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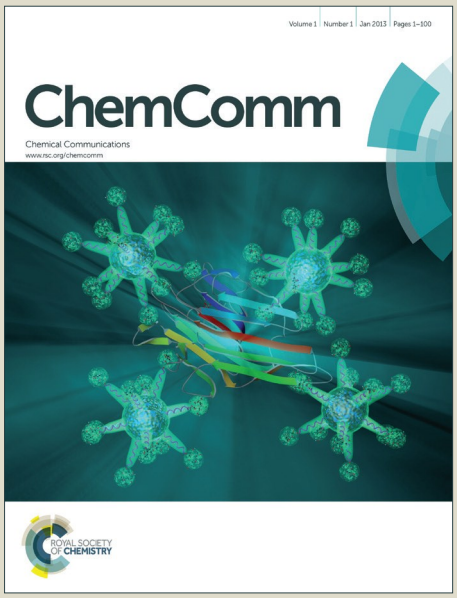

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Synthesis of 2-BMIDA 6,5-bicyclic heterocycles by Cu(I)/Pd(0)/Cu(II) cascade catalysis of 2-iodoaniline/phenols

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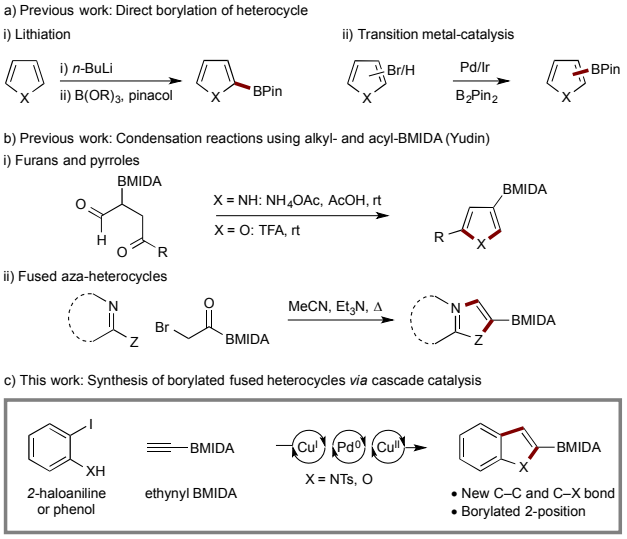
A one-pot cascade reaction for the synthesis of 2-BMIDA 6,5-bicyclic heterocycles has been developed using Cu(I)/Pd(0)/Cu(II) catalysis. 2-Iodoanilines and phenols undergo a Cu(I)/Pd(0)-catalyzed Sonogashira reaction with ethynyl BMIDA followed by in situ Cu(II)-catalyzed 5-endo-dig cyclization to generate heterocyclic scaffolds with a BMIDA functional group in the 2-position. The method provides efficient access to borylated indoles, benzofurans, and aza-derivatives, which can be difficult to access through alternative methods.

Bicyclic heterocycles are valuable throughout synthetic and medicinal chemistry due to their prevalence as the core scaffold of many bioactive molecules.[1] The utility of heterocyclic building blocks in chemical synthesis can be greatly enhanced by the addition of a reactive boron functional group. These motifs enable relatively facile installation of additional functionality *via* various well-established chemistries including the Suzuki–Miyaura and Chan–Evans–Lam reactions.[2,3] Accordingly, methods for the preparation of borylated heterocyclic scaffolds remain highly prized.

Typical methods for the formation of borylated heterocycles involve the formation of a C-B bond *via* stoichiometric metallation (Scheme 1a(i))[4] or transition metal-catalyzed borylation using Pd[5] or Ir[6] catalysts (Scheme 1a(ii)). Recent advances from the Yudin group have exploited the stability of alkyl BMIDA reagents in condensation reactions, providing a route to various borylated heterocycles but without the formation of a C-B bond (Scheme 1b).[7]

Herein, we report the synthesis of 2-borylated 6,5-bicyclic heterocycles using a Cu(I)/Pd(0)/Cu(II) cascade catalysis approach (Scheme 1c).[8,9] This method enables the one-pot, modular preparation of 2-borylated indoles and benzofurans, including aza-derivatives, using simple iodoanilines or iodophenols in conjunction with ethynyl BMIDA. In addition, we demonstrate the utility of the generated products within subsequent chemoselective cross-coupling processes as well as their application as precursors toward the formation of oxindoles and benzofuranones.



Scheme 1 Approaches towards borylated heterocycles.

The formation of indoles and benzofurans *via* the Sonogashira reaction of 2-haloanilines and phenols with alkynes, followed by *in situ* Cacchi-type intramolecular cyclization has been thoroughly investigated.[10] We identified that the use of a suitable borylated alkyne could enable the same annulation but generate products that are borylated in the 2-position. Acetylynic BMIDA reagents have been used under Rh- and Au-catalysis to effect similar annulation processes.[11-13] Accordingly, our study commenced with the reaction of *N*-tosyl 2-iodoaniline (**1**) with ethynyl BMIDA (**3**). Initial experiments based on literature reaction conditions[10] led to good conversion to the Sonogashira product intermediate (not shown);[14] however, the subsequent cyclization event was inefficient, providing the desired product **4a** in only 19% yield (entry 1). Increasing the quantity of CuI led only to a small increase in conversion to **4a** (entry 2). $Cu(OAc)_2$ is known to facilitate similar 5-*endo*-dig cyclizations[15] and while addition of 50 mol

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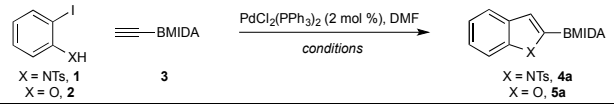
% $Cu(OAc)_2$ delivered a significant increase in conversion to **4a**, we noted a considerable quantity of Glaser–Hay homocoupling of **3** (entry 3).[16] However, following a survey of reaction conditions including catalyst loading, base, and temperature, alkyne homocoupling could be mitigated, delivering an efficient set of reaction conditions that produced **4a** in 83% yield (entry 4 – see Electronic Supporting Information (ESI) for full details). The balance of base and temperature was particularly crucial to avoid premature hydrolysis of the generated heterocyclic BMIDA residue and subsequent protodeboronation of the resulting heterocyclic boronic acid. In addition, control reactions demonstrated the requirement of all three catalysts – removal of either CuI or $Cu(OAc)_2$ led to diminished yields (entries 5 and 6). Removal of $Cu(OAc)_2$ gave effective Sonogashira cross-coupling but ineffective ring closure, providing **4a** in only 22% yield (entry 5). Removal of CuI was found to hinder the Sonogashira step; however, **4a** was obtained in a moderate 63% yield. We believe this was due to adventitious Cu(I) arising from either trace levels in the unpurified $Cu(OAc)_2$ or disproportionation of Cu(II) to Cu(I).[17]

Table 1 Reaction development.[a]

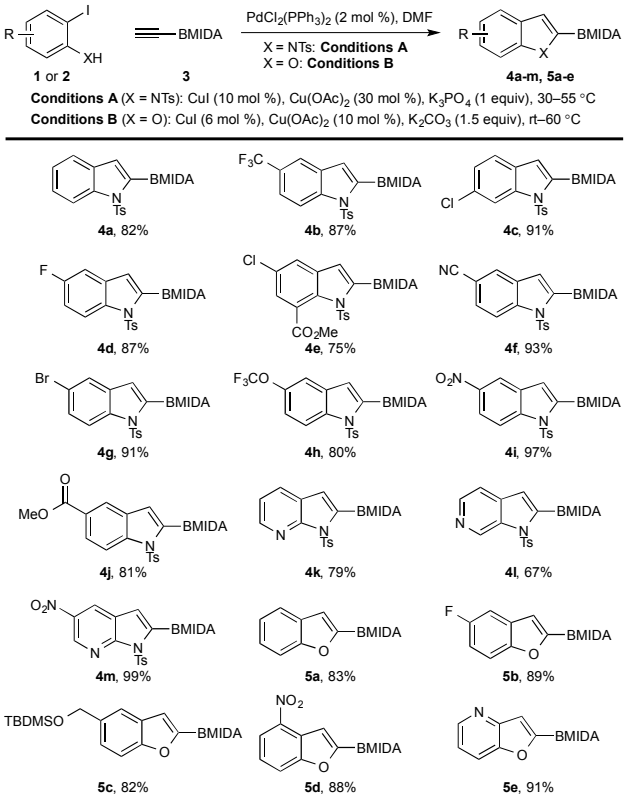


entry	reaction conditions	X	yield (%)[b]
1	CuI (20 mol %), Et_3N, 60 °C	NTs	19%
2	CuI (50 mol %), Et_3N, 60 °C	NTs	31%
3	CuI (50 mol %), $Cu(OAc)_2$ (50 mol %), Et_3N, 60 °C	NTs	62%
4	CuI (10 mol %), $Cu(OAc)_2$ (30 mol %), K_3PO_4, 30–55 °C	NTs	83%
5	CuI (10 mol %), K_3PO_4, 30–55 °C	NTs	22%
6	$Cu(OAc)_2$ (30 mol %), K_3PO_4, 30–55 °C	NTs	63%
7	CuI (10 mol %), $Cu(OAc)_2$ (30 mol %), K_3PO_4, 30–55 °C	O	32%
8	CuI (10 mol %), $Cu(OAc)_2$ (30 mol %), K_3PO_4, rt–60 °C	O	51%
9	CuI (10 mol %), $Cu(OAc)_2$ (30 mol %), K_2CO_3, rt–60 °C	O	62%
10	CuI (6 mol %), $Cu(OAc)_2$ (10 mol %), K_2CO_3, rt–60 °C	O	87%

[a] **1/2** (1 equiv, 0.25 mmol, 0.125 M), **3** (1.2 equiv, 0.3 mmol), $PdCl_2(PPh_3)_2$ (2 mol %), Cu cat. (see Table), base (see Table), DMF, temp. (see Table), N_2. [b] Determined by HPLC analysis using an internal standard.

With effective conditions for substrate **1** established, we turned our attention to the analogous benzofuran formation from 2-iodophenol, **2**. However, the preferred conditions for indole formation delivered only 32% yield of **5a**, with the mass balance consisting of unreacted starting material and homocoupled alkyne (entry 7). Alteration of the temperature profile improved conversion but Glaser–Hay coupling remained problematic (entry 8). Modification of the base to K_2CO_3 provided an additional increase (entry 9) while lowering the loading of Cu-catalysts provided the most significant improvements to deliver 87% yield of **5a** with minimal alkyne homocoupling (Table 1, entry 10).

With effective reaction conditions in place, we assessed the generality of the process (Scheme 2).



Scheme 2 Scope of the annulation process.

The developed process was found to be generally high yielding for indole (**4a-m**) and benzofuran (**5a-e**) substrates, including various aza-derivatives (**4k**, **4l**, **4m**, **5e**). Due to the mild reaction conditions, a wide range of standard functional groups was tolerated, including esters (**4e**, **4j**), ethers (**4h**, **5c**), halides (**4c**, **4d**, **4e**, **4g**, **5b**), nitriles (**4f**), and nitro groups (**4i**, **4m**, **5d**). In addition, the process was also found to be amenable on preparatively useful (mmol) scale (Figure 1) and chromatographic purification was often not required – products could be isolated cleanly following aqueous work-up and subsequent precipitation/filtration.[18]

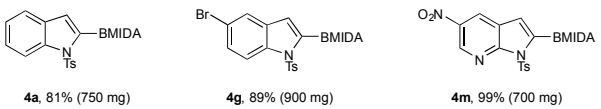


Figure 1 Annulation reactions on 1.5-2.0 mmol scale. Values in parentheses are isolated masses of material.

Electrophile-chemoselective Sonogashira cross-coupling allowed use of dihalide starting materials to furnish Br- and Cl-bearing products (**4c**, **4e**, **4g**), providing a handle for further functionalisation *via* cross-coupling processes. For example, **4g** participates in chemoselective Suzuki–Miyaura cross-coupling

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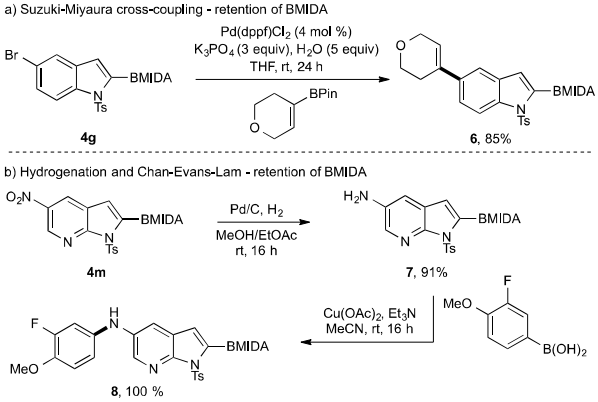
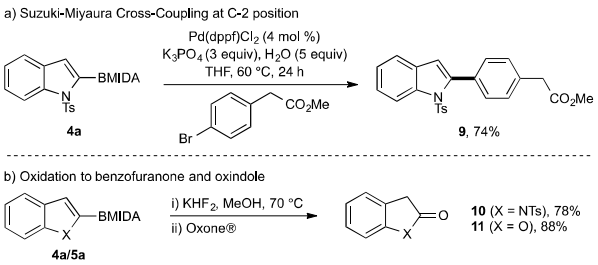
with retention of the BMIDA unit (Scheme 3a).[11,19] The robust BMIDA protecting group allows hydrogenation of nitro aza-indole **4m** to give the corresponding amino aza-indole **7**, which can undergo chemoselective Chan–Evans–Lam coupling to generate products such as **8** in excellent yield (Scheme 3b). As 7-aza-indoles are valuable kinase hinge-binders,[20] the developed method therefore provides expedient access to desirable multi-functional intermediates that can be used for exploration of this chemotype in kinase drug discovery.



Scheme 3 Product utility with retention of BMIDA.

Importantly, the BMIDA unit of the products was amenable to manipulation. Suzuki–Miyaura cross-coupling was effective under our previously developed, mild reaction conditions (Scheme 4a);[19,21] increased temperatures or imbalance in the base/H_2O stoichiometry led to considerable levels of protodeboronation. Lastly, oxidation of the BMIDA unit of both indole **4a** and benzofuran **5a** could be achieved using Oxone®, *via in situ* preparation of the BF_3K derivative,[22,23] to deliver oxindole **10** and benzofuranone **11** (Scheme 4b). Oxindoles are also an important kinase hinge-binding motif; the developed process allows access to intermediates that can be diverted to two different chemotypes and therefore gives a new approach to diversity-oriented synthesis within kinase drug discovery.[24]



Scheme 4 Manipulation of the BMIDA unit.

In summary, we have developed a one-pot tandem reaction for the synthesis of borylated heterocycles from simple and readily available starting materials. Synthetically valuable functionalized 2-BMIDA-substituted indoles and benzofurans, as well as aza-derivatives, are generated using the described chemoselective Cu(I)/Pd(0)/Cu(II) catalysis method. Based on the utility of the BMIDA unit, the products can be manipulated in several ways to allow access to functionalised heterocyclic scaffolds that have significant potential for application, particularly within drug discovery.

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