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A Robust Protocol for Pd(II)-catalyzed C-3 Arylation of (1*H*) Indazoles and Pyrazoles: Total Synthesis of Nigellidine Hydrobromide

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Abstract

C3-arylated indazole and pyrazoles are privileged structural motifs in agrochemicals and pharmaceuticals. C-3 C-H arylation of (1*H*) indazole and pyrazole has been a significant challenge due to the poor reactivity of the C-3 position. Herein, we report a practical Pd(II)/Phen catalyst and conditions for direct C-3 arylation of indazole and pyrazole with ArI or ArBr without using Ag additives as halide scavengers. The use of toluene, chlorobenzene, trifluoromethylbenzene and mesitylene as the solvent was found to be crucial for the selectivity and reactivity. We further demonstrate the robustness of this protocol through the first total synthesis of Nigellidine hydrobromide as well as expedient preparation of heterocycles structurally related to pesticides and drug molecules.

Introduction

Transition metal-catalyzed arylation of heteroarene C-H bonds has regained considerable attention over recent years.¹ These reactions can potentially provide concise routes for constructing bi(hetero)aryls, as well as late-stage diversification of bioactive target molecular scaffolds.² As an important class of heteroarenes, indazole and pyrazole motifs are embedded in numerous pharmaceuticals and agrochemicals with broad range of biological activities,³ including anti-inflammatory (Celebrex, Fig. 1),^{3a} antiemetic (Granisol),^{3b} antipsychotic (CDPPB),^{3c} and anticancer (Pyrazolanthrone)^{3d} drugs, as well as herbicide (Fluazolate),^{3e} and insecticide (Chlorantraniliprole).^{3f}

As a result, extensive efforts have been directed towards the development of practical and efficient catalytic systems for direct arylation of indazole and pyrazole in recent years. These protocols have been applied to the rapid syntheses of indazole or pyrazole

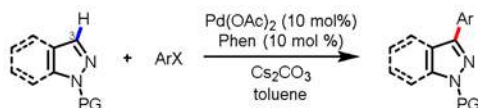
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[†]Electronic Supplementary Information (ESI) available: Data for new compounds and experimental procedures. See DOI: 10.1039/b000000x/

[‡]General procedure for C-3 Arylation of Indazoles and Pyrazoles: To a 35 mL sealed tube, were added Pd(OAc)₂ (5.6 mg, 0.025 mmol), 1,10-phenanthroline (4.5 mg, 0.025 mmol), Cs₂CO₃ (82 mg, 0.25 mmol), aryl halide (0.25 mmol), indazole derivative (0.25 mmol), and toluene (1 mL). The tube was capped and stirred at 160 °C for 48–72 h. The reaction mixture was cooled to room temperature and diluted with EtOAc, filtered through a short pad of Celite, washed with EtOAc, and concentrated in *vacuo*. The resulting residue was purified by PTLC using hexanes: EtOAc (10:1 to 6:1, depending on different substrates) as the eluent.

bi(hetero)aryls, or late-stage modification of complex indazole or pyrazole scaffolds.⁴⁻⁹ Despite the development of several efficient protocols for C-4,^{4,5} C-5 arylation of pyrazole,⁶ and C-3 arylation of (*2H*) indazole,^{7,8} C-3 arylations of pyrazole and (*1H*) indazole remain formidable challenges due to lack of reactivity (Fig. 2).⁹ Indeed, installation of an aryl group at C-3 of pyrazole via C-H activation can only be achieved by using a elegantly devised protecting-group-switch strategy.^{6a} This strategy essentially converted the C-3 position into the more reactive C-5 position. It has also been shown that an efficient arylation protocol for C-3 arylation of (*2H*) indazole is not applicable to (*1H*) indazole substrates.⁸

Building on our previous success of C-3 selective arylation and olefination of pyridines using Pd(II)/Phen(phenanthroline) catalysts,¹⁰ we embarked on the development of related protocols for C-3 arylation of (*1H*) indazoles and pyrazoles. While our manuscript was in preparation, the Itami and Kazzouli groups independently reported Pd/Phen (phenanthroline) catalysts for C-3 arylation of (*1H*) indazole.¹¹ In Itami's protocol, the reaction was run with 10 mol% PdCl₂, 10 mol% Phen, 2.0 equiv K₃PO₄, and 1.5 equiv Ag₂CO₃ in DMA.11a Kazzouli's conditions required 20 mol% Pd(OAc)₂ and 40 mol% Phen in polar DMA.11b While these reactions represent exciting development for C-3 arylation of (*1H*) indazole, both yields and substrate scope remain to be substantially improved. The use of stoichiometric amount of Ag additive as halide scavenger, or high catalyst loading (20 mol% Pd) is also a drawback. Herein, we report a highly efficient Pd/Phen catalytic system for the C-3 arylation of (*1H*) indazole and pyrazole without using Ag additive (eq 1). We demonstrate the utility of this protocol by achieving the first total synthesis of Nigellidine.

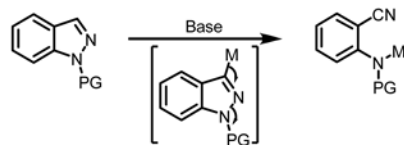


(1)

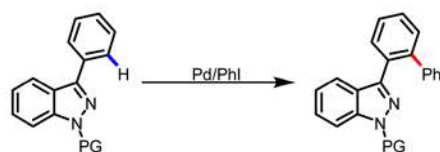
Results and Discussion

Initial Studies and Reaction Optimization

There exist two major challenges in the development of selective C-H functionalization methods for heterocycles, namely, controlling the regioselectivity among C-H bonds with subtle electronic and steric differences, and preventing the non-productive coordination of the heteroatom of the substrates with the metal catalysts. In search for solutions to these two problems, we found phenanthroline ligand coordinate strongly with Pd(II) center and weakens coordination of the N-atom of pyridine substrates, most likely through sterics.¹⁰ The dissociation of the pyridine enhances the local concentration of substrate nearby the Pd(II) catalysts for productive π -binding which triggers the C-3 C-H functionalizations. Computational studies suggest that the C-3 selectivity can be attributed to the recognition of the highest electron density at this carbon by the catalyst.¹² Encouraged by these preliminary results, we began to test if Pd(II)/Phen system could be adapted for C-3 arylation of (*1H*) indazole and pyrazole. We were aware of several potential problems that we could encounter in applying this Pd/Phen system to C-3 arylation of pyrazole and indazole. Firstly, N-N bond is known to be unstable under previously reported conditions (eq 2).¹³ Secondly, the sp² nitrogen at the 2-position could direct further arylation of the newly installed aryl groups (eq 3).



(2)



(3)

Based on our previous protocol for C-3 arylation of pyridines, we began to screen conditions for arylation of 1-methyl indazole **1a**. We found that the reaction of 1 equiv **1a** with 1 equiv iodobenzene in DMF in the presence of 10 mol% Pd(OAc)₂, 30 mol% Phen and 3.0 equiv Cs₂CO₃ under air at 140 °C gave the desired arylated product **2a** in 24% yield after 48 h (entry 1, Table 1). The undesired byproduct **3** from further directed arylation of product **2a** was also isolated in 3% yield. Increasing the amount of iodobenzene to 2 equiv improved the yield of **2a** to 51%. Unfortunately, the yield of side product **3** also increased to 14% (entry 2, Table 1). We reasoned that bulkier or tridentate ligand would prevent the nitrogen at the 2-position from directing further arylation of product **2a**. Indeed, bulkier ligand (Phen-PhMe, entry 3) and tridentate (Dpya, entry 4) inhibited the formation of **3**, with ligand Dpya affording **2a** in 42% yield (entry 4). Although the result obtained with Dpya was promising, we further optimized conditions using phenanthroline due to its ready availability, and found that the use of K₃PO₄ as the base in DMF diminished the formation of **3** (entry 5) while affording **2a** in 47% yield. Disappointingly, the material balance under all these conditions was only around 60%.

To improve the material balance, we examined the solvent effect using K₃PO₄ as a base (entries 1–4, Table 2). Strikingly, the use of PhCl as the solvent completely suppressed the formation of the side product **3** (entry 4). Most importantly, the material balance in PhCl reached above 90%. The stability of indazole substrate in this solvent prompted us to raise the reaction temperature to 160 °C which improved the yield to 60% (entry 5). This dramatic solvent effect urged us to revisit the use Cs₂CO₃ as the base. To our delight, Cs₂CO₃ in PhCl improved the yield to 89% with the formation of only 3% of byproduct **3** (entry 6). Either reducing the loading of ligand (entry 7) or the amount of base resulted in a lower yield (entry 8). We also observed that PhCl reacted with indazole in the absence of PhI (entry 9) which could be a potential problem in synthetic applications. In light of these two drawbacks, we further screened arene-based solvents and found that toluene, PhCF₃ and mesitylene also gave comparable results (entries 10–12). Importantly, the loading of phen ligand and base can be reduced to 10 mol% and 1 equiv, respectively only when toluene is used as solvent (entries 13, 14). Control experiments showed that the Pd(OAc)₂, Phen and base are essential for the observed reactivity (entries 15, 16).

Substrate Scope

With this significantly improved protocol in hand, we examined the scope of arylhalide coupling partners for C-3 arylation of indazoles. Both aryl iodides and bromides worked well to give the corresponding 3-arylated indazoles in high to excellent yield (**2a-2p**, Table 3). Aryl chlorides also reacted under these conditions to give the arylated product in 29% yield, albeit requiring use of excess phenyl chloride (entry 9, Table 2). The possibility of using aryl chlorides as coupling partners upon further development is appealing from the practical perspective. A wide range of functional groups on the aryl iodides were tolerated including electron-donating and -withdrawing groups, OMe, MeS, F, Cl, CF₃, CN and CO₂Et (**2g-2m**). The tolerance of a strongly chelating MeS group is a valuable feature for making sulfur containing compounds. Most importantly, arylation with heteroaryl bromides also proceeded smoothly to afford biologically important biheteroaryls in good to excellent yields (**2n-2p**), which speaks to the robustness of the Pd/Phen catalysts and conditions.

Next, we focused our attention on the scope of the indazoles and pyrazoles. Unprotected indazole and pyrazole gave no reaction under the optimal conditions. To improve the versatility of this protocol, we tested various synthetically useful N-protecting groups. Unfortunately, electron-withdrawing protecting groups such as Ac, Boc, and Ts inhibit the reaction severely. To our delight, the practically useful alkyl protecting group, such as Bn (**2q**, **2r**), SEM (**2s**), and THP (**2t**) were compatible with this reaction (Table 4).¹⁴ It is worth noting that the undesired directed ortho-arylation of the benzyl groups was not observed. The synthetic utility C-3 arylation of Bn-protected indazole was demonstrated by a one-step synthesis of biologically active agent YD-3 (**2r**) in 89% yield using *para*-methoxycarbonylaryliodide coupling partner.¹⁵ Various substituents including fluoro, chloro and ester on indazole phenyl rings were tolerated (**2u-2y**), although 4-Cl substituted indazole reacted very slowly due to the sterics, giving 44% yield in 72 h (**2u**). We were pleased that azaindazole, a biologically important structural motif, was also successfully arylated to give the desired product in 81% yield (**2y**), without any reaction of the highly activated chloro group at the 2-position of the pyridyl ring, thus allowing subsequent further cross couplings at this position. Finally, C-3 arylations of substituted pyrazoles including a hindered triphenyl pyrazole were also successful (**4a-4c**).¹⁶ Prior to our work, a single example of tris(trifluoromethyl)phenylation of N-methylpyrazole in a moderate yield (52%) using [Pd(Phen)₂](PF₆)₂ catalyst was reported by Murai.¹⁷

As expected, arylation of (*2H*) indazole under these reaction conditions gave the desired products in 91% yield (Fig. 3). Competition experiments using (*1H*) indazole and (*2H*) indazole in the same reaction afforded 75% C-3-arylated (*2H*) indazole and 8% C-3-arylated (*1H*) indazole, confirming that the reactivity of (*2H*) indazole is superior to that of (*1H*) indazole.

Synthetic Application

Developing C-H activation reactions as enabling synthetic disconnections to allow for highly convergent synthesis is one major impetus for our efforts in this field.^{18,19} We therefore sought to demonstrate the utility of our C-3 indazole arylation in a total synthesis of the natural alkaloid nigellidine (**12**). Nigellidine was isolated in 1995 from the seeds of *Nigella sativa*, which are used to treat various diseases.²⁰ While related indazole natural products have been synthesized by Kelly,²¹ no total synthesis of nigellidine has yet been reported. We envisioned a convergent synthesis of nigellidine could be rapidly accomplished using this C-3 arylation reaction as a key step. Thus, commercially available 4-methoxy-6-methyl-(*1H*)-indazole was first protected using the readily removable THP group to give **7**. C-3 arylation of **7** under the optimized conditions furnished **8** in 54% isolated yield on gram scale (Fig. 4). Deprotection of the THP group and stepwise *N*-

alkylations with 1,4-dibromobutane afforded precursor **11**. Subsequent demethylation by treating **11** with BBr_3 afforded the natural product nigellidine hydrobromide (**12**), which was confirmed by X-ray crystallographic analysis. Thus, the first total synthesis of nigellidine hydrobromide was completed in six steps with an overall yield of 18%.

Conclusions

In summary, we have developed a practical Pd/Phen catalyst system for C-3 arylation of indazole and pyrazole. This protocol in general gives high yields and accommodates broad range of substrates and coupling partners. The robustness of this catalytic reaction was demonstrated in the first total synthesis of natural alkaloid Nigellidine hydrobromide as well as one-step synthesis of drug molecule YD-3.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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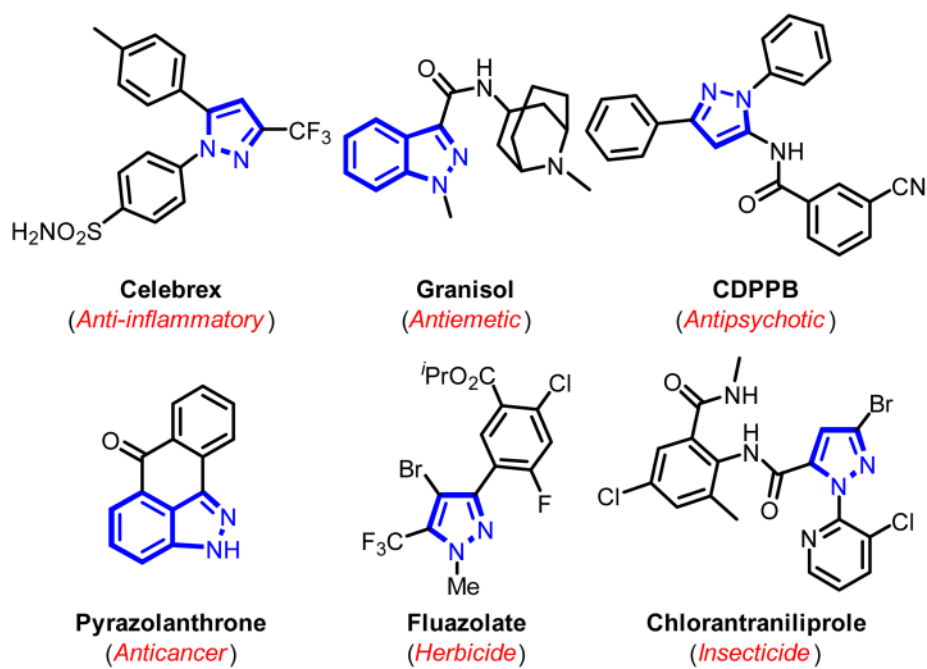


Fig. 1.
Biologically active indazoles and pyrazoles.

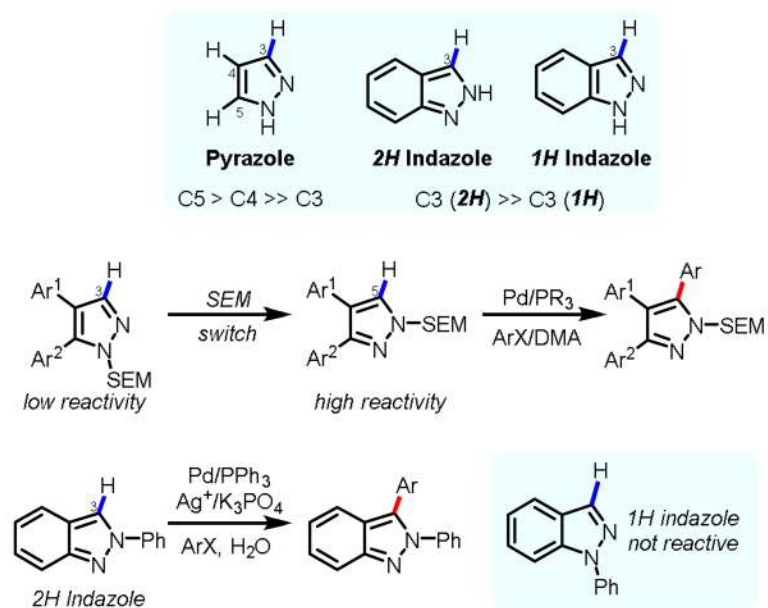


Fig. 2. Reactivity of indazole and pyrazole towards C-H arylation.

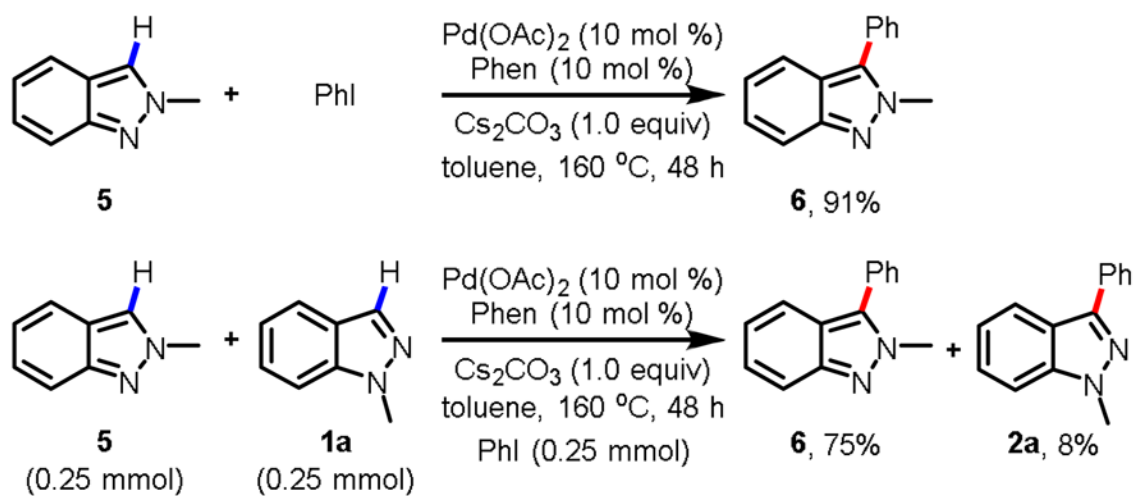


Fig. 3. Competition reaction between (1*H*) indazole and (2*H*) indazole.

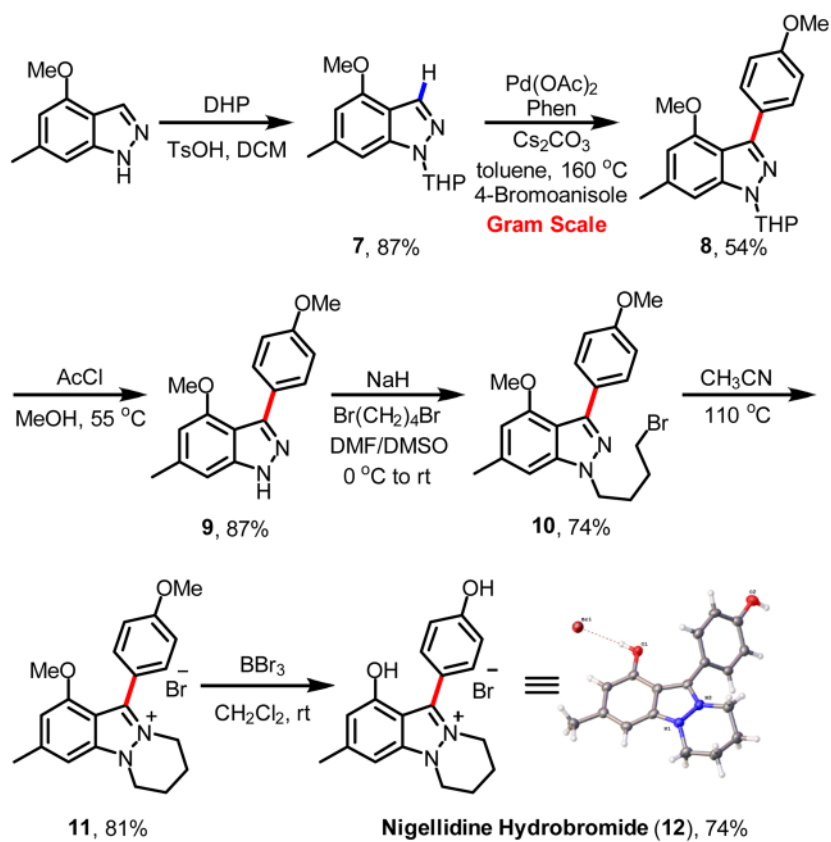


Fig. 4. Total synthesis of nigellidine hydrobromide.

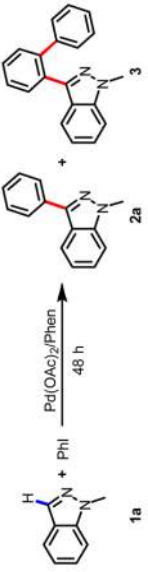
Table 1

Discovery of C-3 C-H arylation of indazole.^a

entry	PhI (equiv)	ligand	base	2a (%) ^b	3 (%) ^b
1	1.0	Phen	Cs ₂ CO ₃	24	3
2	2.0	Phen	Cs ₂ CO ₃	51	14
3	2.0	Phen-PhMe	Cs ₂ CO ₃	21	0
4	2.0	Dpya	Cs ₂ CO ₃	42	0
5	2.0	Phen	K ₃ PO ₄	47	6
6	2.0	Phen	K ₂ HPO ₄	3	0

^aReaction conditions: Indazole (0.25 mmol) in solvent (1 mL) at 140 °C for 48 h.^bYield was determined by ¹H NMR using CH₂Br₂ as an internal standard.

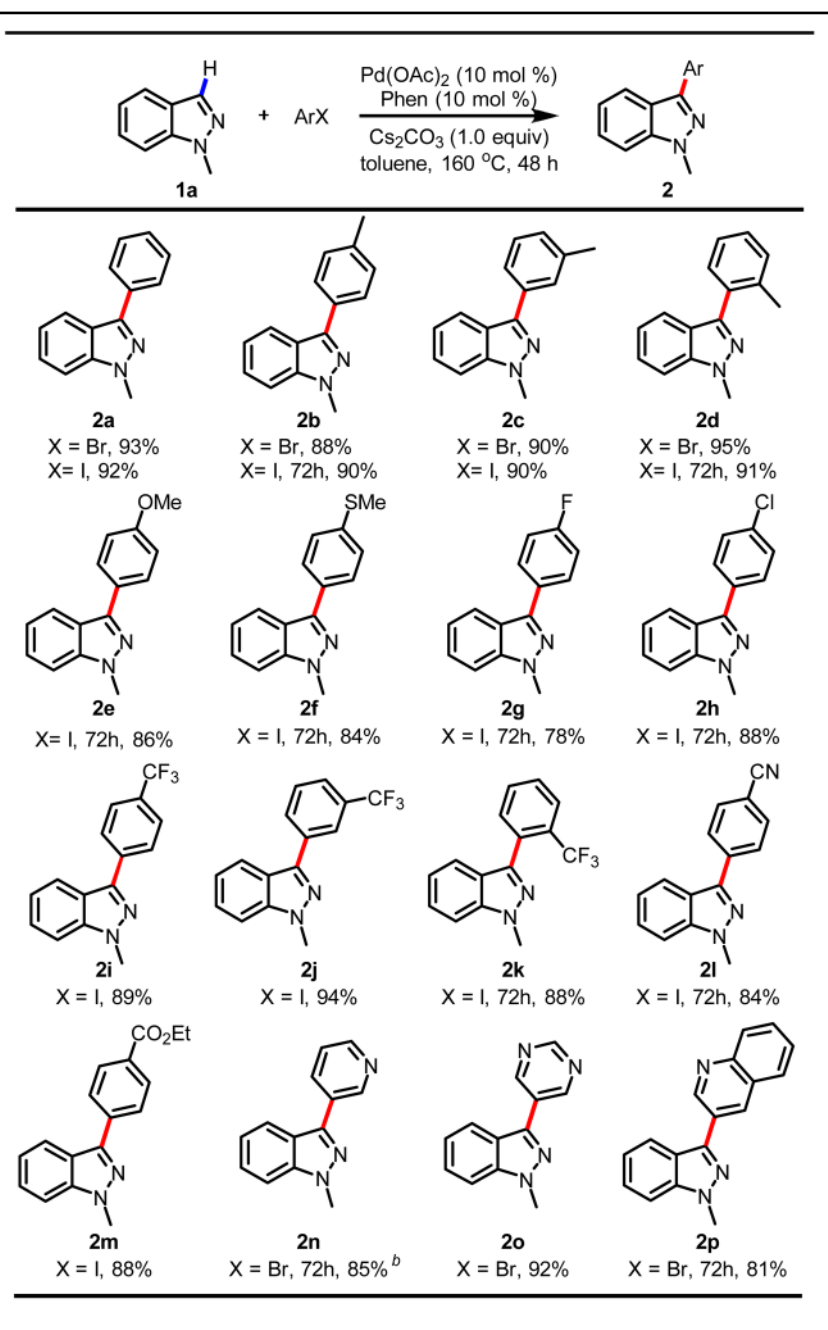
Table 2

Optimization for C-3 arylation of indazole.^a


entry	Pd(OAc) ₂ (mol %)	Phen (mol %)	base (equiv)	solvent (1 mL)	temp. (C)	yield (%) ^b	2a (3)
1	10	30	K ₃ PO ₄ (3.0)	Dioxane	140	0	(0)
2	10	30	K ₃ PO ₄ (3.0)	DMSO	140	45	(0)
3	10	30	K ₃ PO ₄ (3.0)	o-xylene	140	19	(0)
4	10	30	K ₃ PO ₄ (3.0)	PhCl	140	45	(0)
5	10	30	K ₃ PO ₄ (3.0)	PhCl	160	60	(0)
6	10	30	Cs ₂ CO ₃ (3.0)	PhCl	160	89	(3)
7	10	10	Cs ₂ CO ₃ (3.0)	PhCl	160	72	(1)
8	10	30	Cs ₂ CO ₃ (1.0)	PhCl	160	64	(0)
9	10	30	Cs ₂ CO ₃ (3.0)	PhCl	160	29	(0) ^c
10	10	30	Cs ₂ CO ₃ (3.0)	PhCF ₃	160	87	(0)
11	10	30	Cs ₂ CO ₃ (3.0)	mesitylene	160	77	(4)
12	10	30	Cs ₂ CO ₃ (3.0)	toluene	160	85	(3)
13	10	10	Cs ₂ CO ₃ (1.0)	toluene	160	93	(0)
14	5	5	Cs ₂ CO ₃ (1.0)	toluene	160	23	(0)
15	10	0	Cs ₂ CO ₃ (1.0)	toluene	160	0	
16	0	10	Cs ₂ CO ₃ (1.0)	toluene	160	0	

^aReaction conditions: Indazole (0.25 mmol) and PhI (0.5 mmol) in solvent (1 mL) for 48 h.^bYield was determined by ¹H NMR using CH₂Br₂ as an internal standard.^cNo PhI was added.

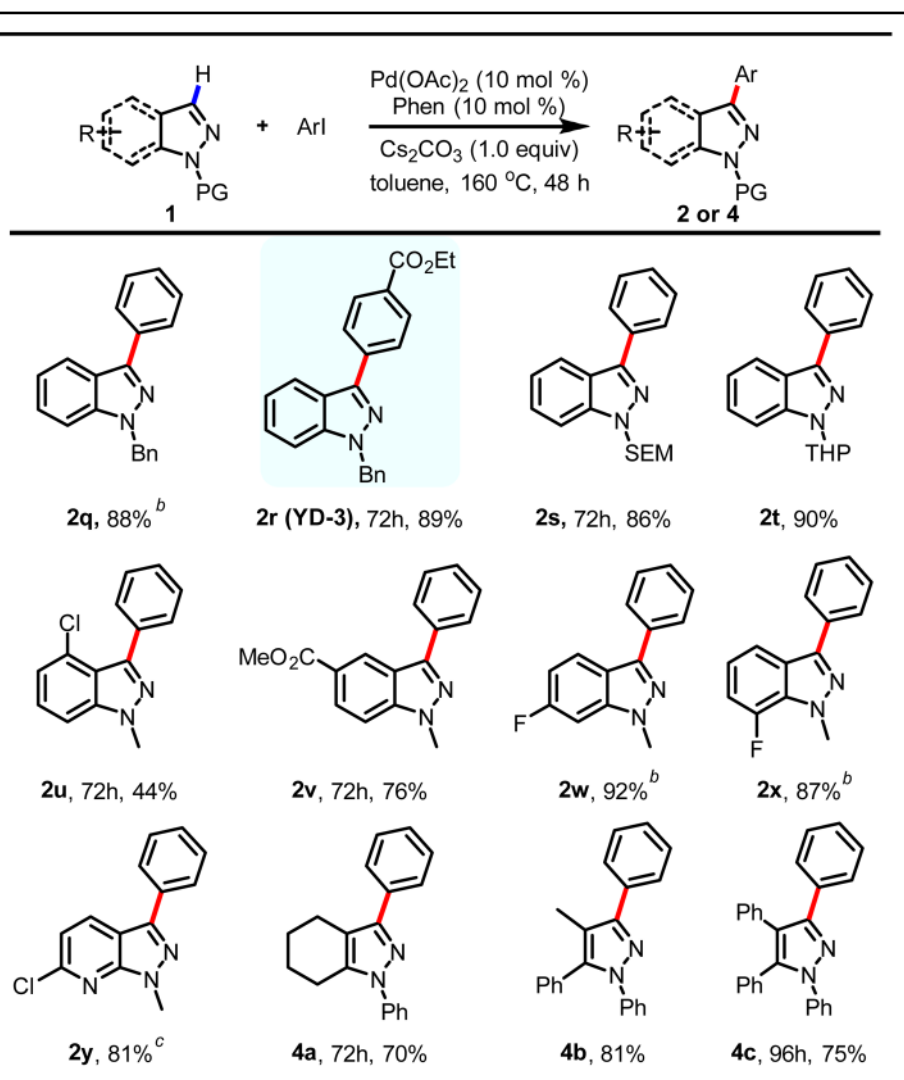
Table 3

Various aryl halides in C-3 arylation^a

^aReaction conditions: Pd(OAc)₂ (10 mol %), Phen (10 mol %), Cs₂CO₃ (1.0 equiv), indazole (0.25 mmol), ArX (0.5 mmol) in toluene (1 mL) for 48 h and then isolated yield was obtained.

^b3-Bromopyridine (1.0 mmol) was used.

Table 4

Various substituted indazoles and pyrazoles^a

^aReaction conditions: Pd(OAc)₂ (10 mol %), Phen (10 mol %), Cs₂CO₃ (1.0 equiv), indazole (0.25 mmol), ArI (0.5 mmol) in toluene (1 mL) for 48 h and then isolated yield was obtained.

^b30 mol % of Phen was used.

^cReaction was run for 12 h to give the same yield when chlorobenzene was used.