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Solvent/Ligand Controlled Switchable C3 or C7 C–H Arylations of 1-Methyl-4-Nitro-1*H*-Indazole

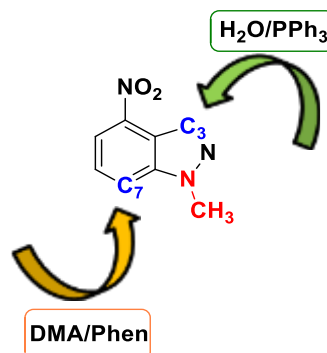
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Abstract A new solvent/ligand controlled switchable C–H arylation of 1-methyl-4-nitro-1*H*-indazole catalyzed by Pd(OAc)₂ was achieved. A bidentate ligand in DMA promoted the activation at C7 position, while a phosphine ligand in H₂O oriented the arylation at C3 position. The C3 and C7 arylation products were obtained in moderate to good yields and in high regioselectivity.

Key words Heteroarenes, indazole, C–H activation, C–H arylation, regioselectivity

C–H arylation is nowadays well known for the functionalization of a wide variety of arenes and heteroarenes.^{1–7} This reaction is accomplished without the need for the prefunctionalization of the starting materials, thus providing a more atom-economical and green sustainable process in contrast to conventional cross-coupling methods which require, in addition to aryl halides, the use of either boronic acids or derivatives,⁸ organostannanes,⁹ organozinc compounds,^{10,11} Grignard reagents,¹² or other organometallic species.

Although progress has been made in the field of direct arylation towards site-selective arylation of more than one position on fused bicyclic heterocyclic systems, especially 6, 5-fused heterocycles, few reports have been published until now on site-selective arylation of the six-membered ring.¹³ In fact, in 6, 5-fused heterocyclic systems, more efforts have been devoted to direct arylation of the five-membered ring because of the lack of reactivity of the six-membered ring. Consequently, the site-selective arylation of different positions on 6, 5-fused heterocycles is of significant interest.

The regioselective control of the C–H activation reactions presents a highly challenging task which has sometimes been overcome by approaches such as the use of directing groups or the careful choice of specific ligands.^{14–18} Although solvent

controlled C–H functionalization has also been used as a strategy, very few examples have been published so far. In an interesting report, Lin and Yao demonstrated that the solvent media could control the site-selective C2/C5 C–H alkenylation of 4-aryl-1*H*-pyrrole-3-carboxylates *via* a Pd(OAc)₂ catalyzed oxidative Heck reaction.¹⁹ Also, Gaunt *et al.* reported a regioselective palladium-catalyzed C2 or C3 alkenylation of indoles controlled by solvents and oxidants.²⁰ To the best of our knowledge, only very few examples have been reported so far in the literature on a direct arylation reaction controlled by solvents.²¹ Larrosa *et al.* described an interesting Ru-catalyzed *ortho* C–H arylation of benzoic acids which was extended to direct arylation of the benzoic ring of indole containing carboxylic acid on the six-membered ring.²² By taking advantage of -CO₂H as a directing group, the *ortho* arylation on the benzoic ring was achieved. Interestingly, when 3 equivalents of H₂O were added to the reaction media, it led to bis-arylation at both *ortho* positions of the carboxylic acid group. In another example, Bedford's group developed solvent/ligand controlled regioselective C3 and C7 arylations of the pyrazolo[1,5-*a*]pyrimidine.²³ In this Pd(OAc)₂ catalyzed reaction, the C3 direct arylation was achieved using 1,4-dioxane as the solvent under phosphine-free conditions, while the C7 arylation was favored in toluene using SPhos as the ligand. In our very recent report we showed that the use of *N*-oxide as directing group led to solvent/ligand controlled regioselective C5 and C7 arylation of 4-azaindazole *N*-oxides catalyzed by palladium without any need to block the C3 position.²⁴ In fact, the reaction catalyzed by PdCl₂ in the presence of a combination of DMA/triphenylphosphine (PPh₃) as solvent and ligand respectively, led to site-selective C7 arylation, while the use of Pd(OAc)₂ as catalyst in the presence of 1,10-phenanthroline (phen) in toluene provided the selective C5 arylation.

In our previous reports we showed that the C7 functionalization of indazoles by either direct arylation²⁵ or oxidative alkenylation²⁶ required the blockage of the C3 position of the

fused pyrazole ring. In the case of the 4-nitro-1*H*-indazole, C7 arylation using a Pd(OAc)₂/phen system was achieved without the blockage of the C3 position, but the reaction yield was low even when a large excess of iodotoluene was used.²⁵ In continuation of our research program toward the development of site-selective C–H activation of the six-membered rings of 6, 5-fused heterocyclic systems,^{24–26} we report herein a site-selective arylation of the 4-nitro-1*H*-indazole at either the C3 or the C7 position by means of new reaction conditions that allow perfect control of the regioselectivity. This control of the arylation reaction is mainly governed by the nitro group at the C4 position as well as the nature of the solvent assisted by the ligand. Both C3 and C7 arylation reactions were catalyzed by Pd(OAc)₂ in the presence of bases at high temperature. The C3 arylation was promoted by the use of water as solvent and PPh₃ as ligand while the switch to the C7 arylation was favored by the choice of DMA as solvent and phen as ligand.

The investigation of the reaction conditions began with 1-methyl-4-nitro-1*H*-indazole (**2**), prepared from 4-nitro-1*H*-indazole (**1**), as starting material (Table 1). The treatment of **2** with iodotoluene as coupling partner, Pd(OAc)₂ as catalyst, phen as ligand and Cs₂CO₃ as the base in DMA at 160 °C led only to degradation compounds and neither the starting material **2** nor the desired compound **3a** were isolated (entry 1). When the reaction mixture was heated at 140 °C instead of 160 °C, no degradation was noticed. However, the desired compound **3a** was isolated in a moderate yield (48%) along with 39% of the recovered starting material **2** (entry 2). When Cs₂CO₃ was replaced by K₂CO₃, the reaction yield decreased to 21% and 64% of starting material was recovered (entry 3). Taking PPh₃ as the ligand instead of phen led to a complete loss of reactivity and

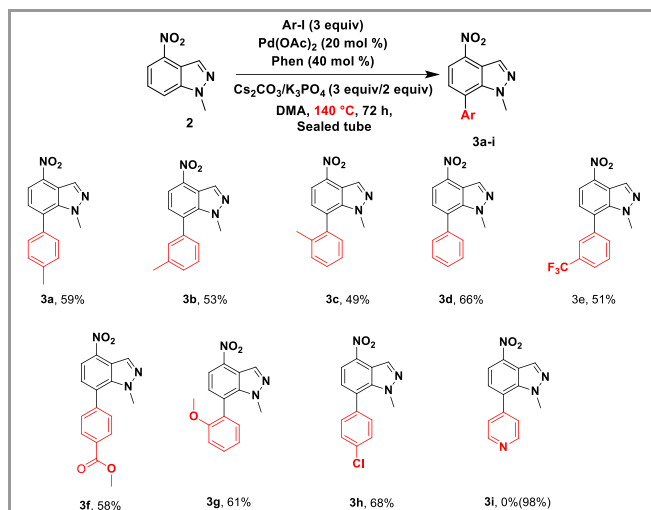
only starting material **2** was recovered (92%, entry 4). The same result was observed with Pd(PPh₃)₂Cl₂ as the catalyst (entry 5). A mixture of two different bases (Cs₂CO₃ and K₃PO₄) slightly improved the reaction yield (entry 6). Unfortunately, the replacement of DMA by either DMSO or DMF as solvent led to a total loss of reactivity (entries 7 and 8). Interestingly, when the reaction time was extended to 72 h, the conversion was total and the desired compound **3a** was isolated in 62% yield (entry 9). The replacement of Pd(OAc)₂ by PdCl₂ under the latter reaction conditions was deleterious, leading to a very low yield (12%) with a large amount of starting material **2** recovered (77%, entry 10). The use of PPh₃ instead of phen as ligand was not effective either, giving the compound **3a** as traces (entry 11). More bidentate ligands were tested, such as 2,2'-bipyridine and tetramethylethylenediamine (TMEDA), but only starting material **2** was recovered in 88 and 94% yield, respectively (entries 12 and 13). The phen ligand was crucial to achieve the C7 arylation, because no traces of the desired compound **3a** were observed when the reaction was conducted without ligand (entry 14). The reaction yield dramatically decreased when the reaction mixture was heated at 120 °C instead of 140 °C (compare entry 15 with entry 9). In an attempt to limit the quantity of the 4-iodotoluene partner, we found that 2 equivalents were not sufficient for a total conversion of the substrate (entry 16), compared to 3 equivalents which gave 59% yield of the desired compound **3a** (entry 17). The reaction with 4-bromotoluene instead of 4-iodotoluene as arylating agent led to a very low yield of the desired compound **3a** (23%) along with 61% of the recovered starting material **2** (entry 18).

Table 1 Optimization of the direct C7 arylation of 1-methyl-4-nitro-1*H*-indazole **2**

Entry	X (equiv)	Cat (0.2 equiv)	Ligand (0.4 equiv)	Base 3 equiv or 3 equiv/2 equiv	Solvent	Time	T °C Sealed tube	Yield % 2/3a
1	I (5)	Pd(OAc) ₂	Phen	Cs ₂ CO ₃	DMA	48 h	160 °C	Degradation
2	I (5)	Pd(OAc) ₂	Phen	Cs ₂ CO ₃	DMA	48 h	140 °C	39/48
3	I (5)	Pd(OAc) ₂	Phen	K ₂ CO ₃	DMA	48 h	140 °C	64/21
4	I (5)	Pd(OAc) ₂	PPh ₃	Cs ₂ CO ₃	DMA	48 h	140 °C	92/0
5	I (5)	Pd(PPh ₃) ₂ Cl ₂	Phen	Cs ₂ CO ₃	DMA	48 h	140 °C	88/traces
6	I (5)	Pd(OAc) ₂	Phen	Cs ₂ CO ₃ /K ₃ PO ₄	DMA	48 h	140 °C	24/53
7	I (5)	Pd(OAc) ₂	Phen	Cs ₂ CO ₃	DMSO	48 h	140 °C	87/traces
8	I (5)	Pd(OAc) ₂	Phen	Cs ₂ CO ₃	DMF	48 h	140 °C	93/traces
9	I (5)	Pd(OAc) ₂	Phen	Cs ₂ CO ₃ /K ₃ PO ₄	DMA	72 h	140 °C	Traces/62
10	I (5)	Pd(Cl) ₂	Phen	Cs ₂ CO ₃ /K ₃ PO ₄	DMA	72 h	140 °C	77/12
11	I (5)	Pd(OAc) ₂	PPh ₃	Cs ₂ CO ₃ /K ₃ PO ₄	DMA	72 h	140 °C	90/Traces
12	Br (3)	Pd(OAc) ₂	2,2'-bipyridine	Cs ₂ CO ₃ /K ₃ PO ₄	DMA	72 h	140 °C	88/0
13	Br (3)	Pd(OAc) ₂	TMEDA	Cs ₂ CO ₃ /K ₃ PO ₄	DMA	72 h	140 °C	94/0
14	I (5)	Pd(OAc) ₂	-	Cs ₂ CO ₃ /K ₃ PO ₄	DMA	72 h	140 °C	91/0
15	I (5)	Pd(OAc) ₂	Phen	Cs ₂ CO ₃ /K ₃ PO ₄	DMA	72 h	120 °C	68/24
16	I (2)	Pd(OAc) ₂	Phen	Cs ₂ CO ₃ /K ₃ PO ₄	DMA	72 h	140 °C	50/32
17	I (3)	Pd(OAc) ₂	Phen	Cs ₂ CO ₃ /K ₃ PO ₄	DMA	72 h	140 °C	Traces/59
18	Br (10)	Pd(OAc) ₂	Phen	Cs ₂ CO ₃ /K ₃ PO ₄	DMA	72 h	140 °C	61/23

^a Insert table footnotes here.

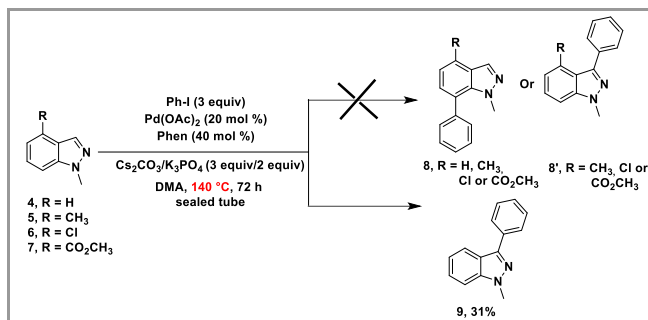
With the optimized reaction conditions in hand, we set out to study the scope and limitations of this reaction using various aryl iodides bearing either electron donating or electron withdrawing groups (Scheme 1). Compared to the reaction with 4-iodotoluene which gave 59% yield of the desired compound **3a**, results with 3-iodo or 2-iodo isomers were slightly lower, giving 53% yield of **3b** and 49% yield of **3c**, respectively, indicating a weak impact of the steric hindrance of the methyl group at the *ortho*-position of 2-iodotoluene on this coupling reaction. The use of iodobenzene as coupling partner led to its corresponding C7 arylated compound **3d** in 66% yield. The use of aryls containing electron withdrawing groups such as $-\text{CF}_3$ and $-\text{CO}_2\text{CH}_3$ led to the expected compounds **3e** and **3f** in comparable yields of 51 and 58%, respectively. The best results were obtained with aryls bearing electron donating groups, giving **3g** (61%) and **3h** (68%). Unfortunately, when 4-iodopyridine was employed as coupling partner, no compound **3i** was observed and only starting material **2** was recovered in 98% yield.



Scheme 1 Scope and limitations of the C7 arylation of 1-methyl-4-nitro-1H-indazole (**2**)

Then we decided to study the arylation reaction with 1-methyl-1H-indazole (**4**) and 4-substituted analogues bearing either electron donating or electron withdrawing groups at the C4 position of the indazole ring (starting materials **5–7**, Scheme 2). As expected, the reaction between 1-methyl-1H-indazole (**4**) and iodobenzene did not lead to the C7 arylated compound **8**. However, the C3 arylated indazole **9** was isolated in 31% yield along with 60% of the recovered starting material. When the reactions were carried out using either the substrate **5** or **6**, no reaction occurred and only starting materials were recovered in

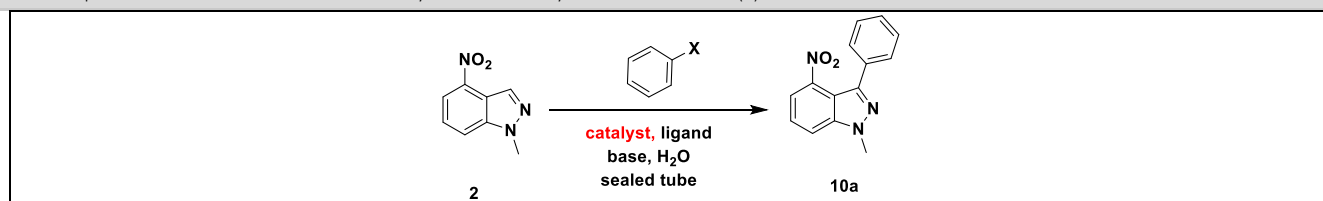
97 and 94% yield, respectively. Then, we studied the reactivity of the 4-substituted indazole **7** bearing an electron withdrawing $-\text{CO}_2\text{CH}_3$ group to compare with the $-\text{NO}_2$ group. Unfortunately, under the reaction conditions the ester group was not stable and only degradation was observed (Scheme 2)



Scheme 2 Limitations of the C7 arylation reaction

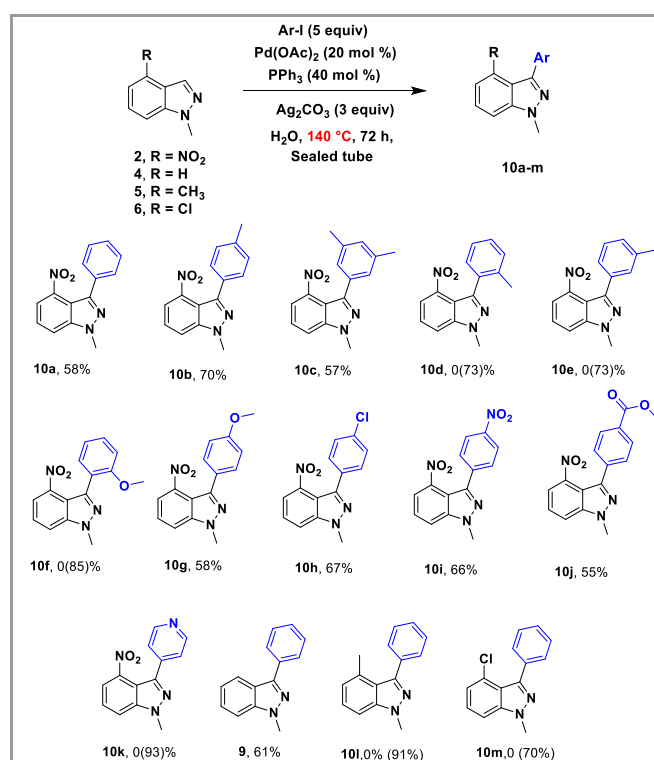
As a green approach, we decided to test the arylation reaction on water (Table 2). Selecting iodobenzene as arylating agent gave 66% yield of the C7 substituted indazole **3d**. Under the previous study conditions (see *supra*), no reaction occurred using water instead of DMA (Table 2, entry 1). Then, drawing on our previous work,^{24,25} we tested various Pd(II) as catalysts in the presence of 3 equivalents of 4-iodobenzene, PPh_3 as ligand, Ag_2CO_3 as the base in H_2O as solvent at 140 °C for 48 h in a sealed tube. With $\text{Pd}(\text{PPh}_3)\text{Cl}_2$ or PdCl_2 , only starting material **2** was recovered in 88 and 70% yield, respectively (entries 2 and 3). When $\text{Pd}(\text{OAc})_2$ was used, we were excited to see that the reaction led to the desired C3 arylation compound **10a** in 31% isolated yield along with 53% of the recovered starting material **2**. Importantly, no traces of the C7 arylation compound **3d** were observed (entry 4). When the reaction time was extended to 72 h, the desired compound **10a** was isolated in 45% yield; however, 28% of starting material was recovered (entry 5). Heating the reaction mixture for 72 h at 120 °C instead of 140 °C led to a notable decrease in the reaction yield (24%, entry 6). Interestingly, when 5 equivalents of iodobenzene were used instead of 3 equivalents, the reaction conversion was total and the desired compound **10a** was isolated in 58% yield (entry 7). Remarkably, when H_2O was replaced by a mixture of $\text{H}_2\text{O}/\text{EtOH}$, the reaction was not effective and only starting material **2** was recovered in 78% yield (entry 8). The use of a mixture of $\text{Ag}_2\text{CO}_3/\text{K}_3\text{PO}_4$ instead of Ag_2CO_3 gave almost the same result (compare entries 7 and 9). When conducted without ligand, no reaction occurred (entry 10). The reaction with bromobenzene as the coupling partner provided the expected compound **10a** in a very low yield (18%, entry 11).

Table 2 Optimization of the “on water” direct C3 arylation of 1-methyl-4-nitro-1H-indazole (**2**)



Entry	X (equiv)	Cat (0.2 equiv)	Ligand (0.4 equiv)	Base 3 equiv or 3 equiv/2 equiv	Solvent	Time	T °C Sealed tube	Yield % 2/10a
1	I (5)	Pd(OAc) ₂	phen	Cs ₂ CO ₃ / K ₃ PO ₄	H ₂ O	72 h	140 °C	93/0
2	I (3)	Pd(PPh ₃) ₂ Cl ₂	PPh ₃	Ag ₂ CO ₃	H ₂ O	48 h	140 °C	88/traces
3	I (3)	PdCl ₂	PPh ₃	Ag ₂ CO ₃	H ₂ O	48 h	140 °C	70/traces
4	I (3)	Pd(OAc) ₂	PPh ₃	Ag ₂ CO ₃	H ₂ O	48 h	140 °C	53/31
5	I (3)	Pd(OAc) ₂	PPh ₃	Ag ₂ CO ₃	H ₂ O	72 h	140 °C	28/45
6	I (3)	Pd(OAc) ₂	PPh ₃	Ag ₂ CO ₃	H ₂ O	72 h	120 °C	59/24
7	I (5)	Pd(OAc) ₂	PPh ₃	Ag ₂ CO ₃	H ₂ O	72 h	140 °C	0/58
8	I (5)	Pd(OAc) ₂	PPh ₃	Ag ₂ CO ₃	H ₂ O/EtOH	72 h	140 °C	78/traces
9	I (5)	Pd(OAc) ₂	PPh ₃	Ag ₂ CO ₃ /K ₃ PO ₄	H ₂ O	72 h	140 °C	Traces/56
10	I (5)	Pd(OAc) ₂	None	Ag ₂ CO ₃	H ₂ O	72 h	140 °C	98/0
11	Br (5)	Pd(OAc) ₂	PPh ₃	Ag ₂ CO ₃ /K ₃ PO ₄	H ₂ O	72 h	140 °C	73/18

Having in hand the optimized reaction conditions for the regioselective C3 arylation of 1-methyl-4-nitro-1*H*-indazole (**2**), we decided then to study the scope and limitations of this method. Thus, the starting material **2** was coupled with various aryl iodides under the following reaction conditions [5 equiv of aryl iodide, 20 mol% of Pd(OAc)₂, 40 mol% of PPh₃, 3 equiv of Ag₂CO₃ in H₂O at 140 °C for 72 h in a sealed tube]. With 4-iodotoluene and 5-iodo-*m*-xylene as the halogenated aryls, the expected compounds **10b** and **10c** were isolated in good (70%) and acceptable (57%) yields, respectively. Surprisingly, no reaction occurred using 2-iodo or 3-iodotoluene as starting material (**10d** and **10e**), probably due to steric hindrance. The same problem was observed when 1-iodo-2-methoxybenzene was employed as coupling partner **10f**. Nevertheless, when 1-iodo-4-methoxybenzene was used as a coupling partner, the expected compound **10g** was obtained in 58% yield. The reaction with 4-substituted iodobenzene partners furnished the C3 arylation compounds **10h-j** in acceptable yields (67, 66 and 55% yield, respectively), and did not seem to strongly discriminate iodoaryl partners bearing donating or withdrawing groups. Here too, the use of 4-iodopyridine as coupling partner was not effective and no traces of the arylated compound **10k** were observed. When the non-substituted indazole **4** was used as the starting material, the expected C3 arylated compound **9** was isolated in 61% yield, compared to 31% in the previous non aqueous conditions (see *supra*). Unfortunately, with 1,4-dimethyl-1*H*-indazole (**5**) or 4-chloro-1-methyl-1*H*-indazole (**6**) no C3 arylation reaction was observed (**10l** and **10m**, Scheme 3).



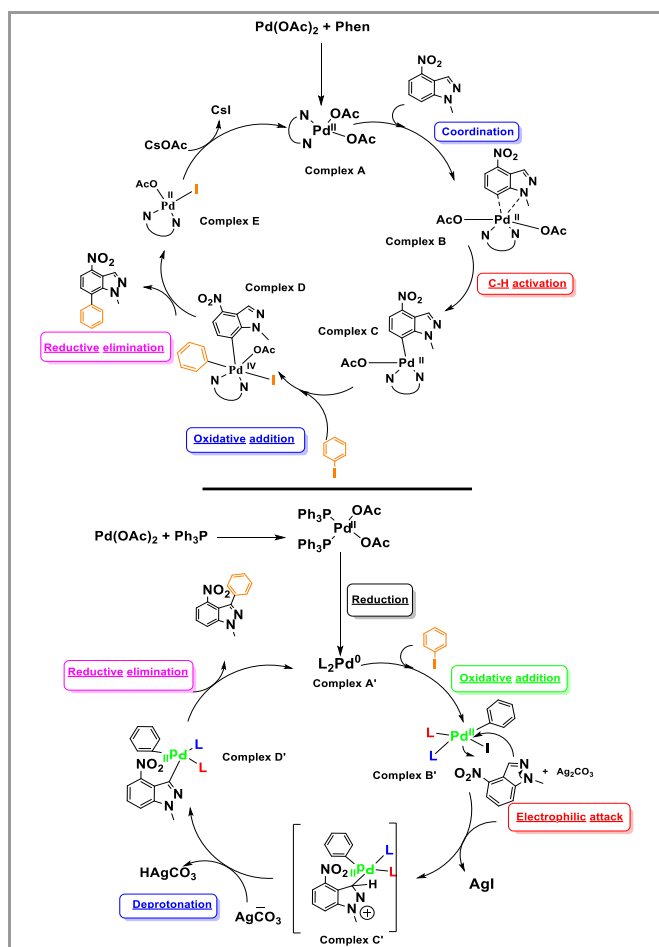
Scheme 3 Scope and limitations of the direct C3 arylation reaction

We believe that the C3 versus C7 direct arylation of 1-methyl-4-nitro-1*H*-indazole (**2**) is limited by the steric hindrance of the -NO₂ group when phen is used as the ligand in DMA. Indeed, we previously found that when starting indazoles containing a -NO₂ group on either C5, C6 or C7 position were used as substrates under these conditions, direct arylation took place preferably at the C3 position.²⁵ We therefore presume that for compound **2**, when H₂O was chosen as the solvent and Ph₃P as the ligand, this may have overcome the steric problem. In this case the solvent assisted by the ligand played a crucial role in achieving this regioselective C3 arylation.

On the basis of previous studies²⁵⁻²⁸ we propose a plausible mechanism for both C3 and C7 functionalizations (Scheme 4).

First catalytic cycle of C7 arylation: 1-methyl-4-nitro-1*H*-indazole (**2**) is coordinated with the catalyst (complex A) generated in situ from Pd(OAc)₂ and phen to give complex B. Complex B leads to complex C by C–H activation of the C7 position of **2**. Subsequently, the oxidative addition of the C–I bond of iodoaryl to complex C leads to complex D, followed by a reductive elimination giving the C7 arylation compound.

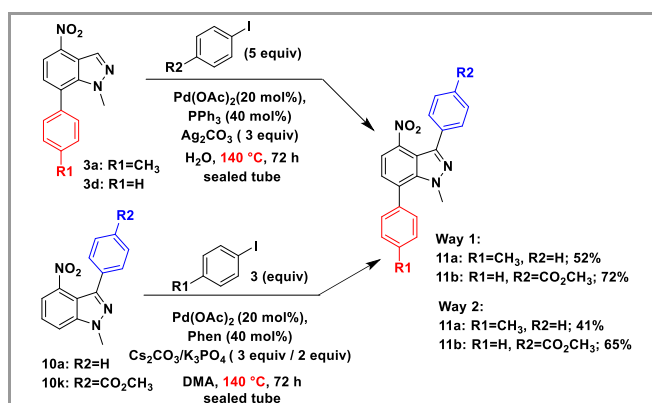
Second catalytic cycle of C3 arylation: iodoaryl reagent is coordinated with the catalyst (complex A') generated in situ from Pd(OAc)₂ and PPh₃ to give complex B'. Complex B' leads to complex C' by C–H activation of the C3 position of the indazole under Ph₃P/H₂O conditions. Subsequently deprotonation of complex C' leads to complex D' followed by the reductive elimination to give the C3 arylation compound.



Scheme 4 Plausible mechanism of C3 and C7 arylation reactions

We then pursued our investigations with the synthesis of the unsymmetrical C3, C7 bis-arylated indazoles **11a–b**. Thus, we explored two different pathways starting from either C3 arylation then C7 arylation or C7 arylation followed by C3 arylation. It should also be pointed out here that both methods gave C3, C7 bis-arylated indazoles. So, when the C7 arylated compounds **3a** and **3d** were treated under the optimized reaction conditions found for C3 arylation, the expected compounds **11a** and **11b** were obtained in 52 and 72% yield, respectively (pathway 1). Using pathway 2, when **10a** and **10k** were treated under the reaction conditions developed for C7 arylation, the

desired compounds **11a** and **11b** were isolated in 41 and 65% yield, respectively (Scheme 5).



Scheme 5 Unsymmetrical C3, C7 bis-arylation of 1-methyl-4-nitro-1*H*-indazole

In summary, we have found the reaction conditions to achieve site-selective arylation at either the C3 or the C7 position of 1-methyl-4-nitro-1*H*-indazole (**2**) by means of a palladium catalyzed C–H activation reaction. The regioselectivity at either C3 or C7 arylation was directed and controlled by the nitro group at the C4 position as well as the nature of the solvent and ligand. The use of DMA as the solvent and phen as the ligand in the presence of Pd(OAc)₂ and Cs₂CO₃/K₃PO₄ provided C7 arylation of 1-methyl-4-nitro-1*H*-indazole (**2**). It is important to note that in 6, 5-fused heterocyclic systems, direct C7 arylation with a free C3 position is extremely rare. The use of water as solvent and PPh₃ as ligand in the presence of Pd(OAc)₂, Ag₂CO₃ promoted the C3 arylation of 1-methyl-4-nitro-1*H*-indazole (**2**), which represents the first example of C3 direct arylation of this substrate. These results encourage us to continue our investigation in the development of site-selective C–H functionalization of heterocycles.

All chemicals, starting materials and solvents used in this study were commercially available from Sigma-Aldrich or Alfa Aesar and were used without further purification. The 4-nitro-1*H*-indazole (**1**) and the 1-methyl-4-nitro-1*H*-indazole (**2**) were prepared as described in the literature.^{25,29,30}

TLC was performed on silica-covered aluminum (Kieselgel 60F254, Merck) and visualized using ultraviolet light ($\lambda = 254$ nm). Column chromatography was performed on silica gel 60 (ACC 40–63 μ m 5SDS-ChromatErba). Infrared spectroscopic analyses were recorded on an IRTF Bruker Tensor Spectrophotometer Specac Quest ATK system (samples were neat). NMR spectra were recorded on a Bruker AC300 (300 MHz for ¹H and 75 MHz for ¹³C), on a Bruker 400 (400 MHz for ¹H and 101 MHz for ¹³C) or on a Jeol 600 (600 MHz for ¹H and 151 MHz for ¹³C) spectrometer at room temperature, and the samples were dissolved in an appropriate deuterated solvent. Tetramethylsilane (TMS) for ¹H and the solvent signal for ¹³C were used as references. 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. Melting points (mp [°C]) were recorded with an Electrothermal Digital Melting Point apparatus from Cole – Parmer.

General procedure of C7 Arylation

To a solution of 1-methyl-4-nitro-1*H*-indazole (**2**) (1.0 equivalent) in DMA, iodoaryl (3.0 equivalents), palladium acetate (0.2 equivalent), 1,10-phenanthroline (0.4 equivalent), Cs₂CO₃ (3 equivalents), and K₃PO₄ (2 equivalents) were added. The mixture was degassed for few minutes, and stirred at 140 °C for 72 h in a sealed tube. After the reaction mixture was cooled to room temperature, filtered through celite, washed with water and extracted three times with ethyl acetate. The combined organic layers were dried over magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using DCM/Hexane (2/3 (v/v)) as eluent to provide the desired compounds

1-Methyl-4-nitro-7-(*p*-tolyl)-1*H*-indazole (**3a**)

Yellow solid; yield: 59% (51 mg); mp 206–208 °C

¹H NMR (600 MHz, CDCl₃): δ = 8.67 (s, 1H), 8.15 (d, *J* = 7.8 Hz, 1H), 7.39–7.18 (m, 5H), 3.68 (s, 3H), 2.46 (s, 3H).

¹³C NMR (151 MHz, CDCl₃): δ = 139.6, 139.4, 139.1, 133.9, 133.8, 132.7, 129.3 (2C), 129.2 (2C), 127.3, 118.4, 118.1, 39.7, 21.4.

IR (neat): 3060, 2926, 2848, 1724, 1486, 1275, 821, 696 cm⁻¹.

HRMS (ASAP⁺): *m/z* [M+H]⁺ calcd for C₁₅H₁₄N₃O₂: 268.1086; found: 268.1091.

1-Methyl-4-nitro-7-(*m*-tolyl)-1*H*-indazole (**3b**)

White solid; yield: 53% (48 mg); mp 164–166 °C.

¹H NMR (400 MHz, CDCl₃): δ = 8.61 (s, 1H), 8.09 (d, *J* = 7.9 Hz, 1H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.25 (t, *J* = 7.0 Hz, 2H), 7.18–7.12 (m, 2H), 3.60 (s, 3H), 2.38 (s, 3H).

¹³C NMR (101 MHz, CDCl₃): δ = 139.7, 139.3, 138.3, 136.8, 133.7, 132.7, 130.0, 129.6, 128.3, 127.1, 126.5, 118.2, 118.1, 39.5, 21.4.

IR (neat): 3041, 2922, 2851, 1511, 707 cm⁻¹.

HRMS (ASAP⁺): *m/z* [M+H]⁺ calcd for C₁₅H₁₄N₃O₂: 268.1086; found: 268.1089.

1-Methyl-4-nitro-7-(*o*-tolyl)-1*H*-indazole (**3c**)

Yellow solid; yield: 49% (45 mg); mp 209–211 °C.

¹H NMR (400 MHz, CDCl₃): δ = 8.60 (s, 1H), 8.11 (d, *J* = 7.8 Hz, 1H), 7.34 (dd, *J* = 7.4, 1.6 Hz, 1H), 7.31–7.23 (m, 3H), 7.17 (d, *J* = 1.6 Hz, 1H), 3.47 (s, 3H), 1.98 (s, 3H).

¹³C NMR (101 MHz, CDCl₃): δ = 139.3, 139.0, 136.2, 132.7, 130.2, 129.7, 129.6, 129.3, 126.7, 125.9, 118.3, 117.7, 38.1, 29.7.

IR (neat): 3094, 2946, 1614, 1515, 1329, 1277, 1078, 746, 662 cm⁻¹.

HRMS (ASAP⁺): *m/z* [M+H]⁺ calcd for C₁₅H₁₄N₃O₂: 268.1086; found: 268.1089.

1-Methyl-4-nitro-7-phenyl-1*H*-indazole (**3d**)

Yellow solid; yield, 66% (53 mg); mp 172–173 °C.

¹H NMR (400 MHz, CDCl₃): δ = 8.62 (s, 1H), 8.10 (d, *J* = 7.9 Hz, 1H), 7.48–7.42 (m, 3H), 7.39–7.33 (m, 2H), 7.25 (d, *J* = 7.9 Hz, 1H), 3.60 (s, 3H).

¹³C NMR (101 MHz, CDCl₃): δ = 138.7, 138.2, 135.8, 132.4, 131.7, 128.3 (2C), 127.9, 127.4 (2C), 126.1, 117.1, 117.0, 38.5.

IR (neat): 3054, 2924, 2852, 1514, 627 cm⁻¹.

HRMS (ASAP⁺): *m/z* [M+H]⁺ calcd for C₁₄H₁₂N₃O₂: 254.0930; found: 254.0934.

1-Methyl-4-nitro-7-(3-(trifluoromethyl)phenyl)-1*H*-indazole (**3e**)

White solid; yield: 51% (57 mg) mp 133–135 °C.

¹H NMR (600 MHz, Acetone-*d*₆): δ = 8.56 (s, 1H), 8.21 (d, *J* = 7.8 Hz, 1H), 7.96–7.95 (m, 1H), 7.93 (s, 1H), 7.91–7.90 (m, 2H), 7.83 (t, *J* = 8.1 Hz, 1H), 7.53 (d, *J* = 7.8 Hz, 1H), 3.66 (s, 3H).

¹³C NMR (151 MHz, Acetone-*d*₆): δ = 140.0, 139.1, 138.1, 133.7, 132.0 (q, *J*_{Cq} = 55.3 Hz, C_q-F), 131.8, 129.5, 127.7, 126.4 (q, ³*J*_{CHAR-F} = 3.7 Hz, 2C, CH_{Ar}), 126.3, 125.7 (q, ¹*J*_{C-F} = 109.5 Hz, CF₃), 125.6, 123.1, 118.1, 39.3.

IR (neat): 2922, 2852, 1517, 1326, 705 cm⁻¹.

HRMS (ASAP⁺): *m/z* [M+H]⁺ calcd for C₁₅H₁₁N₃O₂F₃: 322.0803; found: 322.0800.

Methyl 4-(1-methyl-4-nitro-1*H*-indazol-7-yl)benzoate (**3f**)

Orange solid; yield: 58% (32 mg); mp 157–162 °C.

¹H NMR (600 MHz, CDCl₃): δ = 8.70 (s, 1H), 8.20–8.17 (m, 3H), 7.52 (d, *J* = 8.6 Hz, 2H), 7.33 (d, *J* = 7.9 Hz, 1H), 3.98 (s, 3H), 3.66 (s, 3H).

¹³C NMR (151 MHz, CDCl₃): δ = 166.4, 141.4, 140.2, 139.1, 132.9, 132.1, 130.8, 129.7 (2C), 129.5, 127.1 (2C), 118.3, 118.1, 52.5, 31.9.

IR (neat): 2921, 2850, 1716, 963 cm⁻¹.

HRMS (ASAP⁺): *m/z* [M+H]⁺ calcd for C₁₆H₁₄N₃O₄: 312.0984; found: 312.0984.

7-(2-Methoxyphenyl)-1-methyl-4-nitro-1*H*-indazole (**3g**)

Colorless oil; yield: 61% (36 mg); mp 187–189 °C

¹H NMR (400 MHz, CDCl₃): δ = 8.58 (s, 1H), 8.08 (d, *J* = 7.8 Hz, 1H), 7.43 (ddd, *J* = 8.3, 7.5, 1.8 Hz, 1H), 7.22 (d, *J* = 1.8 Hz, 1H), 7.19 (d, *J* = 0.7 Hz, 1H), 7.04 (td, *J* = 7.5, 1.0 Hz, 1H), 6.96 (dd, *J* = 8.3, 1.0 Hz, 1H), 3.67 (s, 3H), 3.59 (s, 3H).

¹³C NMR (101 MHz, CDCl₃): δ = 156.9, 139.9, 139.8, 132.3, 131.1, 130.8, 130.3, 127.4, 125.8, 120.8, 118.2, 117.6, 110.6, 55.4, 37.8.

IR (neat): 3072, 2919, 2850, 1501, 963 cm⁻¹.

HRMS (ASAP⁺): *m/z* [M+H]⁺ calcd for C₁₅H₁₄N₃O₃: 284.1035; found: 284.1038.

7-(4-Chlorophenyl)-1-methyl-4-nitro-1*H*-indazole (**3h**)

Yellow solid; yield: 68% (31 mg); mp 112–113 °C.

¹H NMR (600 MHz, CDCl₃): δ = 8.69 (s, 1H), 8.16 (d, *J* = 7.9 Hz, 1H), 7.52–7.37 (m, 3H), 7.32 (d, *J* = 7.3 Hz, 2H), 3.70 (s, 3H).

¹³C NMR (151 MHz, CDCl₃): δ = 132.7, 130.0, 129.7, 129.3, 129.2 (2C), 128.3, 127.2 (2C), 127.1, 126.5, 126.0, 118.2, 39.6.

IR (neat): 2923, 2852, 1519, 1338, 963 cm⁻¹.

HRMS (ASAP⁺): *m/z* [M+H]⁺ calcd for C₁₄H₁₁N₃O₂Cl: 288.0537; found: 288.0538.

General procedure of C3 Arylation.

To a solution of 1-methyl-4-nitro-1*H*-indazole (**2**) (1.0 equivalent) in H₂O, iodoaryl (3.0 equivalents), palladium acetate (0.2 equivalent), PPh₃ (0.4 equivalent) and Ag₂CO₃ (3 equivalents) were added. The mixture was stirred for a few seconds to ensure that all solids were well mixed, then, 3 mL of distilled water was added. The solution was degassed for few minutes, and stirred at 140 °C for 72h in a sealed tube. After the reaction mixture was cooled to room temperature, filtered through celite, washed with water and extracted three times with ethyl acetate. The combined organic layers were dried over magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using DCM/ Hexane (2/3 (v/v)) as eluent to provide the desired compounds

1-Methyl-3-phenyl-1*H*-indazole (**9**)

Yellow solid; yield: 61% (41 mg); mp 78–80 °C.

IR (neat): 2932, 1490, 1337, 1261, 780, 735, 697 cm⁻¹.

HRMS (ES⁺): *m/z* [M+H]⁺ calcd for C₁₄H₁₃N₂: 209.1073; found: 209.1071.

The ¹H and ¹³C NMR spectra were in accordance with those described in the literature.³⁰

1-Methyl-4-nitro-3-phenyl-1*H*-indazole (**10a**)

Yellow solid; yield: 58% (42 mg); mp 234.9–236.7 °C.

¹H NMR (400 MHz, CDCl₃): δ = 7.79 (dd, *J* = 7.5, 0.8 Hz, 1H), 7.68 (dd, *J* = 8.4, 0.8 Hz, 1H), 7.46 (dd, *J* = 8.5, 7.5 Hz, 1H), 7.35–7.45 (m, 5H), 4.15 (s, 3H).

¹³C NMR (101 MHz, CDCl₃): δ = 143.9, 143.4, 142.8, 133.4, 128.7, 128.6 (2C), 128.3, 128.1 (2C), 125.5, 117.8, 114.7, 36.1.

IR (neat): 2922, 2324, 1518, 1329, 1153, 636 cm⁻¹

HRMS (ES⁺): *m/z* [M+Na]⁺ calcd for C₁₄H₁₁N₃O₂Na: 276.0749; found: 276.0749.

1-Methyl-4-nitro-3-(*p*-tolyl)-1*H*-indazole (**10b**)

Yellow solid; yield: 70% (62 mg); mp 234.9–236.7 °C.

¹H NMR (300 MHz, CDCl₃): δ = 7.85 (dd, *J* = 7.5, 0.8 Hz, 1H), 7.75 (dd, *J* = 8.5, 0.8 Hz, 1H), 7.53 (dd, *J* = 8.5, 7.5 Hz, 1H), 7.36 (d, *J* = 8.1 Hz, 2H), 7.27 (d, *J* = 8.1 Hz, 2H), 4.23 (s, 3H), 2.44 (s, 3H).

¹³C NMR (75 MHz, CDCl₃): δ = 130.9, 129.1, 128.8 (2C), 128.7, 128.4 (2C), 128.3, 125.4, 117.8, 117.6, 114.7, 114.6, 36.1, 21.4.

IR (neat): 3065, 2938, 1497, 1410, 1278, 1253, 1134, 878, 772, 696 cm⁻¹.

HRMS (ES⁺): *m/z* [M+H]⁺ calcd for C₁₅H₁₄N₃O₂: 268.1086; found: 268.10782.

3-(3,5-Dimethylphenyl)-1-methyl-4-nitro-1*H*-indazole (**10c**)

Yellow solid; yield: 48% (28 mg); mp 234.9–236.7 °C.

¹H NMR (600 MHz, Acetone-*d*₆): δ = 8.04 (d, *J* = 8.5 Hz, 1H), 7.82 (d, *J* = 7.4 Hz, 1H), 7.63 (dd, *J* = 8.5, 7.5 Hz, 1H), 7.02 (s, 3H), 4.22 (s, 3H), 2.31 (s, 6H).
¹³C NMR (151 MHz, Acetone-*d*₆): δ = 140.5, 138.7, 138.1, 135.7, 135.6, 133.0, 131.9, 130.8, 128.5, 128.3, 119.5, 119.1, 40.4, 20.1 (2C).
 IR (neat): 2877, 2599, 1687, 1137, 1078, 566, 414 cm⁻¹.
 HRMS (ASAP⁺): *m/z* [M+H]⁺ calcd for C₁₆H₁₅N₃O₂: 282.1243; found: 282.1243.

3-(4-Methoxyphenyl)-1-methyl-4-nitro-1H-indazole (10g)

Yellow solid; yield: 58% (58 mg); mp 177–179 °C.
¹H NMR (600 MHz, CDCl₃): δ = 7.82 (d, *J* = 8.5 Hz, 1H), 7.72 (d, *J* = 8.5 Hz, 1H), 7.51 (dd, *J* = 8.5, 7.5 Hz, 1H), 7.37 (d, *J* = 8.7 Hz, 2H), 6.97 (d, *J* = 8.7 Hz, 2H), 4.19 (s, 3H), 3.85 (s, 3H).
¹³C NMR (151 MHz, CDCl₃): δ = 140.7, 138.1, 136.1, 129.8, 129.7 (2C), 129.5, 129.1 (2C), 128.7, 128.6, 127.6, 114.0, 52.3, 40.0.
 IR (neat): 2919, 2850, 2639, 2323, 1717, 1275 cm⁻¹.
 HRMS (ASAP⁺): *m/z* [M+H]⁺ calcd for C₁₅H₁₄N₃O₃: 284.1035; found: 284.1034.

3-(4-Chlorophenyl)-1-methyl-4-nitro-1H-indazole (10h)

White solid; yield: 67% (61 mg); mp 234.9–236.7 °C.
¹H NMR (400 MHz, CDCl₃): δ = 7.81 (dd, *J* = 7.5, 0.8 Hz, 1H), 7.67 (dd, *J* = 8.5, 0.8 Hz, 1H), 7.45 (dd, *J* = 8.5, 7.5 Hz, 1H), 7.34 (d, *J* = 8.8 Hz, 2H), 7.29 (d, *J* = 8.8 Hz, 2H), 4.13 (s, 3H).
¹³C NMR (101 MHz, CDCl₃): δ = 143.2, 142.8, 134.3, 130.7, 130.0 (2C), 128.8, 128.3 (2C), 125.6, 118.1, 115.0, 112.9, 36.1.
 IR (neat): 3052, 2938, 1511, 1429, 963, 626 cm⁻¹.
 HRMS (ES⁺): *m/z* [M+H]⁺ calcd for C₁₄H₁₁ClN₃O₂: 288.0534; found: 288.0534.

1-Methyl-4-nitro-3-(4-nitrophenyl)-1H-indazole (10i)

Orange solid; yield: 53% (58 mg); mp 234.9–236.7 °C.
¹H NMR (600 MHz, CDCl₃): δ = 8.31 (d, *J* = 8.8 Hz, 2H), 7.99 (d, *J* = 8.5 Hz, 1H), 7.81 (d, *J* = 7.6 Hz, 1H), 7.60 – 7.57 (m, 3H), 4.25 (s, 3H).
¹³C NMR (151 MHz, CDCl₃): δ = 147.6, 143.0, 142.8, 141.8, 140.3, 129.7 (2C), 126.1, 123.3 (2C), 119.0, 115.6, 113.1, 36.5.
 IR (neat): 2920, 2323, 1511, 1343, 1108, 768 cm⁻¹.
 HRMS (ES⁺): *m/z* [M+H]⁺ calcd for C₁₄H₁₁N₄O₄: 299.0775; found: 299.0786.

Methyl 4-(1-methyl-4-nitro-1H-indazol-3-yl)benzoate (10j)

White solid; yield: 55% (60 mg); mp 234.9–236.7 °C.
¹H NMR (600 MHz, CDCl₃): δ = 8.06 (d, *J* = 8.6 Hz, 2H), 7.84 (dd, *J* = 7.5, 0.8 Hz, 1H), 7.70 (dd, *J* = 8.5, 0.8 Hz, 1H), 7.48 (dd, *J* = 8.5, 7.5 Hz, 1H), 7.46 – 7.42 (m, 2H), 4.16 (s, 3H), 3.88 (s, 3H).
¹³C NMR (151 MHz, CDCl₃): δ = 166.9, 143.1, 142.9, 138.0, 129.3 (2C), 128.7 (2C), 125.7, 118.3, 115.0, 113.3, 113.0, 109.0, 52.1, 36.2.
 IR (neat): 2921, 2850, 1716, 963 cm⁻¹.
 HRMS (ES⁺): *m/z* [M+H]⁺ calcd for C₁₆H₁₄N₃O₄: 312.0984; found: 312.0981.

1-Methyl-4-nitro-3-phenyl-7-(*p*-tolyl)-1H-indazole (11a)

Yellow solid; yield way 1: 52% (31 mg); yield way 2: 41% (24 mg); mp 78–80 °C.
¹H NMR (300 MHz, CDCl₃): δ = 7.87 (d, *J* = 7.5 Hz, 1H), 7.49–7.46 (m, 5H), 7.40–7.36 (m, 4H), 7.32 (d, *J* = 7.7 Hz, 1H), 3.74 (s, 3H), 2.51 (s, 3H).
 IR (neat): 2919, 2850, 1519, 1337, 1037, 1020, 815, 699 cm⁻¹.
 The ¹H and ¹³C NMR spectra were in accordance with those described in the literature.²⁵

Methyl 4-(1-methyl-4-nitro-7-phenyl-1H-indazol-3-yl)benzoate (11b)

Yellow solid; yield way 1: 72% (55 mg); yield way 2: 65% (49 mg); mp 212–214 °C.
¹H NMR (600 MHz, CDCl₃): δ = 8.07 (d, *J* = 8.3 Hz, 2H), 7.97 (d, *J* = 7.7 Hz, 1H), 7.64 – 7.54 (m, 7H), 7.47 (d, *J* = 7.7 Hz, 1H), 3.90 (s, 3H), 3.70 (s, 3H).
¹³C NMR (151 MHz, CDCl₃): δ = 167.0, 140.7, 138.1, 136.8, 132.5, 130.9, 129.8, 129.7, 129.6 (2C), 129.5 (2C), 129.1, 128.7 (2C), 128.6 (2C), 127.6, 118.3, 114.0, 52.3, 40.0.
 IR (neat): 2922, 2851, 2644, 2613, 733 cm⁻¹.
 HRMS (ASAP⁺): *m/z* [M+H]⁺ calcd for C₂₂H₁₈N₃O₄: 388.1297; found: 388.1303.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

Yes

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