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Mild, base-free copper-catalyzed N-arylations of heterocycles using potassium aryltrifluoroborates in water under air

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ABSTRACT

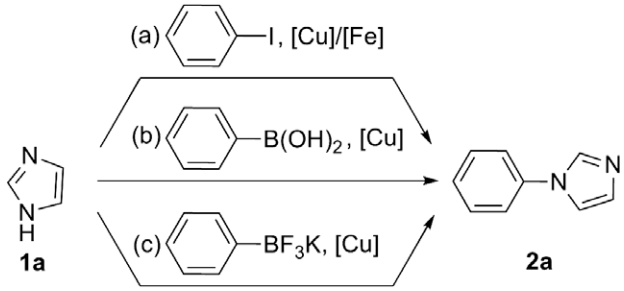
An economic, mild and efficient copper-catalyzed methodology for the N-arylation of heterocycles was optimized using potassium aryltrifluoroborates in water.

C–N bond formation by transition-metal-catalyzed cross-coupling reactions has been an old[1] but powerful strategy[2] for chemical, pharmaceutical and materials applications. N-Arylation of nitrogen nucleophiles with aryl halides is one of the most important methods, early developed with copper-mediated Ullmann condensation,[3] then extended to Buchwald's palladium-catalyzed cross-coupling reaction.[4] The latter has been extremely successful, despite its prior limitations to non-heterocyclic N–H bond cross-coupling. In parallel, the development of Ullmann condensation has been slowed by notable drawbacks including harsh conditions and required stoichiometric amounts of copper. Then, high costs of palladium and limitations in terms of generality made researchers turn towards less expensive, less toxic and more efficient catalysts.[5] Indeed, Buchwald and Taillefer first described copper-catalyzed cross-coupling reactions of N–H heterocycles with aryl halides,[6–11] while Taillefer developed its iron/copper- or iron-catalyzed counterparts.[12]

As an interesting alternative, a Chan–Evans–Lam modified Ullmann condensation[13–15] employs arylboronic acids to perform a copper-catalyzed N-arylation of amines[16–18] including nitrogen heterocycles.[15,19–22] The replacement of halides by organometallic reagents facilitates the transmetallation step in comparison with the oxidative addition, and reactions were found to be highly compatible with water.[23,24] However, boronic acids still present several drawbacks associated with tedious purification and relative instability which generates by-products in reactions.

Fortunately, the development of trifluoro(organo)borate as boronic acid surrogates for coupling reactions by both Genet[25,26] and Molander[27] opened new horizons. These compounds are more stable towards air and humidity. The faster transmetallation step allowed the development of various Pd-[28] or Rh-catalyzed[29–34] reactions, some in water.[35] Batey et al. realized Cu-catalyzed N-arylation of amines with borates, but use of anhydrous solvent and limited substrate scope narrowed its applicability.[36] Similarly, Kabalka showed a similar transformation using microwave irradiation in the absence of solvent.[37]

Most approaches (Scheme 1) suffer rather from lack of generality, use of expensive ligands/catalysts, base as an additive, anhydrous solvent and/or high temperature. Therefore, there is still a



Scheme 1. Evolution of the reported synthesis of phenylimidazole: (a) Cu- and/or Fe-catalyzed coupling of arylhalides (Buchwald/Taillefer); (b) Cu-catalyzed coupling of phenyl boronic acid (Collman/Lam/Chan); (c) Cu-catalyzed coupling of potassium trifluorophenylborate (Batey).

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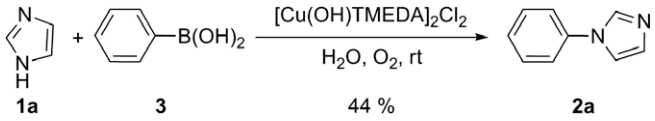


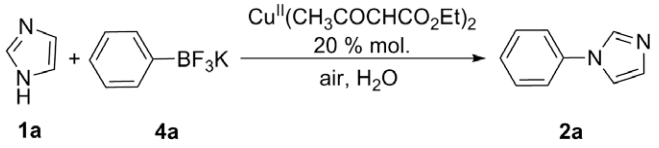
Scheme 2. Previously reported synthesis of phenylimidazole in water.

need for a general, mild and inexpensive methodology for the N-arylation of heterocycles compatible with water. Herein, we wish to report such methodology, using aryltrifluoroborates in water under air atmosphere. Our selected approach of choice for the formation of phenylimidazole **2a** was based on the coupling between imidazole **1a** and potassium trifluorophenylborate **4a** in water. N-Arylation of imidazole using phenylboronic acid **3** proceeds smoothly in organic solvents,[19,24] but only moderate yield is observed in water, using $[Cu(OH)TMEDA]_2Cl_2$ as the best catalyst (Scheme 2).[23,24]

Therefore, our first efforts were devoted to the screening of a large choice of metal catalysts (including Cu, Fe, Pd, Au, Rh or Ru) for the coupling between imidazole **1a** and potassium trifluorophenylborate **4a**. Catalyst (20%) loading was chosen as a standard with 40% of ligand if required; the reaction was carried out at 40 °C, in open air at 0.08 M in water. Surprisingly, only copper led to significant conversion in the desired product, no reaction occurred with any other metal including iron.[5,11] Replacing the borate salt by phenylboronic acid failed, most certainly due to solubility problem (of the boronic acid) at this concentration.

Having selected copper as the metal of choice, we investigated several types of ligands such as diamines, mono- and diketones, diesters and ketone-esters according to various literature references (Table 1). Most gave traces of compound, but ethyl acetoacetate quickly stood out to be the best ligand resulting in a moderate yet encouraging 27% yield (Table 1, entry 4). Catalyst and ligand loadings were critical: 2 equiv of ligand were not required (entry 5), while a diminishing amount of catalyst resulted in a spectacular decrease of reactivity (entries 4, 6 and 7), leading to almost no reaction with 5% or less catalyst loading. Copper precatalyst appeared crucial: copper chloride and copper acetate (entries 8 and 9) were less reactive than copper iodide. Copper(I) seemed relatively less efficient than copper(II) (entries 8 and 10), and copper(II) triflate gave a result among our best attempts with 25% yield (entry 11). A pre-formed copper(II) ethyl acetoacetate complex was also used (entry 12), and unsurprisingly gave a similar result to the combined use of copper(II) triflate and ethyl acetoacetate.

Table 2
N-Arylation of imidazole: catalytic system optimization

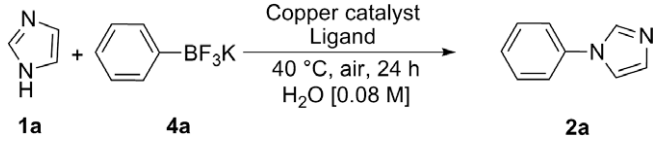


Entry	*T* (°C)	Time	Parameters[a]	Yield (%)
1	40	1 d	[0.08 M]	26
2	40	1 d	[0.02 M]	<1
3	40	1 d	[0.5 M]	55
4	40	1 d	[1.0 M]	33
5	40	1 d	[0.5 M], pH 11	63
6	40	1 d	[0.5 M], pH 3	60
7	60	1 d	[0.5 M]	62
8	20	1 d	[0.5 M]	30
9	60	4 d	[0.5 M]	72
10	40	4 d	[0.5 M]	76

[a] Concentration in imidazole, pH.

We studied medium influence (concentration, temperature, pH and time), using commercially available copper(II) ethyl acetoacetate (Table 2). Interestingly, among protic solvents, water stood as the best choice as yields were largely decreased in methanol or ethanol. Concentrated media favoured the reaction (entries 2, 3 and 4): 0.5 M solution afforded the product in 55% yield. Although protodeboronation side reaction is usually limited by fine adjustment of pH, it did not surprisingly affect reactivity (entries 3, 5 and 6), while 40 °C was required and sufficient to achieve good conversions. 60 °C did not improve much the results and room temperature showed a large decrease in reactivity. Gratifyingly, a longer reaction time, at 40 °C, in open air, allowed us to reach an optimized 76% yield (entry 10). These last conditions were used for all following N-arylations.

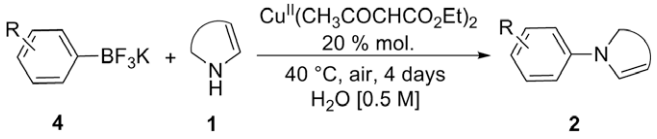
Table 1
N-Arylation of imidazole: catalytic system optimization

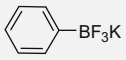
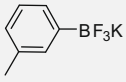
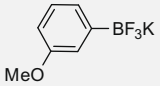
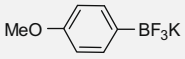
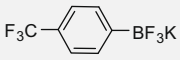
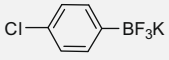
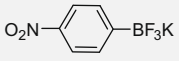
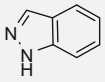
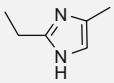


Entry	Catalyst	Ligand[a]	Mol %[b]	Yield (%)
1	$[Cu(OH)TMEDA]_2Cl_2$		20	14
2	$Cu(acac)_2$		20	8
3	CuI	$CH_2[CO_2Me]_2$	20	13
4	CuI	$CH_3COCH_2CO_2Et$	20	27
5	CuI	$CH_3COCH_2CO_2Et$[c]	20	26
6	CuI	$CH_3COCH_2CO_2Et$	10	12
7	CuI	$CH_3COCH_2CO_2Et$	5	<1
8	CuCl	$CH_3COCH_2CO_2Et$	20	15
9	CuOAc	$CH_3COCH_2CO_2Et$	20	20
10	$CuCl_2$	$CH_3COCH_2CO_2Et$	20	20
11	$Cu(OTf)_2$	$CH_3COCH_2CO_2Et$	20	25
12	$Cu(CH_3COCHCO_2Et)_2$		20	26

[a] 2 equiv/metal.
[b] Metal loading.
[c] 10 equiv/metal.

Table 3
Arylation of N-heterocyles



Entry	$ArBF_3K$	ArN–H	Product	Yield (%)
1	 **4a**	 **1b**	**2b**	78
2	**4a**	 **1c**	**2c**	72
3	**4a**	 **1d**	**2d**	59
4	 **4b**	 **1a**	**2e**	77
5	 **4c**	**1a**	**2f**	68
6	 **4d**	**1a**	**2g**	80
7	 **4e**	**1a**	**2h**	64
8	 **4f**	**1a**	**2i**	66
9	**4e**	**1c**	**2j**	41
10	 **4g**	**1a**	**2k**	0
11	**4b**	**1b**	**2l**	92
12	**4d**	**1b**	**2m**	89
13	**4d**	**1d**	**2n**	89
14	**4d**	 **1e**	**2o**	73[a] (53/47)
15	**4d**	 **1f**	**2p**	45
16	**4d**	**1c**	**2q**	62

[a] Isolated as mixture of isomers.

Having in hand an optimized procedure[38] for the coupling between imidazole **1a** and potassium trifluorophenylborate **4a**, we evaluated the reactivity of various N–H heterocycles and potassium aryltrifluoroborates (Table 3). N-Arylation of pyrazoles (entries 1 and 2) and benzimidazole (entry 3) with potassium trifluorophenylborate **1a** afforded the desired compounds **2b–d** in good yields from 59% to 78%. N-Arylation using aryltrifluoroborates in water appears more effective than the previously reported methodologies involving boronic acids.[23] N-Arylation of imidazole with *para*-, *meta*- or *ortho*-substituted phenylborates **4b–g** was studied (entries 4–8 and 10). With methoxy-substituted aryl groups (entries 5–7), the reaction was favoured when the substituent was in *para* position (**4d**), leading to the 4′-methoxyphenylimidazole **2g** in an excellent 80% yield (entry 6). For the *meta*-substituted borate, with lowered electron donating effect, the desired compounds **2f** was isolated in 68% yield (entry 5). For the *ortho*-substituted aryl group for which the steric hindrance is limiting, no N-arylated compound was isolated, and only the corresponding boronic acid was recovered.

No clear electronic effects were observed regarding the electron demand of the aryl substitution and N-arylation occurred smoothly giving **2e–i** in decent to excellent yields (entries 4–8 and 10). The only limitation was found using trifluoro(4-nitrophenyl)borate **4g**, which gave only the homocoupling product (4,4′-dinitrobiphenyl) in 79% yield[39–41] (entry 10). Finally, the reaction of 4-methoxyphenylborate on pyrazole, benzimidazole and indazole afforded the expected N-arylated products **2m, 2n** and **2o** in satisfying yields ranging from 73% to 89% (entries 12–14). N-Arylation of 2-ethyl-4-methylimidazole **1f** with **4d** gave the N-arylated compound **2p** in a moderate 45% yield, while reaction with dimethylpyrazole **1c** afforded the desired compound **2q** in 62% yield. Further studies into the scope of the reaction, specially using more complex heterocycles are currently underway and will be reported in due course.

In summary, we have developed a mild, efficient methodology for the N-arylation of various nitrogen heterocycles with trifluoro(organo)borates, using inexpensive commercially available copper as a catalyst, in water under air atmosphere. This simple method could be adapted for the synthesis of more advanced intermediates.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.03.118.

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38. *Typical procedure for the N-arylation of N–H heterocycle*: Potassium aryltrifluoroborate **4** (1 mmol), N–H heterocycle **1** (0.5 mmol) and copper(II) ethylacetoacetate (0.1 mmol) were dissolved in water (1 mL) and stirred for 4 days at 40 °C under an air atmosphere. After cooling down, 1 M aqueous ammonia was added (10 mL) and the mixture was extracted with ethyl acetate (40 mL × 3). The combined organic phases were dried on $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude N-arylated derivative, which was then purified by flash column chromatography, eluting with heptane/ethyl acetate mixtures, to give the pure N-arylated derivative **2**.
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