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Sequential Metal-Catalyzed *N*-Heteroarylation and C–C Cross-Coupling Reactions: An Expedient Route to Tris(hetero)aryl Systems

Jamie S. Siddle,[a] Andrei S. Batsanov,[a] and Martin R. Bryce*[a]

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This paper describes copper-catalyzed N–C heteroarylation of benzimidazole, 1-methylbenzimidazolone, imidazole and pyrrole. The products of these reactions then undergo palladium-catalyzed C–C cross-couplings with aryl or heteroarylboronic acids under Suzuki–Miyaura conditions to provide a rapid entry, from readily-available reagents, into tris(hetero)aryl scaffolds comprising two or three N-heterocyclic rings. The sequential N–C and C–C couplings can be performed in a one-pot process (two examples are given: >50 % overall yields).

Introduction

Arylated heterocycles are key structural motifs in a wide range of pharmaceuticals, agrochemicals, and organic functional materials, hence great effort has been devoted to their synthesis by a range of metal-catalyzed protocols.[1] Contemporary procedures can be readily performed with low catalyst loadings and good functional-group tolerance. These include C–heteroaryl bond formation by palladium-catalyzed Suzuki–Miyaura cross-coupling reactions of arylboronic acids/esters with heteroaryl halides,[2] or by direct functionalization of heterocyclic C–H bonds with aryl halides[1d] catalyzed by palladium[3] or copper species.[4] For heterocyclic *N*-arylation, which is relevant to the present work, the classical copper-promoted Ullmann reaction has been improved by the addition of a variety of ligands, such as diamines,[5] pipecolinic acid,[6] sterically hindered phosphanes,[7] a mixture of 1,10-phenanthroline and dibenzylideneacetone,[8] 4,7-dimethoxy-1,10-phenanthroline,[9] (*S*)-pyrrolidinylmethylimidazole,[10] *N*-hydroxyimides[11] or ninhydrin.[12] A CuCl-catalyzed *N*-arylation of imidazole with arylboronic acids has been developed in the absence of an additional chelating ligand.[13] Combined N(1)- and C(3)-arylations of 3-iodoindazole using boronic acids and $Cu(OAc)_2$ have been reported.[14] However, these methods require additional steps to synthesize the arylboronic acid. You et al. have very recently shown that imidazoles can be *N*-arylated with aryl and heteroaryl halides in the presence of base and a catalytic amount of CuI: an excess of imidazole improved the product yield and it was noted that the imidazole substrate may also function as a ligand in this process.[15] The CuOAc-mediated *N*-arylation of indoles and carbazole with aryl iodides under base-free and ligandless conditions has been reported.[16] New developments in palladium-[17] and iron-catalysed[18] *N*-arylations have also been reported recently.

While many important results have been achieved for *N*-arylations, it is notable that much less progress has been made for *N*-heteroarylations, i.e. analogous reactions with heteroaryl halides.[15] The development of this methodology is, therefore, of considerable interest. Herein we present a series of heterocyclic *N*-heteroarylation reactions and exploit further reaction at an active halide site in the products via Suzuki–Miyaura cross-coupling reactions leading to the expedient construction of tris(hetero)aryl scaffolds comprising two or three N-heterocyclic rings.[19]

Results and Discussion

We chose benzimidazole **1** and 1-methylbenzimidazolone **2** as starting reagents for the optimization of our strategy for two reasons: (i) their derivatives are widespread in structures of biological and medicinal importance;[20] (ii) their arylation reactions have been relatively neglected compared to other NH heterocycles; imidazole is most commonly used in this context.[3d,8,10,12,15,21] To confirm the versatility of the procedures, analogous reactions are also reported for imidazole (**3**) and pyrrole (**4**). The general concept of sequential N–C and C–C couplings leading to tris(hetero)aryl systems is depicted for benzimidazole in Scheme 1. The higher reactivity of iodides compared to bromides was exploited for selectivity in the reactions of the dihaloarenes in step 1. Scheme 2 depicts the N–C couplings and the specific examples are shown in Table 1.

In test reactions benzimidazole (**1**) reacted smoothly with 2-iodopyrimidine (**5a**) and 2-iodopyrazine (**6**) under modi-

[a] Department of Chemistry, Durham University, Durham DH1 3LE, UK
Fax: +44-191-384-4737
E-mail: m.r.bryce@durham.ac.uk
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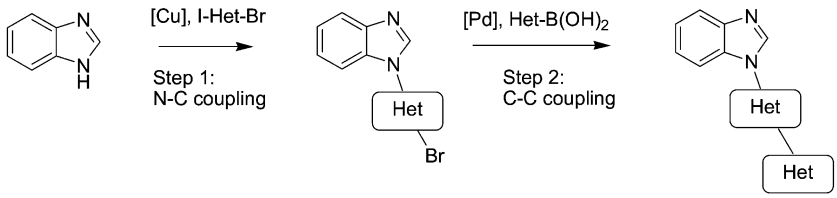
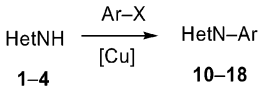


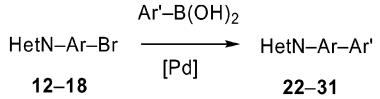
Scheme 1. Construction of tris(hetero)aryl scaffolds by sequential N–C and C–C couplings.



Scheme 2. Synthesis of **10**–**18**. For conditions see Table 1.

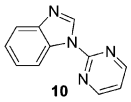
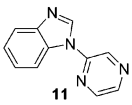
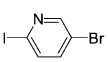
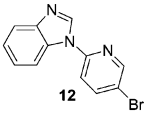
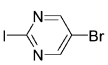
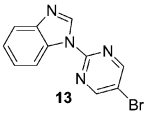
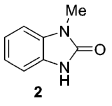
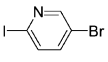
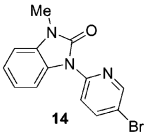
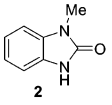
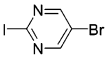
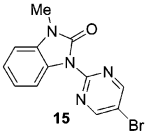
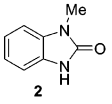
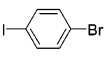
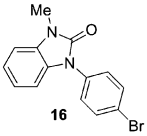
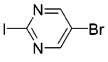
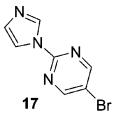
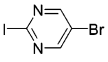
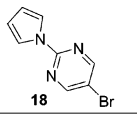
fied Ullmann conditions (Cs_2CO_3, CuI, 1,10-phenanthroline, DMF, 110 °C)[22] to afford the *N*-heteroarylated products **10** and **11** in 50% and 70% isolated yields, respectively (Table 1, Entries 1 and 2). The comparable reaction of **1** with 2-bromopyrimidine (**5b**) using the conditions developed by Cristau, Taillefer, et al.[5d] (Cs_2CO_3, Cu_2O, Schiff base ligand Chxn-py-al, acetonitrile, reflux) gave **10** in 78% yield. These workers found that the reaction of imidazole with 4-bromo-1-iodobenzene (1 equiv.) took place with complete regioselectivity at the iodine site. We have found that for reactions of the dihalo reagents **7** and **8** with the NH heterocycles **1**–**4** the optimum conditions to achieve selective displacement of the iodo substituent[23] are: **1**–**4** (1.2 equiv.), **7** or **8** (1.0 equiv.) Cs_2CO_3 (2.0 equiv.) CuI (10 mol-%) and 1,10-phenanthroline (10 mol-%) in DMF at 80 °C (Table 1, Entries 3–6, 8 and 9). Higher reaction temperatures (e.g. 110 °C as used in Entries 1 and 2) resulted in considerably lower product yields for reactions of **7** and **8**. The reaction of the less activated 4-bromo-1-iodobenzene (**9**) with benzimidazolone **2** (Entry 7) required a higher temperature (100 °C) for efficient formation of **16**. Table 1, Entries 3–9, show that moderate to high isolated yields were obtained for all the products **12**–**18**, which possess a bromo substituent suitable for a subsequent C–C (hetero)arylation reaction. The reactions of 5-bromo-2-iodopyridine (**7**) were especially efficient (Entries 3 and 5).

To accomplish step 2 of our strategy (Scheme 1) the compounds **12**–**18** were treated with the methoxyphenylboronic acid derivatives **19** and **20**, and the pyridylboronic acid derivative **21**[24–26] in Pd-catalyzed Suzuki–Miyaura reactions[2] to obtain the tris(hetero)aryl scaffolds **22**–**31** comprising two or three N-heterocyclic rings (Scheme 3). The alkoxy substituents on the aryl/heteroaryl boronic acids were chosen to ensure good solubility of the products. The results are collated in Table 2. Standard conditions using $Pd(PPh_3)_2Cl_2$ (ca. 5 mol-%) as catalyst, Na_2CO_3 (1 M) as base, in dioxane at 80 °C gave the products **22**–**26** in high



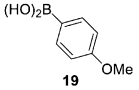
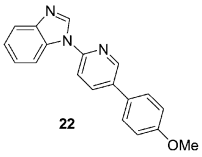
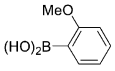
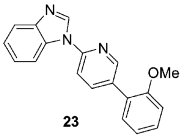
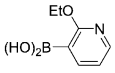
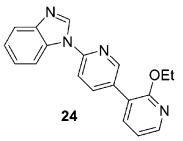
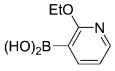
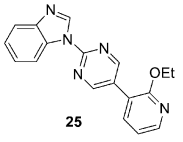
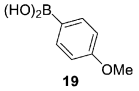
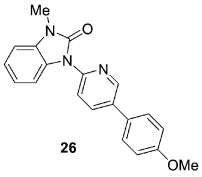
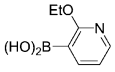
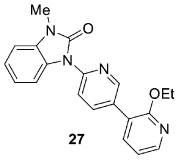
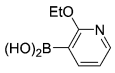
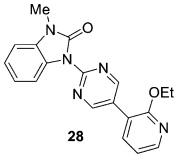
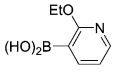
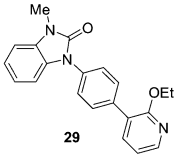
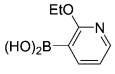
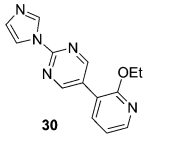
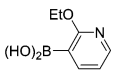
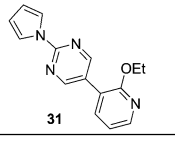
Scheme 3. Synthesis of **22**–**31**. For conditions see Table 2.

Table 1. Catalytic *N*-arylation/heteroarylation (N–C bond formation)[a].

Entry	HetNH	Ar–X	Product	Conditions, isolated yield (%)[b]
1	 **1**	 **5a** X = I **b** X = Br	 **10**	a, 50 (X = I) b, 78 (X = Br)
2	 **1**	 **6**	 **11**	a, 70
3	 **1**	 **7**	 **12**	c, 90
4	 **1**	 **8**	 **13**	c, 57
5	 **2**	 **7**	 **14**	c, 94
6	 **2**	 **8**	 **15**	c, 76
7	 **2**	 **9**	 **16**	d, 81
8	 **3**	 **8**	 **17**	c, 65
9	 **4**	 **8**	 **18**	c, 84

[a] Reaction conditions, a: **5a**, Cs_2CO_3, CuI, 1,10-phenanthroline, DMF, 110 °C; b: **5b**, Cs_2CO_3, Cu_2O, Schiff base ligand Chxn-py-al, acetonitrile, reflux; c: Cs_2CO_3, CuI, 1,10-phenanthroline, DMF, 80 °C; d: Cs_2CO_3, CuI, 1,10-phenanthroline, DMF, 80→100 °C. [b] The quoted yields are for isolated product after purification by chromatography and/or recrystallization.

Table 2. Suzuki–Miyaura cross-couplings (C–C bond formation).[a]

Entry	HetN-Ar-Br	Ar–B(OH)$_2$	Product	Conditions, isolated yield (%)[b]
1	**12**	 **19**	 **22**	a, 74
2	**12**	 **20**	 **23**	a, 96
3	**12**	 **21**	 **24**	a, 96
4	**13**	 **21**	 **25**	a, 79
5	**14**	 **19**	 **26**	a, 76
6	**14**	 **21**	 **27**	a, 0 b, 67 c, 54
7	**15**	 **21**	 **28**	a, 0 b, 43
8	**16**	 **21**	 **29**	a, 30 b, 83
9	**17**	 **21**	 **30**	a, 48
10	**18**	 **21**	 **31**	a, 78

[a] Reaction conditions, a: $Pd(PPh_3)_2Cl_2$, 1,4-dioxane, Na_2CO_3 (1 M), 80 °C; b: $Pd(PPh_3)_4$, 1,4-dioxane, Na_2CO_3 (1 M), 80–90 °C; c: $[Pd_2(dba)_3]$, 1,4-dioxane, K_3PO_4 (1.27 M), 100 °C. [b] The quoted yields are for the isolated product after purification by chromatography and/or recrystallization.

yields (Entries 1–5). To our surprise, applying these conditions to attempted reactions of **14** and **15** with boronic acid derivative **21** failed to yield any product – unreacted starting materials were recovered in near quantitative yield (Entries 6 and 7, conditions a). When the catalyst was changed to $Pd(PPh_3)_4$ (with Na_2CO_3 as base) or $[Pd_2(dba)_3]$ (with K_3PO_4 as base)[27] product **27** was obtained in 67 and 54% yields, respectively (Entry 6, conditions b, c). Similarly, conditions b gave **28** in 43% yield. A general trend was that the Suzuki–Miyaura reactions were less efficient in the benzimidazolone series, especially Entries 6–8, compared to benzimidazole, imidazole and pyrrole analogs (Entries 1–4, 9, 10).

Analogous one-pot, two-stage procedures gave compounds **25** and **28** starting from benzimidazole (**1**) and 1-methylbenzimidazolone (**2**) in 67% and 52% overall yields, respectively.

The molecular structure of **22** obtained by X-ray crystallographic analysis is shown in Figure 1.

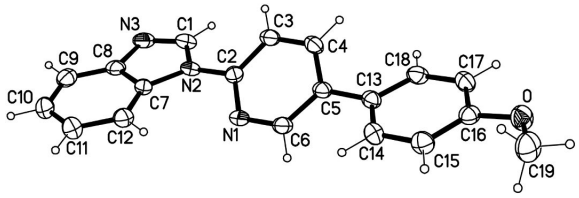


Figure 1. X-ray molecular structure of compound **22** (50% thermal ellipsoids). Dihedral angles [°]: benzimidazole/pyridine 30.7, pyridine/benzene 27.2, benzene/methoxy 10.2.

Conclusions

In summary, we have disclosed a series of reactions which constitute expedient and powerful methodology for the synthesis of new multi-heteroaryl scaffolds by a combination of N–C heteroarylation and C–C cross-couplings. Functionalized benzimidazole, benzimidazolone, imidazole and pyrrole derivatives have thereby been obtained. This protocol complements existing strategies which are of great importance in diverse areas of heterocyclic chemistry, especially the development of new molecular templates for drug discovery and materials chemistry applications. The practical benefits include readily-available and inexpensive starting materials, substrate versatility, experimentally straightforward procedures and good product yields. The sequential N–C and C–C couplings can be performed in a one-pot process in >50% overall yields.

Experimental Section

General: Details of equipment and techniques used are the same as those we have reported previously.[28] All synthetic reagents were used as supplied. Solvents were dried and distilled using standard procedures. All reactions were performed under dry argon.

General Procedure for the *N*-Arylation/Heteroarylation Reactions of N-Heterocycles with Aryl/Heteroaryl Iodides: The halide (4.1 mmol)

and 1,10-phenanthroline (0.40 mmol) was added sequentially to a mixture of the N-heterocycle (4.8 mmol), CuI (0.20 mmol) and Cs_2CO_3 (8.0 mmol) in dry degassed DMF (4 mL). The mixture was stirred and heated under argon at 80 °C until TLC monitoring showed that the reaction was complete (typically ca. 24 h). The reaction mixture was cooled to room temperature, diluted with ethyl acetate (10 mL) and washed through a pad of silica gel with ethyl acetate (ca. 40 mL) to remove inorganic materials. The eluent was concentrated in vacuo and the product was purified either by recrystallization or by chromatography on a silica gel column.

1-(5-Bromopyridin-2-yl)-1*H*-benzimidazole (12): Chromatography (eluent EtOAc/Et_2O, 9:1 v/v) yielded **12** as a white solid in 90% yield, m.p. 159.6–160.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.61 (d, J = 2.0 Hz, 1 H), 8.51 (s, 1 H), 8.00–7.94 (m, 2 H), 7.86–7.84 (m, 1 H), 7.44 (dd, J = 8.4, 0.4 Hz, 1 H), 7.39–7.32 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.7, 148.8, 145.0, 141.7, 141.3, 132.2, 124.7, 123.8, 121.1, 117.9, 115.4, 112.9 ppm. IR ($\tilde{\nu}_{max}$ =): $\tilde{\nu}$ = 3080, 3051, 1578, 1499, 1476, 1203, 741 cm^{-1}. MS (EI): m/z = 273 (100) [M^+, ^{79}Br], 275 (97) [^{81}Br]. $C_{12}H_8BrN_3$ (274.1): calcd. C 52.58, H 2.94, N 15.33; found C 52.53, H 2.83, N 15.19.

General Procedure for the Suzuki–Miyaura Cross-Coupling Reactions with Aryl/Heteroaryl Boronic Acids: Aqueous Na_2CO_3 (1 M, 4 mL) was added to a mixture of the aryl halide (1.8 mmol), the boronic acid (2.0 mmol) and catalyst (0.1 mmol) in 1,4-dioxane (8 mL). The mixture was stirred and heated at 80 °C until TLC monitoring showed that reaction was complete. The mixture was cooled to room temperature, solvent was removed in vacuo and EtOAc (50 mL) was added to the residue which was washed with brine (3 × 50 mL). The organic layer was separated, concentrated in vacuo and the product was purified by chromatography on a silica gel column.

1-[5-(2-Ethoxypyridin-3-yl)pyridin-2-yl]-1*H*-benzimidazole (24): Chromatography (eluent EtOAc/dichloromethane, 10:1 v/v) yielded **24** as a white solid in 96% yield, m.p. 106.9–107.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.80 (d, J = 2.0 Hz, 1 H), 8.62 (s, 1 H), 8.21 (dd, J = 4.8, 1.6 Hz, 1 H), 8.15 (dd, J = 8.8, 2.8 Hz, 1 H), 8.11 (dd, J = 7.2, 1.2 Hz, 1 H), 7.88 (dd, J = 7.2, 1.6 Hz, 1 H), 7.69 (dd, J = 7.2, 2.0 Hz, 1 H), 7.63 (d, J = 8.0 Hz, 1 H), 7.42–7.34 (m, 2 H), 7.02 (dd, J = 7.2, 5.2 Hz, 1 H), 4.47 (q, J = 7.2 Hz, 2 H), 1.41 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.9, 149.7, 149.0, 147.3, 145.1, 141.7, 139.7, 138.6, 132.5, 131.3, 124.6, 123.6, 121.0, 120.3, 117.4, 113.8, 113.0, 62.5, 14.9 ppm. MS (EI) m/z 316 (M^+ 100%). HRMS (ES+) calcd. for $C_{19}H_{16}N_4O$+H: m/z 317.13969; found m/z 317.13975. IR: $\tilde{\nu}$ = 3141, 2975, 2901, 1589, 1494, 1457, 1230, 1037, 731 cm^{-1}.

1-[5-(2-Ethoxypyridin-3-yl)pyrimidin-2-yl]-1*H*-benzimidazole (25). One-Pot Procedure: 5-Bromo-2-iodopyrimidine (**7**, 0.570 g, 2.0 mmol) and 1,10-phenanthroline (0.072 g, 0.40 mmol) were added to a mixture of benzimidazole (**1**, 0.284 g, 2.4 mmol), Cs_2CO_3 (1.304 g, 4.0 mmol) and CuI (0.038 g, 0.20 mmol) in dry degassed DMF (4 mL). The mixture was stirred and heated under argon at 80 °C until TLC monitoring showed the reaction was complete (17 h). There was then added, under argon, (2-ethoxypyridin-3-yl)boronic acid (**21**, 0.367 g, 2.2 mmol), $Pd(PPh_3)_2Cl_2$ (0.084 g, 0.12 mmol), 1,4-dioxane (10 mL) and Na_2CO_3 (1 M, 4.4 mL) and stirring was continued at 80 °C for 17 h. The reaction was cooled to room temperature, the solvent removed in vacuo and EtOAc (100 mL) was added to the residue which was washed with brine (3 × 50 mL). The organic layer was separated, dried with $MgSO_4$ and concentrated in vacuo. The product was purified by column chromatography on silica (eluent DCM/EtOAc, 1:1 v/v) to yield **25** as a white solid (0.425 g, 67%) spectroscopically identical to the sample prepared by the two-step procedure, as described in the Supporting Information.

Supporting Information (see also the footnote on the first page of this article): Experimental methods (p. S2–S9), copies of NMR spectra (p. S10–S28.

CCDC-665603 contains supplementary crystallographic data for compound **22**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk./data_request/cif.

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