

serve the dual roles of radical initiation and aryl trapping of the distal C' (Fig. 1b). In our proposed mechanism, an *in situ* generated Cu(I) complex undergoes transmetalation with a (hetero)aryl boronic acid to afford a Cu(I)Ar species. We expected this more electron-rich Cu complex to be well-suited to initiate reduction of the N–F bond of amide **A** *via* either a single-electron-transfer or atom-transfer mechanism. The resultant N-centered radical **B** would then undergo selective 1,5-HAT to afford δ C' amide **C**. In the second vital role of the Cu catalyst, an oxidized Cu(II)Ar complex could combine with C' in the mechanism described by Kochi,¹⁵ as well as Liu.^{10e} The highly oxidized organometallic **D** should then reductively eliminate Cu(I) and δ aryl amide **E**. This final step simultaneously affords turnover of the catalytic cycle and sp³–sp² C–C coupling. Importantly, we were intrigued by the possibility that ligand tunability could enable control of both reactivity and stereoselectivity in this δ C–H arylation.

Results and discussion

To test our hypothesis, we combined *p*-F-phenylboronic acid, an *N*-fluoro-tosylamide, and 5% Cu(OTf)₂ (Fig. 2). Upon optimization of ligand, base, and solvent mixtures (all crucial factors to enable maximum reaction efficiency, see ESI† for details), we were pleased to find the radical relay mechanism could indeed be interrupted to afford δ arylation (**1**, 79%). Control experiments reveal that both bisoxazoline ligand (\pm) **L1** and an aryl boronic acid are necessary for efficient amide consumption, suggesting the Cu complex requires both donating ligands to reduce the N–F.

We next turned our attention to investigating the scope and generality of this δ C–H arylation (Fig. 2). Interestingly, electronic variation of the sulfonamide does not greatly affect reaction efficiency (**1**–**3**). Heteroarenes, such as indole, can be incorporated on the amide (**4**; without 6-*exo*-trig cyclization), or



Fig. 2 Scope of δ C–H (hetero)arylation by Cu-catalyzed radical relay and coupling with aryl boronic acids. Conditions: sulfonamide (0.2 mmol), arylboronic acid (2 equiv.), Li₂CO₃ (1 equiv.), 5% Cu(OTf)₂, 7.5% (\pm) **L1**, PhH : DMAc (4 mL; 9 : 1), r.t. isolated yields. ^aNMR yield. ^b10% Cu(OTf)₂, 15% (\pm) **L1**. ^cBased on recovered starting material.



within the aryl boronic acid (Ar^2). In the latter case, we found the difluoropyridyl arene products to be particularly easy to isolate. Notably, we found that it is not necessary to abstract the H-atom from a benzylic position. In fact, secondary C–H bonds are readily arylated (5–9), in accordance with our previous work on δ C–H aminations.¹⁶ α -Branched amides are also viable (8), although they afford lower diastereoselectivity (1 : 1) than γ substitution (9, 3 : 1).

To showcase the synthetic utility of employing aryl boronic acids within this remote Cu-catalyzed cross-coupling, we embarked on an exhaustive investigation of this component. As shown in Fig. 2, this δ arylation is amenable to electronic perturbation of the $\text{ArB}(\text{OH})_2$ – with both donating and accepting groups tolerated (10–31) – ranging from –OMe to –NO₂ and including orthogonal functional handles, such as bromides, ketones, esters, and sulfones. Similarly, both *ortho* and *meta* substitution, as well as polyaromatics (32), readily participate in this reaction. As further demonstration of the likely utility of this approach to the synthesis of medicinal agents, we employed a family of heteroaryl boronic acids, including those containing N, O, S, and F, and all are amenable to this δ C–H arylation (33–37).

The robust δ regioselectivity observed in these reactions, including an arylation of a single 1-of-15 methylenes (7), led us to further investigate the limits of the selectivity in the key HAT step (Fig. 3). With this question in mind, we subjected an amide with two benzylic C–H bonds at δ and ϵ positions to these catalytic conditions. Selective δ arylation of this probe (38; 14 : 1) confirms 1,5-HAT is highly favored over 1,6-HAT in this reaction. However, this kinetic preference can be thermodynamically overridden if a weaker, benzylic ϵ C–H is pitted against a secondary δ C–H. In this case, 1,6-HAT is slightly favored (39; 1.7 : 1). Importantly, and as a complement to previous work on α C–H arylation,^{10–12} when a molecule containing a distal benzylic C–H bond is employed, no undirected arylation is observed (40; > 20 : 1 δ). Finally, in a three-way competition between δ/ϵ secondary C–H bonds and a ζ benzylic C–H bond, only the product of 1,5-HAT is observed, rather than either 1,6 or 1,7 HAT (41–42; > 20 : 1 δ).



Fig. 3 Regioselectivity probes of intramolecular HAT.



Fig. 4 Pyrrolidine synthesis via iterative δ C–H arylation and δ C–H amination.

Although this δ C–H arylation was enabled by interrupting the classic Hofmann–Löffler–Freitag (HLF) reaction, we questioned if these complementary transformations could be sequentially combined (Fig. 4). For example, we have demonstrated that this Cu-catalyzed δ arylation (I) yields 4-aryl-butyl amides (II), and subsequent AcOI-mediated δ amination affords α diaryl pyrrolidines (III), bearing a tetra-substituted carbon (43–46). We expect this two-step, double C–H functionalization sequence will provide a synthetically enabling route to access medicinally relevant pyrrolidines,¹⁷ in a rapid, modular, and non-classical fashion.

Finally, given the strong dependence of reaction efficiency on ligand choice, as well as the ready availability of enantioenriched bisoxazoline ligands, we tested whether a catalytic, asymmetric version of this δ C–H arylation is possible (eqn (1)). To our delight, we found that employing enantiopure **L1**¹⁸ affords enantioenriched diaryl amide (1, 48% ee). Moreover, decreasing the temperature to –4 °C (and employing a co-solvent with a lower mp) allows access to this 1,1-diaryl-product with 65% ee – affording the first example of an enantioselective, radical C–H arylation.



Conclusions

In summary, we have interrupted the HLF reaction to afford a δ C–H arylation. The regioselectively translocated C[•] of this classic mechanism was intercepted and employed in C–C bond formation by using a Cu catalyst. The two key roles of this catalyst are: (i) to generate N[•] without also forming a δ halogenating X[•], and (ii) to trap the translocated C[•] as an organometallic intermediate. This organocopper species enables cross-coupling with a range of (hetero)aryl boronic acids at the δ position of sulfonamides in a regioselective (and stereoselective) manner. We expect this strategy will facilitate further development of methods to interrupt the classic HLF reaction with valuable C–C bond formation.



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