EurJOC
European Journal of Organic Chemistry

Chemistry Europe
European Chemical Societies Publishing

Accepted Article

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To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.202001313

Link to VoR: https://doi.org/10.1002/ejoc.202001313

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Palladium-Catalyzed Oxidative Arylation of 1*H*-Indazoles with Arenes

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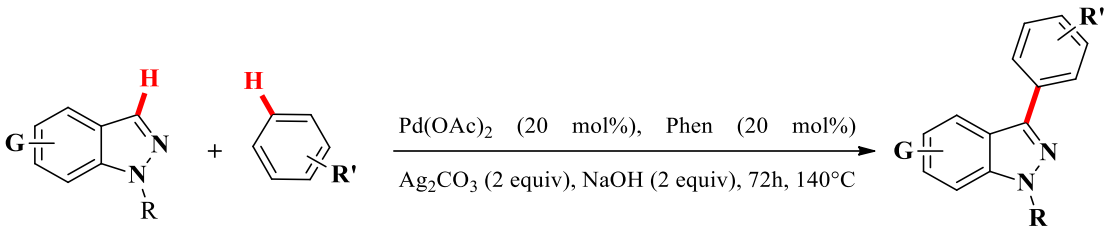
Key words: 1H-indazole, oxidative arylation, palladium, C-H/C-H activation, arenes.

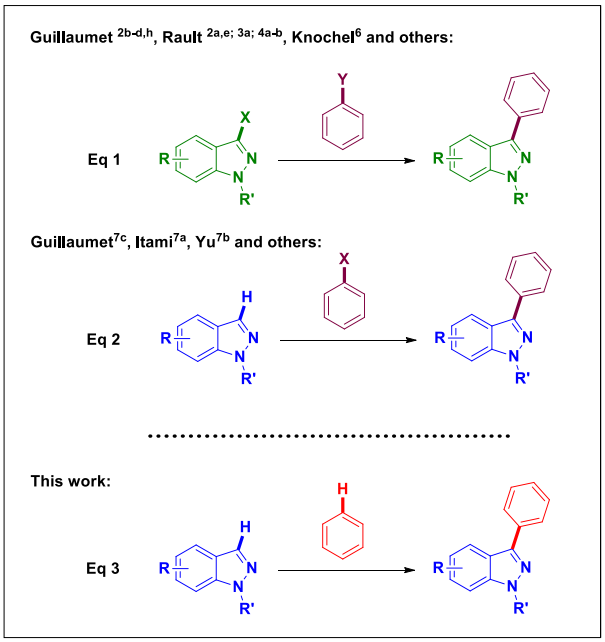
ABSTRACT



A simple method for the direct $Pd(OAc)_2$-catalyzed oxidative arylation of inactivated 1*H*-indazole derivatives with simple arenes is reported. This method exhibits good reaction efficiency and good functional-group tolerance. Using the method developed, twenty-eight arylated products were prepared in yields up to 80%.

INTRODUCTION:

In many natural products, pharmaceuticals, functional materials, and biologically active compounds, arylated 1*H*-indazoles are paramount motifs[1]. The construction of C−C bonds, which links indazole with arenes and heteroarenes, was ordinarily achieved by transition-metal-catalyzed reactions such as Suzuki-Miyaura[2], Heck[3], Sonogashira[4], Stille[5] and Negishi[6]. Since these methods use arylboronic acids, aryl halides, or other aryl organometallic compounds, they are less atom economical and less green than more recently developed C-H activation methods (eq 1, scheme 1). The subsequent development of C−H activation led to the direct arylation of 1*H*-indazole without the need for the prefunctionalization of the starting material[7]. This method increasingly gained interest because of its ability to further the development of efficiency in synthesis (eq 2, scheme 1). Another major advance in the development of C−H arylation is oxidative arylation[8], which provides a highly step- and atom-economical process in which neither of the partners requires prefunctionalization.



Scheme 1: C-H activation of indazole

To date, the transition metal-catalyzed direct oxidative C−H/C−H arylation of benzo[*h*]quinolines[9], benzoxazoles[10], xanthine[11], and imidazo[1,2-*a*]pyridine[12] have been reported with good yields. In addition, Goa and You[13] reported a palladium-catalyzed oxidative cross-coupling of electron-deficient 2*H*-indazole with electro-rich heteroarenes to construct a large library of biheteroaryl fluorophores, using $Pd(PPh_3)_4$ (5 mol %), $Cu(OAc)_2 \cdot H_2O$ (1.5 equiv.), and pyridine (1.0 equiv.) in 1,4-dioxane at 120 °C for 24 hours. Notably, while our manuscript was in preparation, an elegant

mechanochemical oxidative arylation of 1*H*-indazole in position 3 with 5-membered heteroarenes using 20 mol % of $Pd_2(dba)_3$ in the presence of $Cu(OAc)_2 \cdot H_2O$ and Na_2SO_4 has been described[14].This new protocol afforded C3-heteroarylated indazoles in moderate yields up to 45%.

Based on the previous antitumor drug candidates' structures (Figure 1, **E7070**[15-17] and **ER35745**[18,19]), indazole derivatives having sulfonamide moieties at C7 position (**A**) have been developed in our laboratory,[2d]. This compound has significant cytotoxicities *in vitro* (Figure 1, A) against human (colon and prostate) and murine (leukemia) cancer cell lines. Also, 7-NO_2-1*H*-indazoles, known as 7-NI, are believed to play a key role in the inhibition of all nitric oxide synthase isoforms[20]. They have shown substantial neuroprotective effects against hypoxic damage (such as stroke) and animal models of Parkinson disease[21-25]. Accordingly, we selected 1-methyl-7-nitro-1*H*-indazole **1** as the benchmark reaction partner.

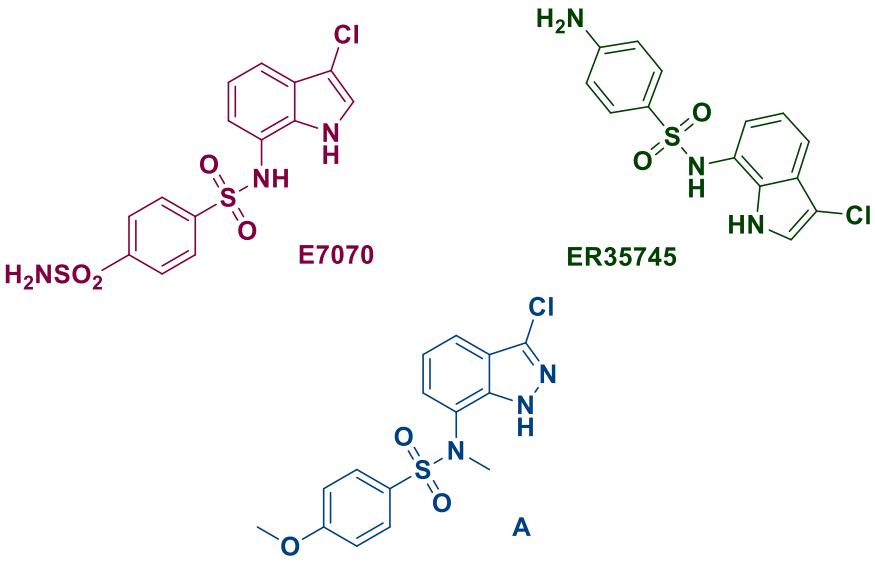


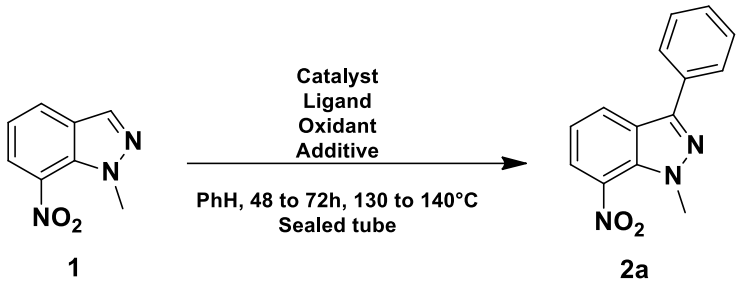
Figure 1: Examples of bioactive compounds containing indole or indazole.

To the best of our knowledge, so far, no examples of oxidative C3 arylation of 1*H*-indazole with simple arenes have been reported. Herein, we wish to report the first example of a palladium-catalyzed oxidative arylation of 1*H*-indazole using arenes as coupling partners in the presence of 10 mol % of $Pd(OAc)_2$, 10 mol % of phenanthroline (Phen), Ag_2CO_3 and NaOH at 130 °C for 48 hours. Another coupling cycle was found necessary to achieve total reaction conversions by adding 5 mol % of $Pd(OAc)_2$ and 5 mol % of Phen and heating the reaction mixture again for an additional 24 hours at the same temperature.

RESULTS AND DISCUCSSION:

With indazole **1** and benzene as a substrate, we initiated our screening of different oxidants, bases, palladium sources and ligands. The coupling partners also played the role of solvent.

Table 1: Optimization of direct oxidative arylation of 1-methyl-7-nitro-1*H*-indazole.



Entry	Catalyst	Ligand	Oxidant (2 equiv.)	Base	T °C	Time (h)	Yield (%)
1	$Pd(OAc)_2$ 20%	Phen 20%	$Cu(OAc)_2.H_2O$	-	130	48	Traces[a] (95)[b]
2	$Pd(OAc)_2$ 20%	Phen 20%	$Cu(OAc)_2$	-	130	48	0 (98)
3	$Pd(OAc)_2$ 20%	Phen 20%	Ag_2CO_3	-	130	48	15 (77)
4	$Pd(OAc)_2$ 20%	Phen 20%	Ag_2CO_3	K_2CO_3 (1 eq)	130	48	33 (50)
5	$Pd(OAc)_2$ 20%	Phen 20%	Ag_2CO_3	K_2CO_3 (2 eq)	130	48	48 (41)
6	$Pd(OAc)_2$ 20%	Phen 20%	Ag_2CO_3	K_2CO_3 (2.5 eq)	130	48	16 (72)
7	$Pd(OAc)_2$ 20%	PPh_3 20%	Ag_2CO_3	K_2CO_3 (2 eq)	130	48	0 (92)
8	$Pd(PPh_3)_2Cl_2$ 20%	Phen20%	Ag_2CO_3	K_2CO_3 (2 eq)	130	48	27 (65)
9	$Pd(OAc)_2$ 20%	Phen 20%	Ag_2CO_3	Cs_2CO_3 (2 eq)	130	48	0 (94)
10	$Pd(OAc)_2$ 20%	Phen 20%	Ag_2CO_3	NaOH (2 eq)	130	48	57 (36)
11	$Pd(OAc)_2$ 10 + 5%	Phen 10 +5%	Ag_2CO_3	NaOH (2 eq)	130	48 + 24	68 (traces)[c]
12	$Pd(OAc)_2$ 10%	Phen 10%	Ag_2CO_3	NaOH (2 eq)	140	72	49 (40)[d]
13	$Pd(OAc)_2$ 15%	Phen 15%	Ag_2CO_3	NaOH (2 eq)	140	72	55 (32)[d]
14	$Pd(OAc)_2$ 20%	Phen 20%	Ag_2CO_3	NaOH (2 eq)	140	72	67 (traces)[d]

[a] yield of isolated product 2a; [b] yield of recovered starting material 1 in parentheses. [c] in this case the reaction was carried out using two cycles 1 and 2. For cycle 1 the reaction was heated at 130 °C for 48 h, the 5 mol of $Pd(OAc)_2$ 10 % and 5 mol % of Phen were added and the reaction was heated again for 24h. [d] in this case, the reaction mixture was heated at 140 °C for 72 h.

In initial screens, the use of 20 mol % of $Pd(OAc)_2$, 20 mol % of Phen in the presence of 2 equiv. of $Cu(OAc)_2.H_2O$ or $Cu(OAc)_2$ as oxidant gave only traces or no arylated product **2a** (Table 1, entries 1 and 2). In contrast, the use of 2 equiv. Ag_2CO_3 as oxidant provided more promising results (Table 1, entry 3). This oxidant was then selected for further optimization studies. Remarkably, the yield of product **2a** was nearly trebled to 33 % by adding 1 equiv. of K_2CO_3 as base (Table 1, entry

4). When using 2 equiv. of K_2CO_3, the desired product was isolated with a promising 48 % yield (Table 1, entry 5). With 2.5 equiv. of K_2CO_3, the yield dropped to 16 % (Table 1, entry 6). We decided then to test $Pd(PPh_3)_2Cl_2$ and PPh_3 as the catalyst and ligand system. This proved unsuccessful as only a slight amount of product **2a** and unreacted starting material were recovered (Table 1, entries 7 and 8). When employing 20 mol% of $Pd(OAc)_2$ and 20 mol% of Phen in the presence of both Ag_2Co_3 and Cs_2CO_3 at 130°C for 48 hours, no reaction was observed and only starting material was recovered in 94%. Other bases were investigated and NaOH appeared to give **2a** in the highest yield of 57 % (Table 1, entry 10).

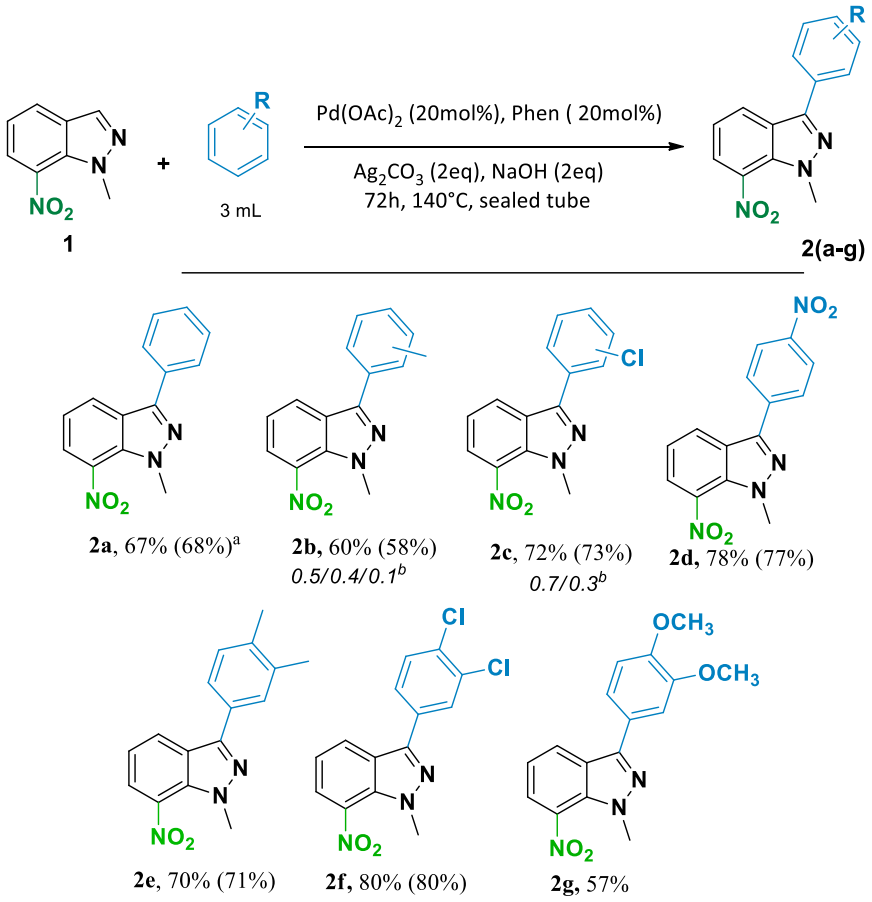
Nevertheless, we noticed that after 48 hours, the reaction reached a stagnation point, with the reaction mixture still containing the arylated product **2a**, starting product **1** and benzene. Based on this observation, we decided to add 10 mol% of $Pd(OAc)_2$ and 5 mol% of the ligand and extend the reaction to 24 hours. With this strategy, we were pleased to observe the completion of the reaction and the arylated product **2a** was isolated in 68% yield (entry 11, table 1). In order to avoid the use of two reaction cycles, we decided to further optimize the reaction conditions. When the mixture was heated at 140 °C instead of 130 °C for 72 hours using under the same reaction conditions used for reaction cycle 1, the desired product **2a** was isolated in 49% yield and the starting material **1** was recovered in 40% yield (Table 1, entry 12). The increase of both the catalyst and the ligand charges from 10 to 15 mol% led to the expected product **2a** in 55% yield. But again, 32% of starting material was recovered (Table 1, entry 13). Finally, when using 20 mol % of $Pd(OAc)_2$ and 20 mol % of Phen, the reaction led to compound **2a** in 67 % yield and only traces of starting material **2** were observed (Table 1, entry 14). Interestingly, this yield was almost the same as that obtained when using two reaction cycles (Table 1, entries 11 and 14).

With the optimized reaction conditions in hand, multiple simple arenes as coupling partners were investigated to study the scope and limitation of this reaction. The arylated 1*H*-indazole **2a-f** were isolated with yields ranging from 60 to 80 % (from 58 to 80 % with two cycles, Table 2). In some cases, the use of monosubstituted arenes generated a mixture of isomers regardless of electron-donating or electron-withdrawing substituents, and the reaction took place mainly at less hindered *meta*- and *para*-positions.

First, the starting material 1-methyl-7-nitro-1*H*-indazole was used with differently substituted arenes (Table 2). The arylation partners toluene and chlorobenzene generated a mixture of isomers

(compounds **2b** and **2c**), while nitrobenzene provided only the *para*-arylated isomer **2d** with a good yield of 78 % (77 % with two cycles). When using disubstituted arenes, the reaction was sensitive to steric hindrance and only occurred at the less hindered position. The use of *o*-xylene and *o*-dichlorobenzene afforded the single coupling products **2e** and **2f** with good yields, 70 % and 80 % respectively (71 % and 80 % respectively, with two cycles). The use of 2,3-dimethoxybenzene as coupling partner led to the expected product **2g** as one isomer in 57 % yield (Table 2).

Table 2: Oxidative arylation of 1-methyl-7-nitro-1*H*-indazole with arenes

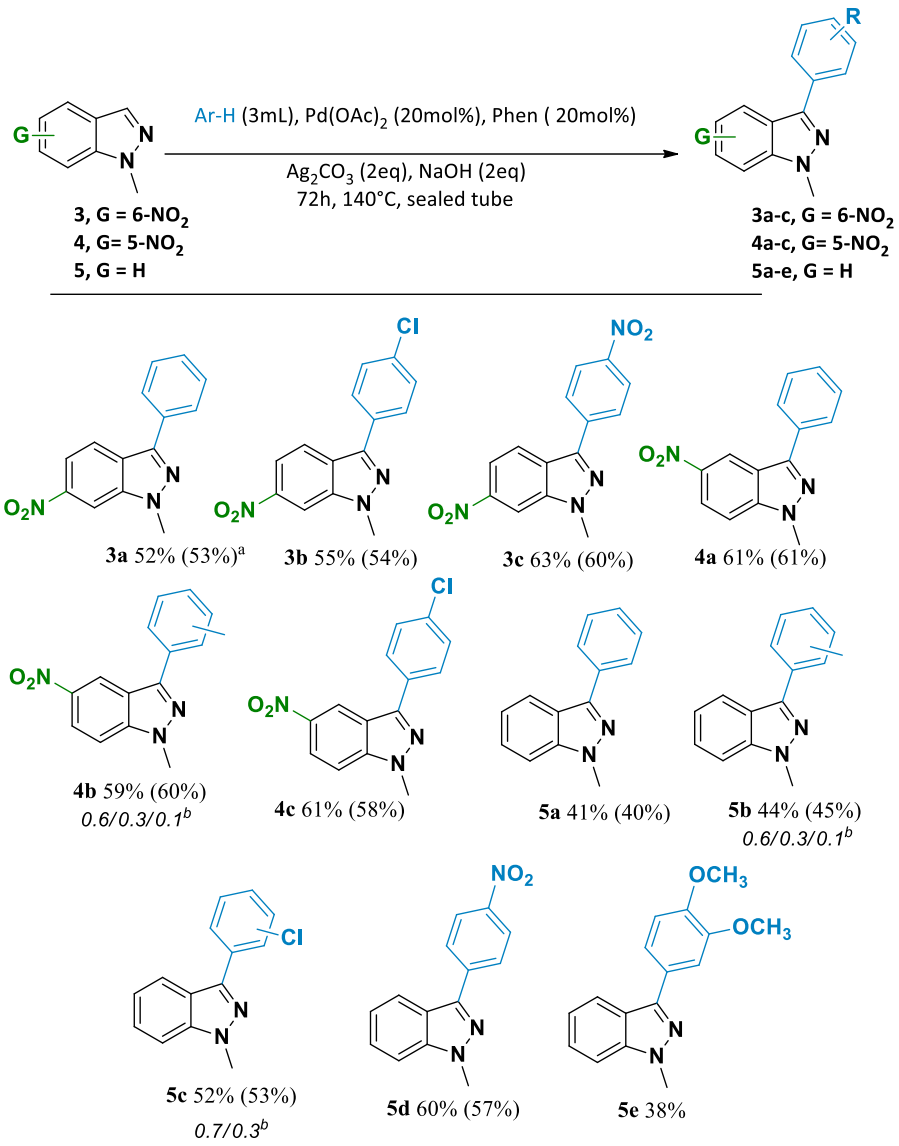


[a] the yields calculated for reactions carried out using two cycles are in parentheses. [b] mixture of isomers (*p/m/o*): ratio calculated by NMR integration.

Likewise, substrates bearing a nitro group at either the 6- or the 5-position gave the desired 3-arylated products group (Table 3) in good yields (52-61 %). Regardless of the arenes involved bearing either electron donating or electron withdrawing groups, the reaction yield was only slightly impacted (compounds **3(a-c)**, **4(a-c)** and **5(a-e)**). In the case of the arylation of 5-

nitroindazole with toluene, a mixture of isomers was obtained **4b**. Subsequently,1-methyl-1*H*-indazole **4** was also investigated as starting material. Indazole **5** underwent the oxidative arylation reaction to give the expected C3-arylated indazoles in moderate yields (Table 3). One isomer **5a** was obtained when using benzene as a coupling partner in a yield of 41 % (40 % yield with two reaction cycles). Using monosubstituted arenes led to a mixture of isomers, with electron-withdrawing groups giving slightly better yields than the electron-donor groups (compounds **5b** and **5c**), while only the *para*-arylated indazole **5d** was isolated with a moderate yield of 60 % (57 % yield with two reaction cycles) when using nitrobenzene as coupling partner. When employing 2,3-dimethoxybenzene as coupling partner, the expected product **5e** was isolated as one isomer in 38 % yield (Table 3).

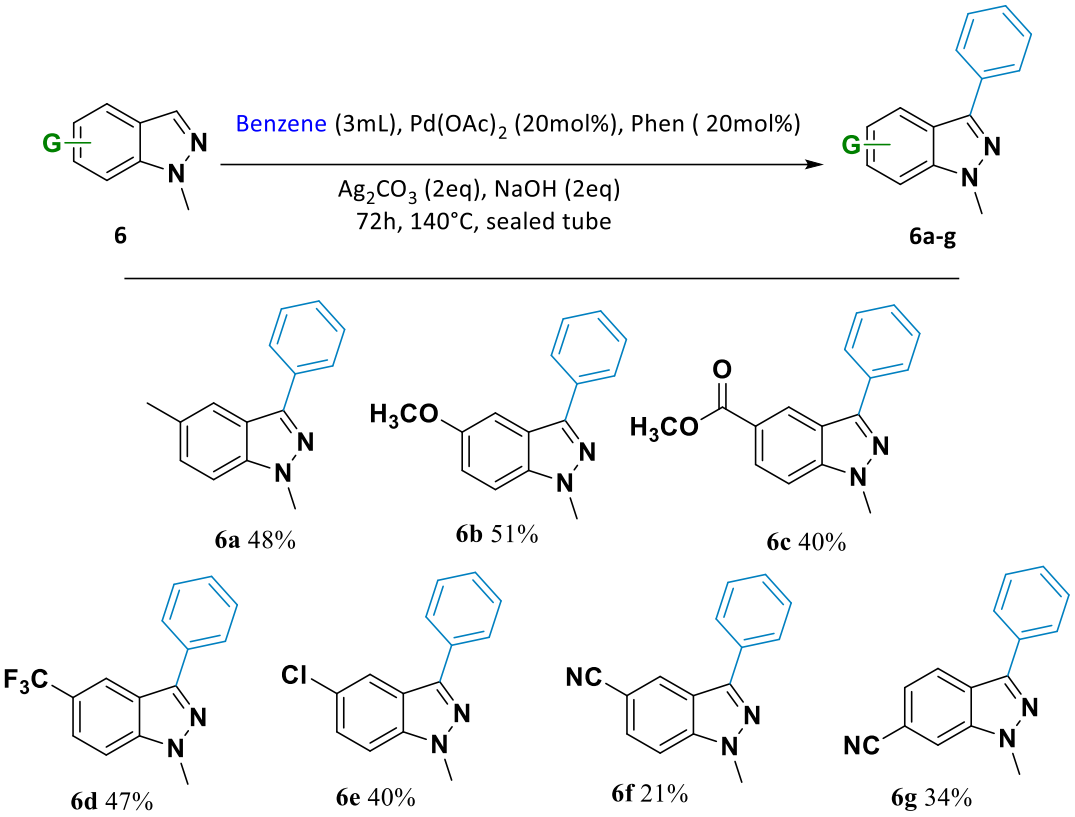
Table 3: Oxidative arylation of 1-methyl-1*H*-indazole derivatives with arenes



[a] the yields calculated for reactions carried out using two cycles are in parentheses. [b] mixture of isomers (*p/m/o*): ratio calculated by NMR integration

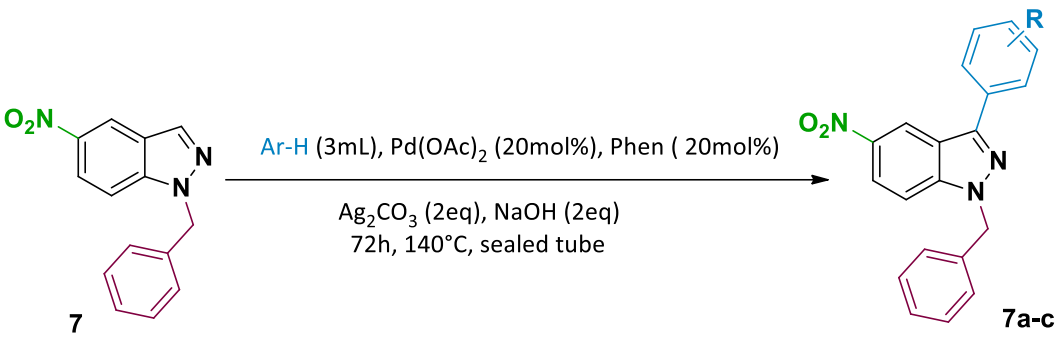
Then, we decided to investigate the oxidative arylation reaction using benzene and various indazoles containing electron withdrawing or electron donating functional groups at either positions 5 or 6 as coupling partners. Regardless of the nature of the functional group (either electron donating or electron withdrawing groups) on the indazoles employed as coupling partners, the reaction yields were only slightly impacted (Table 4). The desired products **6(a-e)** were isolated in moderate yields ranging between 40 and 51 %. Nevertheless, when 1-methyl-1*H*-indazole-5-carbonitrile was used as starting material, the arylated product **6f** was isolated in a low yield (21 %). An improved yield was obtained with 1-methyl-1*H*-indazole-6-carbonitrile: in this case, the expected product **6g** was achieved in 34 % yield (Table 4).

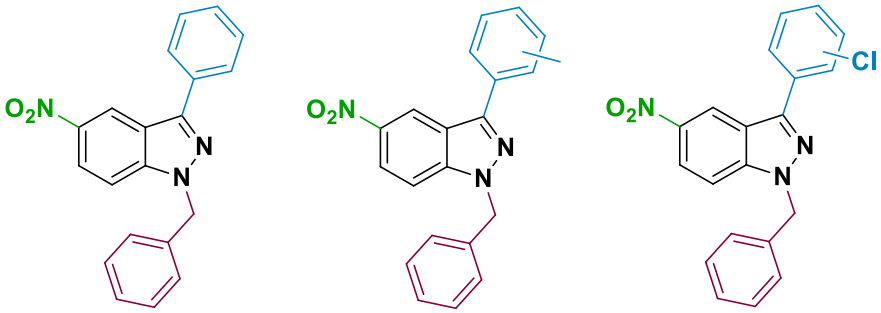
Table 4: Oxidative arylation of 1-methyl-1*H*-indazole derivatives with benzene



Notably, the optimized conditions turned out to be effective also for 1-benzyl-5-nitro-1*H*-indazole **7**. This starting material reacted with benzene to give **7a** in 54 % yield (55 % with two reaction cycles), while the reaction with toluene **7b** and chlorobenzene **7c** generated a mixture of isomers with yields of 51% and 54% yield, respectively (53 to 57 % yield, respectively with two reaction cycles, Table 5).

Table 5: Oxidative arylation of 1-benzyl-5-nitro-1*H*-indazole with arenes.

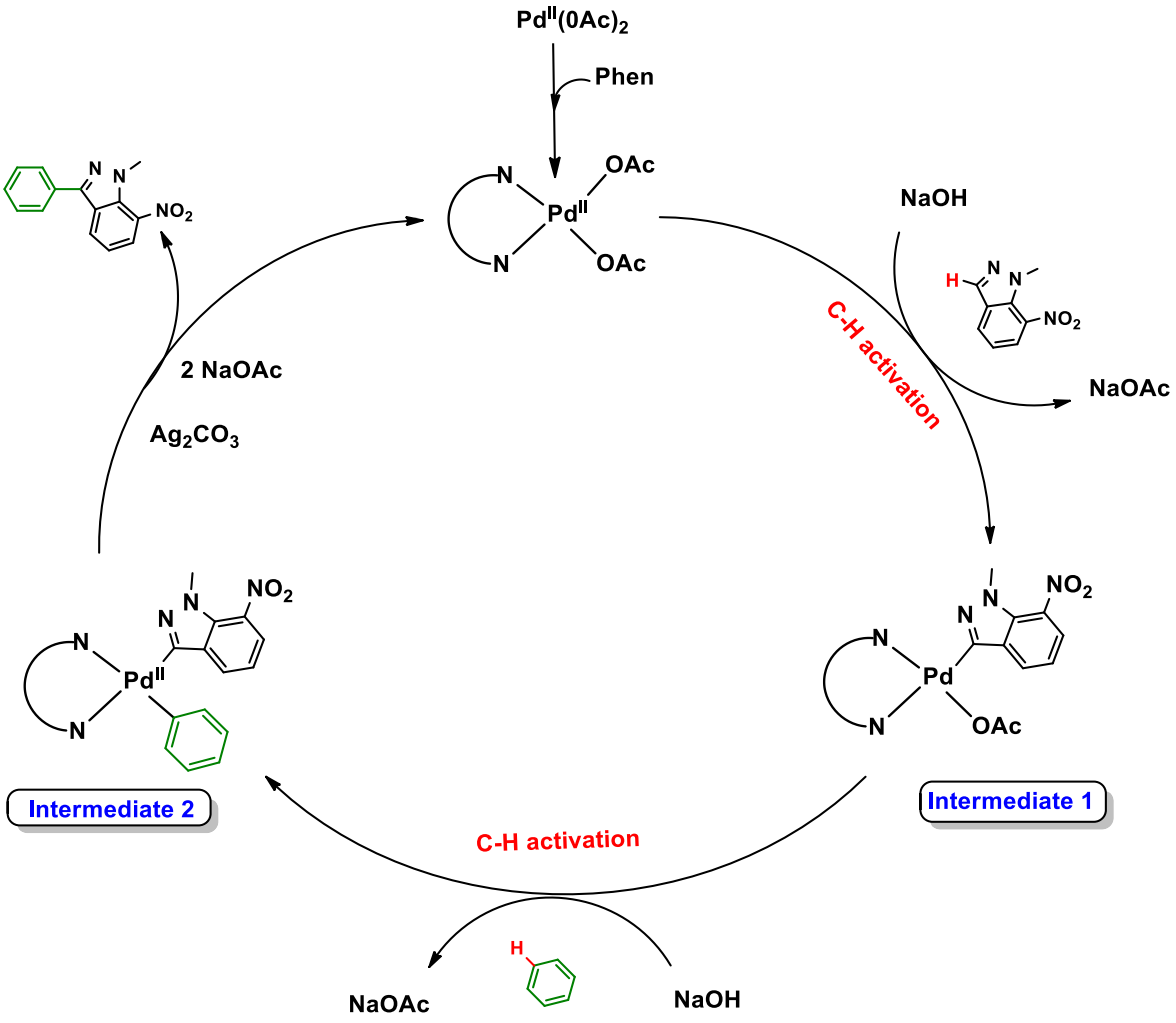




7a 54% (55%)[a] **7b** 53% (51%) *0.6/0.3/0.1*[b] **7c** 57% (54%) *0.7/0.3*

[a] the yields calculated for reactions carried out using two cycles are in parentheses. [b] mixture of isomers (*p/m/o*): ratio calculated by NMR integration.

Based on previous mechanistic studies[1,12,25], a plausible mechanism is proposed for this reaction in Scheme 2. First, the starting material 1-methyl-7-nitro-1*H*-indazole **1** coordinates with the catalyst, formed in situ from $Pd(OAc)_2$ and 1,10- phenanthroline, to assemble the intermediate 1. Afterward, the intermediate 1 reacts with benzene, leading to the intermediate 2 *via* a C-H activation of the C3 position of indazole. Then, the intermediate 2 undergoes reductive elimination to give the desired product **2a**. Finally, the Pd is oxidized by Ag^+ to regenerate $Pd(OAc)_2$.



Scheme 2. Plausible mechanism of oxidative arylation of indazole **1**.

CONCLUSION

In conclusion, we have developed the first C3-oxidative arylation of 1*H*-indazole using arenes as coupling partners. The optimized reaction conditions showed good compatibility with different 1*H*-indazole derivatives and tolerance to arenes bearing various functional groups. In some cases, good regioselectivities were observed while in other cases, mixtures of two or three isomers were obtained.

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