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Palladium-Catalyzed Site-Selective C7 Oxidative Arylation of 4-EWG-1*H*-Indazoles

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Abstract: An efficient palladium-catalyzed oxidative arylation of substituted 1*H*-indazole with various arenes and heteroarenes as coupling partners is reported. A site selective C7 oxidative arylation was perfectly achieved with a directing electron-withdrawing groups (EWG) located at the C4 position of the 1*H*-indazole. The desired products are obtained in moderate to good yields from 4-NO₂ or 4-CO₂Me 1*H*-indazoles and various (hete)aryls as coupling partners in the presence of Pd(OAc)₂ as catalyst, phenanthroline as ligand, Ag₂CO₃ as oxidant and NaOH as the base. Density functional theory was also conducted for reaction mechanism comprehension. This approach provides a highly effective, direct, and atom economical way to build C7- (het)arylated 1*H*-indazole compounds.

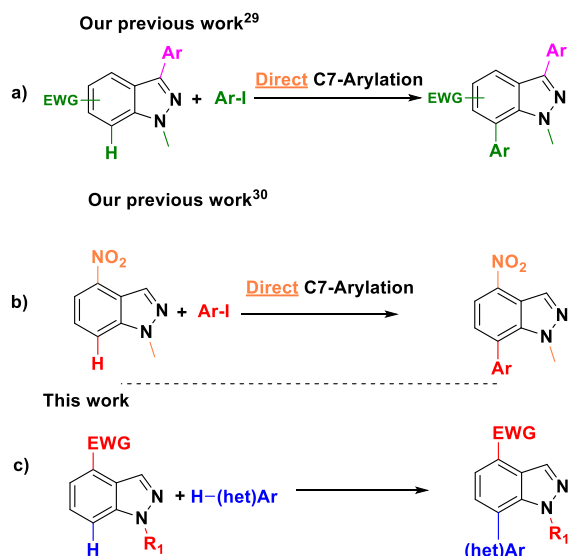
Introduction

The synthesis of heterocyclic compounds has always been a major research focus for chemists. Heterocycles represent privileged structures in the drug discovery process and they are found in a wide plethora of drugs and biological active compounds.^[1–5] However, their preparation and functionalization remain a delicate challenge.^[6,7] Processes using transition metal catalysis have nowadays a privileged place in organic chemistry. For more than a century, the use of transition metals has made a major contribution to the field of organic synthesis, especially for the formation of carbon-carbon bonds,^[8–10] permitting the development of cleaner synthesis processes compared to conventional methods that required the use of alkyl or aryl halides and organometallic derivatives (examples: Suzuki-Miyaura,^[11] Heck,^[12] Sonogashira,^[13] Stille^[14] and Negishi^[15] cross-couplings).

Due to their biological properties, 1*H*-indazole molecules are extensively studied in organic chemistry,^[16] material science,^[17,18] and nanotechnology.^[19,20] Nevertheless, the regioselective functionalization at the six membered ring still remains a challenging task. In particular, these compounds can be efficiently functionalized by C-H activation reactions, especially by direct C3 arylation.^[21–24] Recently, oxidative arylation has attracted a significant interest, especially in the context of more efficient chemistry in terms of the number of steps and atom economy.^[25–28] This approach avoids the use of pre-functionalized reagents such as organic halides or organometallic reagents. Although this transformation is very attractive and efficient, the regioselective activation of a specific C-H bond remains a major limitation. Since a few years, our group and others have focused their work on the development of new strategies for the regioselective functionalization of indazole heterocycles. In 2014, our group described for the first time a direct palladium catalyzed C7-arylation of C3-substituted indazoles using iodoaryls as coupling partners (**Scheme 1a**).^[29] Very recently, we have reported a regioselective C7-direct arylation of 4-nitro-1*H*-indazoles utilizing iodoaryls, as coupling partners (**Scheme 1b**).^[30] Notably, in this case, the coupling reactions under optimized conditions were effective with iodoaryls as arylation agents, while no product was formed with iodo(hetero)aryls as coupling partners. Interestingly, Gao group has developed a palladium-catalyzed oxidative C3-arylation of 2*H*-indazole derivatives using a Pd(PPh₃)₄/Cu(OAc)₂ system and heteroarenes^[31]. Recently, we have also performed an oxidative C3-arylation of substituted 1*H*-indazole with arenes using palladium as catalyst.^[32] Here, we describe the first example of a palladium-catalyzed oxidative C7-arylation of C4-substituted 1*H*-indazole bearing an electron-withdrawing group

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(NO₂, CO₂Me) on the C4 position as a para directing group and with arenes or heteroarenes as coupling partners. The reaction was achieved under the following conditions: 10 mol% Pd(OAc)₂, 15 mol% phenanthroline (Phen), Ag₂CO₃, and NaOH at 140 °C for 72 hours in sealed tube. The optimization of the reaction conditions allowed the preparation of various C7-(het) arylated 1*H*-indazoles (**Scheme 1c**).



Scheme 1: C7-oxidative (het)arylation of indazoles vs the previously reported C7-arylation methods.

Results and Discussion

We have initiated our investigation using 1-methyl-4-nitro-1*H*-indazole **1** as a substrate and benzene as both coupling partner and solvent. As a starting point, the screening of different reaction conditions was performed including varying solvent, base, nature of catalyst and ligand, as summarized in (**Table 1**).

First, we have tested Pd(OAc)₂ (20 mol%) as the catalyst with Phen (20 mol%) as ligand in the presence of Cu(OAc)₂·H₂O or Cu(OAc)₂ (2 equiv.) as the oxidant at 140 °C for 72 hours (**entries 1 and 2, Table 1**). Unfortunately, with TLC no traces of C7-arylation compound was observed, but traces of the biaryl product arising from homocoupling reaction was detected by the NMR analysis of the crude reaction mixture. In this case, the starting material **1** was recovered. The same result was observed with 2 equivalents of benzoquinone (BQ) or AgNO₃ instead of Cu(OAc)₂·H₂O as oxidative agent in the presence of 15 mol% of Pd(OAc)₂ and 15 mol% of Phen (**entries 3 and 4, Table 1**). Interestingly, using the Ag₂CO₃ (2 equiv.) instead of AgNO₃ as the oxidant afforded the desired product **2a** in a low yield (13%) (**entry 5, Table 1**). Adding K₂CO₃ (2 equiv.) as a base slightly increased the yield (32%) of the desired product,^[32] along with a large amount of the recovered starting material **1** (**entry 6, Table 1**). On the other hand, using the Pd(PPh₃)₂Cl₂ (20 mol%) instead of Pd(OAc)₂ as the catalyst has led to the recovery of the starting material **1** along with traces of the desired product **2a** (**entry 7, Table 1**). Given these results, the Pd(OAc)₂ catalyst was selected for further optimization studies. Therefore, with Pd(OAc)₂ (20

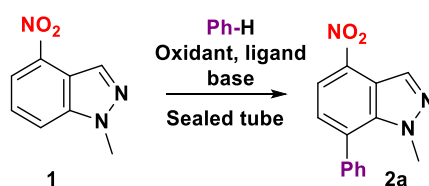
mol%), Phen (20 mol%) and Ag₂CO₃ (2 equiv.) as the oxidant, the addition of NaOH (2 equiv.) as the base at 140 °C for 48 hours gave the expected product **2a** in 47% isolated yield (**entry 8, Table 1**). Increasing the reaction time from 48 to 72 hours (**entry 9, Table 1**) has led to complete conversion of the starting material **1** to give 70% yield of the desired product **2a**.

A decreased loading of both catalyst and ligand from 15 to 10 mol% and 20 to 15 mol% respectively, left the reaction yield almost unaltered (**entry 10, Table 1**). Further attempts that have been made to replace the sealed tube by heating the reaction mixture at reflux in open flask was not successful (**entry 11, Table 1**), only starting material **1** was recovered. We then conducted an experiment utilizing 1.5 equivalents of Ag₂CO₃ instead of 2 equivalents. Unfortunately, these conditions yielded only 55% of the desired product along with 30% of the recovered starting material **1** (**entry 12, Table 1**). Subsequently, we replaced NaOH by tBuOK as a stronger base while maintaining the optimized reaction conditions. Unexpectedly, this modification did not lead to the formation of the desired product only starting material **1** was recovered in 45% yield along with inseparable py-products probably due to homocoupling reactions (**entry 13, Table 1**).

Next, we have evaluated the scope and the limitations of this oxidative C7 arylation by applying the reaction conditions of (**entry 10, Table 1**), with either the starting 1*H*-indazoles **1** or **1'** and various simple arenes and heteroarenes as coupling partners (arenes with electron-donating (EDG) and electron-withdrawing groups (EWG), or steric hindrance). The expected products **2a-i** were isolated in yields ranging between 20 to 80% (**Scheme 2**).

In the case of the 1-methyl-4-nitro-1*H*-indazole **1** as a starting material, the reaction with EDG monosubstituted arenes, used as arylation agents, generated a mixture of isomers, especially, when arenes such as toluene, and tert-butylbenzene were employed (compounds **2b**, and **2d**). The arylation occurred predominantly at the less hindered positions (para and meta). When EWG monosubstituted arenes are used, such as (trifluoromethyl)benzene, chlorobenzene and nitrobenzene were used, the arylation reaction provided only the meta-arylated compounds **2e**, **2f** and **2g** with 24, 68 and 50% yield, respectively. Also, we have observed that the nature of the substituents on the arene ring affect the reaction yields. Thus, arylation agents bearing EDG led to better yields than those containing EWG. Interestingly, the optimized reaction conditions showed good tolerance to various substituents on the arene rings.

Regarding the di-substituted arenes, the reaction appears to be sensitive to steric factors, only occurring at a position that is less hindered. The use of *o*-xylene and 1,3-dichlorobenzene gave the meta-arylated isomers (compounds **2c** and **2h**) with good yields of 70 and 72%, respectively. When the reaction was carried out with 2-methyl thiophene as arene partner, the expected thiophene adduct **2i** was isolated in a moderate yield of 40%. It is very important to note that the oxidative arylation has allowed the introduction of heteroaryl by C-H/C-H activation at the C7 position in contrast to direct arylation conditions previously reported.^[29, 30]

Table 1. Optimization of the oxidative C7 arylation of 1 - methyl - 4 - nitro - 1*H* - indazole (**1**). Table Caption.

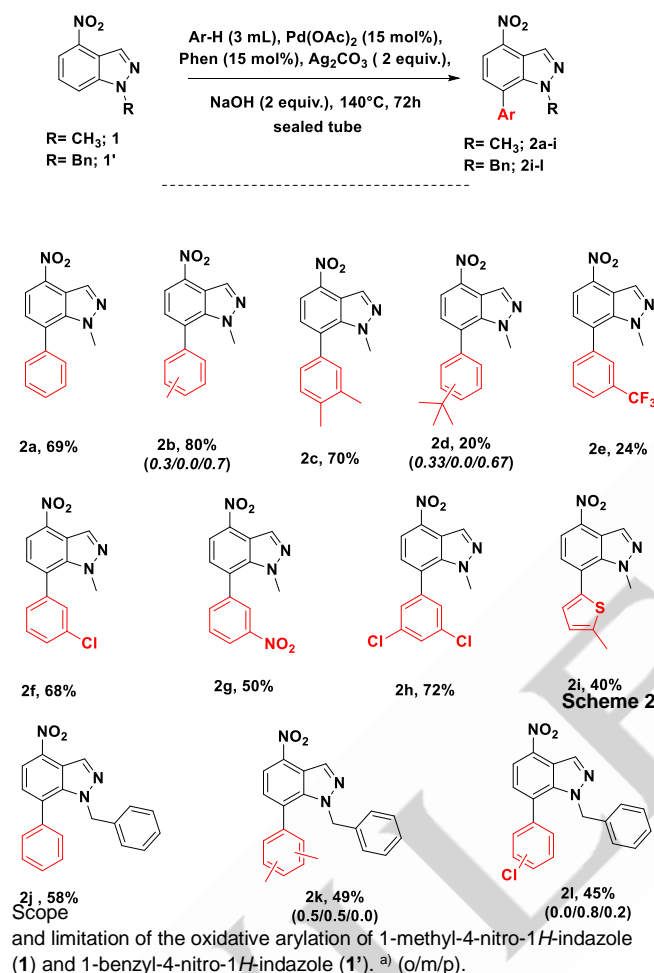
Entry	Cat mol%	Ligand mol%	Oxidant 2 equiv.	Base 2equiv.	T°C	Time	Yield% 1/2a
1	Pd(OAc) ₂ 20%	Phen 20%	Cu(OAc) ₂ ·H ₂ O	-	140	72h	94/0
2	Pd(OAc) ₂ 20%	Phen 20%	Cu(OAc) ₂	-	140	72h	98/0
3	Pd(OAc) ₂ 15%	Phen 15%	BQ	-	140	72h	98/0
4	Pd(OAc) ₂ 15%	Phen 15%	AgNO ₃	-	140	72h	94/traces
5	Pd(OAc) ₂ 20%	Phen 20%	Ag ₂ CO ₃	-	140	72h	80/13
6	Pd(OAc) ₂ 20%	Phen 20%	Ag ₂ CO ₃	K ₂ CO ₃	140	72h	61/32
7	Pd(PPh ₃) ₂ Cl ₂ 20%	Phen 20%	Ag ₂ CO ₃	K ₂ CO ₃	140	72h	87/traces
8	Pd(OAc) ₂ 20%	Phen 20%	Ag ₂ CO ₃	NaOH	140	48h	32/47
9	Pd(OAc) ₂ 15%	Phen 20%	Ag ₂ CO ₃	NaOH	140	72h	Traces/70
10	Pd(OAc) ₂ 10%	Phen 15%	Ag ₂ CO ₃	NaOH	<u>140</u>	<u>72h</u>	<u>Traces/69</u>
11	Pd(OAc) ₂ 15%	Phen 15%	Ag ₂ CO ₃	NaOH	Reflux	72h	92/0
12	Pd(OAc) ₂ 15%	Phen 15%	Ag ₂ CO ₃ 1.5 equiv.	NaOH	140	72h	30/55
13	Pd(OAc) ₂ 15%	Phen 15%	Ag ₂ CO ₃	tBuOK	140	72h	45/0

Then, the starting material **1'** with benzyl as a protecting group at the N1 position was used instead of the starting material **1** bearing a methyl group. Under the same oxidative arylation conditions with benzene as coupling partner, the reaction has led to the

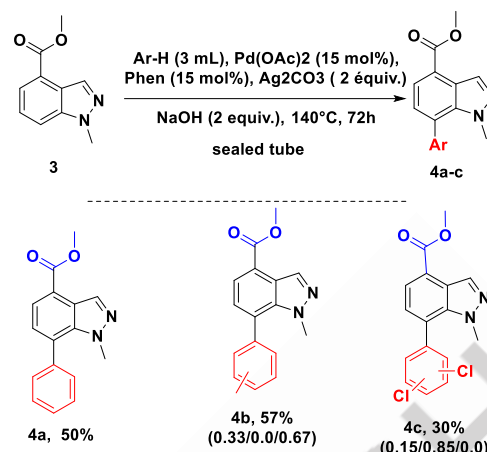
expected product **2j** with lower yield (58%) compared to the analog **2a** (69%). The same tendency was observed when using either xylene or chlorobenzene as arylating agent. In these cases,

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the arylated products **2k** and **2l** were isolated in 49 and 45% yield, respectively (**Scheme 2**). The decrease in the reaction yield could be attributed to the steric hindrance of the benzyl group at N1. Surprisingly, with *o*-xylene and chlorobenzene, oxidative arylation, gave in both cases, a mixture of two isomers (**2k** and **2l**, **Scheme 2**), while in the case of starting material **1**, both arylating agents led to their corresponding meta-products as a single isomer in higher yields (compounds **2c** and **2f**, **Scheme 2**).

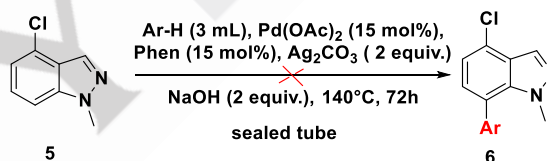


When methyl 1-methyl-1*H*-indazole-4-carboxylate **3** was involved as a starting material, whatever selected unsubstituted or substituted arene reagents, the yield of the arylation reaction decreased compared to the same experiment with 1-methyl-4-nitro-1*H*-indazole **1** as substrate (see supra). The desired products **4a-c** were isolated in moderate to acceptable yields ranging from 30 to 57% (**Scheme 3**) with recovering of a significant amount of starting material **3**. Moreover, a mixture of two isomers was obtained with 1,3-dichlorobenzene, while nitro substrate **1** gave the single meta-isomer **2h** with 72% yield, (**Scheme 2**).



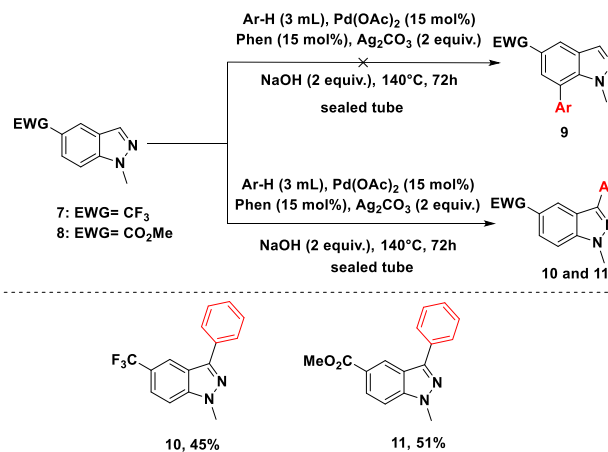
Scheme 3. Examples (**4a-c**) of the oxidative arylation of methyl 1-methyl-1*H*-indazole-4-carboxylate (**3**).^{a)} (o/m/p)

In the case of 4-chloro-1-methyl-1*H*-indazole **5**, no arylation reaction was observed at the C7 position and only starting material **5** was quantitatively recovered. This observation indicates that the chlorine substituent lacked the directing ability necessary to perform the desired reaction. These valuable insights shed light on the importance of substituent selection for successful orientation of this arylation (**Scheme 4**).



Scheme 4. Oxidative arylation of 4-chloro-1-methyl-1*H*-indazole **5**

To highlight the importance of the para direction of electron-withdrawing groups at C4 position of 1-methyl-1*H*-indazole, we conducted arylation reactions involving either 1-methyl-5-(trifluoromethyl)-1*H*-indazole **7** or methyl 1-methyl-1*H*-indazole-5-carboxylate **8** as substrates under the optimized conditions in the presence of benzene as arylating agent. As expected, only C3 arylated products **10** and **11** were obtained in 45 and 51% yield, respectively. These results are consistent with the findings previously obtained by our research group.^[32] (**Scheme 5**).

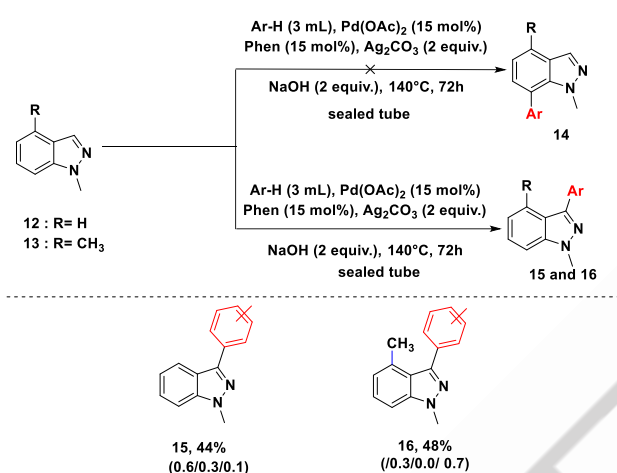


Scheme 5. Oxidative arylation of 5-EWG-1-methyl-1*H*-indazoles **7** and **8**.

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In order to illustrate the crucial role of these EWG (NO_2 or CO_2Me) for site directing C7 arylation of 1H-indazole, we have tested our optimized reaction conditions with 1-methyl-1H-indazole, compound **12** or with compound **13** bearing an EDG (methyl group) at the C4 position of the 1-methyl-1H-indazole. Selecting toluene as the arene reagent, with both substrates **12** or **13**, the oxidative arylation only occurred at the C3 position to give the products **15** and **16** in 44 and 48% yield, respectively, without any traces of C7-arylated products **14**. We have obtained before similar results with C5, or C6 nitro substituted 1-methyl-1H-indazol.^[32]

Unlike the electron-donating group at C4 position (starting material **13**), which enriches the six membered ring and makes the proton C7 less acid. In this case, the C3 position became more acid and thus more appropriate for C-H activation (Scheme 6).



Scheme 6. Oxidative arylation of 1-methyl-1H-indazole (**6**) and 1,4-dimethyl-1H-indazole (**7**).

To understand the seen regioselectivity, we have examined the pKa values of compounds (**1**) and (**6**) that have been predicted by the Jaguar pKa software.^[33] For 1-Methyl-4-nitro-1H-indazole (**1**), the lowest pKa values correspond to the C7 position, in contrast to 1,4-dimethyl-1H-indazole (**6**) where the lowest pKa values correspond to the C3 position (Figure 1).

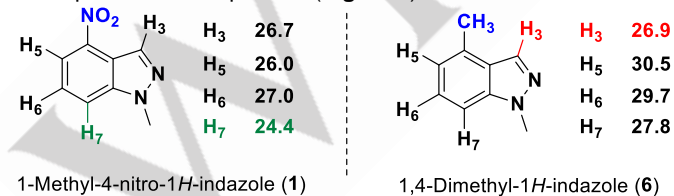
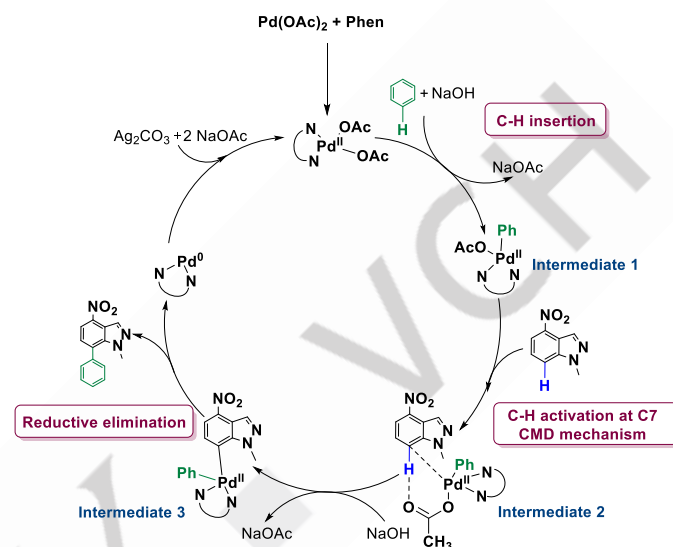


Figure 1. pKa values calculated for starting materials **1** and **6**.

In addition, in starting materials (**1** or **3**) the nitro or the ester group have weakened the benzene ring in electron and have made the protons at C7 position more acid. Thus, C-H bond activation under concerted metalation-deprotonation (CMD) process is more suitable in this case.^[34,35]

Inspired by previous mechanistic studies^[30-32] and pKa calculation, we propose a plausible CMD mechanism for this

oxidative arylation in (Scheme 7). Thus, a C-H insertion of Pd(II) to the benzene in basic conditions, forms the intermediate 1. Then, intermediate 1 interacts with 4-nitro-1-methyl-1H-indazole **1** to give intermediate 2 through a concerted metalation deprotonation and the CMD process led to intermediate 3. Finally, the reductive elimination furnished arylation product **2a** and Pd(0) which is oxidized to Pd(II) by Ag₂CO₃ and NaOAc.



Scheme 7. Plausible mechanism of oxidative arylation of 4-EWG-1-methyl-1H-indazole (**1**).

Conclusion

To conclude, we have created a new C-H functionalization of the six membered ring of C4-substituted 1H-indazole derivatives using oxidative arylation reaction. This strategy has allowed the site selective introduction of substituted (hete)arenes at the C7 position of the 1H-indazole assisted by an EWG directing group at the C4 position. When no substituent or when an EDG group is present at the C4 position only the C3-arylation products were observed. DFT calculation has allowed us to propose a plausible CMD mechanism for this reaction. The development of this new C-H/C-H arylation reaction has led to the synthesis of a series of C7-arylated 1H-indazoles, in an economical and efficient manner.

Supporting Information

Thin layer chromatography analysis (TLC) was performed by using silica gel (60 F254) plates, and visualized by ultraviolet light ($\lambda = 254$ nm). Column chromatography was performed on silica gel 60 (ACC 40–63 μm 5SDS-CarloErba). Melting points (mp [°C]) were taken on samples in open capillary tubes and are uncorrected using BioCote Thermo scientific digital melting point IA9200. The infrared spectra (FT-IR) were recorded at room temperature on a Thermo Scientific Nicolet IS50 FT-I and are given in cm⁻¹. Nuclear magnetic resonance (NMR) spectra were

recorded on a Bruker AC350 (300 MHz for ¹H and 75 MHz for ¹³C), and on a Jeyol 600 (600 MHz for ¹H and 100.6 MHz for ¹³C) with the solvent peak or tetramethylsilane used as the internal reference. Assignments of individual signals were carried out using COSY, NOESY, HSQC, HMBC, and DEPT experiments. Chemical shifts (δ) are expressed in parts per million (ppm), and coupling constants (J) in Hertz (Hz). Resonances are described as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and dd (double doublet). High-resolution mass spectrometry (HRMS) was recorded on a Waters Xevo GL-XS Qtof spectrometer coupled with an Acquity H-Class LC apparatus. Ionization sources were performed with the available methods among electrospray ionization (ESI⁺ or ESI⁻) or Atmospheric Solid Analysis Probe (ASAP⁺ or ASAP⁻). For HRMS, a tolerance of 5 ppm was applied to discriminate the difference between calculated and experimental values Materials.

All chemicals, starting materials, and solvents used in this work were commercially available from Sigma-Aldrich or Alfa Aesar and used without further purification.

The starting materials and products **1**^[30], **1'**^[36], **5**^[21], **6**^[37], **10**^[32] and **11**^[32] were prepared as described in the literature.

Synthesis of Starting Material Methyl 1-methyl-1H-indazole-4-carboxylate (3). In a 50 mL flask, the methyl 1H-indazole-4-carboxylate (1.0 g, 1 equiv.) was dissolved in acetone (10 mL) at 0 °C in a 50 mL flask. KOH (3 equiv.) was added and the contents of the flask, sealed with a septum, were stirred for 60 minutes. Then, CH₃I (1.5 equiv.) was added dropwise using a syringe and the reaction mixture was warmed to room temperature and this temperature maintained for 18 hours. The reaction mixture was filtered to remove the inorganic base then separated by flash chromatography on silica gel (Hexane/EtOAc, 9:1).

General procedure of C7-arylation of indazoles. To a solution of (100mg) 1H-indazole derivatives (**1**, **1'**, **3**, **5**, **6**) in arenes (as partner agent and solvents (3 mL)), or in dioxane when we used heteroarene derivatives (5 equiv.), Pd(OAc)₂ (0.15 equiv.), Phen (0.15 equiv.), Ag₂CO₃ (2 equiv.) and NaOH (2 equiv.) were added. The reaction mixture was stirred at 140 °C for 72 hours, then filtration through celite. Then, the mixture was poured into 20 mL of H₂O and extracted twice with AcOEt (2 x 5 mL). The combined organic layers were dried over anhydrous MgSO₄, filtered, and concentrated under a vacuum. The crude product was purified by column chromatography over silica gel (hexane/ethyl acetate 9.5/0.5) to provide the desired products.

Products **2a**, **2e**, and **7** are well known, we found out their structure by a comparison between our spectral analysis and others that exist in the literature.^{30,21} For the new products their data are collected in supporting information.

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Keywords: directing groups; 1H-indazoles; Oxidative arylation; palladium; regioselectivity.

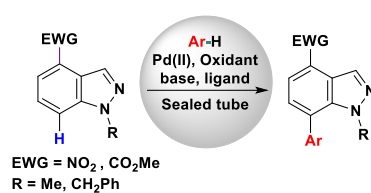
References

- [1] A. P. Taylor, R. P. Robinson, Y. M. Fobian, D. C. Blakemore, L. H. Jones, O. Fadeyi, *Org. Biomol. Chem.* **2016**, *14*, 6611–6637.
- [2] Y. Zhang, A. Pike, *Bioorg. Med. Chem.* **2021**, *38*, 127849.
- [3] M. Heravi, V. Zadsirjan, *RSC Adv.* **2020**, *10*, 44247–44311.
- [4] St. D. J. C. Jean, C. Fotsch, *J. Med. Chem.* **2012**, *55*, 6002–6020.
- [5] L. Amini-Rentsch, E. Vanoli, S. Richard-Bildstein, R. Marti, G. Vilé, *Ind. Eng. Chem. Res.* **2019**, *58*, 10164–10171.
- [6] X.X. Guo, D.W. Gu, Z. Wu, W. Zhang, *Chem. Rev.* **2015**, *115*, 1622–1651.
- [7] P. Thansandote, M. Lautens, *Chem. Eur. J.* **2009**, *15*, 5874–5883.
- [8] A.P. Kozikowski, H.F. Wetter, *Synthesis* **1976**, 561–590.
- [9] B. Soderberg, *Coord. Chem. Rev.* **2003**, *247*, 79–145.
- [10] B. Liégault, D. Lapointe, L. Caron, A. Vlassova, K. Fagnou, *J. Org. Chem.* **2009**, *74*, 1826–1834.
- [11] K. Boujdi, N. El Brahmi, J. Graton, D. Dubreuil, S. Collet, M. Mathé-Allainmat, M. Akssira, J. Lebreton, S. El Kazzouli, *RSC Adv.* **2021**, *11*, 7107–7114.
- [12] S. El Kazzouli, L. Bouissane, M. Khouili, G. Guillaumet, *Tetrahedron* **2005**, *46*, 6163–6167.
- [13] C.W.D. Gallop, M-T. Chen, O. Navarro, *Org. Lett.* **2014**, *16*, 3724–3727.
- [14] S.P.H. Mee, V. Lee, J.E. Baldwin, *Angew. Chem. Int. Ed.* **2004**, *43*, 1132–1136.
- [15] A. Unsinn, P. Knochel, *Chem. Commun.* **2012**, *48*, 2680.
- [16] S. El Kazzouli, G. Guillaumet, *Tetrahedron* **2016**, *72*, 6711–6727.
- [17] A. A García-Valdivia, E. Echenique-Erandonnea, G.B. Ramírez-Rodríguez, J.M. Delgado-López, B. Fernández, S. Rojas, J. Cepeda, A. Rodríguez-Diéguez, *Inorganics* **2021**, *9*, 20.
- [18] X. Sang, X. Hu, R. Tao, Y. Zhang, H. Zhu, D.A Wang, *ChemPlusChem.* **2020**, *85*, 123–129.
- [19] S.-G. Zhang, C.-G. Liang, W.-H. Zhang, *Molecules* **2018**, *23*, 2783.
- [20] P. Emayavaramban, K. Kadirvelu, N. Dharmaraj, *J. Nanosci. Nanotechnol.* **2016**, *16*, 9093–9103.
- [21] A. Ben-Yahia, M. Naas, M. S. El Kazzouli, E. M. Essassi, G. Guillaumet, *Eur. J. Org. Chem.* **2012**, 7075–7081.
- [22] K. Gambouz, A. El Abbouchi, S. Nassiri, F. Suzenet, M. Bousmina, M. Akssira, G. Guillaumet, S. El Kazzouli, *Molecules* **2020**, *25*, 2820.
- [23] F. Belkessam, M. Aidene, J.-F. Soulé, H. Doucet, *ChemCatChem.* **2017**, *9*, 2239–2249.
- [24] S.A. Ohnmacht, A.J. Culshaw, M.F. Greaney, *Org. Lett.* **2010**, *12*, 224–226.
- [25] M. C. Kozlowski, *Acc. Chem. Res.* **2017**, *50*, 638–643.
- [26] C.-J. Li, *Acc. Chem. Res.* **2009**, *42*, 335–344.
- [27] T. W. Lyons, M.S. Sanford, *Chem. Rev.* **2010**, *110*, 1147–1169.
- [28] J. Wencel-Delord, T. Dröge, F. Liu, F. Glorius, *Chem. Soc. Rev.* **2011**, *40*, 4740–4761.
- [29] M. Naas, S. El Kazzouli, E.M. Essassi, M. Bousmina, G. Guillaumet, *J. Org. Chem.* **2014**, *79*, 7286–7293.
- [30] K. Boujdi, K.; N. El Brahmi, S. Collet, D. Dubreuil, M. Mathé-Allainmat, M. Akssira, G. Guillaumet, J. Lebreton, S. El Kazzouli, *Synthesis* **2022**, *54*, 4834–4842.
- [31] Y. Cheng, G. Li, Y. Liu, Y. Shi, G. Gao, D. Wu, J. Lan, J. You, *J. Am. Chem. Soc.* **2016**, *138*, 4730–4738.
- [32] K. Gambouz, A. E. Abouchi, S. Nassiri, F. Suzenet, M. Bousmina, M. Akssira, G. Guillaumet, S. El Kazzouli, *Eur. J. Org. Chem.* **2020**, 7435–7439.
- [33] A.D. Bochevarov, E. Harder, T.F. Hughes, J.R Greenwood, D.A. Braden, D.M. Philipp, D. Rinaldo, M.D. Halls, J. Zhang, R.A. Friesner, *Int. J. Quantum Chem.* **2013**, *113*, 2110–2142.

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- [34] M. Lafrance, C.N. Rowley, T.K. Woo, K. Fagnou, *J. Am. Chem. Soc.* **2006**, *128*, 8754–8756.
- [35] S.I. Gorelsky, D. Lapointe, K. Fagnou, *J. Am. Chem. Soc.* **2008**, *130*, 10848–10849.
- [36] M.E. Rakib, N. Abbassi, A. Hannoui, M. Alaoui, M. Benchidmi, M.E. Essassi, D. Geffken, *Heterocycles* **2011**, *83*, 891-900.
- [37] A.M. Haydl, J. F. Hartwig, *Org. Lett.* **2019**, *21*, 1337–1341.

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This study presents an efficient method for the palladium-catalyzed oxidative arylation of substituted 1H-indazole with various arenes and heteroarenes as coupling partners. Using an EWG at the C4 position of the 1H-indazole, a site-selective C7 oxidative arylation was successfully achieved. The catalytic system comprised Pd(OAc)₂ as the catalyst, phenanthroline as the ligand, Ag₂CO₃ as the oxidant, and NaOH as the base.