Domino C–O/C–N Bond Formation

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Copper-Catalyzed Cross-Coupling Interrupted by an Opportunistic Smiles Rearrangement: An Efficient Domino Approach to Dibenzoxazepinones**

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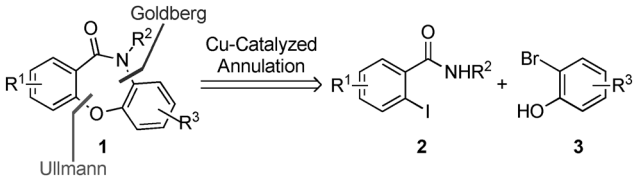
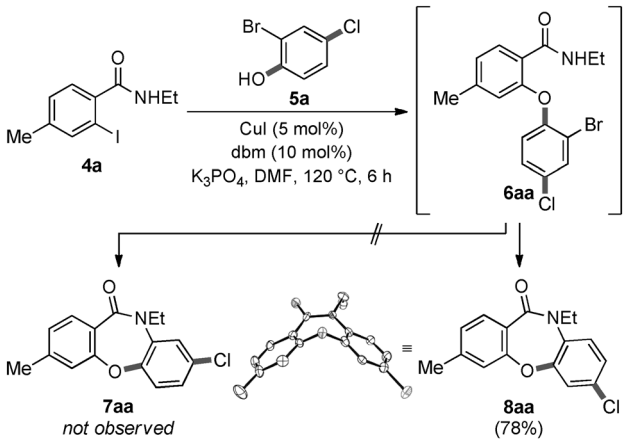
The construction of C–O and C–N bonds by palladium- and copper-mediated cross-coupling approaches has undergone a renaissance in the last decade.[1] Although the utility of these coupling approaches to effect a single-bond construction event has now been established, the quest to improve efficiency has driven the further exploration of one-pot procedures for effecting multiple transformations, often by a domino[2] approach. Success in this area has come from impressive examples of ligand control,[3] finely tuned multicatalyst systems,[4] and exploitation of established multicomponent reactions.[5] Based on our previous experience with Ullmann[6] couplings of 2-halobenzamides,[7] combined with the established Goldberg *N*-arylation methods,[1b,8] we envisaged that a copper-catalyzed one-pot annulation between 2-iodobenzamides **2** and 2-bromophenols **3** would allow access to dibenzoxazepinones **1** by selective C–O and C–N bond forming events (Scheme 1).[9]



Scheme 1. Initial retrosynthetic analysis of dibenzoxazepinones **1**.

We herein report an unusual and highly selective copper-initiated domino synthesis of dibenzoxazepinones that includes the formal C–N coupling of secondary benzamides assisted by an unexpected Smiles rearrangement. Most strategies to **1** are classical, multistep processes.[10] Our efficient, modular, and convergent approach utilizes either commercially available or readily prepared starting materials and incorporates the effective directed *ortho* metalation strategy.[11] This allows for rapid construction, either singly or in library format, of this class of tricyclics, which constitute attractive synthetic targets due to their varied and extensive biological activity.[12]

Considerable optimization (see the Supporting Information) demonstrated that using CuI as catalyst, dibenzoylmethane (dbm) as ligand, K_3PO_4 as base, and DMF as solvent is optimal for this process, giving a tricyclic product in 78% yield (Scheme 2). A remarkable switch in selectivity was



Scheme 2. Initial study of copper-catalyzed annulations to dibenzoxazepinones.

observed when the apolar solvent toluene was used. This produced the diaryl ether **6aa** (69% yield), arising from an Ullmann coupling, as the only product. Control experiments performed without ligand showed that CuI alone was capable of catalyzing the transformation, albeit in reduced and irreproducible yield. Performing the reaction in the absence of both CuI and ligand led to complete recovery of iodide **4a**. The structure of the tricyclic product was established by 2D NMR spectroscopy and X-ray crystallographic analysis. To our surprise, the expected Goldberg arylation product **7aa** had not been formed. Instead, the rearranged compound **8aa**, in which the oxygen and chlorine atoms share a *meta*- rather than the expected *para*-relationship, was the sole product. We reasoned that this product arose from interception of the initially formed diaryl ether **6aa** by a Smiles rearrangement, instead of the expected C–N Goldberg coupling process (see below). Having established optimized conditions, we examined the reaction scope with respect to the amide

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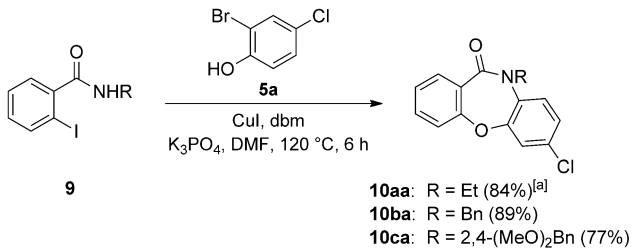
N-substituent, which demonstrated that simple alkyl, benzyl, and 2,4-dimethoxybenzyl groups were equally well tolerated (Scheme 3).



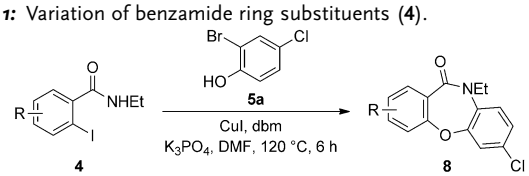
Scheme 3. Copper-catalyzed coupling–annulation of benzamides **9** with 2-bromo-4-chlorophenol (**5a**). [a] 78% yield was obtained when the reaction was conducted using 10 g (36 mmol) of **9a**.

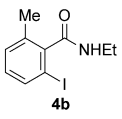
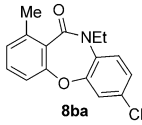
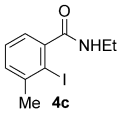
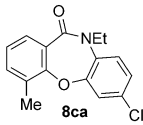
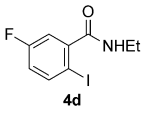
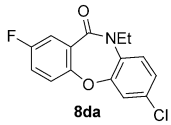
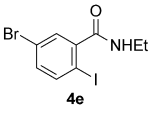
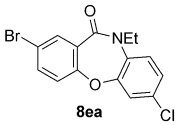
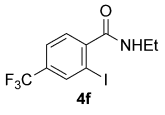
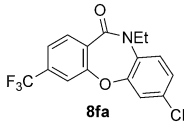
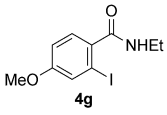
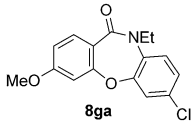
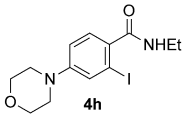
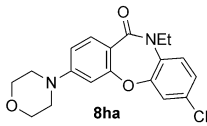
With these encouraging results in hand, the coupling–annulation of variously substituted *N*-ethyl-2-iodobenzamides **4** with 2-bromo-4-chlorophenol (**5a**) was undertaken (Table 1). In terms of the effect of structural features, introducing steric hindrance *ortho* to the amide proved detrimental to the reaction, with the desired product **8ba** being isolated in only 14% yield after 6 h. However, increasing the reaction time to 24 h led to a synthetically useful 50% yield of **8ba** (entry 1), along with small amounts of an isomeric tricyclic compound, which was assigned as the Goldberg coupled product **7ba** on the basis of 2D NMR spectroscopy (see the Supporting Information).[13] A hindered 3-methyl benzamide **4c** was well tolerated, as were amides bearing halogens (entries 3 and 4), an electron withdrawing group (entry 5), and electron donating groups (entries 6 and 7). Significantly, the Smiles rearranged products were formed in all cases, as shown by either X-ray crystallographic analysis or 2D NMR spectroscopy.

To explore the scope of electronically and sterically differentiated 2-bromophenols in the observed Smiles rearrangement (Table 2), the isomeric 2-bromocresols **5c** and **5d** were exposed to the standard reaction conditions, resulting in the formation of rearranged products **8ac** and **8ad**, albeit in low yield, with large amounts of the uncyclized biaryl ethers also isolated. As in the previous case, simply extending the reaction time to 24 h and 48 h, respectively, led to increased yields (entries 2 and 3). 1-Bromo-2-naphthol also performed well in the reaction to give the benzonaphthoxazepinone **8ae** (entry 4). However, sluggish reactivity was observed when 2-bromo-4-methoxyphenol **5f** was used. Upon extended heating, **8af** was obtained as the major product in 31% yield (entry 5), along with small amounts of the isomeric compound **8ag**. This result suggests that electron-rich phenols undergo rearrangement at a greatly reduced rate, allowing Goldberg cyclization as a competing pathway. To confirm this result, **8ag** was independently prepared from 2-bromo-5-methoxyphenol **5g** under the standard conditions (entry 6), furnishing material that was identical to the minor product **8ag** of entry 5.

Electronically impoverished phenols gave more varied results. While a high yield of **8ah** bearing a fluoro substituent

Table 1: Variation of benzamide ring substituents (**4**).



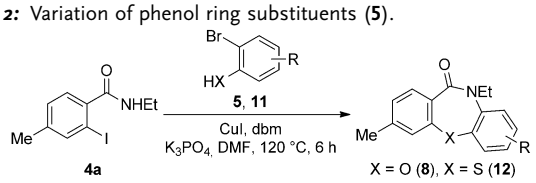
Entry	Substrate	Product	Yield [%]
1	 **4b**	 **8ba**	50[a,b]
2	 **4c**	 **8ca**	80[a]
3	 **4d**	 **8da**	73[a]
4	 **4e**	 **8ea**	85
5	 **4f**	 **8fa**	86
6	 **4g**	 **8ga**	86
7	 **4h**	 **8ha**	74

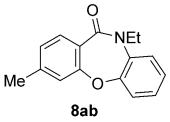
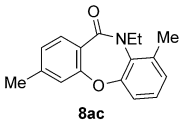
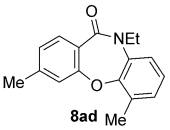
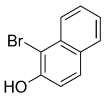
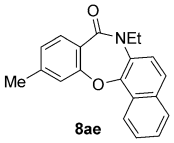
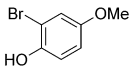
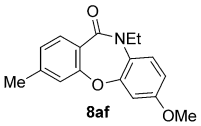
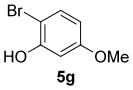
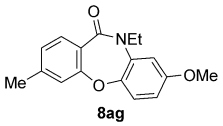
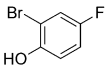
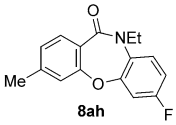
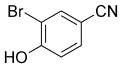
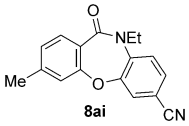
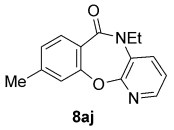
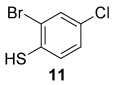
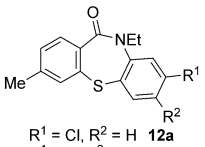
[a] 24 h reaction time. [b] The Goldberg coupled product **7ba** was also isolated in 12% yield.

was obtained (entry 7), the corresponding nitrile **8ai** was formed in poor yield (entry 8). Heterocycle-derived substrates also appear to be excellent coupling partners, based on the formation of pyridobenzoxazepinone **8aj** in excellent yield (entry 9). To further test the reaction scope, the one-pot coupling–annulation of 2-bromo-4-chlorothiophenol (**11**) was attempted. Unfortunately, the coupling of **4a** with **11** proved sluggish at 120°C. However, an equimolar mixture of both Goldberg and rearranged products (**12a** and **12b**), was obtained after heating at 150°C for 48 h (entry 10).

Having established the scope of the dibenzoxazepinone synthesis, we turned our attention to investigation of the mechanism of this unusual process. With the requirement for copper to initiate the process already established (see the Supporting Information), the analogous single-step Ullmann and Goldberg couplings were conducted. When a mixture of *N*-ethyl toluamide and model phenol **5a** were exposed to the standard reaction conditions, no Goldberg coupling product

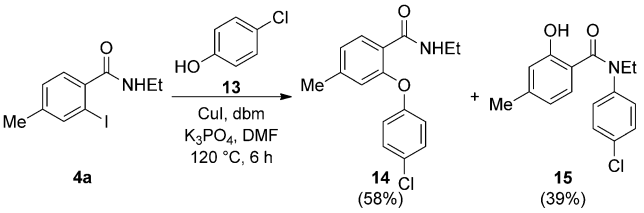
Table 2: Variation of phenol ring substituents (**5**).



Entry	Substrate	Product	Yield [%]
1	 **5b**	 **8ab**	75[a]
2	 **5c**	 **8ac**	37[a]
3	 **5d**	 **8ad**	74[b]
4	 **5e**	 **8ae**	67
5	 **5f**	 **8af**	31[c,d]
6	 **5g**	 **8ag**	70[a]
7	 **5h**	 **8ah**	72[b]
8	 **5i**	 **8ai**	32[a]
9	 **5j**	 **8aj**	95
10	 **11**	 R^1 = Cl, R^2 = H **12a** R^1 = H, R^2 = Cl **12b**	41 (**12a**)[e] 38 (**12b**)[e]

[a] 24 h reaction time. [b] 48 h reaction time. [c] 72 h reaction time. [d] The Goldberg coupled product **8ag** was also isolated in 7% yield. [e] 150°C for 48 h.

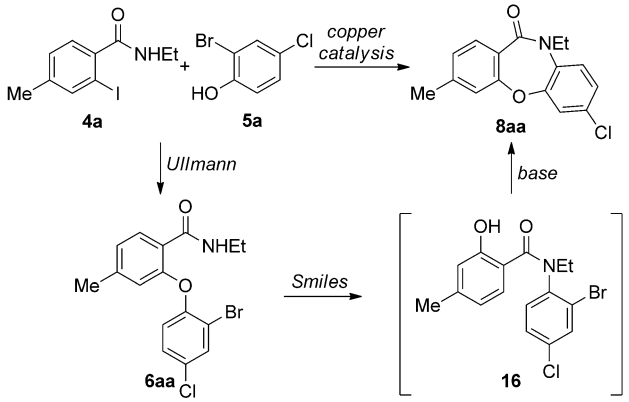
was detected; rather, unreacted amide was recovered (98% yield) instead. In contrast, when 4-chlorophenol (**13**) and model amide **4a** were combined under identical conditions (Scheme 4), the Ullmann product **14** was obtained (58% yield) along with the Smiles-rearranged tertiary salicylamide **15** (39% yield), whose structure was unambiguously confirmed by X-ray crystallography (see the Supporting Information).



Scheme 4. Single-step Ullmann coupling control experiment.

Although Smiles rearrangements of diaryl ethers bearing secondary amides have been previously reported,[14] the systems investigated typically involve arenes bearing multiple electron-withdrawing groups (for example, NO_2, CN, F) or strongly electron-deficient heteroaromatic rings, such as pyridine.[15] In stark contrast, our reaction progresses smoothly in the presence of both electron-neutral and electron-rich phenols. Perhaps most surprisingly, these substrates often outperform their electron-poor counterparts, which are less-tolerated. Our results constitute, to the best of our knowledge, the first report on the generality of the Smiles rearrangement of electron-rich diaryl ethers bearing secondary amides. Furthermore, in all but three cases examined, exclusive regioselectivity for the Smiles rearrangement product is observed.[16,17]

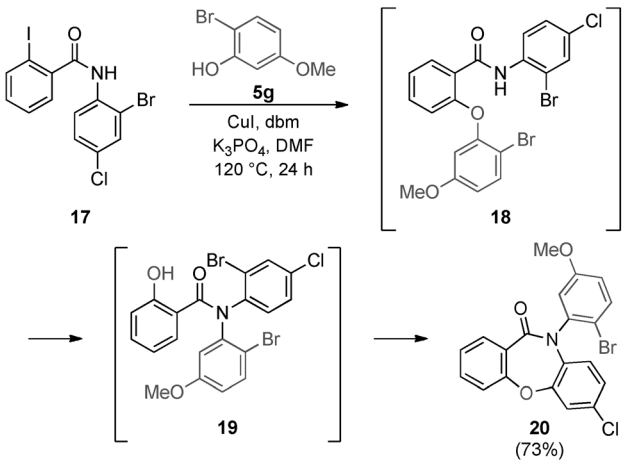
To further support the intermediacy of the Ullmann product **6**, and to investigate the Smiles rearrangement in more depth, we examined the progress of the reaction from isolated diaryl ether **6aa** (Scheme 5). As expected, exposure of **6aa** to the optimized, copper-catalyzed conditions afforded the Smiles rearranged product **8aa** in quantitative yield, providing further evidence for **6aa** as an intermediate in the reaction pathway. We reasoned that, as with the initiation of



Scheme 5. Proposed Ullmann–Smiles-cyclization reaction pathway to dibenzoxazepinones.

this domino process, the final ring closure of **16** to produce **8aa** resulted from a copper-catalyzed Ullmann coupling between the newly generated phenol and the residual aryl bromide. To confirm this assumption, the reaction of **6aa** was also conducted both without copper and ligand (base only) and under purely thermal conditions (no copper, ligand, or base). Although no reaction was observed in the latter case, we were surprised to find that the dibenzoxazepinone product **8aa** was obtained in quantitative yield under base-mediated copper-free conditions,[18,19] demonstrating that copper is not a prerequisite for the ring-closing etherification.[20] Based on these observations, we propose a mechanism involving a copper-catalyzed Ullmann coupling, followed by a base-mediated Smiles rearrangement and final ring-closure (Scheme 5).

As a final point of mechanistic significance, our inability to isolate or detect a Smiles rearrangement product from any of our reaction mixtures gave us pause for concern. To demonstrate the transient generation of rearrangement product **19** under the reaction conditions, we investigated the possibility of trapping **19** in situ to confirm its presence in the reaction mixture (Scheme 6). Towards this aim, amide **17** was treated with phenol **5g** under our standard reaction conditions. To our delight, product **20** was obtained in 73% yield, thus demonstrating the intermediacy of **19** in the reaction pathway.



Scheme 6. In situ trapping of Smiles rearrangement intermediate **19**.

In summary, we have uncovered an unusual and highly regioselective copper-initiated domino reaction which provides a general route to dibenzoxazepinones **8** from 2-iodobenzamides **4** and 2-bromophenols **5**. As supported by detailed mechanistic studies, the reactions proceed first by a copper-catalyzed Ullmann coupling, followed by a base-mediated Smiles rearrangement and final ring-closing process (Scheme 5). Our initial observation of a Smiles reaction was unexpected owing to the absence of strong electron withdrawing groups.[14] It therefore provides a caveat to those in the currently active area of C–O and C–N bond coupling studies.

This method provides an efficient, scalable (see Scheme 3, footnote a), and modular approach for the rapid construction of dibenzoxazepinones, with significant advantages over established multi-step processes. Further work to expand the scope of this method, to extend it to an analogous coupling–annulation process with 2-iodobenzenesulfonamides, and to study its mechanism in detail will be reported in due course.

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[17] In the two examples using phenolic substrates, the Smiles product remains the dominant product (ratios of isolated products **8ba**/**7ba** 4.2:1, **8af**/**8ag** 4.4:1). Only in the case of dibenzothiazepinones **12a** and **12b** is no selectivity observed.

[18] To rule out the possibility of metal contamination, **8aa** was also prepared from *N*-ethyl-2-fluoro-4-methylbenzamide under copper-free conditions. See the Supporting Information for details.

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[20] It is not possible to rule out catalysis by homeopathic quantities of copper or other metals present in commercially available bases (see ref. [19]). However, the use of the same batch of K_3PO_4 did not catalyze either the overall transformation or the initial Ullmann reaction (see the Supporting Information).

