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First combined selective N- and C-arylations with boronic acids: application to the synthesis of 1,3-diarylindazoles

Valérie Collot,[a] Philippe R. Bovy[b] and Sylvain Rault[a,*]

[a]*Centre d'Etudes et de Recherche sur le Médicament de Normandie, UFR des Sciences Pharmaceutiques, 5 rue Vaubénard, 14032 Caen, France*
[b]*Synthelabo Recherche, 10 rue des Carrières, 92500 Rueil-Malmaison, France*

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Abstract

3-Iodoindazole allows combined N1- and C3-arylations with boronic acids. These two reactions work independently of one another and can be combined in a one pot procedure.

To obtain mild and flexible strategies to design new indazole libraries, we were interested in the reactivity of 3-iodoindazoles in metal-catalysed coupling reactions. Thus, we recently published a general and versatile pathway leading to 2-azatryptamines via a Heck cross-coupling reaction of 3-iodoindazole with methyl acrylate.[1] We also developed a Suzuki-type cross-coupling reaction of 3-iodoindazoles with aryl and heteroaryl boronic acids as a general route to 3-aryl indazoles.[2]

Whereas the well-known application of aryl boronic acid in palladium-catalyzed coupling with aryl halides to produce biphenyls is one of the most powerful tools in C–C bond formation,[3] the corresponding aryl/heteroaryl C–N bond cross-coupling reactions are less common,[4] especially those involving mild conditions.

In our search for a general and mild methodology for the aryl/heteroaryl C–N bond cross-coupling reaction toward the synthesis of biologically active indazoles, we have explored the newly discovered aryl boronic acid/cupric acetate N-arylation reaction,[5] and studied its combination with C–C Suzuki type cross coupling reactions.

Only two examples of the N-arylation of indazole have been described in the literature. This has been shown to work with catalytic cupric acetate/*p*-tolyllead triacetate[6] or cupric acetate/*p*-tolylboronic acid[7] but gave a mixture of N1 and N2 substituted derivatives, the ratio being in agreement with the general features of indazole reactivity.[8]

* Corresponding author. E-mail: rault@pharmacie.unicaen.fr

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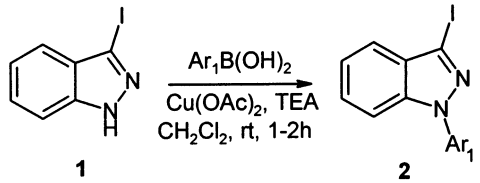
The general conditions for this latter aryl/heteroaryl C–N bond coupling reaction involve the addition of 2.0 equivalents of *p*-tolylboronic acid and 2.0 equivalents of triethylamine to 1.0 equivalent of indazole in methylene chloride at room temperature, followed by 1.5 equivalent of anhydrous cupric acetate.

We observed that the same conditions applied to 3-iodoindazole **1** gave a quantitative coupling after a brief reaction time (1 h) and provided 67% of isolated product **2c** after column chromatography.[9]

Beside *p*-tolyl boronic acid, three different aryl boronic acids (phenyl, *p*-trifluoromethylphenyl, and *p*-methoxyphenyl) ranging from electron-deficient to electron-rich rings were studied. The yields are in general good, indicating that this copper-promoted N-arylation of 3-iodoindazole **1** can tolerate aryl boronic acids of various electronic nature (Table 1).

Table 1
Regioselective copper-promoted N1-arylation of 3-iodoindazole **1**[a]



1 **2**

	Ar_1	Time (h)	Yield (%)
2a	Phenyl	2	71
2b	*p*-CF_3-phenyl	1	62
2c	*p*-Tolyl	1	67
2d	*p*-OCH_3-phenyl	1	61

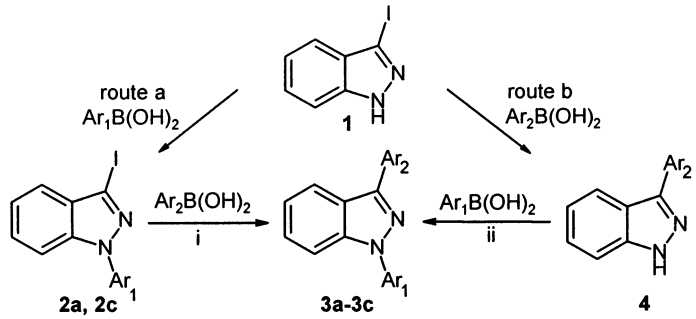
[a] Couplings were carried out at rt in CH_2Cl_2 in the presence of 2 equiv. of $Ar_1B(OH)_2$, 2 equiv. of TEA and 1.5 equiv. of $Cu(OAc)_2$.

With this first exploration, we showed the N1-regioselectivity of the arylation of 3-iodoindazole **1**. In contrast with indazole, a single reaction product is obtained here because of the steric hindrance in position 3 induced by the presence of iodine, avoiding the formation of regioisomers. Moreover, the iodine in position 3 remains unchanged, thus allowing further reactions. This prompted us to investigate its reactivity in a Suzuki-type coupling reaction. We observed that arylboronic or heteroarylboronic acids gave with compounds **2** quantitative couplings after a short time of reaction (Table 2, compounds **3**) and provided 67–75% yield of isolated product after column chromatography.

We also examined the reverse strategy and observed that compounds **3** could be obtained by N-arylation of the appropriate 3-arylindazoles **4** (route b) in the conditions depicted in Table 1. Indeed the 1,3-diaryl derivatives **3** could be obtained according to two different successive routes starting from 3-iodoindazole **1**, providing a flexible and selective N- and C-arylations of 3-iodoindazole.

We also investigated whether it could be possible to combine those two selective catalytic N1- and C3-arylations of 3-iodoindazole in the same reaction. For this purpose, we searched for compatible experimental conditions (Table 3) able to provide the corresponding 1,3-diaryl compounds **3**.

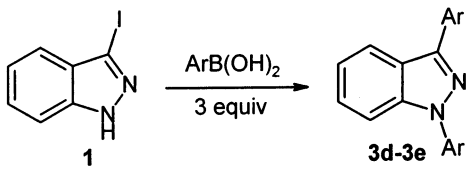
Table 2
Two different routes to access to 1,3-diarylindazoles **3a**–**3c**[a]



	Ar_1	Ar_2	Yield (%)
3a	Phenyl	*p*-OCH_3-phenyl	71
3a	Phenyl	*p*-OCH_3-phenyl	68
3b	*p*-Tolyl	2-Thienyl	67
3c	Phenyl	2-Furyl	75

[a] (i) Couplings were carried out at 80°C in DME (2–3 h) in the presence of 5% of $Pd(PPh_3)_4$, 1.1 equiv. of $Ar_2B(OH)_2$ and 3.0 equiv. of $NaHCO_3$. (ii) Cf reaction conditions depicted in Table 1.

Table 3
Combined N- and C-arylations of 3-iodoindazole in a 'one pot' procedure[a]

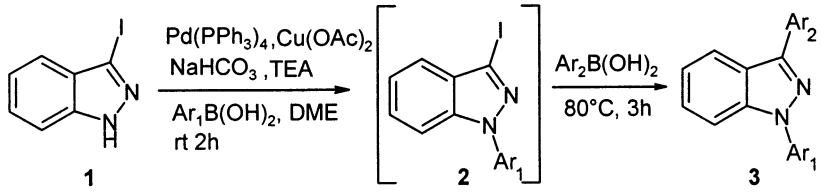


	Ar	Time (h)	Yield (%)
3d	Phenyl	5	65
3e	OCH_3-phenyl	2.5	69

[a] Reactions were carried out at 80°C in DME in the presence of 3.0 equiv. of $ArB(OH)_2$, 5% of $Pd(PPh_3)_4$, 1.5 equiv. of $Cu(OAc)_2$, 3.0 equiv. of $NaHCO_3$ and 2.0 equiv. of TEA.

Thus, we observed that in Suzuki coupling conditions (Table 2), addition of copper acetate and at least one further equivalent of arylboronic acid allowed the N-arylation without preventing the C3-arylation to give 1,3-diaryl compounds **3d**–**e** in excellent conditions (Table 3). Moreover, as we observed that the N-arylation proceeded faster and at lower temperature than the C-arylation, we managed to dissociate the two reactions to functionalize 3-iodoindazole with two different aryl substituents in a 'one pot' procedure (Table 4).

Table 4
Dissociated N- then C-arylations of 3-iodoindazole with two different boronic acids in a 'one pot' procedure[10]



	Ar_1	Ar_2	Yield (%)
3c	Phenyl	2-Furyl	71
3f	*p*-OCH_3-Phenyl	3,5-di-Cl-phenyl	68

Finally we found that treatment of **1** in DME with only one equivalent of a first aryl boronic acid in the presence of a mixture of the two different catalysts ($Pd(PPh_3)_4$, $Cu(OAc)_2$) totally consumed this boronic acid and gave firstly the N1-aryl derivative **2**. This was then converted in situ into the diaryl compound **3** by addition of a second boronic acid in the reaction mixture.[10] The reaction was completed after 3 h at 80°C.

In conclusion, this study demonstrates for the first time the possibility of conducting in a 'one pot' procedure two different coupling reactions (N- and C-arylations) with arylboronic acids in the presence of two catalysts able to work independently of one another. This approach could provide a flexible and selective scheme to design new libraries from haloarylamines.

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9. General procedure for N-arylation: The resulting dark blue to turquoise mixture of 3-iodoindazole[2] (1.0 mmol), aryl boronic (2.0 mmol), anhydrous cupric acetate (1.0 mmol), triethylamine (2.0 mmol) in dry CH_2Cl_2 (7 mL) was stirred at room temperature for 1–2 h. The progress of the reaction was monitored by TLC. The products were isolated by direct flash column chromatography of the crude reaction mixture with pre-absorption on silica gel (EtOAc/cHex 1:8). Compound **2d**: mp 110°C. ^1H NMR ($CDCl_3$) δ 7.59–7.53 (m, 4H), 7.46 (t, 1H, $J=7.9$ Hz), 7.27 (t, 1H, $J=7.4$ Hz), 7.04 (d, 2H, $J=7.3$ Hz), 3.88 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 158.7, 139.6, 132.7, 129.1, 128.0, 124.6, 122.0, 121.8, 119.5, 114.7, 114.6, 110.3, 94.1, 55.6; MS *m*/*z* 350. Anal. calcd for $C_{14}H_{11}N_2OI$: C, 48.02; H, 3.17; N, 8.00. Found: C, 48.30; H, 3.01; N, 7.82.
10. Preparation of compound **3f**: The resulting green mixture of 3-iodoindazole[2] (1.0 mmol), *p*-OCH_3phenylboronic (1.0 mmol), anhydrous cupric acetate (1.0 mmol), $Pd(PPh_3)_4$ (5%), triethylamine (2.0 mmol), $NaHCO_3$ (3.0 mmol) in DME (10 mL) was stirred at room temperature. The progress of the reaction was monitored by TLC. After

1 h 3,5-di-Cl-phenylboronic (1.0 mmol) was added and the mixture was heated at 80°C for 3 h. After filtration, **3f** was isolated by flash column chromatography (EtOAc/cHex 1:4; **3f**: mp 174°C. ^{1}H NMR ($CDCl_3$) δ 8.04 (d, 1H, $J=8.2$ Hz), 7.94 (s, 1H), 7.68–7.64 (m, 3H), 7.46 (t, 1H, $J=7.8$ Hz), 7.39 (s, 1H), 7.32 (t, 1H, $J=7.9$ Hz), 7.08 (d, 2H, $J=8.3$ Hz), 3.85 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 158.8, 143.1, 140.7, 136.6, 136.3, 135.4, 132.8, 127.9, 127.2, 125.8, 125.0, 122.2, 120.8, 114.8, 110.8, 55.6; MS m/z 369. Anal. calcd for $C_{20}H_{14}N_2OCl_2$: C, 65.06; H, 3.82; N, 7.58. Found: C, 65.31; H, 3.75; N, 7.72.