Intramolecular cross-coupling of *gem*-dibromoolefins: a mild approach to 2-bromo benzofused heterocycles†‡

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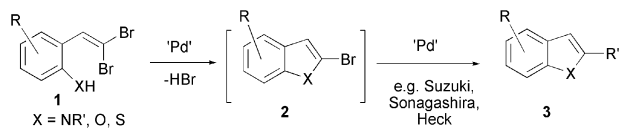
Highly useful halogenated benzofurans and benzothiophenes are prepared from readily available *gem*-dibromoolefins using a mild, ligand-free copper catalyzed cross-coupling procedure.

Halogenated heterocycles are of significant value in the synthesis of natural and unnatural products due to their reactivity and ease of derivatization.[1] The most straightforward method for their synthesis is by treatment of the unsubstituted parent substrate with an electrophilic halogen source. For benzofused heterocycles such as benzofurans, benzothiophenes, and indoles, this typically provides access to 3-halogenated substrates, which have found frequent application in organic synthesis.[2] In contrast, 2-substituted benzofused heterocycles are less accessible, typically requiring lithiation,[3] which introduces issues of regioselectivity, scalability, and functional group compatibility. There is a clear need for the development of milder conditions for the formation of 2-halogenated benzofused heterocycles.

We and others have recently devoted attention to the synthesis of 2-substituted indoles and other benzofused heterocycles by tandem intra- and intermolecular cross-coupling reactions of *gem*-dihaloolefins **1** (Scheme 1).[4] Mechanistic studies suggest that the predominant reaction pathway involves first an intramolecular carbon–heteroatom coupling to form heterocycles **2**, followed by intermolecular cross-coupling (*e.g.* Suzuki, Sonagashira, Heck) to form substrates **3**.[4e] This is in contrast to the more commonly observed selectivity for the cross-coupling of *gem*-dihaloolefins, which typically react first at the (*E*)-halide.[5] Interestingly, in the absence of an external coupling partner, the proposed intermediate **2** is not observed, instead providing only recovered starting material. Herein, we report our findings on how to gain access to desirable 2-bromobenzofused heterocycles by a selective intramolecular cross-coupling procedure.



Scheme 1 Synthesis of 2-substituted heterocycles by tandem cross-coupling.

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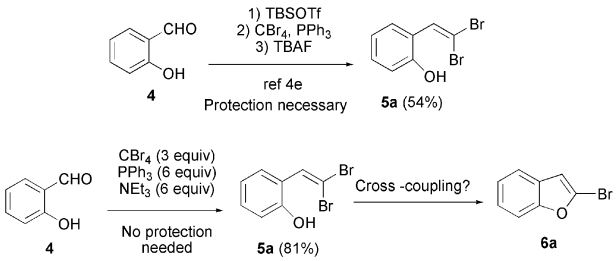
‡ Electronic supplementary information (ESI) available: Experimental procedures and characterization data. See DOI: 10.1039/b912093a

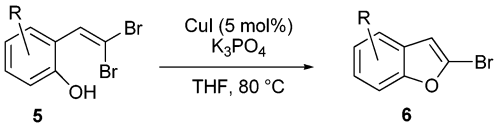


Scheme 2 Protecting group-free synthesis of *gem*-dibromovinyl phenols.

Our initial efforts focused on the synthesis of 2-bromobenzofurans. A very limited number of this family of substrates have been previously reported, most of which are synthesized through a lithiation protocol. While this method has proven effective for unsubstituted benzofuran, it is incompatible with substrates bearing substituents around the aryl ring, especially base sensitive or *ortho*-directing groups.[6] Previous studies in our lab used commercially available salicylaldehyde **4** and derivatives as precursors to *gem*-dibromoolefin **5a** by a 3-step route (Scheme 2). We believed that **5a** and derivatives could be used for the synthesis of 2-bromobenzofurans such as **6a**. In the interest of making this route more attractive, we first investigated the Ramirez olefination[7] of salicylaldehydes, and identified protecting group-free conditions. Preformation of 3 equivalents of the active PPh_3CBr_2 ylid, followed by slow addition of NEt_3 and salicylaldehyde **4**, provided *gem*-dibromoolefin **5a** in 81% yield. The use of excess ylid and the slow addition of reagents were necessary for high yields. This protocol may be applicable to the protecting group-free Ramirez olefination of other aldehydes containing Lewis basic groups.

With this improved starting material synthesis in hand, we screened conditions for the selective intramolecular cross-coupling reaction of phenol **5a** to form benzofuran **6a**. Studies with palladium catalysis proved ineffective, often providing recovered starting material or a complex mixture of products. Conversely, the use of copper as a cross-coupling catalyst gave cleaner reaction and enabled us to develop a highly effective catalytic system.[8] When phenol **5a** was treated with K_3PO_4 and catalytic CuI at 80 °C in THF, 2-bromobenzofuran **6a** was formed with complete selectivity in 89% yield (Table 1, entry 1). Many different copper species were effective catalysts, with good conversion being obtained with 5 mol% CuI, $CuCl_2$, and Cu^0 (powder). The choice of base was important, with organic bases such as NEt_3 giving reduced reactivity, and Cs_2CO_3

Table 1 Synthesis of benzofurans by intramolecular Ullmann coupling[a]



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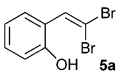
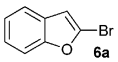
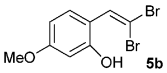
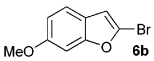
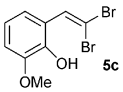
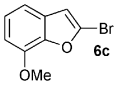
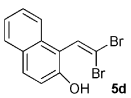
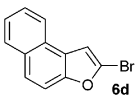
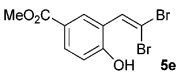
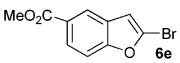
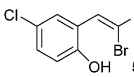
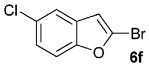
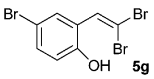
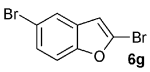
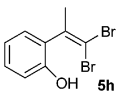
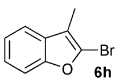
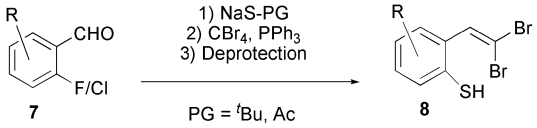
1			93
2			89
3			95
4			89
5			93
6			99
7			96
8			52[b]

[a] Conditions: 5 mol% CuI, 2 equiv. K_3PO_4, 80 °C, 6 h, THF (0.2 M). [b] Purification by flash chromatography.

giving complex reaction mixtures. The choice of solvent and temperature was also important, with several unidentified by-products being formed at higher temperatures, especially in non-polar solvents such as toluene.[9] Of particular note is the use of ligand-free conditions, which greatly simplifies the reaction and work-up procedure, enabling purification to be accomplished by simple filtration of the reaction mixture through silica gel.[10]

Following optimization, the scope of the reaction was evaluated (Table 1). Subjecting a number of *gem*-dibromoolefins with electron-withdrawing (entries 2 and 3) and -donating (entries 4 and 5) substituents to the optimized reaction conditions gave the expected 2-bromobenzofurans in excellent yields. Halogen substituents on the aryl ring were also tolerated, giving polyhalogenated benzofurans **6f** and **6g** which may be useful for regioselective cross-coupling (entries 6 and 7).[11] More sterically encumbered tetra-substituted olefin **5h** could also undergo regioselective cross-coupling to give 3-substituted benzofuran **6h** (entry 8).

Following the study of benzofurans, we turned our attention to the synthesis of benzothiophenes. Our lab has recently developed a general methodology for the synthesis of

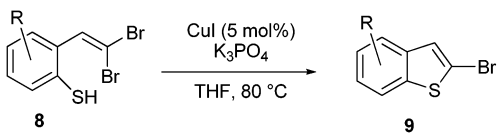


Scheme 3 Synthesis of benzothiophene precursors.

thiophenols **8** by nucleophilic aromatic substitution, Ramirez olefination, and deprotection of commercially available 2-fluoro- and 2-chlorobenzaldehydes **7** (Scheme 3).[12] Treatment of these substrates with the conditions optimized for the synthesis of benzofurans gave the corresponding 2-bromobenzothiophenes **8** in excellent yields (Table 2). Electron-neutral (entry 1), -poor (entry 2), and -rich (entries 3 and 4)[13] substrates smoothly underwent cross-coupling. Halogenated derivatives could also be used with complete selectivity (entries 5–8). Notably, *gem*-dichloroolefin **8i** could be converted to 2-chlorobenzothiophene **9i** under the general conditions (entry 9).

Having developed a novel procedure for the synthesis of halogenated benzofurans and benzothiophenes, we sought to

Table 2 Synthesis of benzothiophenes by intramolecular Ullmann coupling[a]



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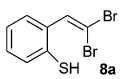
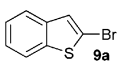
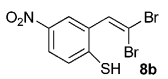
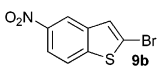
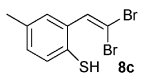
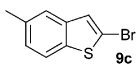
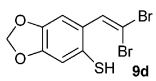
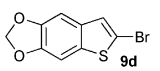
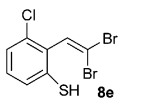
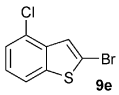
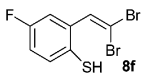
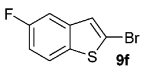
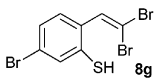
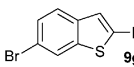
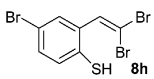
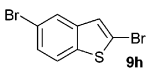
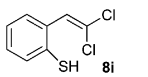
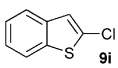
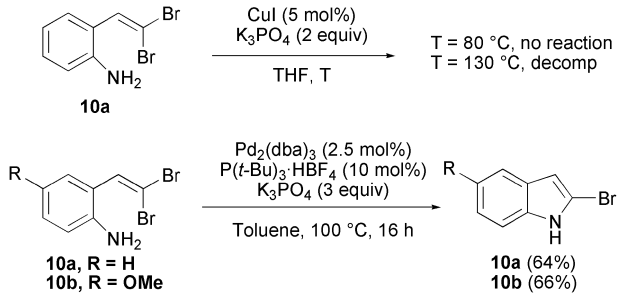
1			84
2			88
3			99
4			74[b]
5			91
6			82
7			91
8			96
9			62[b]

[a] Conditions: 5 mol% CuI, 2 equiv. K_3PO_4, 80 °C, 6 h, THF (0.2 M). [b] Purification by flash chromatography.



Scheme 4 Preliminary finding on the synthesis of 2-bromoindoles.

extend this methodology to indoles. Unfortunately, applying the general copper conditions to aniline **10a** gave complete recovery of starting material (Scheme 4). Increasing the reaction temperature gave no conversion until approximately 130 °C, at which point starting material decomposed. Exhaustive screening of bases, solvents, and ligands failed to reveal effective conditions. Reinvestigation of palladium catalyzed Buchwald–Hartwig conditions generally gave no conversion of starting material. However, when P(*t*-Bu)$_3$ was used as a ligand, 2-bromoindoles **11a** and **11b** could be obtained in 64% and 66% yield.[14] Further studies into the optimization, scope, and mechanism of this transformation are currently underway.

In summary, we have developed a method for the synthesis of a wide range of novel halogenated benzofused heterocycles. *gem*-Dibromoolefins are used as readily accessible precursors, ligand-free conditions were employed, and purification by flash chromatography is unnecessary, making this method highly efficient. We expect these substrates will become useful building blocks for the synthesis of more complex heterocycles, similar to the better known 3-halogenated isomers.

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Notes and references

1 For reviews on halogenated and metalated heterocycles, see: (*a*) R. Chinchilla, C. Nájera and M. Yus, *Chem. Rev.*, 2004, **104**, 2667–2722; (*b*) S. Cacchi and G. Fabrizi, *Chem. Rev.*, 2005, **105**, 2873–2920.

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