

REGULAR ARTICLE

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BINOL accelerated Ru(II)-catalyzed regioselective C-H functionalization of arenes with disulfides and diselenides

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Abstract. A BINOL accelerated Ru-catalyzed *ortho*-selective C-H coupling of arenes tethered to 7-azaindoles is described with disulfides and diselenides under air. The thioether can be readily oxidized to sulfoxide and sulfone. The use of less expensive Ru-catalysis, substrate scope and scale-up are the important practical features.

Keywords. Arenes; C-H functionalization; regioselective; Ru-catalysis; chalcogen.

1. Introduction

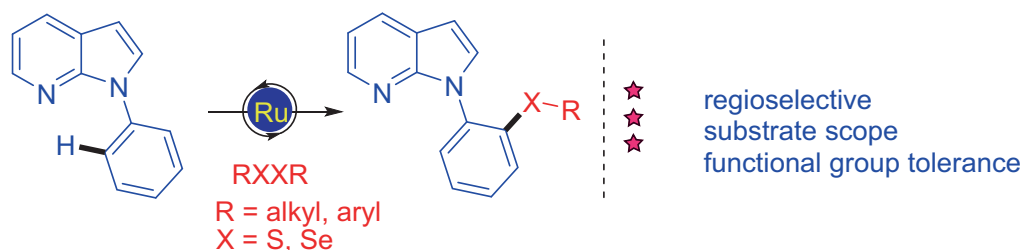
Recent advances in the directed C-H functionalization using transition-metal-catalysis have led to the development of effective synthetic tools for regioselective carbon-heteroatom bond formation.¹ Among them, the C-S/Se bond formation is attractive^{2,3} as these motifs are the structural constituents of numerous pharmaceuticals,⁴ materials⁵ and fluorescent probes.⁶ In 2006, Yu and co-workers demonstrated a Cu-catalyzed C-H thiolation of 2-phenylpyridines utilizing disulfides.^{7a} Since then, efforts are made on the directing group assisted C-H functionalization of arenes with disulfides using Cu,⁷ Co,⁸ Ni,⁹ Rh,¹⁰ Ru¹¹ and Pd¹²-based catalytic systems. 7-Azaindoles are important structural scaffolds found in a plethora of bioactive natural products and marketed drugs.¹³ Their unique structural feature with electron-rich azole and electron-deficient azine ring make them attractive in therapeutic agents, such as anti-cancer vemurafenib and glucokinase activator.¹³ Considerable attention is thus devoted to the C-H functionalization of 7-azaindole scaffolds.¹⁴ Recently, an Rh-catalyzed coupling of *N*-aryl-7-azaindoles with disulfides is reported.^{10d} However, the high cost of Rh-catalysis limit its potential applications. Herein, we present a BINOL enabled Ru-

catalyzed¹⁵ *ortho*-selective coupling of arenes tethered to 7-azaindoles with disulfides and diselenides under air (Scheme 1). The use of less expensive catalyst and large scale reaction are important practical features.

2. Results and Discussion

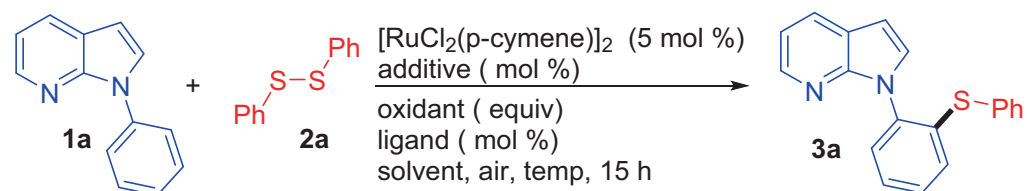
First, we commenced the optimization studies with *N*-phenyl-7-azaindole **1a** and diphenyl disulfide **2a** as the model substrates (Table 1). Pleasantly, the coupling occurred to deliver the *ortho*-thioether **3a** in 35% yield when **1a** and **2a** were stirred with 5 mol % [RuCl₂(*p*-cymene)]₂, 20 mol % AgSbF₆ and 1.0 equiv. Ag₂CO₃ in toluene at 100 °C for 15 h (entry 1). Subsequent screening with ligand led to accelerating the reaction to produce **3a** in 72% yield employing BINOL, whereas PCy₃, bipyridyl and Boc-Phe-OH showed inferior results (entries 2–5). Toluene was found to be the solvent of choice, while 1,4-dioxane, DMF, (CH₂Cl)₂, *m*-xylene and chlorobenzene furnished <42% yield (entries 6–10). In a set of oxidants studied, Ag₂CO₃, AgOAc, Cu(OAc)₂, K₂S₂O₈, Ag₂O and AgNO₃, the former gave the best result (entries 11–15). Among the additives, AgSbF₆ was superior to AgBF₄, KPF₆, AgOTf and AgNTf₂ (entries 16–19).

*For correspondence



Scheme 1. Ru-BINOL-catalyzed C-H functionalization arenes tethered to 7-azaindole with disulfides and diselenides.

Table 1. Optimization of the reaction conditions.^a



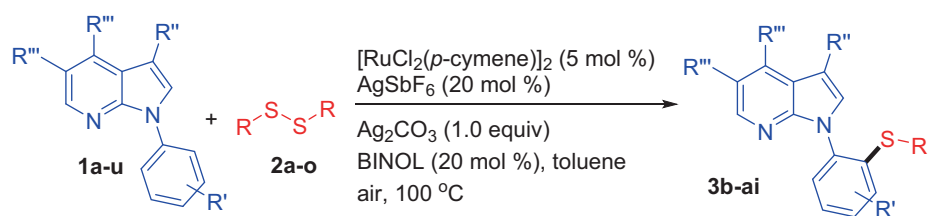
Entry	Additive	Oxidant	Ligand	Solvent	Yield (%) ^b
1	AgSbF ₆	Ag ₂ CO ₃	–	Toluene	35
2	AgSbF ₆	Ag ₂ CO ₃	BINOL	Toluene	72
3	AgSbF ₆	Ag ₂ CO ₃	PCy ₃	Toluene	35
4	AgSbF ₆	Ag ₂ CO ₃	bipyridyl	Toluene	27
5	AgSbF ₆	Ag ₂ CO ₃	Boc-Phe-OH	Toluene	25
6	AgSbF ₆	Ag ₂ CO ₃	BINOL	1,4-dioxane	25
7	AgSbF ₆	Ag ₂ CO ₃	BINOL	DMF	Trace
8	AgSbF ₆	Ag ₂ CO ₃	BINOL	(CH ₂ Cl) ₂	42
9	AgSbF ₆	Ag ₂ CO ₃	BINOL	<i>m</i> -xylene	38
10	AgSbF ₆	Ag ₂ CO ₃	BINOL	C ₆ H ₅ Cl	40
11	AgSbF ₆	AgOAc	BINOL	Toluene	35
12	AgSbF ₆	Cu(OAc) ₂	BINOL	Toluene	43
13	AgSbF ₆	K ₂ S ₂ O ₈	BINOL	Toluene	Trace
14	AgSbF ₆	Ag ₂ O	BINOL	Toluene	60
15	AgSbF ₆	AgNO ₃	BINOL	Toluene	35
16	AgBF ₄	Ag ₂ CO ₃	BINOL	Toluene	Trace
17	KPF ₆	Ag ₂ CO ₃	BINOL	Toluene	20
18	AgOTf	Ag ₂ CO ₃	BINOL	Toluene	52
19	AgNTf ₂	Ag ₂ CO ₃	BINOL	Toluene	47
20	AgSbF ₆	Ag ₂ CO ₃	BINOL	Toluene	63 ^c
21	–	Ag ₂ CO ₃	BINOL	Toluene	n.r.
22	AgSbF ₆	Ag ₂ CO ₃	BINOL	Toluene	n.r. ^d

^aReactions conditions: **1a** (0.2 mmol), **2a** (0.2 mmol), [RuCl₂(*p*-cymene)]₂ (5 mol %), additive (20 mol %), oxidant (0.2 mmol), ligand (20 mol %), solvent (2 mL), air, 100 °C, 15 h. ^bIsolated yield. ^c80 °C. ^dNo Ru-catalyst. n.r. = no reaction.

Decreasing the reaction temperature (80 °C) led to drop the yield to 63% yield (entry 20). Control experiments confirmed that the combination of AgSbF₆ and [RuCl₂(*p*-cymene)]₂ plays a crucial role (entries 21 and 22). The coupling was selective and the monothiolation was obtained as the sole product.

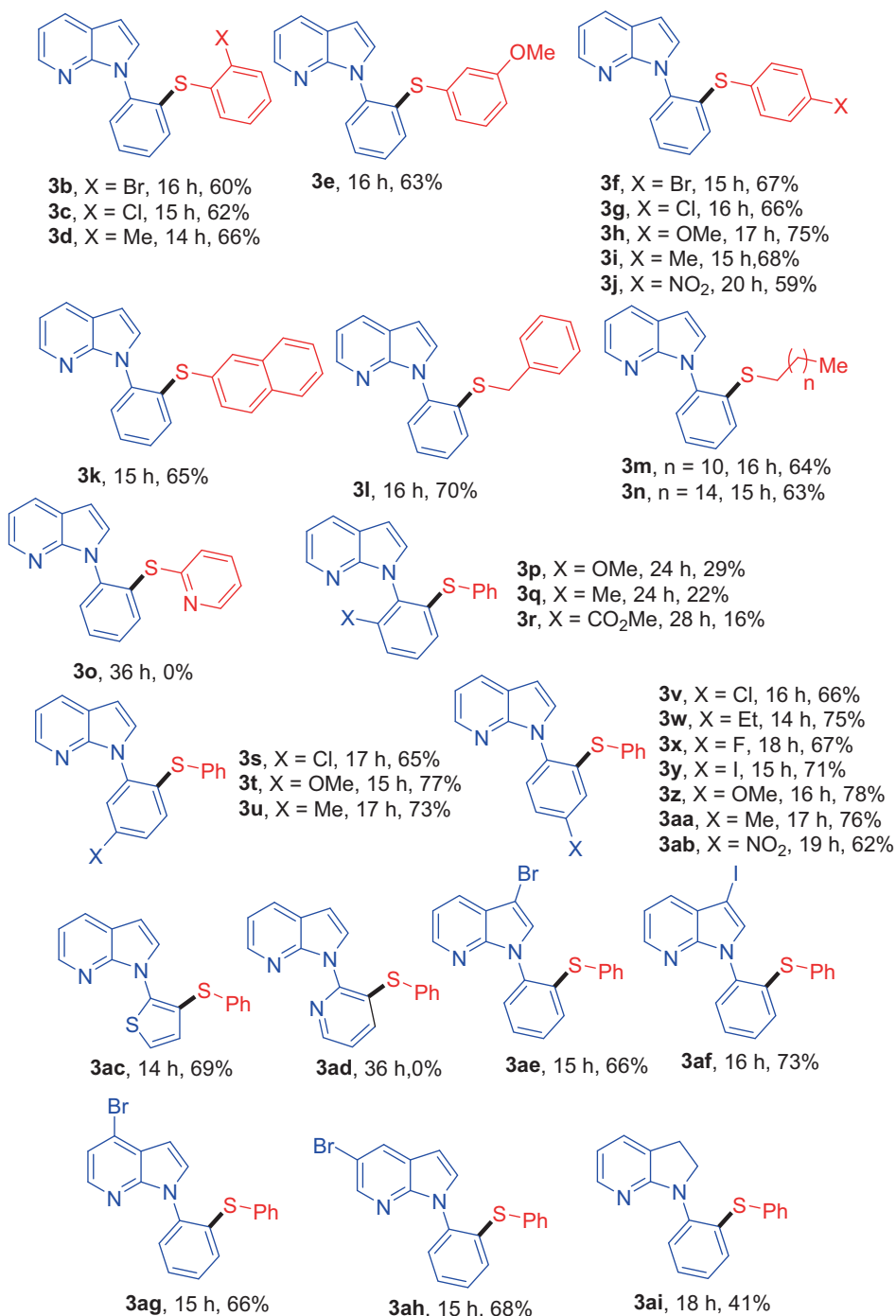
Having optimized the reaction condition, we studied the scope of the reaction using a series of substituted disulfides **2b-o** with *N*-phenyl-7-azaindole **1a** as a standard substrate (Scheme 2).

Disulfides having the substitution at the 2-position of the aryl ring with bromo **2b**, chloro **2c** and methyl

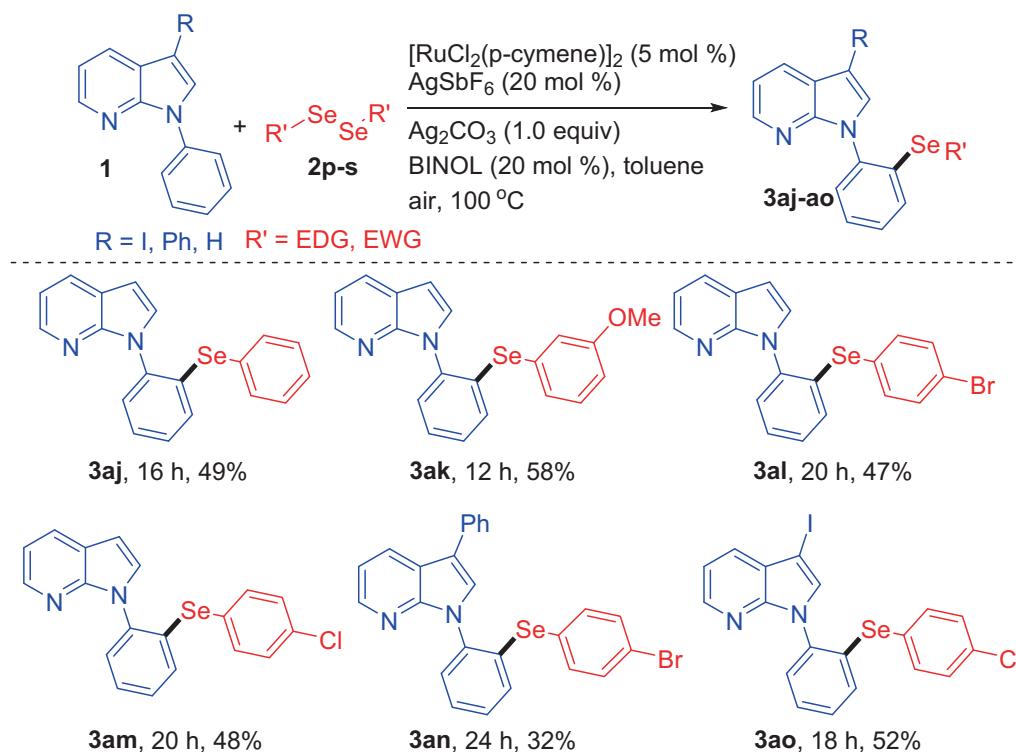


$\text{R}' = \text{EDG, EWG}$; $\text{R}'' = \text{Br, I, H}$; $\text{R}''' = \text{Br, H}$

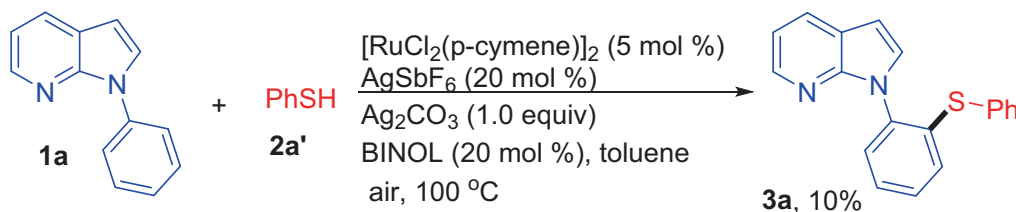
$\text{R} = \text{alkyl, aryl, benzyl, heteroaryl}$



Scheme 2. Reaction of disulfides **2a-o** with N-phenyl-7-azaindole **1a-u**.^{a,b} **1a-u** (0.2 mmol), **2a-o** (0.2 mmol), $[\text{RuCl}_2(p\text{-cymene})]_2$ (5 mol %), AgSbF_6 (20 mol %), Ag_2CO_3 (0.2 mmol), BINOL (20 mol %), toluene (2 mL), air, 100 °C. ^bIsolated yield.



Scheme 3. Reaction of *N*-aryl-7-azaindoles with diaryl diselenides **2p-s**:^{a,b} **1** (0.2 mmol), **2p-s** (0.2 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), $AgSbF_6$ (20 mol %), Ag_2CO_3 (0.2 mmol), toluene (2 mL), air, 100 °C. ^bIsolated yield.

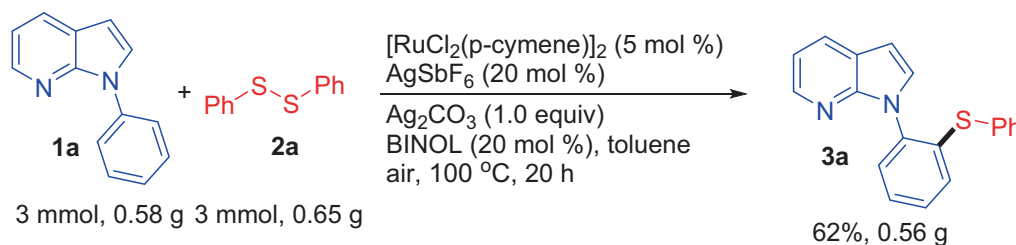


Scheme 4. Reaction of **1a** with thiophenol **2a'**.

2d groups underwent a reaction to produce the thioethers **3b–d** in 60–66% yields.

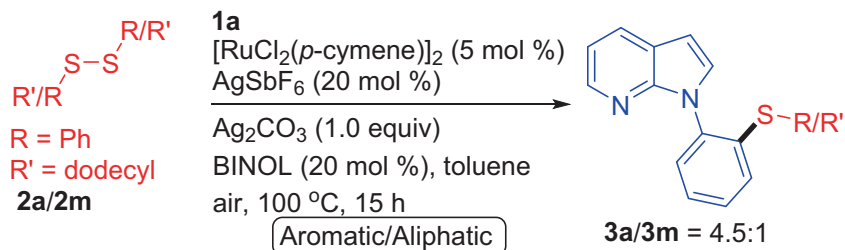
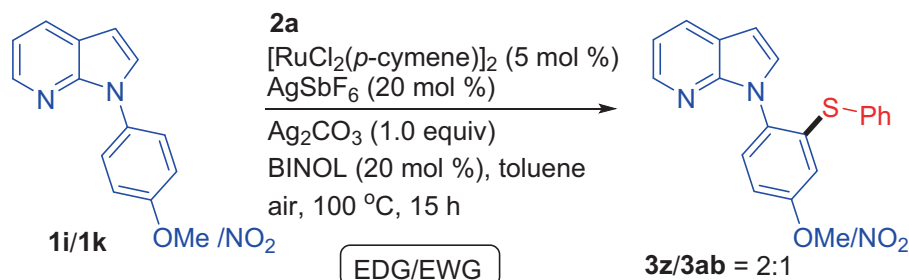
The reaction of the disulfide bearing methoxy **2e** functionality at the 3-position furnished **3e** in 63% yield, whereas the disulfides containing bromo **2f**, chloro **2g**, methoxy **2h**, methyl **2i** and nitro **2j** groups

at the 4-position could be coupled to deliver the thioethers **3f–j** in 59–75% yields. Recrystallization of **3g** in CH_2Cl_2 gave single crystals, whose structure was determined using X-ray analysis (See Supplementary Information). Naphthyl disulfide **2k** could be reacted to afford the thioether **3k** in 65% yield. Similar results

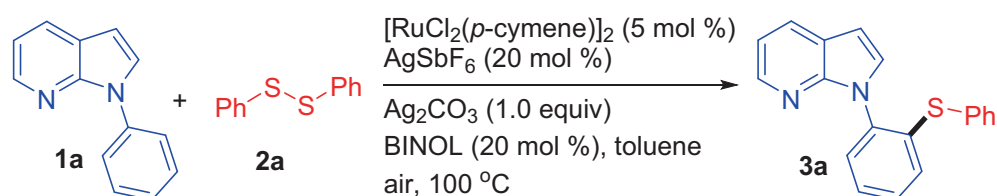


Scheme 5. Large-Scale Reaction.

A. Intermolecular competitive experiments



B. Radical scavenger experiments



Radical Scavenger (2.0 equiv)	Yield (%)
TEMPO	55
BHT	63

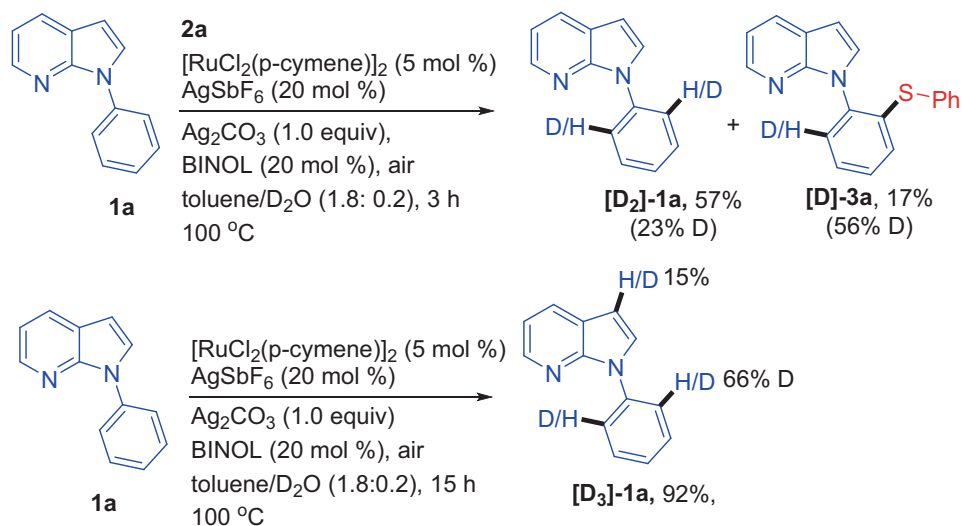
Scheme 6. Preliminary mechanistic experiments.

observed with benzyl disulfide **2l**, affording **3l** in 70% yield, while didodecyl disulfide **2m** and dihexadecyl disulfide **2n** were tolerated to furnish the thioethers **3m** and **3n** in 64% and 63% yields, respectively. However, the reaction of dipyrindyl disulfide (**1o**) was not successful, which may be due to the chelation of pyridine nitrogen to the Ru species.

Next, the reaction was extended to the coupling of a series of *N*-aryl-7-azaindoles **1b–u** with **2a** as a standard substrate (Scheme 2). The reaction of the substrates bearing the substitution at the 2-position with methoxy **1b**, methyl **1c** and ester **1d** groups produced **3p–r** in 16–29% yields, which may be attributed to the steric hindrance of the substituents. However, the substrates having the substitution at the 3-position with chloro **1e**, methoxy **1f** and methyl **1g** groups

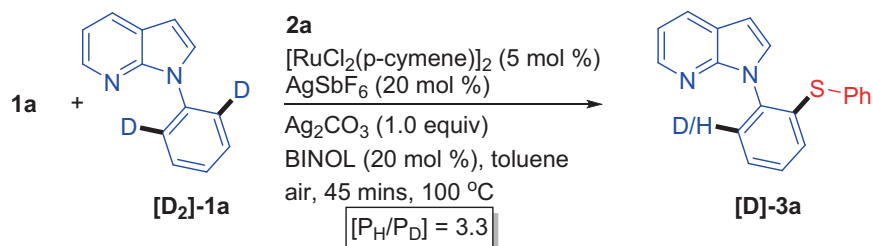
underwent a reaction to afford the target thioethers **3s–u** in 65–77% yields. Similar results were observed with the substrates bearing chloro **1h**, ethyl **1i**, fluoro **1j**, iodo **1k**, methoxy **1l**, methyl **1m** and nitro **1n** groups at the 4-position, giving the thioethers **3v–ab** in 62–78% yields. The reaction of heterocycle-containing azaindole **1o** gave **3ac** in 69% yield, whereas the azaindole having pyridine **1p** failed to produce the target thioether. However, 7-azaindoles bearing bromo **1q** and iodo **1r** substituents at the 3-position afforded **3ae** and **3af** in 66 and 73% yields, respectively. Furthermore, the reaction of 7-azaindole containing 4-Br (**1s**) and 5-Br (**1t**) groups furnished **3ag** and **3ah** in 66 and 68% yields, respectively, whereas 7-azaindoline **1u** underwent reaction to afford the thioether **3ai** in 41% yield. These results suggest that the reaction of

A. H/D-Exchange experiments

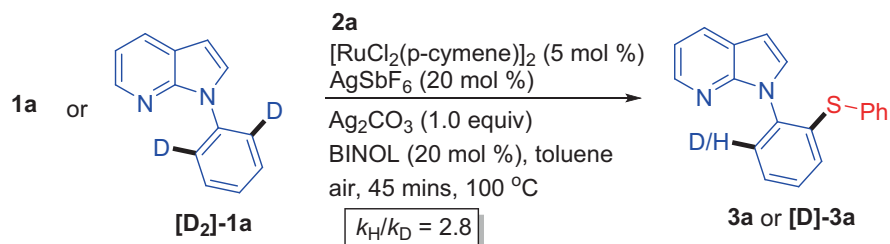


B. Kinetic isotope experiments

I. Intermolecular



II. Parallel



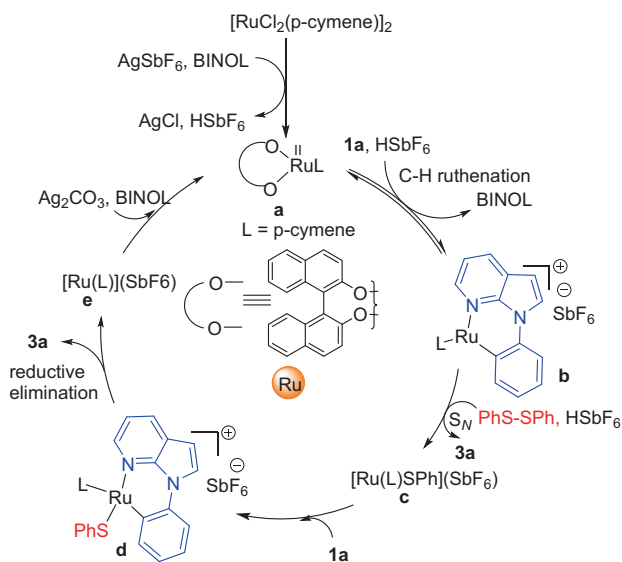
Scheme 7. H/D exchange and kinetic isotope experiments.

both the 7-azaindole and 7-azaindoline can be accomplished.

The scope of the procedure was further studied for the coupling of analogue diselenides (Scheme 3). The reaction of *N*-phenyl-7-azaindole **1a** with diselenide **2p** produced **3aj** in 49% yield. Similar result observed with diselenide bearing methoxy **2q** group at the 3-position, giving **3ak** in 58% yield, whereas diselenide containing bromo **2r** and chloro **2s** functional groups at the 4-position delivered **3al** and **3am** in 47% and 48% yields, respectively. In addition, the reaction of 7-azaindole having phenyl **1v** group at the

3-position with **2r** gave **3an** in 32% yield. Moreover, 7-azaindole having 3-iodo group **1r** underwent reaction with **2s** to afford **3ao** in 52% yield.

The utility of the protocol was further studied for the coupling of thiophenol **2a'** with 7-azaindole **1a** as the representative example (Scheme 4). However, the reaction was less effective, giving **3a** in 10% yield. Next, the scalability of the protocol was studied employing **1a** and **2a** as the representative substrates (Scheme 5). The coupling occurred with 62% yield, which suggests that the large scale reaction can be performed.



Scheme 8. Plausible catalytic cycle.

To get insight into the reaction pathway, intermolecular competitive experiments were performed using electronically varied *N*-aryl-7-azaindoles **1l** and **1n** with **2a** (Scheme 6A). The substrate with the electron-donating 4-methoxy group exhibited greater reactivity compared to that having electron-deficient 4-nitro group. In addition, the reaction of **1a** with diaryl disulfide **2a** showed greater reactivity compared with dialkyl disulfide **2m** (Scheme 6A). Further, the radical scavenger experiments using TEMPO and BHT gave **3a** in 55 and 63% yields, respectively which suggests that radical process may not be involved (Scheme 6B).

Moreover, the reaction using D₂O as a co-solvent exhibited H/D exchange at the *ortho*-position of the aryl ring (Scheme 7A). The intermolecular kinetic isotope experiment using **1a** and [D₂]-**1a** with **2a** provided [P_H/P_D] = 3.3 (Scheme 7BI) and the parallel experiment yielded *k_H/k_D* = 2.8 (Scheme 7BII). These experimental results and literature reports suggest that [RuCl₂(*p*-cymene)]₂ with BINOL and AgSbF₆ may generate an active cationic Ru^{II} species **a**, which may

react with *N*-aryl-7-azaindole **1a** reversibly to form a Ru^{II}-metallacycle **b** (Scheme 8).^{11,16–18}

The latter can undergo nucleophilic substitution (S_N) with disulfide to give the thiolated **3a** and the Ru(II)-species **c** that can participate in a second C-H activation with **1a** to afford ruthenated species **d**. Reductive elimination of **d** can deliver **3a** and the Ru(I)-species **e**, which can undergo Ag(I)-mediated oxidation and reassociation of the BINOL ligand to regenerate the active Ru(II) species. Thus, BINOL may facilitate the generation of the active Ru(II) complex.

Finally, the synthetic utility was studied using the oxidation of **3a** as an example (Scheme 9). The thioether **3a** underwent oxidation with oxone in THF/H₂O to give the sulfoxide **4** in 72% yield, whereas the reaction using *m*-CPBA delivered the sulfone **5** in 48% yield.

3. Conclusions

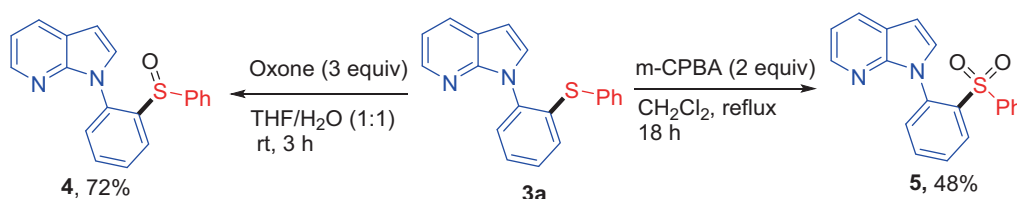
In conclusion, we have presented a BINOL-accelerated Ru-catalyzed *ortho*-selective C-H functionalization of arene tethered to 7-azaindole^{17a} with disulfides^{17c} and diselenides^{17b} under air. The reaction is selective with broad substrate scope and functional group diversities using the less expensive Ru-catalysis.

Supplementary Information (SI)

The experimental procedure, characterization data, NMR spectra (¹H and ¹³C) and Crystal structure and data of **3g** are available at www.ias.ac.in/chemsci.

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Scheme 9. Post synthetic applications.

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