mol higher than that of **Spinol-ts-*S***. The geometry information of transition state **Spinol-ts-*S*** shows that the distance between H1 and H2 atoms is 2.59 Å, which indicates less steric interaction between quinolone group and isopropyl group on C5 position. On the other hand, in geometry of transition state **Spinol-ts-*R***, the distance of H1···H2 and H3···H4 are 2.63 and 2.73 Å, which reveals a significant steric repulsion between quinoline and two isopropyl groups (C5 and C6 position). As such, the *S*-configuration phenylacrylate is the major product. These computational observations suggest that the enantioselective is determined by the CMD type C-H bond cleavage step. An 97% of ee value is predicted by theoretical calculation based on the energy difference between transition states **Spinol-ts-*S*** and **Spinol-ts-*R***, which is in good agreement with the experimental result, where the *S*-configuration phenylacrylate is formed preferentially (ee = 96%, in Table 2).

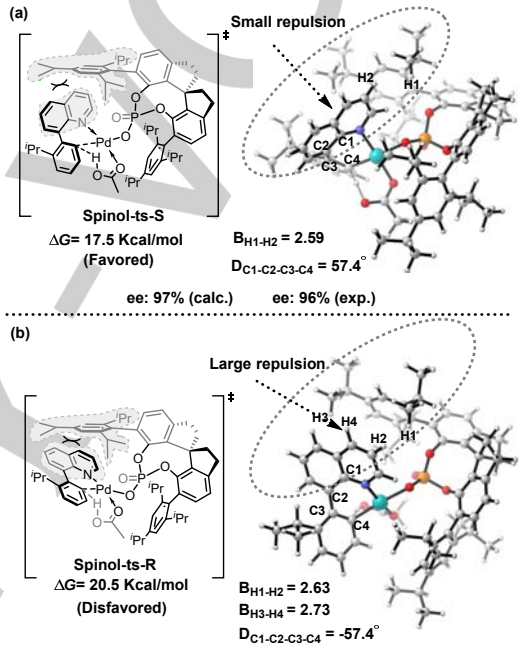
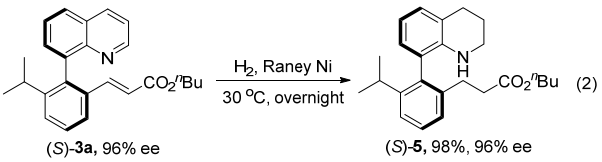


Figure 2. One scenario for C−H cleavage via CMD pathway.

Due to the importance of tetrahydroquinoline derivatives in numerous bioactive natural products and pharmaceuticals,[17] the reduction of the resulting axially chiral quinolines was conducted. We were pleased to find tetrahydroquinoline (*S*)-**5** was obtained in 98% yield with complete retention of chirality (eq 2).



In summary, we have developed a Pd(II)/STRIP catalytic system to enable the synthesis of axially chiral quinoline atropoisomers via enantioselective C-H olefination, which expanding the existing systems of catalytic atroposelective C-H functionalizations. Furthermore, SPA is one of the most widely used chiral ligands in asymmetric synthesis, which means this strategy might offer a practical and promising opportunity and fills a major methodology gap.

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Keywords: palladium • C-H olefination • chiral spiro phosphoric acids • atroposelectivity • quinoline biaryls

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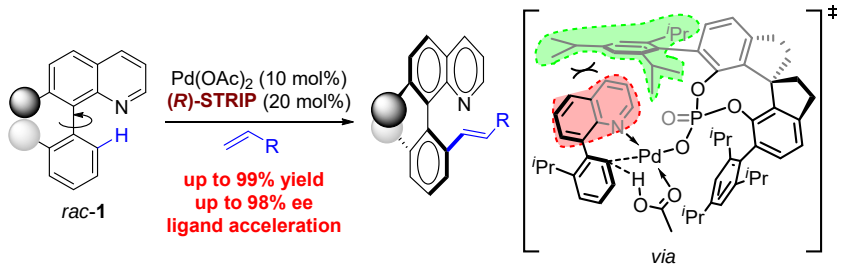

Jun Luo, Tao Zhang, Lei Wang, Gang Liao, Qi-Jun Yao, Yong-Jie Wu, Bei-Bei Zhan, Yu Lan, Xu-Feng Lin,* and Bing-Feng Shi**

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Enantioselective Synthesis of Biaryl Atropisomers via Pd-Catalyzed C–H Olefination using Chiral Spiro Phosphoric Acid Ligands

The discovery of proper ligands to simultaneously modulate the reactivity and effectively control the stereoselectivity is a central topic in the field of enantioselective C-H activation. Herein, we reported the synthesis of axially chiral biaryls via Pd-catalyzed atroposelective C-H olefination. A novel chiral spiro phosphoric acid, STRIP, was identified as a superior ligand for this transformation. A broad range of axially chiral quinoline derivatives were synthesized in good yields with excellent enantioselectivities (up to 98% ee). Density functional theory was used to gain a theoretical understanding of the enantioselectivities in this reaction.