



**HAL**  
open science

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

Soukaina Faarasse, Saïd El Kazzouli, Otmane Bourzikat, Stéphane Bourg, Samia Aci-Seche, Pascal Bonnet, Franck Suzenet, Gérald Guillaumet

► **To cite this version:**

Soukaina Faarasse, Saïd El Kazzouli, Otmane Bourzikat, Stéphane Bourg, Samia Aci-Seche, et al.. Palladium-Catalyzed Regioselective C–H Arylation of 4-Azaindazole at C3, C5 and C7 Positions. *Advanced Synthesis and Catalysis*, 2021, 363 (16), pp.3937-3945. 10.1002/adsc.202001421 . hal-03416452

**HAL Id: hal-03416452**

**<https://hal.science/hal-03416452v1>**

Submitted on 5 Nov 2021

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

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

Soukaina Faarasse <sup>a, b</sup>, Saïd El Kazzouli <sup>b,\*</sup>, Otmane Bourzikat <sup>a</sup>, Stéphane Bourg <sup>a</sup>, Samia Aci-Sèche <sup>a</sup>, Pascal Bonnet <sup>a</sup>, Franck Suzenet <sup>a,\*</sup> and Gérald Guillaumet <sup>a, b,\*</sup>

<sup>a</sup> Institute of Organic and Analytical Chemistry, University of Orleans, UMR CNRS 7311, BP 6759, 45067 Orleans Cedex 2, France. [franck.suzenet@univ-orleans.fr](mailto:franck.suzenet@univ-orleans.fr); [gerald.guillaumet@univ-orleans.fr](mailto:gerald.guillaumet@univ-orleans.fr)

<sup>b</sup> Euromed Research Centre, Engineering School of Biomedical and Biotechnology, Euromed University of Fes (UEMF), Route de Meknès, 30000 Fès, Morocco. [s.elkazzouli@ueuromed.org](mailto:s.elkazzouli@ueuromed.org)

Received: ((will be filled in by the editorial staff))



Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/adsc.201#####>. ((Please delete if not appropriate))

**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)<sub>2</sub> catalyst in toluene promoted the activation of C5 position, while a phosphine ligand and PdCl<sub>2</sub> 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 compound development.

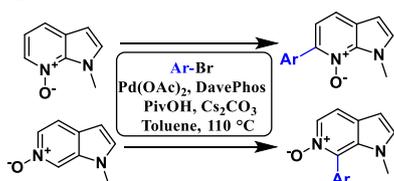
**Keywords:** pyrazolo[4,3-*b*]pyridine *N*-oxide • 4-azaindazole • direct arylation • C-H activation • catalyst

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<sup>1-7</sup>. In contrast, only few examples have been reported to date on direct arylation of the six membered ring<sup>8-14</sup> 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<sup>9,10,12,15-18</sup>. A major breakthrough by Fagnou and collaborators, was the development of direct arylation of azine *N*-oxides<sup>19-22</sup>, allowing the C6 direct arylation of 7-azaindole *N*-oxide as well as the

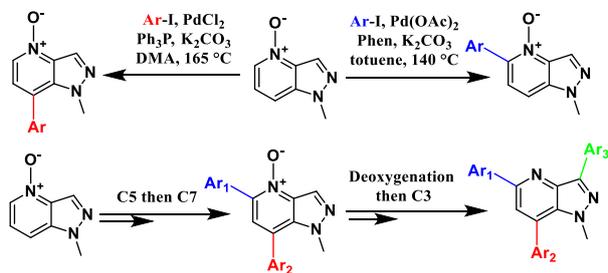
C7 direct arylation of 6-azaindole *N*-oxide<sup>23</sup> (Scheme 1). Remarkably, the direct arylation took place only in the  $\alpha$ -position of the *N*-oxide. So far, only one example has been reported on direct site-selective arylation of two different positions of the six membered ring of indole 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<sup>15</sup>.

Pyrazolo[4,3-*b*]pyridine (azaindazole) and pyrrolo[2,3-*b*]pyridine (azaindole) belong to the family of privileged scaffolds<sup>24</sup> and are widely studied in many medicinal programs<sup>25</sup>. 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 positions 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).

Fagnou et al.



This work

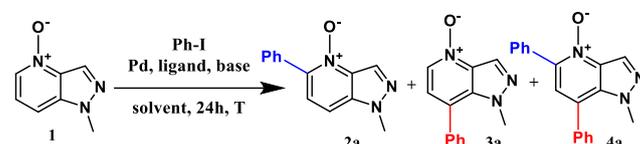


**Scheme 1.** Direct arylation of azaindazole *N*-oxides and of azaindazole *N*-oxides.

The optimization of the reaction conditions (reported in Table 1) began with the iodobenzene as substrate, Pd(OAc)<sub>2</sub> as catalyst, 1,10-phenanthroline (Phen) as ligand in toluene at 130°C and different bases (entries 1-4)<sup>28,29</sup>. The most interesting result was obtained with K<sub>2</sub>CO<sub>3</sub> despite the reaction was not complete (20% of the starting material is recovered, entry 4). Within this entry, 70% of the C-5 arylated product **2a** and 10% of C7-arylated isomer **3a** were formed as determined by LC/MS (see supporting information). The regiochemistry for C5 arylation was assumed by comparison of <sup>1</sup>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<sub>3</sub> as ligand led to a total loss of the reactivity and the starting material was only observed (entry 5). When the reaction mixture was heated at 140°C (entry 6) 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 6). Finally, when 1.5 equiv. of K<sub>2</sub>CO<sub>3</sub> was used instead of 2 equiv., the isomer **2a** was isolated with an improved yield (75%) and only traces of **3a** were observed (entry 7). All the other efforts to reduce ligand loading (entry 8) or to change the solvent (entries 9 and 10) failed. Very interestingly, when DMA was used instead of toluene, the reaction led to the C7 arylated product **3a** as the major isomer in 29% conversion while the C5 arylated product **2a** was formed in only 5%, the rest being the starting material at 66% (entry 10). At higher temperature (165°C), the reaction was complete and more selective towards the C7-arylated product **3a**, (30% conversion), however 68% of C5, C7-diarylated

product **4a** (entry 11) was also identified. The replacement of Phen by PPh<sub>3</sub> under the same reaction conditions discussed above led almost to the same result (entry 12). The replacement of Pd(OAc)<sub>2</sub> by PdCl<sub>2</sub> 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 13). Finally, the best result was obtained when Phen was replaced by Ph<sub>3</sub>P 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 14). 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 15).

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



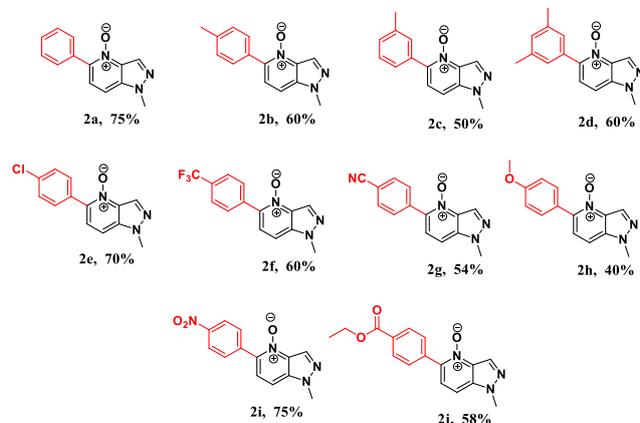
entry	conditions <sup>a</sup>	T °C	1:2a:3a:4a <sup>b</sup>	yield <sup>c</sup> 2a:3a
1	Pd(OAc) <sub>2</sub> , phen, Cs <sub>2</sub> CO <sub>3</sub> , toluene	130	6:18:50:26	-
2	Pd(OAc) <sub>2</sub> , phen, Ag <sub>2</sub> CO <sub>3</sub> , toluene	130	88:7:5:0	-
3	Pd(OAc) <sub>2</sub> , phen, K <sub>3</sub> PO <sub>4</sub> , toluene	130	33:48:19:0	-
4	Pd(OAc) <sub>2</sub> , phen, K <sub>2</sub> CO <sub>3</sub> , toluene	130	20: 70: 10:0	-
5	Pd(OAc) <sub>2</sub> , PPh <sub>3</sub> , K <sub>2</sub> CO <sub>3</sub> , toluene	130	100: 0: 0:0	-
6	Pd(OAc) <sub>2</sub> , phen, K <sub>2</sub> CO <sub>3</sub> , toluene	140	0:74:26:0	70:12
7	Pd(OAc) <sub>2</sub> , phen, K <sub>2</sub> CO <sub>3</sub> <sup>d</sup> , toluene	140	0:98:2:0	75:0
8	Pd(OAc) <sub>2</sub> <sup>e</sup> , phen, K <sub>2</sub> CO <sub>3</sub> , toluene	140	15:85:0:0	-
9	Pd(OAc) <sub>2</sub> , phen, K <sub>2</sub> CO <sub>3</sub> , DMF	130	58:11:31:0	-
10	Pd(OAc) <sub>2</sub> , phen, K <sub>2</sub> CO <sub>3</sub> , DMA	130	66: 5: 29:0	-
11	Pd(OAc) <sub>2</sub> , phen, K <sub>2</sub> CO <sub>3</sub> , DMA	165	0:2:30:68	-
12	Pd(OAc) <sub>2</sub> , PPh <sub>3</sub> , K <sub>2</sub> CO <sub>3</sub> , DMA	165	0:8:30:62	-
13	PdCl <sub>2</sub> , phen, K <sub>2</sub> CO <sub>3</sub> , DMA	165	0:19:70:11	-
14	PdCl <sub>2</sub> , PPh <sub>3</sub> , K <sub>2</sub> CO <sub>3</sub> , DMA	165	0:7:88:5	0:65
15	PdCl <sub>2</sub> , PPh <sub>3</sub> , K <sub>2</sub> CO <sub>3</sub> , toluene	140	76:2:5:17	-

Reaction conditions: [a] 1 equiv. of **1**, 2 equiv. of iodoaryl, Pd(5mol%), ligand (10mol%), base (2 equiv.), solvent, 24h. [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.

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 [ $\text{Pd}(\text{OAc})_2$  (5 mol%), Phen (10 mol%),  $\text{K}_2\text{CO}_3$  (1.5 equiv.), toluene, 140 °C, 24h] (Table 2).

**Table 1.** Summarized results of C5-arylated 4-azaindazole *N*-oxides.

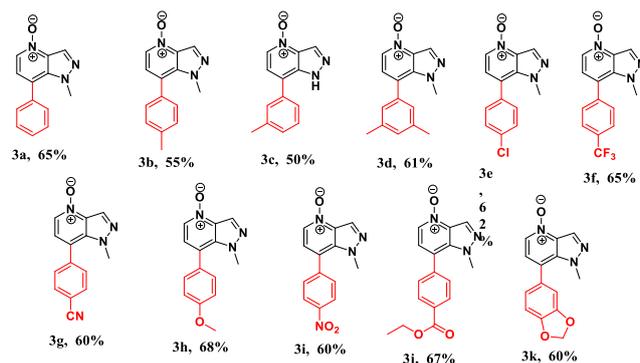


Reaction condition. 1 equiv. of **1**, 2 equiv. of iodoaryl,  $\text{Pd}(\text{OAc})_2$  (5 mol%), Phen (10 mol%),  $\text{K}_2\text{CO}_3$  (1.5 equiv.), toluene, 140 °C, 24h

In general, all the reaction proceeded smoothly to give the expected C5 arylated products **2a-j** in moderate to good yields (40 to 75%). Both electron withdrawing groups and electron donating groups on the iodoaryl moiety afforded good substrates. The reaction was compatible with various valuable functional groups such as Cl,  $\text{CF}_3$ , ethyl ester, CN, methoxy, and  $\text{NO}_2$  (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.

The scope and limitations of C7 direct arylation of 4-azaindazole *N*-oxide was then explored under the optimized reaction conditions [ $\text{PdCl}_2$  (5 mol%),  $\text{PPh}_3$  (10 mol%),  $\text{K}_2\text{CO}_3$  (2 equiv.), DMA, 165°C, 24h] (Table 3).

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



Reaction conditions. 1 equiv. of **1**, 2 equiv. of iodoaryl,  $\text{PdCl}_2$  (5 mol%),  $\text{PPh}_3$  (10 mol%),  $\text{K}_2\text{CO}_3$  (2 equiv.), DMA, 165°C, 24h

Again, various aryl iodides were used as coupling partners which led to desired C7-arylated 4-azaindazole *N*-oxides **3a-k** in isolated yield ranging between 50 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 (Table 3). Unfortunately, again when using 2-iodotoluene as arylating agent the reaction mixture was very difficult to purify and thus the C7-arylated product was not isolated as a pure product.

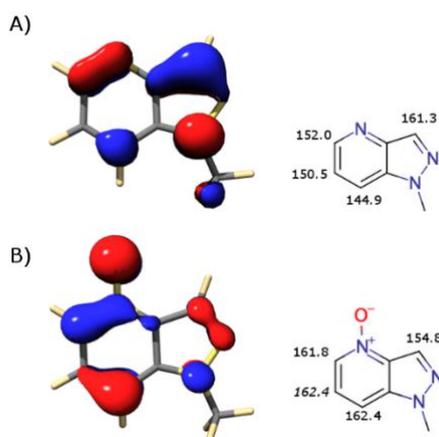
pKa values on 4-azaindazole and 4-azaindazole-*N*-oxide were predicted by Jaguar pKa software. Regarding the 4-azaindazole, the lowest pKa values correspond to C3 and C7 positions, in contrary to the 4-azaindazole-*N*-oxide **1** where the lowest pKa values correspond to C5 and C7 positions (Figure 1).

 4-Azaindazole	H3	24.3	 4-Azaindazole <i>N</i> -oxide ( <b>1</b> )	H3	23.3
	H5	29.1		H5	21.8
	H6	26.7		H6	24.6
	H7	24.8		H7	23.2

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

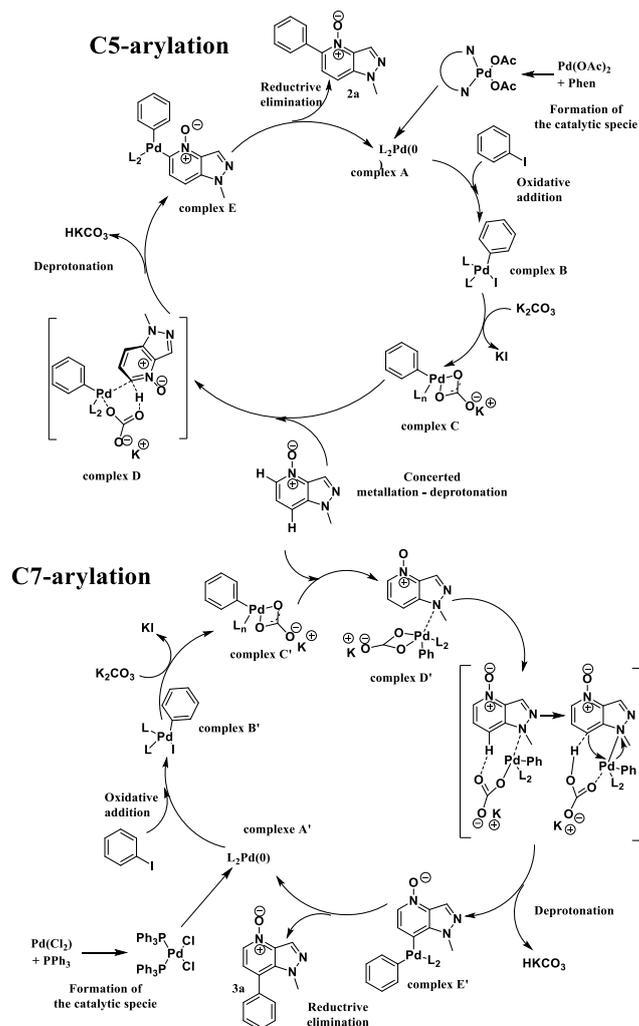
For the two compounds, we observe significant electron density of the HOMO at positions 5 and 7 while the position 6 appears unfavorable for substitution. For the 4-azaindazole compound, the highest electron density is observed at position 3 whereas the electron density is lower at position 3 for the 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 ( $E_a$ ) at positions 5 and 6.  $E_a$  is a theoretical parameter recently proposed to characterize reactivity and positional selectivity. For more information, see Koleva et al.<sup>26</sup> and Galabov et al.<sup>27</sup>. The lowest value of  $E_a$  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 values of  $E_a$  at positions 5 and 7 and the lowest value of  $E_a$  (154.8 kcal/mol) at position 3. The  $E_a$  and HOMO calculations clearly validate the absence of reactivity at C3 position (through a SEAr type mechanism) for the 4-azaindazole *N*-oxide compound and are in agreement with the experimental results (Figure 2).



**Figure 2.** Ea and HOMO calculations for compound **1** and 4-azaindazole.

Analysis of the Ea and HOMO calculations allows us to hypothesize for a plausible mechanism of arylation at C5 position on the 4-azaindazole-*N*-oxide **19** (Scheme 2). We believe that the direct arylation at C5 position is governed by a base-assisted deprotonation mechanism. So, first complex A is formed by Pd(OAc)<sub>2</sub> and Phen, then, oxidative addition led to complex B which generated complex C by coordination with K<sub>2</sub>CO<sub>3</sub> (Scheme 2).

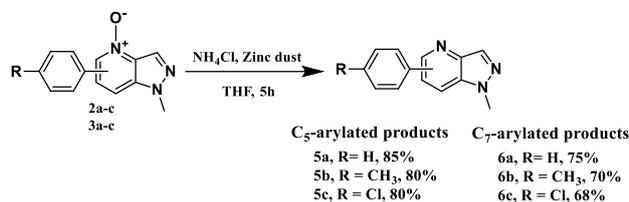


**Scheme 2.** Plausible mechanism for C5 and C7 direct arylations

The reaction between **1** and complex C led to complex D. The deprotonation (complex E) followed by reductive elimination led to **2a**. The switch in the C-H activation from position C5 to C7 is probably due to the coordination of the palladium specie with the single lone pair of nitrogen (*N*-methyl) promoted by the use of a phosphine ligand and PdCl<sub>2</sub> catalyst in DMA. Thus, after formation of complex A' between PdCl<sub>2</sub> and PPh<sub>3</sub> followed by oxidative addition (complex B'), the coordination by K<sub>2</sub>CO<sub>3</sub> led to complex C'. The reaction between **1** and complex C' gave complex D' which after deprotonation provided complex E'. Reductive elimination furnished the desired C7 arylated compound **3a** and generated complex A' (Scheme 2).

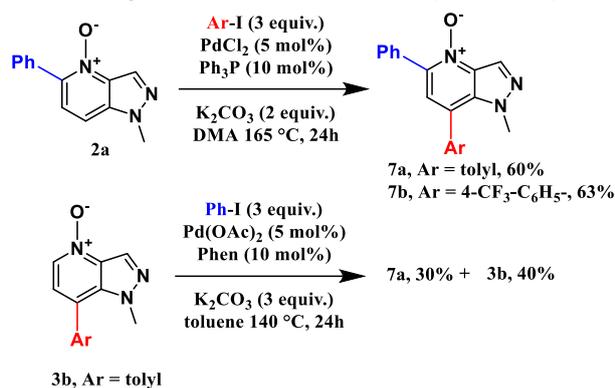
In order to demonstrate the valuable access of the azaindazole privileged scaffold in drug design with the present methodology, we decided to generate the deoxygenated 5-arylated-4-azaindazoles **5a-c** and 7-aryled-4-azaindazoles **6a-c** from their corresponding *N*-oxide precursors. In the case of C5 arylated 4-azaindazole *N*-oxides **2a**, **2b**, **2e**, their treatment with NH<sub>4</sub>Cl in the presence of Zinc dust in THF for 5h led

to desired products **5a-c** in very good yields ranging between 80 and 85 %. When **3a**, **3b** and **3e** were treated under the same following reaction conditions [ $\text{NH}_4\text{Cl}$  in the presence of Zinc dust in THF for 5h], acceptable isolated yields ranging between 68 and 75% were obtained for desired C7 arylated analogues **6a-c** (Scheme 3).



**Scheme 3.** Deoxygenation of C5 and C7 arylated 4-azaindazole *N*-oxides.

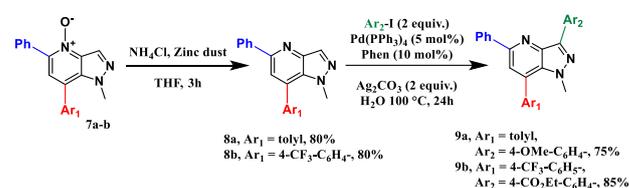
At this stage, we decided to validate another strength of this methodology by preparing C5, C7-unsymmetrical diaryled 4-azaindazole *N*-oxides. The treatment of the monoarylated azaindazole **2a** with 3 equivalents of either 4-iodoluene or 4-iodotrifluorobenzene in the presence of  $\text{PdCl}_2$  as catalyst,  $\text{PPh}_3$  as ligand, and  $\text{K}_2\text{CO}_3$  in DMA for 24h at 165 °C led to C5-, C7-diarylated compounds **7a** and **7b** in 60 and 63% yield, respectively (Scheme 4). It is noticed that the arylation was also investigated starting from the C7 arylated product **3b** which was with the C5 arylation conditions using iodobenzene,  $\text{Pd}(\text{OAc})_2$ , phen,  $\text{K}_2\text{CO}_3$ , in toluene at 140 °C for 24h. In this case, the C5 arylation reaction was not total and the C5, C7-diarylated product **7a** was isolated in low yield of 30% while 40% the starting material was recovered (Scheme 4).



**Scheme 4.** Synthesis of C5, C7 diarylated azaindazole-*N*-oxides.

More interestingly, this method in combination with others from the literature<sup>28,29</sup> could enable the synthesis of C3, C5, C7 triarylated azaindazoles by 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 [ $\text{Pd}(\text{PPh}_3)_4$ , Phen,  $\text{Ag}_2\text{CO}_3$ ,

$\text{H}_2\text{O}$ , 24h, 100 °C].<sup>28,29</sup> 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<sup>23</sup>. Consequently, we decided to first deoxygenate compounds **7a** and **7b** with  $\text{NH}_4\text{Cl}$  in the presence of Zinc dust 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 [ $\text{Ar}_2$ -I,  $\text{Pd}(\text{PPh}_3)_4$ , Phen,  $\text{Ag}_2\text{CO}_3$ ,  $\text{H}_2\text{O}$ , 24h, 100°C]<sup>28,29</sup> successfully led to C3, C5, C7 triarylated 4-azaindazoles **9a** and **9b** in 75 and 85% yield, respectively (Scheme 5).



**Scheme 5.** Synthesis of C3, C5, C7 triarylated azaindazoles.

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 di-arylated 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

### 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  $\text{MgSO}_4$ . After filtration, the solvent was removed in vacuum. The residue was purified by flash chromatography to give 1*H*-pyrazolo[4,3-*b*]pyridine (2g) in 70% yield as a white solid.

### *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 reaction mixture was quenched with water and

extracted with ethyl acetate. The combined organic extracts were dried over anhydrous MgSO<sub>4</sub>. 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 products N1 and N2 with 60 and 30% yield, respectively.

#### General procedures for *N*-Oxidation:

To a solution of 1-methyl-1*H*-pyrazolo[4,3-*b*]pyridine (2g, 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<sub>3</sub> (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.

#### Reduction of the *N*-oxide moiety:

The 5-arylated 4-azaindazole *N*-oxide (0.2 mmol) is dissolved in THF (3 mL). To this mixture is then added saturated NH<sub>4</sub>Cl 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<sub>2</sub>Cl<sub>2</sub>. The organic layer is then separated and the aqueous layer is extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organics are combined, dried with MgSO<sub>4</sub>, 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.

#### Sequential C5-arylation

In a dry sealed tube placed under an argon atmosphere, 100 mg de 1-methyl-1*H*-pyrazolo[4,3-*b*]pyridine-4-oxide is solubilized in 2 ml of toluene. After the introduction of K<sub>2</sub>CO<sub>3</sub> (1,5 eq), 1,10-phenanthroline (10 mol%) and iodoaryl (3eq), the tube and its contents were then purged under argon for 10 minutes and, Pd(OAc)<sub>2</sub> (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<sub>2</sub>Cl<sub>2</sub>. The organics are combined, dried with MgSO<sub>4</sub>, filtered and concentrated under reduced pressure then the crude residue is purified by chromatography on a column of silica gel (toluene/acetone, 6/4).

#### Sequential C7-arylation

In a dry sealed tube placed under an argon atmosphere, 100 mg de 1-methyl-1*H*-pyrazolo[4,3-*b*]pyridine-4-oxide is solubilized in 2 ml of DMA. After the introduction of K<sub>2</sub>CO<sub>3</sub> (2eq), PPh<sub>3</sub> (10 mol%) and iodoaryl (3eq), the tube and its contents were then purged under argon for 10 minutes and, PdCl<sub>2</sub> (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<sub>2</sub>Cl<sub>2</sub>. The organics are combined, dried with MgSO<sub>4</sub>, filtered and concentrated under reduced pressure then the crude residue is purified by chromatography on a column of silica gel (toluene/acetone, 5/5).

#### Palladium catalyzed double direct arylation:

In a dried sealed tube placed under an argon atmosphere, 1-methyl-1*H*-pyrazolo[4,3-*b*]pyridine-4-oxide (solubilized in 2ml of toluene), K<sub>2</sub>CO<sub>3</sub> (1.5eq), 1,10-phenanthroline (10 mol%) and iodobenzene (2 eq) were added. The mixture was then degassed with argon for 10 min and Pd(OAc)<sub>2</sub> (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<sub>2</sub>Cl<sub>2</sub>), 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 is then solubilized in 2ml of DMA in a dry sealed tube placed under an argon atmosphere. After the introduction of K<sub>2</sub>CO<sub>3</sub> (2eq), PPh<sub>3</sub> (10 mol%) and R<sub>1</sub>-I (3eq), the reaction mixture is degassed with argon for 10 min and PdCl<sub>2</sub> (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<sub>2</sub>Cl<sub>2</sub>), 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-R<sub>1</sub>-1*H*-pyrazolo[4,3-*b*]pyridine-4-oxide.

#### Palladium catalyzed triple direct arylation:

The 1-methyl-5-phenyl-7-R<sub>1</sub>-1*H*-pyrazolo[4,3-*b*]pyridine, synthesized by general procedure 4 is dissolved in THF (2mL). To this mixture is then added saturated NH<sub>4</sub>Cl solution (2mL) 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<sub>2</sub>Cl<sub>2</sub>. The organic layer is then separated and the aqueous layer is extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organics are combined, dried with MgSO<sub>4</sub>, 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 R<sub>2</sub>-I (2eq), Pd(PPh<sub>3</sub>)<sub>4</sub> (5 mol%), Ag<sub>2</sub>CO<sub>3</sub> (2eq) 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<sub>2</sub>Cl<sub>2</sub> (5 ml) was added and the contents of the tubes were filtered through a short pad of celite. The filtrates were extracted with CH<sub>2</sub>Cl<sub>2</sub> and the organic phase are concentrated under vacuum. The crudes were purified by silica gel column chromatography (petroleum ether/ethyl acetate, 9/1) to give 3-R<sub>2</sub>-1-methyl-5-phenyl-7-R<sub>1</sub>-1*H*-pyrazolo[4,3-*b*]pyridine tri-arylated products at C5, C7 and C3.

## Acknowledgements

This work was supported by the Euromed University of Fes (Morocco), LabexSynOrg (ANR-11-LABX-0029), Labex IRON

## References

- [1] Q. Zhao, G. Meng, S. P. Nolan, M. Szostak, *Chem. Rev.* **2020**, *120*, 1981–2048.
- [2] P. Gandeepan, T. Müller, D. Zell, G. Cera, S. Warratz, L. Ackermann, *Chem. Rev.* **2019**, *119*, 2192–2452.
- [3] K. Murakami, S. Yamada, T. Kaneda, K. Itami, *Chem. Rev.* **2017**, *117*, 9302–9332.
- [4] L. Théveau, C. Schneider, C. Fruit, C. Hoarau, *ChemCatChem*. **2016**, *8*, 3183–3194.
- [5] T. Bura, J. T. Blaskovits, M. Leclerc, *J. Am. Chem. Soc.* **2016**, *138*, 10056–10071.
- [6] S. El Kazzouli, J. Koubachi, N. El Brahmi, G. Guillaumet, *RSC Adv.* **2015**, *5*, 15292–15327.
- [7] R. Rossi, M. Lessi, C. Manzini, G. Marianetti, F. Bellina, *Adv. Synth. Catal.* **2015**, *357*, 3777–3814.
- [8] Y. Yang, Z. Shi, *Chem. Commun.* **2018**, *54*, 1676–1685.
- [9] M. Naas, S. El Kazzouli, E. M. Essassi, M. Bousmina, G. Guillaumet, *J. Org. Chem.* **2014**, *79*, 7286–7293.
- [10] Y. Yang, X. Qiu, Y. Zhao, Y. Mu, Z. Shi, *J. Am. Chem. Soc.* **2016**, *138*, 495–498.
- [11] F. Abdellaoui, C. Youssef, H. Ben Ammar, T. Roisnel, J.-F. Soulé, H. Doucet, *ACS Catal.* **2016**, *6*, 4248–4252.
- [12] A. Carrër, P. Rousselle, J.-C. Florent, E. Bertounesque, *Adv. Synth. Catal.* **2012**, *354*, 2751–2756.
- [13] B. M. Johnson, M. P. Huestis, *European J. Org. Chem.* **2014**, *2014*, 1589–1593.
- [14] I. Idris, F. Derridj, J.-F. Soulé, H. Doucet, *Adv. Synth. Catal.* **2017**, *359*, 2448–2456.
- [15] Y. Yang, P. Gao, Y. Zhao, Z. Shi, *Angew. Chemie Int. Ed.* **2017**, *56*, 3966–3971.
- [16] R. B. Bedford, S. J. Durrant, M. Montgomery, *Angew. Chemie Int. Ed.* **2015**, *54*, 8787–8790.
- [17] H. C. Seung, J. H. Seung, S. Chang, *J. Am. Chem. Soc.* **2008**, *130*, 9254–9256.
- [18] Y. Yang, R. Li, Y. Zhao, D. Zhao, Z. Shi, *J. Am. Chem. Soc.* **2016**, *138*, 8734–8737.
- [19] D. J. Schipper, M. El-Salfiti, C. J. Whipp, K. Fagnou, *Tetrahedron*. **2009**, *65*, 4977–4983.
- [20] L.-C. Campeau, M. Bertrand-Laperle, J.-P. Leclerc, E. Villemure, S. Gorelsky, K. Fagnou, *J. Am. Chem. Soc.* **2008**, *130*, 3276–3277.
- [21] L.-C. Campeau, S. Rousseaux, K. Fagnou, *J. Am. Chem. Soc.* **2005**, *127*, 18020–18021.
- [22] L. C. Campeau, D. R. Stuart, J. P. Leclerc, M. Bertrand-Laperle, E. Villemure, H. Y. Sun, S. Lasserre, N. Guimond, M. Lecavallier, K. Fagnou, *J. Am. Chem. Soc.* **2009**, *131*, 3291–3306.
- [23] M. P. Huestis, K. Fagnou, *Org. Lett.* **2009**, *11*, 1357–1360.
- [24] P. Schneider, G. Schneider, *Angew. Chem. Int. Ed.* **2017**, *11*, 7971–7974.
- [25] J.-Y. Mèroux, F. Buron, K. Plé, P. Bonnet, S. Routier, *Molecules*. **2014**, *19*, 19935–19979.
- [26] G. Koleva, B. Galabov, J. I. Wu, H. F. Schaefer III, *J. Am. Chem. Soc.* **2009**, *131*, 14722–14727.
- [27] B. Galabov, G. Koleva, H. F. Schaefer III, P. R. Schleyer, *J. Org. Chem.* **2010**, *75*, 2813–2819.
- [28] S. Faarasse, S. El Kazzouli, M. Naas, J. Jouha, F. Suzenet, G. Guillaumet, *J. Org. Chem.* **2017**, *82*, 12300–12306.
- [29] S. Faarasse, S. El Kazzouli, F. Suzenet, G. Guillaumet, *J. Org. Chem.* **2018**, *83*, 12847–12854.

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

*Adv. Synth. Catal.* **Year**, *Volume*, Page – Page

Soukaina Faarasse, Saïd El Kazzouli \*,  
Stéphane Bourg, Samia Aci-Sèche, Pascal  
Bonnet, Franck Suzenet \*and Gérard  
Guillaumet\*

