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Efficient Synthesis and First Regioselective C-3 Direct Arylation of Imidazo[1,2-*b*]pyrazoles

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In recent years, 5,5-fused ring systems have attracted much attention. Such systems that contain three nitrogen atoms are found in compounds showing a wide range of biological activities. For example, imidazo[1,2-*b*]pyrazoles have been designed, prepared, and studied as anticancer,[1] antifungal,[2] and anti-inflammatory agents[3] or for the treatment of neurodegenerative disorders.[4]

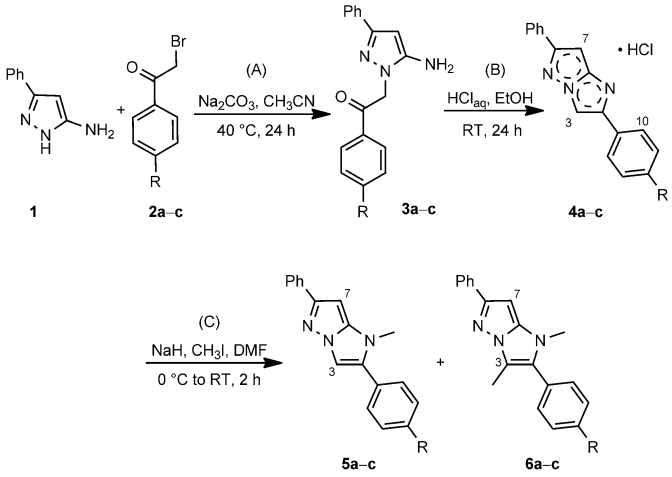
Current strategies for preparing substituted imidazo[1,2-*b*]pyrazole derivatives generally consist in constructing the 5,5-fused ring with the desired substituents in appropriate position.[1a,b,2b,5] Only few methods of direct functionalization of the heterocyclic moiety have been described. In this context, the overall goal of our research was to develop an efficient synthesis of the imidazo[1,2-*b*]pyrazole synthon that permits its subsequent functionalization, thereby enabling molecular diversity.

We started our investigations by using the commercially available 3(5)-phenyl-1*H*-pyrazol-5(3)-amine (**1**), which was selectively N-alkylated with various α-bromoacetophenones **2a–c** in acetonitrile under basic conditions in moderate yields (Table 1).

Optimization procedures were assessed, that is, base, solvent, temperature, and reaction time, but no significant improvement was observed. The regioselectivity of the N-al kylation was established by a single-crystal X-ray study of the pyrazole **3a** (see the Supporting Information). Cyclization of **3a–c** under acidic conditions in ethanol afforded imidazopyrazoles **4a–c** as chlorohydrates in high yields. Compound **4** was N-methylated by using iodomethane in the presence of sodium hydride in *N,N*-dimethylformamide, which afforded two products in good overall yields (77 to 91%): the N-methylated product **5** and the N- and C-3-methylated compound **6** in a 73:27 to 86:14 ratio. These structures were confirmed by single-crystal X-ray studies (see the Supporting Information). To minimize the formation of product **6**, different bases (KH, KOH, Na_2CO_3, K_2CO_3, Cs_2CO_3, Ag_2CO_3, *n*BuLi), a different methylating agent (dimethylsulfate), or different solvents (DMF, THF, acetone)[6] were tested. Nevertheless, in each case, either the two compounds were obtained in lower yields or the reaction afforded degradation products. Regarding the 5,5-fused ring systems, two positions of the imidazo[1,2-*b*]pyrazole core remain potentially functionalizable, enlarging the potential molecular diversity offered by this synthon.

In recent years, the direct C–H arylation of aromatic and heteroaromatic compounds has emerged as an attractive alternative method to the more classic cross-coupling reactions.[7] In contrast to palladium-catalyzed couplings, such

Table 1. Preparation of imidazo[1,2-*b*]pyrazoles **5a–c**.



Entry	R	Step A [%][a]	Step B [%][a]	Step C [%][a]	
1	OCH_3	40 (**3a**)	98 (**4a**)	65 (**5a**)	26 (**6a**)
2	CF_3	48 (**3b**)	90 (**4b**)	60 (**5b**)	17 (**6b**)
3	CH_3	57 (**3c**)	93 (**4c**)	61 (**5c**)	16 (**6c**)

[a] Isolated yields.

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as Suzuki, Stille, or Negishi couplings, which require the preparation of organometallic reagents (boronic acids, tin, or zinc derivatives), preliminary functionalization is avoided in direct C–H arylation. As a result, the number of steps, waste, and solvent and the reaction time are usually reduced. As part of our research effort in direct C–H arylation,[8] we set out to explore the C-3 and C-7 reactivity of **5a** toward C–H arylation. Notably, arylation of electron-poor heterocycles, in particular five-membered heterocycles containing two or three heteroatoms, is the most intriguing challenge in this field today.[9] To the best of our knowledge, no example of direct arylation of the imidazo[1,2-*b*]pyrazole core has been reported.

The Pd^0-mediated arylation of **5a** by using 4-bromo toluene as the coupling partner under thermal heating afforded the desired C-3-arylated imidazopyrazole **7a**, but in a mixture with **8** (Table 2, entry 1). This by-product resulted from the insertion of the phenyl group of triphenylphosphine in C-3. This reactivity is quite rare, but has been reported already.[10] Thus, we replaced triphenylphosphine by tricyclohexylphosphine (PCy_3), which allowed us to isolate **7a** as a single product in a good 70% yield (entry 2). Spectral data (NOESY correlations between H-7 and NCH_3) were in accordance with structure **7a**. In addition, the complete regioselectivity on C-3 was confirmed by a single-crystal X-ray study (Figure 1). We also noted that compound **7a** crystallizes in two polymorphic forms (for details, see the Supporting Information).

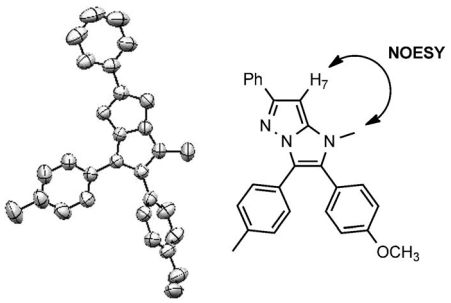
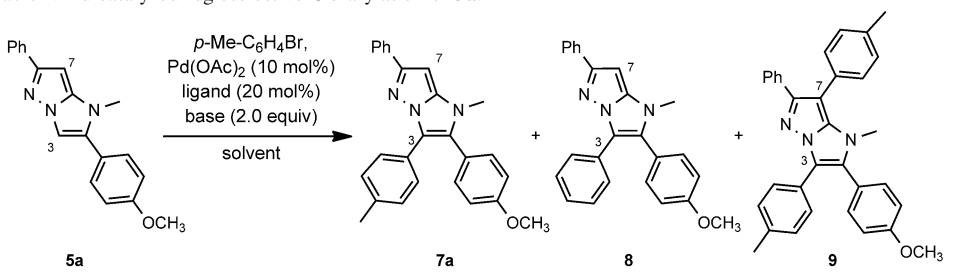


Figure 1. ORTEP representation of **7a**.

To improve the reaction yield, we first used microwave irradiation,[11] which increased the yield to 80% and significantly reduced the reaction time (entry 3). We then increased the quantity of arylbromide (entry 4) or replaced potassium carbonate by caesium carbonate (entry 8). In both cases, the arylation of C-3 and C-7 took place, giving rise to an inseparable mixture of **7a** and **9** (entries 4 and 8). While using a protic solvent decreased the yield to 20% (entry 5), the replacement of toluene by 1,4-dioxane gave a better result (entry 7). Finally, the optimal reaction conditions were found to be imidazopyrazole **5a** (1.0 equiv), 4-bromo toluene (1.0 equiv), palladium acetate (10 mol%), tricyclohexylphosphine (20 mol%), and potassium carbonate (2.0 equiv) in 1,4-dioxane, heated for 1 hour at 160°C under microwave irradiation (entry 9).

Table 2. Pd-catalyzed regioselective C-3 arylation of **5a**.[a]



5a **7a** **8** **9**

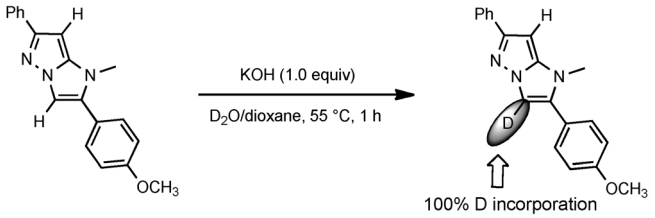
Entry	Ligand	Base	*p*-Me-C_6H_4-Br [equiv]	Solvent	Heating system	*t* [h]	Ratio **7a**/**8**/**9**[b]	Yield [%][c]
1	PPh_3	K_2CO_3	1.5	toluene	reflux	15	64:36:0	81[d]
2	PCy_3	K_2CO_3	1.0	toluene	reflux	41	100:0:0	70
3	PCy_3	K_2CO_3	1.0	toluene	MW, 160°C	4	100:0:0	80
4	PCy_3	K_2CO_3	1.5	toluene	MW, 160°C	4	89:0:11	91[d]
5	PCy_3	K_2CO_3	1.0	toluene/EtOH 2:1	MW, 160°C	4	100:0:0	20
6	PCy_3	K_2CO_3	1.0	1,4-dioxane/EtOH 2:1	MW, 160°C	4	100:0:0	14
7	PCy_3	K_2CO_3	1.0	1,4-dioxane	MW, 160°C	4	100:0:0	83
8	PCy_3	Cs_2CO_3	1.0	1,4-dioxane	MW, 160°C	4	95:0:5	75[d]
9	PCy_3	K_2CO_3	1.0	1,4-dioxane	MW, 160°C	1	100:0:0	86

[a] The reactions were carried out with **5a** (0.329 mmol), 4-bromotoluene (specified quantities), palladium acetate (10 mol%), ligand (20 mol%), and base (2.0 equiv) in solvent (2 mL). [b] ^1H NMR ratio based on the integration of H-7 or OCH_3. [c] Isolated yields after column chromatography. [d] Mixture of inseparable products after column chromatography of the crude mixture.

We tried to understand the origin of this regioselectivity, which is the real challenge in direct C–H arylation studies today.[12] Several mechanistic scenarios have been proposed to explain palladium-catalyzed direct-arylation outcomes, including S_EAr, Heck-like addition, and a CMD (concerted metalation–deprotonation) mechanism.[13]

To identify the role that the C–H bond acidity plays in the site selectivity of this reaction, deuterium-incorporation experiments were carried out. Deuterium exchange of imidazo[1,2-*b*]pyrazole **5a** by treatment with KOH in a mixture of dioxane and D_2O reveals that the C-3 site exchanges exclusively,[14] which shows that C-3 is by far the most acidic position (Scheme 1). A plausible mechanism for this C–H arylation, generally linked to acidity, is a CMD pathway proposed by Fagnou and coworkers.[13g, 15]

To explore the scope of the methodology and detect possible limitations, we applied these selected conditions to the three imidazo[1,2-*b*]pyrazoles **5a–c** by choosing various hetero(aryl) bromides (Table 3). Hence, we could first ob-



Scheme 1. Deuterium incorporation of **5a**.

serve that the C–H arylation on C-3 is not influenced by the nature of the group in C-2 position. Then, it was noticed that aryl bromides that bear a variety of functional groups were well tolerated. More specifically, aryl bromides containing electron-withdrawing (CN, $COOCH_3$, CF_3) or electron-donating groups (CH_3, OCH_3) gave C-3-arylated imidazo[1,2-*b*]pyrazoles in excellent yields. Steric hindrance did not significantly influence the yield, except in the case of 2-cyanophenylbromide for which the yield dropped to 60%.

To enlarge the scope of the method, some heteroaryl bromides were also tested. The use of 3-bromothiophene and 3-bromofurane led to incomplete conversion and the desired products in 24 and 18% yield, respectively. No improvement was observed by increasing the reaction time. Since Fagnou's group described a palladium–pivalic acid combination for the C–H arylation of aromatic heterocycles that exhibited unprecendented reactivity,[16] pivalic acid was added as cocatalyst. In this case, no particular improvement in reactivity was observed. However, when applied to 4-bromopyridine, the optimized conditions gave 3-(pyridin-4-yl)-1*H*-imidazo[1,2-*b*]pyrazoles **7q–s** in good yields.

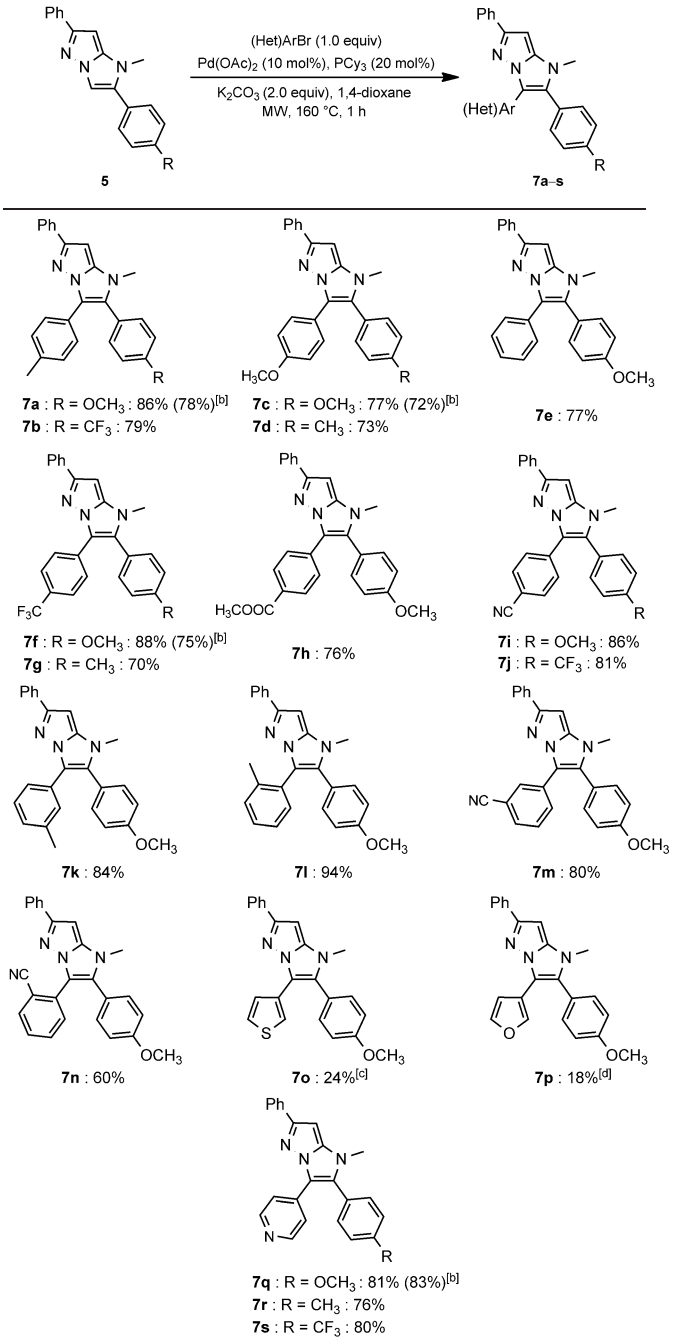
We also extended the methodology to aryl or heteroaryl chlorides, which are often, but not always, less expensive and more readily available than the corresponding bromides and iodides.[17] Remarkably, our conditions could be successfully applied to electron-rich, electron-poor, or heteroaryl chlorides, although they are known to be less reactive (see Table 3, footnote [b]). The compatibility of the strategy with both chlorides and bromides as coupling partners suggests the possibility of introducing a larger range of groups.

Then, arylation of the *NH*-imidazopyrazole **4a** (Table 4) was carried out. Direct arylation under optimized conditions afforded compound **10** as a single product with 40% yield (entry 1). To confirm the regioselectivity of the reaction, **10** was subjected to a methylation reaction by using iodomethane and sodium hydride in *N,N*-dimethylformamide (Scheme 2). All the spectral data of the resulting product were in perfect agreement with those of compound **7a**, which confirms a direct C–H arylation in C-3 position for the free *NH*-imidazopyrazole **4a**.

Optimization of the procedure was carried out, for example, by changing the base, solvent, or ligand or by adding an additive, such as pivalic acid. Unfortunately, the yield never exceeded 40%, presumably owing to the presence of the free NH group, which may disfavor C–H arylation. In addition, we noted a poor stability of **10**. Indeed, we observed its rapid degradation at room temperature, which forced us to keep the product at −20 °C. Consequently, imidazopyrazole **10** was transformed into the corresponding hydrochloride salt **11** (Scheme 2), which is more stable and allows a longer storage.

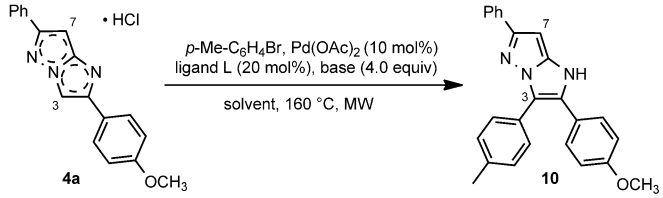
In summary, we developed a novel and efficient synthesis of the imidazo[1,2-*b*]pyrazole core. Then, a palladium-cata-

Table 3. Scope of the Pd-catalyzed C-3 arylation of **5a–c**.[a]



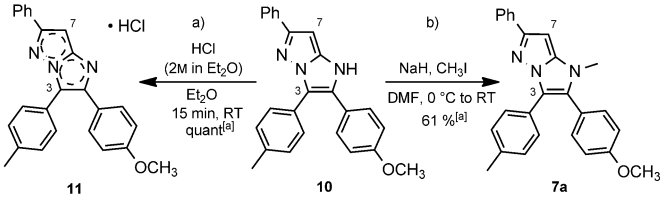
[a] Isolated yields after column chromatography. [b] The reaction was performed by using (hetero)aryl chloride instead of (hetero)aryl bromide. [c] 75% of starting material recovered. [d] 80% of starting material recovered.

Table 4. Pd-catalyzed C-3 arylation of **4a**.



Entry	Ligand	Base	*p*-Me-C_6H_4Br [equiv]	Solvent	*t* [h]	Yield [%][a]
1	PCy_3	K_2CO_3	1.0	1,4-dioxane	4	40
2	PCy_3	K_2CO_3	1.5	1,4-dioxane	4	41
3	PCy_3	K_2CO_3	1.5	1,4-dioxane	4	38[b]
4	PCy_3	K_2CO_3	1.5	toluene	4	31
5	PCy_3	K_2CO_3	1.5	toluene/EtOH 2:1	0.5	–[c]
6	PCy_3	Cs_2CO_3	1.5	toluene	4	–[c]
7	Xts[d]	K_2CO_3	1.5	toluene	4	–[c]

[a] Isolated yields after column chromatography. [b] The reaction was performed with pivalic acid (0.30 equiv). [c] Degradation. [d] Xts = Xantphos.



Scheme 2. a) Stabilization of **10** by formation of the hydrochloride salt **11** and b) structure confirmation by N-methylation. [a] Isolated yields.

lyzed C-3 functionalization was developed. The methodology described is original and the first one able to provide a highly selective C-3 direct arylation. Good to excellent yields were obtained for a wide range of aryl coupling partners with both electron-rich and electron-poor substituents, giving access to a library of diverse imidazo[1,2-*b*]pyrazole compounds. Further studies are currently in progress in our laboratory.

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Keywords: arylation · C–C coupling · fused-ring systems · microwave chemistry · palladium · regioselectivity

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