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Very Important Publication

Palladium-Catalyzed Regioselective C–H Arylation of 4-Azaindazole at C3, C5 and C7 Positions

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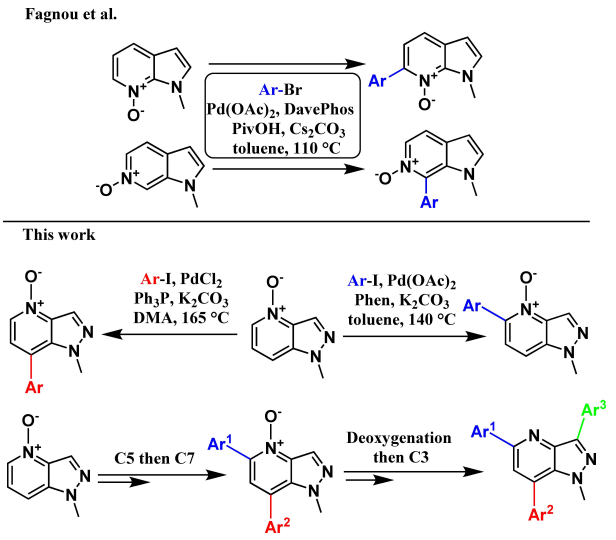
Abstract: Direct and site-selective C5 and C7 palladium-catalyzed C–H arylations of 4-azaindazole *N*-oxide have been achieved. A bidentate ligand and $Pd(OAc)_2$ catalyst in toluene promoted the activation of C5 position, while a phosphine ligand and $PdCl_2$ catalyst in DMA directed the arylation at C7 position. Using this new method, the synthesis of C5, C7-diarylated 4-azaindazole *N*-oxides as well as the C3, C5, C7-triarylated 4-azaindazoles was achieved towards future medicinal compounds development.

Keywords: pyrazolo[4,3-*b*]pyridine *N*-oxide; 4-azindazole; direct arylation; C–H activation; catalyst

Direct arylation of heterocycles is nowadays well-established for selective arylation of one or two different positions on bicyclic heterocycles. Because of the higher reactivity of the five membered ring compared to the six membered ring in 6,5 fused heterocycles, its direct arylation is widely studied.[1–7] In contrast, only few examples have been reported to date on direct arylation of the six membered ring[8–14] and a more rare and challenging issue is its selective arylation on two different positions. Indeed, the regioselective arylation is more easily achieved by functionalization of a first position on the five membered ring and then a second position on the six membered ring.[9,10,12,15–18] A major breakthrough by Fagnou and collaborators, was the development of direct arylation of azine *N*-oxides,[19–25] allowing the C6 direct arylation of 7-azaindole *N*-oxide as well as the C7 direct arylation of 6-azaindole *N*-oxide[26] (Scheme 1). Remarkably, the direct arylation took place only in the α-position of the *N*-oxide. So far, only one example has been reported on direct site-selective arylation of two different positions of the six membered ring of indole on 6,5 fused heterocyclic systems. In this case, a *N*-pivaloyl substituent at position C3 was used to direct the arylation at the C4 and C5 positions, depending on the catalyst system.[15]

Pyrazolo[4,3-*b*]pyridine (4-azaindazole) and pyrrolo[2,3-*b*]pyridine (7-azaindole) belong to the family of privileged scaffolds[27] and are widely studied in many medicinal programs.[28] For a more efficient access to various monosubstituted (on C3, C5 or C7 position) or polysubstituted azaindazole (up to three different substituents over four C–H activatable bonds), pyrazolo[4,3-*b*]pyridine *N*-oxide (4-azaindazole *N*-oxide) appears as an interesting starting substrate. In this paper, we report the direct arylation process leading to the functionalization of two different positions of the 4-azaindazole *N*-oxide. This regioselective C–H activation, either on the C5 or C7 position of the azine ring, depends on the experimental conditions. This methodology was successfully applied to the direct arylation of three different C–H positions of 4-azaindazole (namely, C3, C5 and C7) a real breakthrough in the field of 5,6-fused heterocyclic chemistry (Scheme 1).

In the optimization of the reaction conditions, ratios of all isomers were determined by LC/MS, (see supporting information). This investigation began with iodobenzene as substrate, $Pd(OAc)_2$ as catalyst, 1,10-phenanthroline (phen) as ligand in toluene at 130 °C and two different bases (entries 1–2).[29,30] The most



Scheme 1. Direct arylation of azaindole *N*-oxides and of azaindazole *N*-oxides.

interesting result was obtained with K_2CO_3 despite the reaction was not complete (20% of the starting material is recovered, entry 3). The regiochemistry for C5 arylation was assumed by comparison of ^{1}H NMR chemical shifts of the protons at C5, C6 and C7 positions. In addition, NOESY experiments carried out on compounds **1** and **2a** showed the correlation between the proton at C7 and the protons of the methyl group at N1 (see supporting information). The replacement of phen by PPh_3 as ligand led to a total loss of the reactivity and the starting material was only observed (entry 4). When the reaction mixture was heated at 140 °C (entry 5) the reaction was complete and the desired product **2a** was obtained in 70% isolated yield. In this case, compound **3a** was also isolated in 12% yield (entry 5). Finally, when 1.5 equiv. of K_2CO_3 was used instead of 2 equiv., the isomer **2a** was isolated with an improved yield (75%) and only traces of **3a** were observed (entry 6). The efforts to reduce ligand loading failed (entry 7). Very interestingly, when DMA at higher temperature (165 °C), was used instead of toluene, the reaction was complete and more selective towards the C7-arylated product **3a**, (30% conversion), however 68% of C5, C7-diarylated product **4a** was also identified (entry 8). The replacement of phen by PPh_3 under the same reaction conditions discussed above led almost to the same result (entry 9). While, the use of $PdCl_2$ instead of $Pd(OAc)_2$ led to C7 arylated product in 70% conversion while, diarylated product **4a** and C5-arylated product **2a** were obtained in 11 and 19% conversion, respectively (entry 10). Finally, the best result was obtained when phen was replaced by Ph_3P under the same reaction conditions. In this case, the desired product **3a** was obtained in 65% isolated yield and only traces of compounds **2a** and **4a** were observed (entry 11). We noticed that, the use of toluene instead of DMA at 140 °C led to a total loss of reactivity since 76% of the starting material **1** was observed by LC/MS (entry 12). We observed that the use of either bromobenzene or chlorobenzene instead of iodobenzene under the optimized reaction conditions, led to low yields in the case of bromobenzene and no product was detected in the case of chlorobenzene for which only starting material was recovered. We noticed also that either Fagnou reaction conditions[26] or Hartwig reaction conditions[32] were also tested on starting material **1** but no reaction was observed and only starting material **1** was recovered.

Thanks to the optimized reaction conditions for regioselective arylation at either C5 or C7 position, we explored the scope and limitations of this method. We first prepared a series of C5-arylated-4-azaindazole *N*-oxides using various aryl iodides as coupling partners under the following reaction conditions [$Pd(OAc)_2$ (5 mol%), phen (10 mol%), K_2CO_3 (1.5 equiv.), toluene, 140 °C, 24 h] (Table 2).

In general, all the reactions proceeded smoothly to give the expected C5 arylated products **2a–m** in moderate to good yields (40 to 75%). Both electron with drawing groups and electron donating groups on the aryl iodide moiety afforded good substrates. The reaction was compatible with various valuable functional groups such as Cl, CF_3, ethyl ester, CN, methoxy, and NO_2 (Table 2). It is noticed that the use of 2-iodotoluene as arylating agent led to desired product but the reaction mixture was very difficult to purify and the corresponding C5-arylated product was no isolated as pure product. Unfortunately, heteroaryl iodides such as 4-iodopyridine and 2-iodopyrazine were not effective to achieve their corresponding C5-arylated products (Table 2).

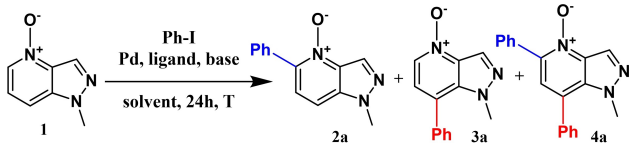
The scope and limitations of C7 direct arylation of 4-azaindazole *N*-oxide was then explored under the optimized reaction conditions [$PdCl_2$ (5 mol%), PPh_3 (10 mol%), K_2CO_3 (2 equiv.), DMA, 165 °C, 24 h] (Table 3).

Again, various aryl iodides were used as coupling partners which led to desired C7-arylated 4-azaindazole *N*-oxides **3a–l** in isolated yields ranging between 40 and 68%. Good compatibility with various valuable functional groups was also observed. In addition, no real effect of the electronic nature of the substituents on the aryl iodides (coupling partners) was observed. Unfortunately, when using ethyl 2-iodobenzoate or ethyl 3-iodobenzoate as arylating agents, only traces of the desired C7-arylated products were observed.

Again, when using 4-iodopyridine and 2-iodopyrazine as arylating agents, the reaction did not give their corresponding C7-arylated products (Table 3).

In order to understand the observed regioselectivity, we looked at pKa values on 4-azaindazole and 4-

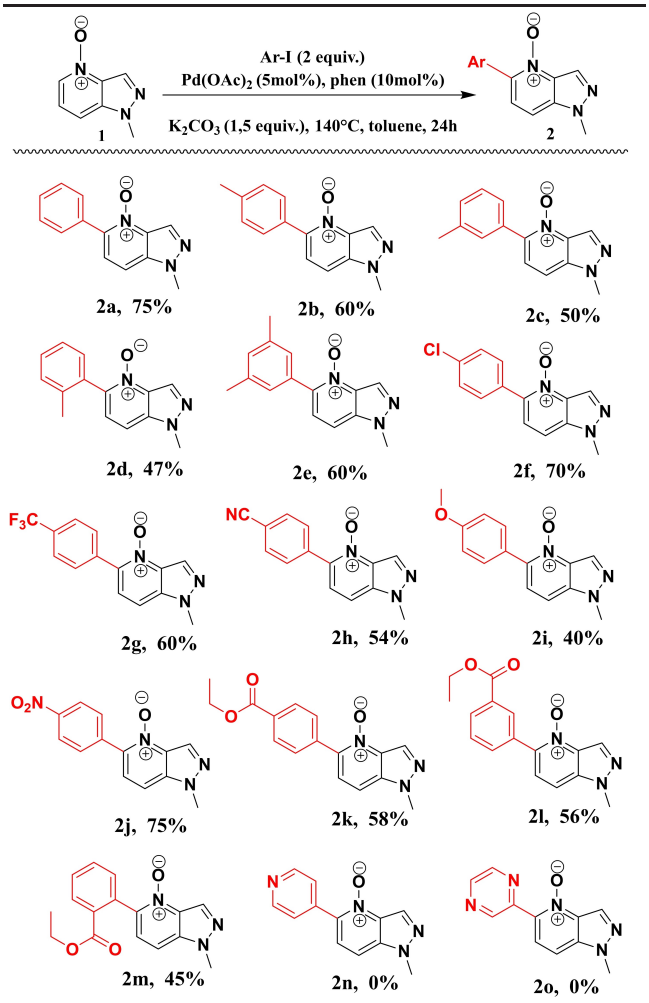
Table 1. Optimisation of C5 and C7 direct arylations on 4-azaindazole.



entry	conditions[a]	T °C	**1**:**2a**:**3a**:**4a**[b]	yield[c] **2a**:**3a**
1	$Pd(OAc)_2$, phen, Cs_2CO_3, toluene	130	6:18:50:26	–
2	$Pd(OAc)_2$, phen, Ag_2CO_3, toluene	130	88:7:5:0	–
3	$Pd(OAc)_2$, phen, K_2CO_3, toluene	130	20:70:10:0	–
4	$Pd(OAc)_2$, PPh_3, K_2CO_3, toluene	130	100: 0: 0:0	–
5	$Pd(OAc)_2$, phen, K_2CO_3, toluene	140	0:74:26:0	70:12
6 [d]	$Pd(OAc)_2$, phen, K_2CO_3, toluene	140	0:98:2:0	75:0
7 [e]	$Pd(OAc)_2$, phen, K_2CO_3, toluene	140	15:85:0:0	–
8	$Pd(OAc)_2$, phen, K_2CO_3, DMA	165	0:2:30:68	–
9	$Pd(OAc)_2$, PPh_3, K_2CO_3, DMA	165	0:8:30:62	–
10	$PdCl_2$, phen, K_2CO_3, DMA	165	0:19:70:11	–
11	$PdCl_2$, PPh_3, K_2CO_3, DMA	165	0:7:88:5	0:65
12	$PdCl_2$, PPh_3,K_2CO_3, toluene	140	76:2:5:17	–

Reaction conditions: [a] 1 equiv. of **1**, 2 equiv. of aryl iodide, Pd (5 mol%), ligand (10 mol%), base (2 equiv.), solvent, 24 h.
[b] Conversions calculated by LC/MS.
[c] isolated yields.
[d] 1.5 equiv. of base was used.
[e] 1.5 equiv. of base and 5 mol% of ligand were used.

Table 2. Summarized results of C5-arylated 4-azaindazole *N*-oxides.



Reaction conditions. 1 equiv. of **1**, 2 equiv. of aryl iodide, Pd $(OAc)_2$ (5 mol%), phen (10 mol%), K_2CO_3 (1.5 equiv.), toluene, 140 °C, 24 h.

azaindazole-*N*-oxide which were predicted by Jaguar pKa software.[32] Regarding the 4-azaindazole, the lowest pKa values correspond to C3 and C7 positions, in contrast to the 4-azaindazole *N*-oxide **1** where the lowest pKa values correspond to C5 and C7 positions (Figure 1).

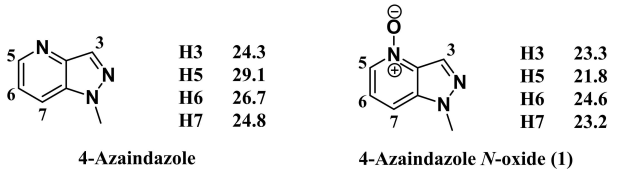
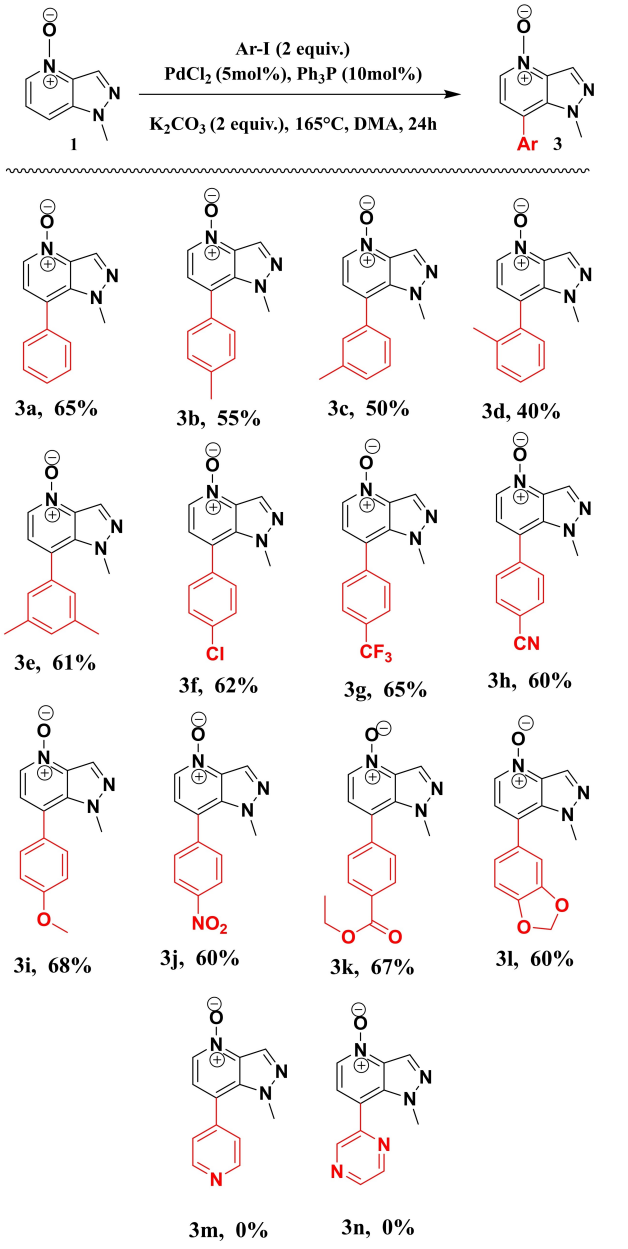


Figure 1. pKa values calculated for 4-azaindazole and 4-azaindazole *N*-oxide **1**.

For the two compounds, we observe significant electron density of the HOMO at positions 5 and 7 while the position 6 appears unfavorable for substitution. For the 4-azaindazole compound, the highest electron density is observed at position 3 whereas the electron density is lower at position 3 for the 4-azaindazole *N*-oxide. This observation could explain the lack of arylation at position 3.

For the 4-azaindazole compound, we observe similar values of electrophile activity (Ea) at positions 5 and 6. Ea is a theoretical parameter recently proposed to characterize reactivity and positional selectivity in C–H functionalisation[16]. For more information, see Koleva et al.[33] and Galabov et al..[34] The lowest value of Ea is obtained at position 7 (144.9 kcal/mol), the highest at position 3 (161.3 kcal/mol). For the 4-azaindazole *N*-oxide compound, we observe similar

Table 3. Summarized results of C7-arylated 4-azaindazole *N*-oxides.



Reaction conditions. 1 equiv. of **1**, 2 equiv. of aryl iodide, $PdCl_2$ (5 mol%), PPh_3 (10 mol%), K_2CO_3 (2 equiv.), DMA, 165 °C, 24 h.

values of Ea at positions 5 and 7 and the lowest value of Ea (154.8 kcal/mol) at position 3. The Ea and HOMO calculations clearly validate the absence of reactivity at C3 position (through a S_EAr type mechanism) for the 4-azaindazole *N*-oxide compound and are in agreement with the experimental results (Figure 2).

Whereas the mechanism of arene C–H activation by Pd^{II} has been the subject of much research,[35] the

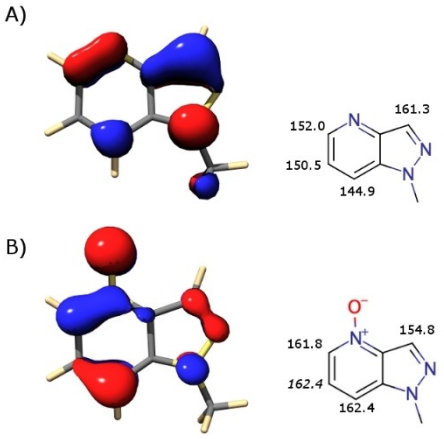


Figure 2. Ea and HOMO calculations for 4-azaindazole (A) and compound **1** (B).

pathway for formation of $Pd^{II}ArAr'$ is steel unclear. The combination of palladium acetate with phen was critical.[36,37] In our case, for the arylation at C5 position, the calculations are more suggestive of an electrophilic aromatic substitution rather than a concerted C–H activation. However, the majority of recent experimental and computational studies indicate that SEAr mechanism is less likely to occur as part of this type of transformation and rather supports C–H bond cleavage by CMD mechanisms.[38]

The acidic nature of H5 (vide supra) and the use of carbonate which is known for its crucial role in CMD process during direct arylation of the C–H bond, imply that this reaction is likely to occur through CMD process, as proposed by many literature reports.[39] However, for the CMD process to be operational, an open coordination site is needed which can be approached by the C–H bond of the arene with the carbonate coordinated to the Pd center to direct the C–H cleavage. In our case, this coordination is not favored due to the presence of a relatively strong coordinating L-type ligand such as phen. Because of phen's lack of flexibility to rotate, it would rigidly bind to Pd as a bidentate ligand[40] (Figure 3).

Alternatively, in recent years, another mechanistic pathway consisting of a cooperative bimetallic mechanism involving parallel C–H activation at two separate Pd^{II} centers followed by transmetalation between the two Pd^{II}–aryl species, was proposed by Hartwig for the

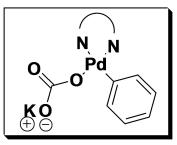


Figure 3. Coordination of phen and carbonate to Pd center.

C–H arylation of pyridine *N*-oxide and was supported by the studies of the direct arylation of simple arenes.[27]

Thus, for a plausible mechanism of C5 arylation of 4-azaindazole *N*-oxide, first catalytic cycle begins with the oxidative addition of aryl iodide to Pd(0). The generated B complex undergoes transmetallation in the presence of the 2nd cyclometallated complex C to give the Ar–Pd–Ar' intermediate E. The latter undergoes a reductive elimination to led to **2 a** and to Pd complex (0). In the other catalytic cycle, the monomeric cyclometallic complex D is involved in the C–H activation step at position 5 of the 4-azaindazole *N*-oxide (Scheme 2).

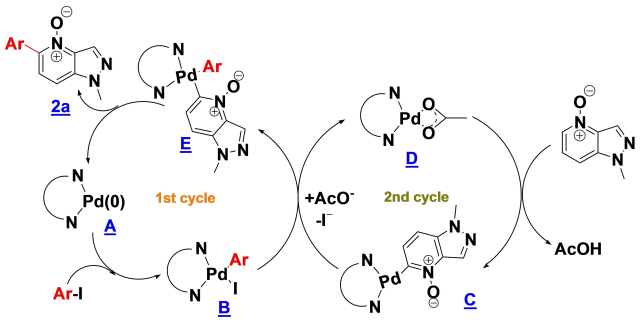
The selectivity for the C5 position with the combination of $Pd(OAC)_2$ and phen is reversed for the C7 position with the use of $PdCl_2$ and PPh_3. This time, following a similar approach, we conjectured a functioning biometallic cooperative pathway[32,41] to explain the functionalization at the C7 position.

The complex B′ undergoes dissociation, generating a complex G′ with a vacant coordination site. The aryl group of the second Pd species H′ binds to the open site of the transition state G′, and sequentially, the anion I^- induces the transfer of the aryl group, completing the transmetalation step to give the Ar–Pd–Ar' intermediate E′. Then a reductive elimination furnished the desired C7 arylated compound **3 a** and generated complex A'. The complete loss of the reactivity with the use of toluene instead of DMA (Table 1, entry 12) demonstrates a significant influence of the solvent on the outcome of the reaction. This result could be attributed to the involvement of an ionic intermediate transition state, stabilized by the polar solvent (DMA)[42] (Scheme 3).

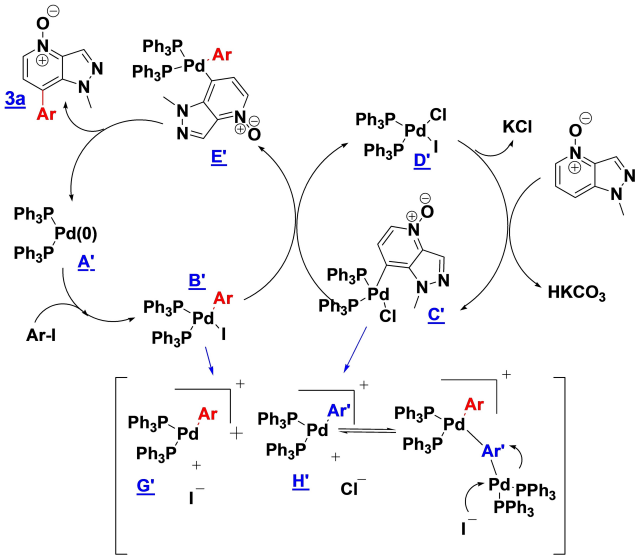
In order to demonstrate the valuable access to the azaindazole privileged scaffold in drug design with the present methodology, we decided to generate the deoxygenated 5-arylated-4-azaindazoles **5 a–c** and 7-aryled-4-azaindazoles **6 a–c** from their corresponding *N*-oxide precursors. In the case of C5 arylated 4-azaindazole *N*-oxides **2 a**, **2 b**, **2 f**, their treatment with zinc dust and NH_4Cl in THF for 5 h led to desired products **5 a–c** in very good yields ranging between 80 and 85%. When **3 a**, **3 b** and **3 f** were treated under the same reaction conditions, acceptable isolated yields ranging between 68 and 75% were obtained for desired C7 arylated analogues **6 a–c** (Scheme 4).

At this stage, we decided to validate another strength of this methodology by preparing C5, C7-unsymetrical diaryled 4-azaindazole *N*-oxides. The treatment of the monoarylated azaindazole **2 a** with 3 equivalents of either 4-iodoluene or 4-iodotrifluorobenzene in the presence of $PdCl_2$ as catalyst, PPh_3 as ligand, and K_2CO_3 in DMA for 24 h at 165 °C led to C5-, C7-diarylated compounds **7 a** and **7 b** in 60 and 63% yield, respectively (Scheme 5). It is noticed that the arylation was also investigated starting from the C7 arylated product **3 b** which was with the C5 arylation conditions using iodobenzene, $Pd(OAc)_2$, phen, K_2CO_3, in toluene at 140 °C for 24 h. In this case, the C5 arylation reaction was not total and the C5, C7-diarylated product **7 a** was isolated in low yield of 30% while 40% the starting material was recovered (Scheme 5).

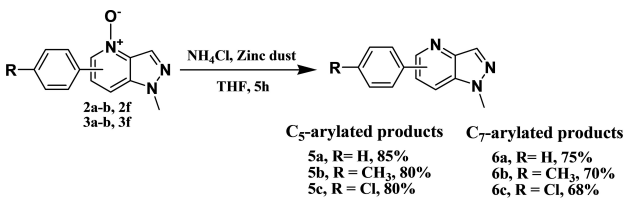
More interestingly, this method in combination with others from the literature[29,30] could enable the synthesis of C3, C5, C7 triarylated azaindazoles by



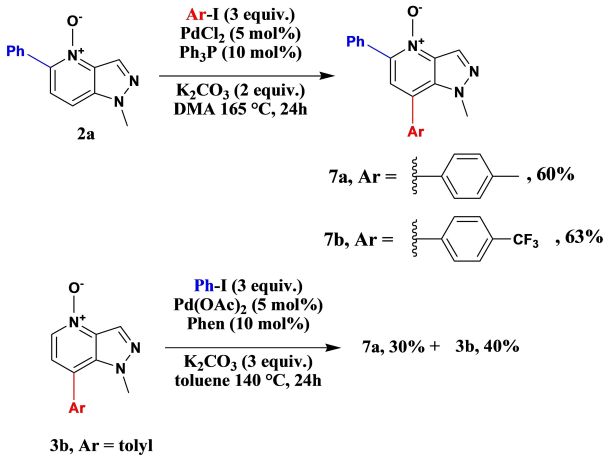
Scheme 2. Tentative mechanism for C5 direct arylation.



Scheme 3. Tentative mechanism for C7 direct arylation.



Scheme 4. Deoxygenation of C5 and C7 arylated 4-azaindazole *N*-oxides.



Scheme 5. Synthesis of C5, C7 diarylatedazaindazole-*N*-oxides.

successive regioselective C–H activation. In preliminary screens, the C3 arylation was investigated from the C5, C7-disubstituted azaindazole *N*-oxide **7a** with 1-iodo-4-methoxybenzene using selective reported experimental conditions [$Pd(PPh_3)_4$, phen, Ag_2CO_3, H_2O, 24 h, 100 °C].[29,30] As obtained by the theoretical calculations (vide supra), the deactivation at C3 position by the *N*-oxide inhibits the reaction and only the starting material **7a** was recovered. This behavior was also observed by Fagnou et al. for the direct arylation of the azole ring of azaindole *N*-oxide.[26] Consequently, we decided to first deoxygenate compounds **7a** and **7b** with zinc dust and NH_4Cl in THF for 3 h. The C5, C7-diarylated 4-azaindazoles **8a** and **8b** were isolated in 80% yields. Then, the C3 arylation of either **8a** or **8b** under the reaction conditions previously mentioned [Ar^2–I, $Pd(PPh_3)_4$, phen, Ag_2CO_3, H_2O, 24 h, 100 °C][29,30] successfully led to C3, C5, C7 triarylated 4-azaindazoles **9a** and **9b** in 75 and 85% yield, respectively (Scheme 6).

Finally, we decided to extend the scope of the reaction conditions developed for either C5 or C7 arylation to the arylation of 7-azaindole *N*-oxide. Thus, starting martial **10** was prepared following Fagnou's report[26] (see supporting information) and treated by 4-iodotoluene in the presence of $Pd(OAc)_2$, phen, K_2CO_3, in toluene at 140 °C for 24 h which led to the desired product **11** in 57% yield. When using 4-bromotoluene, the arylated compound was isolated in low yield (20%). In both cases, the starting material **10** was recovered. We noticed that the treatment of **10** with 4-bromotoluene under the reaction conditions developed for C7 arylation (see vide supra) did not lead to the desired product and only starting material was recovered (Scheme 7).

In summary, we have developed reaction conditions for regioselective C5 and C7 direct arylations of 4-azaindazole *N*-oxides. We have achieved an original access to C5, C7 diarylated 4-azaindazole *N*-oxides. Importantly, for the first time the C–H activation of three of the four C–H bonds available on the 4-azaindazole scaffold can be now controlled and offer unsymmetrical C3, C5, C7 triarylated 4-azaindazoles. This result in the area of direct arylation of 5,6-fused heterocyclic systems, encouraged us to continue the development of site-selective C–H arylation of heteroarenes.

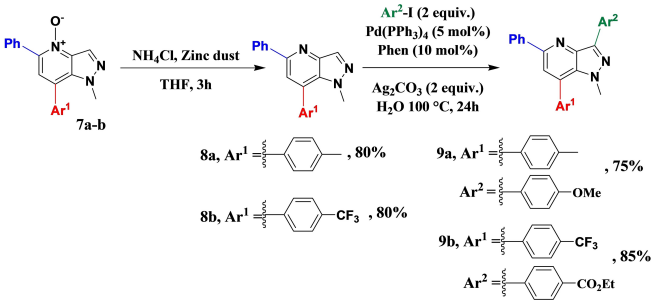
Experimental Section

General Procedure for the Synthesis of 1*H*-pyrazolo[4,3-*b*]pyridine

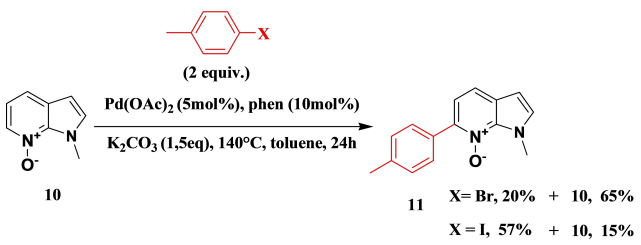
Hydrazine hydrate (10 mL) was added to a mixture of 3- fluoro-2-formylpyridine (3.00 g, 24 mmol) and *p*-TsOH (2.06 g, 12 mmol). The reaction mixture was stirred for 3 h at 130 °C. Upon cooling with cold water, the mixture was extracted three times with ethyl acetate. The combined organic extracts were dried over anhydrous $MgSO_4$. After filtration, the solvent was removed in vacuum. The residue was purified by flash chromatography to give 1*H*-pyrazolo[4,3-*b*]pyridine (2 g) in 70% yield as a white solid.

General Procedure for *N*-Methylation of 1*H*-pyrazolo[4,3-*b*]pyridine

Potassium hydroxide (3 eq) was added to a solution of 1*H*-pyrazolo[4,3-*b*]pyridine (1 g, 8.40 mmol) in acetone (30 mL), and the mixture was maintained for 60 min at 0 °C. Then, iodomethane (1.5 eq) was added. The reaction mixture was warmed to room temperature and maintained for 2 h. The



Scheme 6. Synthesis of C3, C5, C7 triarylatedazaindazoles.



Scheme 7. C6 direct arylation of 7-azaindole *N*-oxide.

reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic extracts were dried over anhydrous $MgSO_4$. After filtration, the solvent was removed in vacuum. The desired products were purified by column chromatography (petroleum ether/ethyl acetate, 9/1) which led to the regioisomeric N1 and N2 methylated products with 60 and 30%yield, respectively.

General Procedures for *N*-oxidation

To a solution of 1-methyl-1*H*-pyrazolo[4,3-*b*]pyridine (2 g, 15 mmol) in DCM (100 mL) at 0 °C was added mCPBA (1,1 eq). After 1 h, the ice-bath was removed and the reaction mixture was stirred overnight at rt. The reaction mixture was diluted with DCM, washed with $NaHCO_3$ (sat), and dried. Concentration followed by purification with flash chromatography afforded 1-methyl-1*H*-pyrazolo[4,3-*b*]pyridine-4-oxide in 90% yield as a yellow solid.

General Procedure for the Preparation of Compounds 5 a–c and 6 a–c

The 5-arylated-4-azaindazole *N*-oxide (0.2 mmol) is dissolved in THF (3 mL). To this mixture is then added saturated NH_4Cl solution (3 mL) and zinc dust (4,5 eq) and mixture is stirred for 3–5 hours. The deposit is then collected by filtration on celite and washed with CH_2Cl_2. The organic layer is then separated and the aqueous layer is extracted with CH_2Cl_2. The organics are combined, dried with $MgSO_4$, filtered and concentrated under reduced pressure. The products are then purified *via* silica gel column chromatography (petroleum ether/ethyl acetate, 4/1) to give the corresponding deoxygenated products.

General Procedure for the Preparation of Compounds 2 a–m, and 11

In a dry sealed tube placed under an argon atmosphere, 100 mg de 1-methyl-*1H*-pyrazolo[4,3-*b*]pyridine-4-oxide is solubilized in 2 ml of toluene. After the introduction of K_2CO_3 (1,5 eq), 1,10-phenanthroline (10 mol%) and aryl iodide (3 eq), the tube and its contents were then purged under argan for 10 minutes and, $Pd(OAc)_2$ (5 mol%) is introduced. The reaction mixture was then heated at 140 °C for 24 hours. After returning to ambient temperature, the contents of the tube were filtered through a short pad of celite. The organic layer is then separated and the aqueous layer is extracted with CH_2Cl_2. The organics are combined, dried with $MgSO_4$, filtered and concentrated under reduced pressure then the crude residue is purified by chromatography on a column of silica gel (toluene/acetone, 6/4).

General Procedure for the Preparation of Compounds 3 a–l

In a dry sealed tube placed under an argon atmosphere, 100 mg de 1-methyl-*1H*-pyrazolo[4,3-*b*]pyridine-4-oxide is solubilized in 2 ml of DMA. After the introduction of K_2CO_3 (2 eq), PPh_3 (10 mol%) and aryl iodide (3 eq), the tube and its contents were then purged under argan for 10 minutes and, $PdCl_2$ (5 mol%) is introduced. The reaction mixture was then heated at 165 °C for 24 hours. After returning to ambient temperature, the contents of the tube were filtered through a short pad of celite. The organic layer is then separated and the aqueous layer is extracted with CH_2Cl_2. The organics are combined, dried with $MgSO_4$, filtered and concentrated under reduced pressure then the crude residue is purified by chromatography on a column of silica gel (toluene/acetone, 5/5).

General Procedure for the Preparation of Compounds 7 a–b

In a dried sealed tube placed under an argon atmosphere, 1-methyl-1*H*-pyrazolo[4,3-*b*]pyridine-4-oxide (solubilized in 2 ml of toluene), K_2CO_3 (1.5 eq), 1,10-phenanthroline (10 mol%) and iodobenzene (2 eq) were added. The mixture was then degassed with argan for 10 min and $Pd(OAc)_2$ (5 mol%) is introduced. The reaction mixture was allowed to stir at 140 °C for 24 hours. After returning to ambient temperature, the reaction is filtered on celite (washing with CH_2Cl_2), the filtrate is concentrated and the residue was purified *via* silica gel column chromatography using (toluene/acetone, 6/4) to give 1-methyl-5-phenyl-1*H*-pyrazolo[4,3-*b*]pyridine-4-oxide. This compound (0.26 mmol) is then solubilized in 2 ml of DMA in a dry sealed tube placed under an argon atmosphere. After the introduction of K_2CO_3 (2 eq), PPh_3 (10 mol%) and Ar^2–I (3 eq), the reaction mixture is degassed with argan for 10 min and $PdCl_2$ (5 mol%) is introduced. The reaction mixture was allowed to stir at 165 °C for 24 hours. After returning to ambient temperature, the reaction is filtered on celite (washing with CH_2Cl_2), the filtrate is concentrated and the residue was purified *via* silica gel column chromatography using (petroleum ether/ethyl acetate, 4/6) to give 1-methyl-5-phenyl-7-Ar^2-1*H*-pyrazolo[4,3-b] pyridine-4-oxide.

General Procedure for the Preparation of Compounds 9 a–b

The 1-methyl-5-phenyl-7-Ar^2-1*H*-pyrazolo[4,3-*b*]pyridine, synthesized by general procedure of double direct arylation is dissolved in THF (2 mL). To this mixture is then added saturated NH_4Cl solution (2 mL) and zinc dust (4,5 eq). This mixture is then stirred for 2 hours and the deposit is then collected by filtration on celite and washed with CH_2Cl_2. The organic layer is then separated and the aqueous layer is extracted with CH_2Cl_2. The organics are combined, dried with $MgSO_4$, filtered and concentrated under reduced pressure. The products are then purified *via* silica gel column chromatography (petroleum ether/ethyl acetate, 4/1) to give the corresponding deoxygenated products. These compounds are placed in sealed tubes and Ar^3–I (2 eq), $Pd(PPh_3)_4$ (5 mol%), Ag_2CO_3 (2 eq) and phenanthroline (10 mol%) were added. Magnetic stirrer bars were added and the mixtures of solids were gently shaken for a few seconds to ensure all solids were well mixed. Distilled water (3 ml) was added and the tubes were covered with a cap. The tubes and their contents were then heated and stirred at 100 °C for 24 h. After this time the reaction mixtures were cooled down to rt. CH_2Cl_2 (5 ml) was added and the contents of the tubes were filtered through a short pad of celite. The filtrates were extracted with CH_2Cl_2 and the organic phase is concentrated under vacuum. The crudes were purified by silica gel

column chromatography (petroleum ether/ethyl acetate, 9/1) to give 1-methyl-3-Ar^3-5-phenyl-7-Ar^2-1*H*-pyrazolo[4.3-*b*] pyridine tri-aryleted products at C5, C7 and C3.

General Procedure for the Preparation of 1H-Pyrrolo[2,3-b]*pyridine-7-oxide and 10*

See reference 26.

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COMMUNICATIONS

Palladium-Catalyzed Regioselective C–H Arylation of 4-Azaindazole at C3, C5 and C7 Positions

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