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Communication

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Rhodium-Catalyzed Atroposelective Oxidative C-H/C-H Cross Coupling Reaction of 1-Aryl Isoquinoline Derivatives with Electron-Rich Heteroarenes

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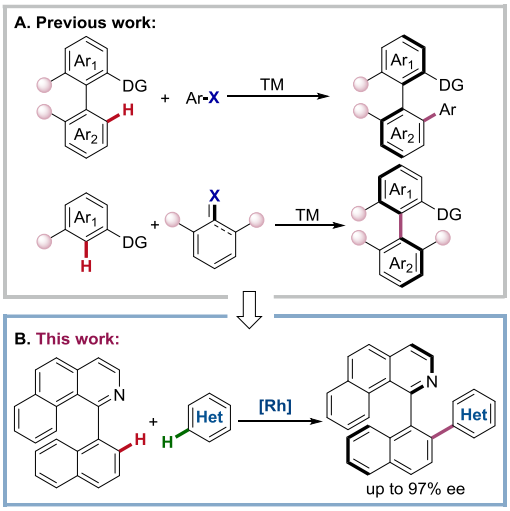
Supporting Information Placeholder

ABSTRACT: Rhodium(III)-catalyzed enantioselective oxidative C–H/C–H cross-coupling reaction between two arenes is disclosed. With the combination of a chiral CpRh(III) complex and a chiral carboxylic acid additive, the direct coupling reactions between 1-aryl isoquinoline derivatives and electron-rich heteroarenes such as thiophenes, furans, benzothiophenes, benzofurans are realized via a double C-H functionalization process. A series of axially chiral compounds are obtained in excellent yields and enantioselectivities (up to 99% yield and 99% ee). Mechanistic studies suggest that both C–H bond cleavages may not be the turnover-limiting step.

Transition metal-catalyzed asymmetric C–H bond functionalization represents an efficient, straightforward and versatile synthetic tool to access chiral molecules.[1] Over the past decade, transition metal-catalyzed oxidative C–H/C–H cross-coupling reaction between two arenes has emerged as a powerful method for the synthesis of biaryls.[2] Compared with conventional cross-coupling reactions, this approach is more direct, efficient and attractive in terms of step- and atom-economy. Various transition metal complexes involving Fe, Co, Ni, Cu, Rh, Ru, Au, and the most frequently used Pd catalysts have been investigated in the oxidative C–H/C–H cross-coupling reaction.[3] In this regard, catalytic asymmetric homo-coupling of 2-naphthol derivatives was achieved in excellent enantioselectivity by using chiral copper[4a], dinuclear vanadium,[4b] and iron complexes,[4c-e] respectively. However, the asymmetric double C–H functionalization reactions beyond 2-naphthol derivatives have been rarely reported.[5] Therefore, the enantioselective twofold oxidative C–H cross-coupling reactions between two arenes are highly desirable.

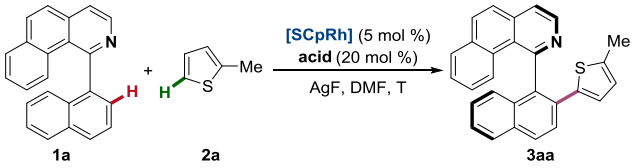
Axially chiral biaryls are important structural motifs in natural products, functional materials, medicinal chemistry, privileged catalysts and ligands.[6-9] Many elegant methods have been developed to access these axially chiral biaryls.[10,11] Recently, asymmetric C–H functionalization reactions have been established as an increasingly important strategy for the synthesis of axially chiral biaryls.[12-15] To be noted, among these previous reports, functionalized arenes such as aryl halides, aryl organometallic reagents, and diazo compounds were generally used (Scheme 1A). Thus, we envisaged that enantioselective twofold oxidative C–H cross-coupling reactions between two arenes would provide direct access to atropisomeric biaryls[16] (Scheme 1B). Herein, we report the details of this study.



Scheme 1. Transition-metal-catalyzed atroposelective C–H functionalization.

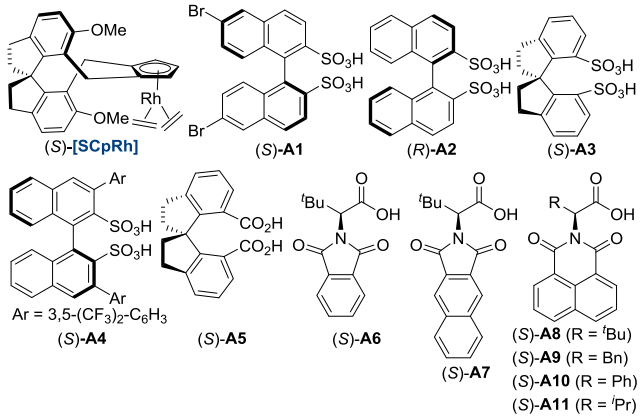
An initial C–H arylation reaction of 1-(naphthalen-1-yl)benzo[h]isoquinoline **1a** with 2-methylthiophene **2a** was carried out at 120 ºC in the presence of 5 mol % of [SCpRh][14b], 20 mol % of 6,6′-Br_2-1,1′-binaphthyl-2,2′ disulfonic acid (6,6′-Br_2-BINSA) (*S*)-**A1**,[17] 10 mol % of $AgNTf_2$, and 3 equivalents of AgF in DMF. To our delight, the reaction did occur and afford the desired coupling product **3aa** in 63% yield and 73% ee (Table 1, entry 1). After screening the oxidants, AgF was found to be the optimal one for this reaction (See SI for details). Interestingly, in the absence of $AgNTf_2$, the reaction proceeded with increased yield and slightly improved enantioselectivity (entry 2, 90% yield and 74% ee). Further investigation of the solvent effect revealed that DMF was the optimal solvent (See SI for details). Next, the reaction temperature for this reaction was

Table 1. Selected condition optimization.[a]



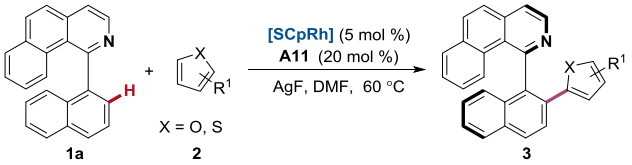
entry	acid	T	time	yield (%)[b]	ee (%)[c]
1[d]	(*S*)-**A1**	120 °C	10 h	63	73
2	(*S*)-**A1**	120 °C	10 h	90	74
3	(*S*)-**A1**	80 °C	12 h	98	82
4	(*S*)-**A1**	60 °C	14 h	98	84
5	(*S*)-**A1**	40 °C	96 h	89	85
6[e]	(*S*)-**A1**	60 °C	14 h	99	86
7[e]	(*R*)-**A1**	60 °C	14 h	99	85
8[e]	(*R*)-**A2**	60 °C	14 h	58	80
9[e]	(*S*)-**A3**	60 °C	14 h	70	77
10[e]	(*S*)-**A4**	60 °C	14 h	59	73
11[e]	(*S*)-**A5**	60 °C	14 h	95	80
12[e]	(*S*)-**A6**	60 °C	14 h	86	84
13[e]	(*S*)-**A7**	60 °C	14 h	72	82
14[e]	(*S*)-**A8**	60 °C	14 h	94	91
15[e]	(*S*)-**A9**	60 °C	14 h	94	93
16[e]	(*S*)-**A10**	60 °C	14 h	93	91
17[e]	(*S*)-**A11**	60 °C	14 h	94 (85)[f]	93
18[e]	(*R*)-**A11**	60 °C	14 h	94	58
19[e]	-	60 °C	14 h	36	76

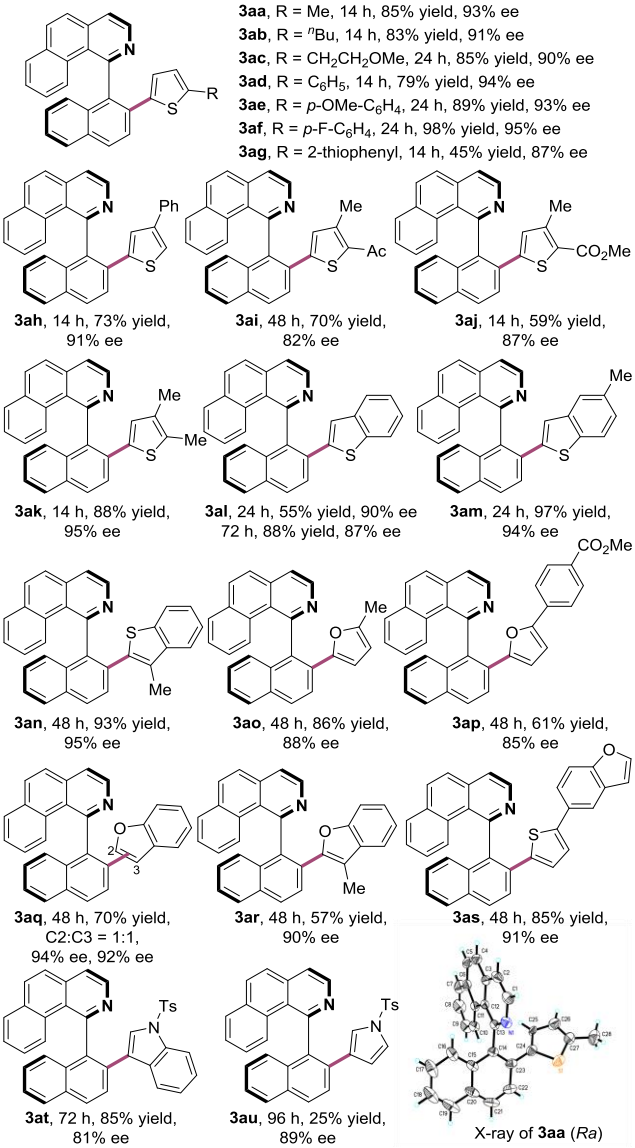
[a] Reaction conditions: **1a** (0.05 mmol), **2a** (0.15 mmol), [SCpRh] (5 mol %), acid (20 mol %), AgF (0.15 mmol), DMF (0.5 mL), under argon atmosphere. [b] Determined by ^{1}H NMR of the reaction mixture using CH_2Br_2 as an internal standard. [c] Determined by HPLC analysis with a chiral stationary phase. [d] With $AgNTf_2$ (10 mol %). [e] 0.05 M of **1a**. [f] Isolated yield of 0.1 mmol scale reaction in parentheses. DMF: *N,N*-dimethylformamide.



studied (entries 2-5). The reaction at 60 °C led to 98% yield and 84% ee within 14 h (entry 4), and much longer reaction time was needed when the reaction was carried out at 40 °C (entry 5, 96 h). Moreover, when the reaction was performed in diluted conditions, the enantioselectivity could be slightly improved (entry 6, 99% yield and 86% ee). Then the chiral acid additives[18] were investigated (entries 6-18). 6,6′-Br_2-BINSA (*S*)-**A1** was found as the optimal disulfonic acid additive for this reaction (entries 6-10). The opposite enantiomer (*R*)-**A1** had no obvious influence on the reactivity and enantioselectivity (entry 7, 99% yield and 85% ee). Further screening on chiral carboxylic acids indicated that (*S*)-**A9** and (*S*)-**A11** performed well

Table 2. Scope of the Rh-catalyzed atroposelective C–H arylation with heteroarenes.[a,b]

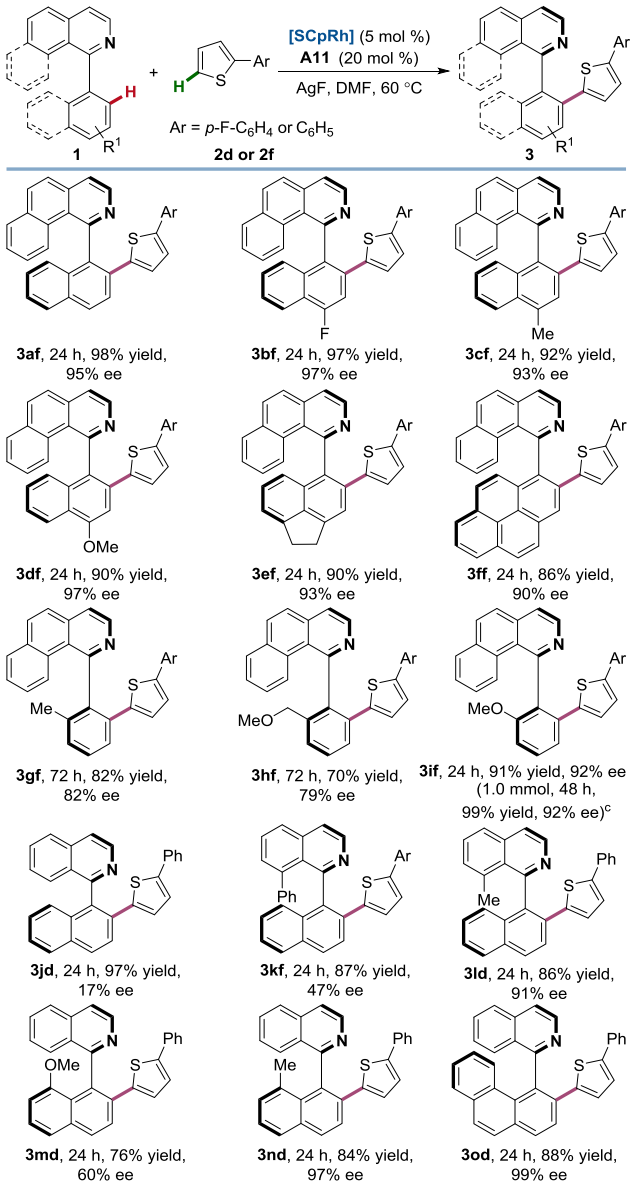




[a] Reaction conditions: **1a** (0.1 mmol), **2** (0.3 mmol), [SCpRh] (5 mol %), **A11** (20 mol %), AgF (0.3 mmol), DMF (2 mL), 60 ºC, under argon atmosphere, unless otherwise noted. [b] Yield of isolated product. Enantiomeric excess (ee) values were determined by HPLC analysis with a chiral stationary phase.

(entries 11-18, (*S*)-**A9** and (*S*)-**A11**: 94% yield and 93% ee), and the naphthaloyl protecting group displayed a very pronounced influence on the reactivity and enantioselectivity. The opposite enantiomer (*R*)-**A11** had no obvious influence on the reactivity but resulted in a significantly eroded enantioselectivity (58% ee vs 93% ee). The control experiment indicated that the chiral acid additive plays an important role in improving both reactivity and enantioselectivity (entry 17 vs entry 19). Overall, the optimized reaction conditions were obtained as the following: **1a** (1 equiv), **2a** (3 equiv), [SCpRh] (5 mol %), (*S*)-**A11** (20 mol %), and AgF (3 equiv) under argon in DMF at 60 ºC for 14 h (entry 17).

Table 3. Scope of the Rh-catalyzed atroposelective C–H arylation of 1-aryl isoquinoline derivatives.[a,b]

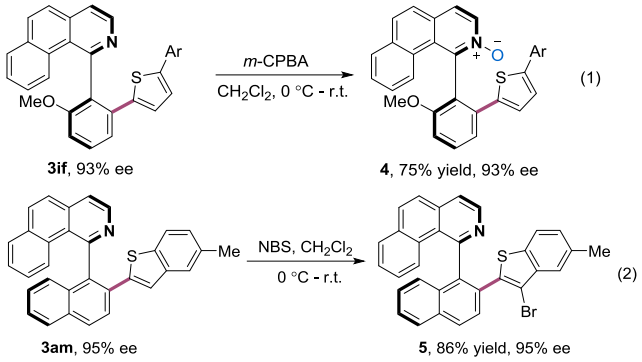


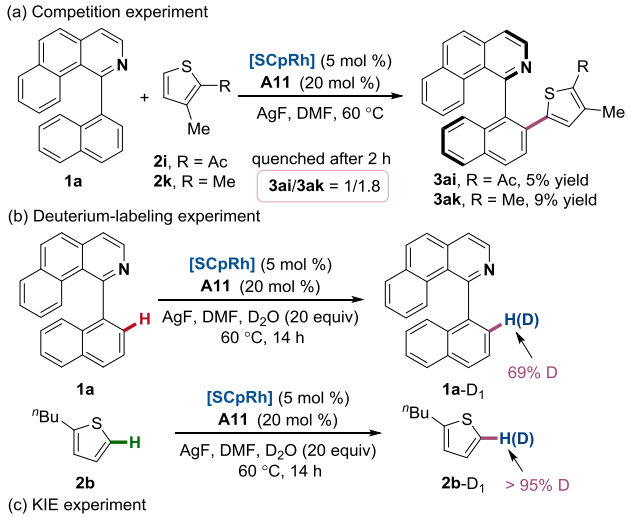
[a] Reaction conditions: **1** (0.1 mmol), **2** (0.3 mmol), [SCpRh] (5 mol %), **A11** (20 mol %), AgF (0.3 mmol), DMF (2 mL), 60 ºC, under argon atmosphere, unless otherwise noted. [b] Yield of isolated product. Enantiomeric excess (ee) values were determined by HPLC analysis with a chiral stationary phase. [c] [SCpRh] (2.5 mol %), DMF (5.0 mL).

With the optimal conditions in hand, enantioselective C–H/C–H oxidative cross-coupling reactions of **1a** with different heteroarenes were first carried out (Table 2). The results showed that thiophenes bearing electronically different substituents reacted smoothly to afford their corresponding products (**3aa-3ag**) in moderate to excellent yields (45-98%) and good to excellent enantioselectivities (87-94% ee). The reaction with 3-phenylthiophene **2h** took place with exclusive C5 regioselectivity, affording **3ah** in 73% yield and 91% ee. The reactions with thiophenes containing both C2 and C3 substituents were also regioselective, regardless of their electronic nature (**3ai-3ak**). The electron-rich thiophene **2k** (**3ak**, 88% yield, 95% ee) reacted more efficiently than the electron-deficient ones such as **2i** (**3ai**, 70% yield, 82% ee) and **2j** (**3aj**, 59% yield, 87% ee). Moreover, the reaction with benzothiophene **2l** gave the C2-functionalized product **3al** regioselectively in 55% yield and 90% ee. When the reaction time was extended to 72 h, product **3al** was isolated in 88% yield and 87% ee, and its C3-isomer was not observed in this reaction. 5-Methylbenzothiophene **2m** was more reactive compared with **2l**, affording product **3am** in 97% yield and 94% ee. Sterically hindered 3-methylbenzothiophene **2n** also reacted smoothly, affording product **3an** in 93% yield and 95% ee. Additionally, furans bearing electronically varied substituents were also compatible in this reaction, giving the products **3ao** and **3ap** in 86% yield and 88% ee, and 61% yield and 85% ee, respectively. However, when benzofuran **2q** was employed in this reaction, inseparable products **3aq**[2] and **3aq**[3] were obtained in a 1:1 ratio with a 70% combined yield. By blocking the C3 position of benzofuran with a methyl group, product **3ar** was afforded in 57% yield and 90% ee. Notably, substrate **2s** bearing multiple reactive sites could be regioselectively coupled at the thiophene ring, affording product **3as** in 85% yield and 91% ee. Furthermore, the reactions of *N*-Ts protected indole and pyrrole gave the C3-functionalized products **3at** and **3au** in 85% yield and 81% ee, and 25% yield and 89% ee, respectively. However, pyrrole, indole, *N*-Ac protected indole, oxazole, thiazole and benzothiazole are not suitable substrates for this reaction. Meanwhile, the absolute configuration of the product **3aa** was assigned as *Ra* by X-ray diffraction analysis (see the Supporting Information for details), and the configurations of all other products **3** were assigned by analogy.

Next, the scope of benzoisoquinolines was examined. As shown in Table 3, an array of benzoisoquinolines were well tolerated in this reaction, and the coupling products **3af-3od** were isolated in 70-99% yields with good to excellent enantioselective control (79-97% ee). Substituents with varied electronic properties on the naphthalene ring did not affect the reaction efficiency and enantioselectivity notably (**3bf-3ff**, 86-97% yields, 90-97% ee). The substrate with a methyl or methoxymethylene group on the phenyl ring showed relatively low reaction efficiency. Products **3gf** and **3hf** were afforded in 82% yield and 82% ee, and 70% yield and 79% ee, respectively. Substrate **1i** with a less bulky methoxy group on the phenyl ring behaved well in this reaction, affording product **3if** in 91% yield and 92% ee. Notably, when the reaction of **1i** with **2f** was performed in the presence of 2.5 mol % of [SCpRh] catalyst in 1.0 mmol scale, product **3if** was obtained in 99% yield and 92% ee. However, when the reaction was carried out with 1-(naphthalen-1-yl)isoquinoline **3j**, poor enantioselective control was observed (**3jd**, 17% ee, 97% yield). By introducing the substituents to the 8-position of the isoquinoline ring or naphthalene ring, the enantioselectivity could be dramatically improved (**3kf-3md**, 76-87% yields, 47-97% ee). Moreover, the reaction with 1-(phenanthren-4-yl)isoquinoline **3o** gave the product

3od in 88% yield and 99% ee. To be noted, one-step oxidation of **3if** by *m*-CPBA could afford *N*-oxide **4**, an analog of QUINOX ligand,[16f] in 75% yield without loss of the enantiopurity (eq 1). Bromination of **3am** by NBS gave product **5** in 86% yield without loss of the enantiopurity, which provide convenient handle for further functionalization (eq 2).



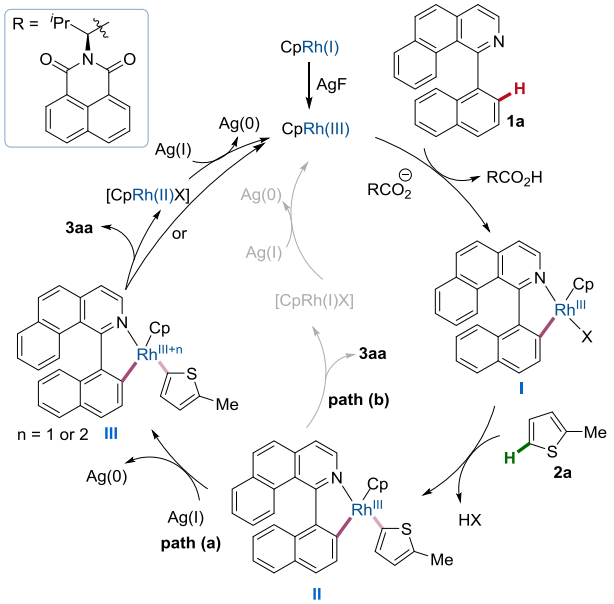


Scheme 2. Mechanistic studies.

To further understand the conformational stability of atropisomers **3**, the barriers to rotation for **3aa** and **3jd** were measured experimentally (**3aa**, $\Delta G^{\ddagger}$ = 39.3 kcal/mol; **3jd**, $\Delta G^{\ddagger}$ = 33.6 kcal/mol). Moreover, density functional theory (DFT) calculations were performed to obtain the rotational barriers of **3ad**, **3gf**, **3hf**, **3if**, and **3jd** (**3ad**, $\Delta G^{\ddagger}$ = 39.9 kcal/mol; **3gf**, $\Delta G^{\ddagger}$ = 39.7 kcal/mol; **3if**, $\Delta G^{\ddagger}$ = 32.9 kcal/mol; **3jd**, $\Delta G^{\ddagger}$ = 34.7 kcal/mol, See SI for details). These results showed that compounds **3** are atropisomerically stable under the reaction conditions.

To shed light on the mechanism of this oxidative cross-coupling reaction, a competitive experiment of **2i** and **2k** was carried out. Notably, products **3ai** and **3ak** were obtained in a 1:1.8 ratio (Scheme 2a). The faster reaction of electron-rich thiophene suggests an electrophilic process for the C-H bond cleavage of thiophene. Next, H/D exchange experiments of **1a** and **2b** were performed under the standard conditions with addition of D_2O. The results showed that both **1a** and **2b** could be easily deuterated, and the desired products **1a**-D_1 and **2b**-D_1 were obtained with 69% and >95% deuterium incorporated, respectively (Scheme 2b). It suggests that the C–H functionalization of both coupling partners are facile. In addition, the kinetic isotope effect (KIE) was measured based on parallel reactions of **1a**-D_7 and **1a** with **2d**-D_1 and **2d** (Scheme 2c). The KIE value was 1.0 for 1-(naphthalen-1-yl)benzo[h]isoquinoline and 1.0 for thiophene, respectively. Moreover, an k_H/k_D value of 1.1 was observed from parallel reactions of **1a** with **2d**, and **1a**-D_7 with **2d**-D_1. These results indicate that both C–H bond cleavages may not be the rate-determining step.[19]

Based on the above results and the previous reports,[3h-k,20] a plausible reaction mechanism was proposed using the reaction of **1a** with **2a** as an example (Scheme 3). Initially, rhodacycle intermediate **I** is generated through coordination with **1a** and subsequent enantioselective C–H bond cleavage via carboxylate-assisted concerted-metalation-deprotonation (CMD).[21] Next, rhodacycle intermediate **I** reacts with 2-methylthiophene **2a** to form rhodacycle intermediate **II** through electrophilic C–H substitution (SEAr).[3j] After oxidation by the Ag(I) salt, the rhodacycle intermediate **II** undergoes oxidation-induced reductive elimination[20b] to afford the cross-coupling product **3aa** and either a $CpRh^{III}$ or $CpRh^{II}$ complex depending on the oxidation state of rhodacycle intermediate **III**. Another pathway through reductive elimination from rhodacycle intermediate **II** cannot be completely excluded at present.[3j]



Scheme 3. Possible reaction mechanism.

In summary, we have developed the first efficient and straightforward rhodium(III)-catalyzed enantioselective oxidative C–H/C–H cross-coupling reaction between 1-aryl isoquinoline derivatives and electron-rich heteroarenes. Good to excellent enantioselectivity and regioselectivity were obtained with a proper choice of a chiral Rh(III) catalyst and a chiral carboxylic acid additive. The preliminary mechanistic experiments indicate that both C–H bond cleavages of two heteroarenes may not be the turnover-limiting step. Further studies of the mechanism and application of this enantioselective oxidative double C–H cross-coupling reaction for the synthesis of other types of atropisomeric compounds are currently underway.

ASSOCIATED CONTENT

Supporting Information

The supporting information is available free of charge via the internet at http://pubs.acs.org. Experimental procedures and spectroscopic data for new compounds (PDF).

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Notes

The authors declare no competing financial interests.

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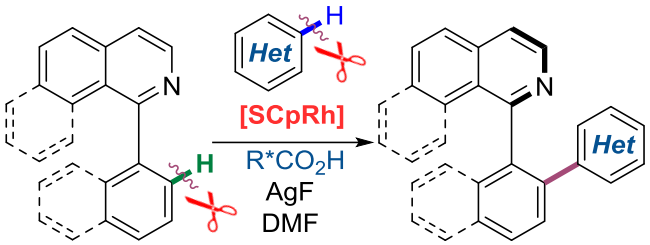

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