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Chemoselective, Scalable Nickel-Electrocatalytic *O*-Arylation of Alcohols

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Abstract: The formation of aryl-alkyl ether bonds through cross coupling of alcohols with aryl halides represents a useful strategic departure from classical S_N2 methods. Numerous tactics relying on Pd-, Cu-, and Ni-based catalytic systems have emerged over the past several years. Herein we disclose a Ni-catalyzed electrochemically driven protocol to achieve this useful transformation with a broad substrate scope in an operationally simple way. This electrochemical method does not require strong base, exogenous expensive transition metal catalysts (e.g. Ir, Ru), and can easily be scaled up in either a batch or flow setting. Interestingly, e-etherification exhibits an enhanced substrate scope over the mechanistically related photochemical variant as it tolerates tertiary amine functional groups in the alcohol nucleophile.

Aryl-alkyl ether bond construction is one of the most often-employed transformations in the pharmaceutical industry.[1] Such linkages are often forged using classical substitution chemistry such as S_N2 displacement represented by Williamson ether synthesis[2] and Mitsunobu reaction[3] or nucleophilic aromatic substitution.[4] The synthesis of BET inhibitor intermediate **1** (Figure 1) is emblematic of this approach wherein a phenol **4** is alkylated with an alkyl halide **3**, followed by the second alkylation to attach the piperazine unit **2** and Miyaura borylation for installing the requisite C-B bond.[5] Although the approach is quite straightforward, step-count and overall yield are not satisfactory. The explosive success of transition-metal catalyzed N-arylation methods [6] has inspired the invention of mild methods for an analogous union of alcohols and aryl halides [7] by using Pd,[8] Cu,[9] and Ni[10-15] catalysis. This coupling strategy is an attractive alternative to classic S_N2-based retrosynthesis; the aryl halide building blocks are often easier to access, and the conditions employed can sometimes be more chemoselective. Continuing with this case study, the coupling approach (Figure 1) requires building blocks **5** and **6**, which are both commercially available. However, the key C-O bond formation was found to be challenging even under the latest state-of-the-art conditions. For example, catalytic reactions based on Pd (conditions **A**[8i] and **B**[8h]) and Cu (conditions **C**[9n] and **D**[9o]) in combination with recently described ligands struggled to forge the C-O bond. Methods based on Ni such as conditions **E**[13] and photochemical conditions **F**[11a] also failed to deliver **1** presumably due to their

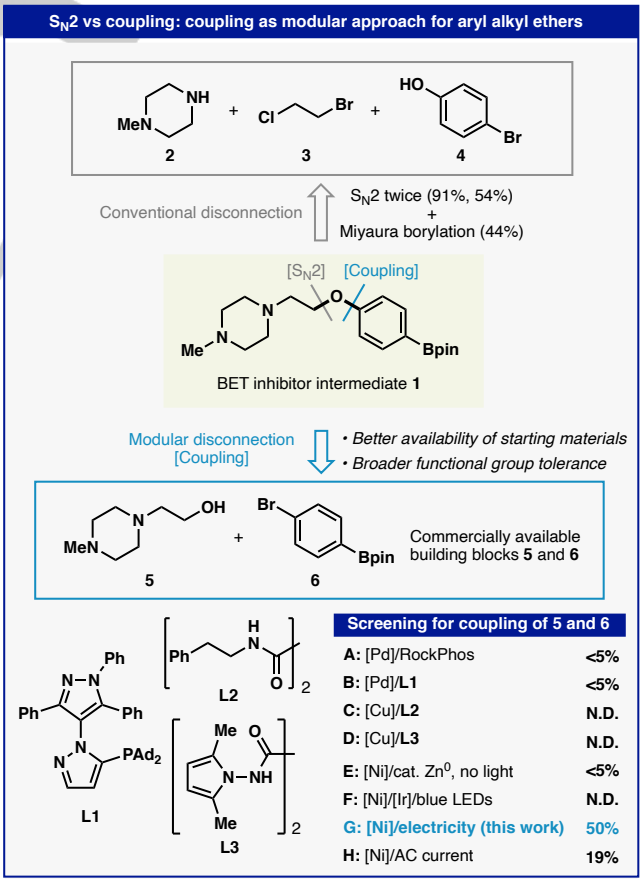

Figure 1. Comparison between S_N2-based strategies and coupling approach in the synthesis of BET inhibitor intermediate **1**. Whereas the S_N2 approach suffers from low overall yield and known methods (A-F) for ether cross coupling fail, e-etherification proceeds smoothly. The yields shown in conditions A-H are crude ^{1}H-NMR yields.

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incompatibility with the tertiary amine motif, which is ubiquitous in pharmaceutical molecules. This study reports the development of a Ni-catalyzed electrochemical etherification (e-etherification) that can succeed in this demanding context (conditions **G**) without recourse to specialized experimental setups (e.g. electrolysis with sinusoidal AC current,[14] conditions **H**) or expensive metals and ligands. This electrochemical method exhibits a broad substrate scope, high chemoselectivity, and represents an economically viable and sustainable means to conduct such etherification reactions on scale.

The development and optimization of the Ni-catalyzed aryl halide etherification commenced with the lessons learned during studies on the analogous e-amination reaction,[16] and employed bromoarene **7** and cyclopentanol **8** to access ether **9** (Figure 2). Prior detailed mechanistic and optimization studies for e-amination pointed to the importance of the ligand/Ni ratio, the use of DBU as a base, and $^{n}Bu_4NBr$ as the electrolyte. In the case of etherification, those variables proved critical; however the maximum yield obtained using those conditions was only 10% yield. Remarkably, by simply changing the ligand from **L5** to **L7** and adding 3Å molecular sieves the yield improved to 62%. Control experiments reinforced several important aspects of this reaction. First, electricity is necessary for the reaction to proceed (shutting off electrical current immediately halts the reaction). Second, the Ni-catalyst is playing a crucial role for the product formation under basic conditions as the omission of Ni or DBU resulted in no ether formation. Third, replacement of electricity with a chemical reductant (Zn powder) resulted in no product formation. These results are consistent with chemical,[17-18] photochemical,[11a,11c,19-21] and electrochemical[16b] mechanistic studies, consistent with the Ni-catalytic cycle being driven in a paired electrolysis fashion,[16,22] requiring both oxidation and reduction. Although it was recently found that sinusoidal AC current may improve yield in such Ni-catalyzed electrochemical coupling,[14] this method was not applicable in our case as the optimal anode and cathode are made of different material. Exclusion of air by using a simple Ar-balloon is sufficient to efficiently perform this reaction, and no laborious procedures for degassing (or a glovebox) are needed. As described below, during scale-up a modified procedure can be used in flow that does tolerate air. DMA and NMP were found to be ideal solvents as they render reactions good solubility and have high conductivity. Finally, the use of a Ni-**L7** precatalyst, $NiCl_2(dtbbpy)_3$, improved the operational simplicity of the reaction without any reduction in yield (64%). This readily prepared, bench-stable, and non-hygroscopic Ni-precatalyst (see SI for preparation) was utilized for the remainder of these studies.

Table 1 provides a snapshot of the broad scope of e-etherification with 41 out of >80 examples shown (see SI for full scope and limitations). The use of a relatively mild organic base DBU and room temperature conditions enabled a range of functional groups to be tolerated. For example, reductively labile C-X bonds (X = Br, Cl, F) and fluoroethers (**10**-**22**, **39**, **40**, **41**, **47**-**48**), ester (**49**) and ketones (**42**, **50**) were well tolerated. Even an aromatic aldehyde (**43**) was compatible in this reaction. Of note, only small amount of di-etherification product was observed when 1,4-dibromobenzene was used as the starting material due to much lower reactivity of **16** to low-valent Ni species. In addition, oxidatively labile groups such as 3° amines (**26**), electron-rich arenes (**23**, **24**) as well as heterocycles (**27**-**33, 45**, **46**), and C-B bond (**38**, **41**-**50**) were found intact. Sensitive or polar (N-H containing) motifs such as carbamates (**18**, **27, 31**-**33**), Lewis-basic heterocycles (**34**, **35**, **40**, **44**), amides (**25**, **26**) and ketals (**28**, **37**, **49**) showed no complications under the reaction conditions. Regarding the scope of alcohol coupling partner, both primary and secondary alcohol were compatible whereas tertiary alcohols were found to be inefficient. The efficient coupling of nucleosides and polyfunctionalized fragments is also notable (**36**-**37**). Taken together, this e-etherification method provides an easy access to small molecules and building blocks for pharmaceutical drug discovery efforts.

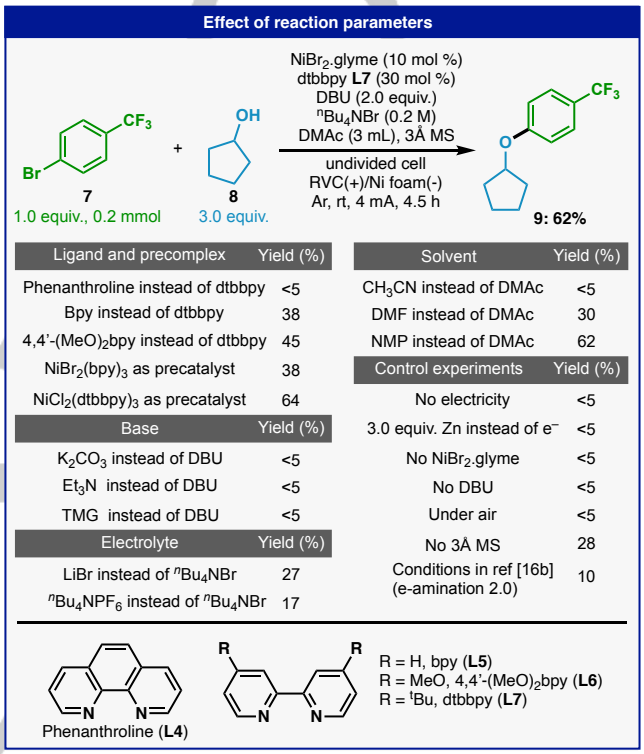

Figure 2. Effects of various reaction parameters. Yields determined by gas chromatography.

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Table 2 illustrates the synthesis of known ether products wherein conventional strategies were used in prior routes and also compares the e-etherification with known Cu, Pd, and Ir/Ni-based methods. The room temperature conditions of e-etherification avoids the use of highly basic metal alkoxides or insoluble inorganic bases, does not require rigorous deoxygenation procedures (simple air/argon exchange), and deletes precious metal catalysts. With regards to the prior routes

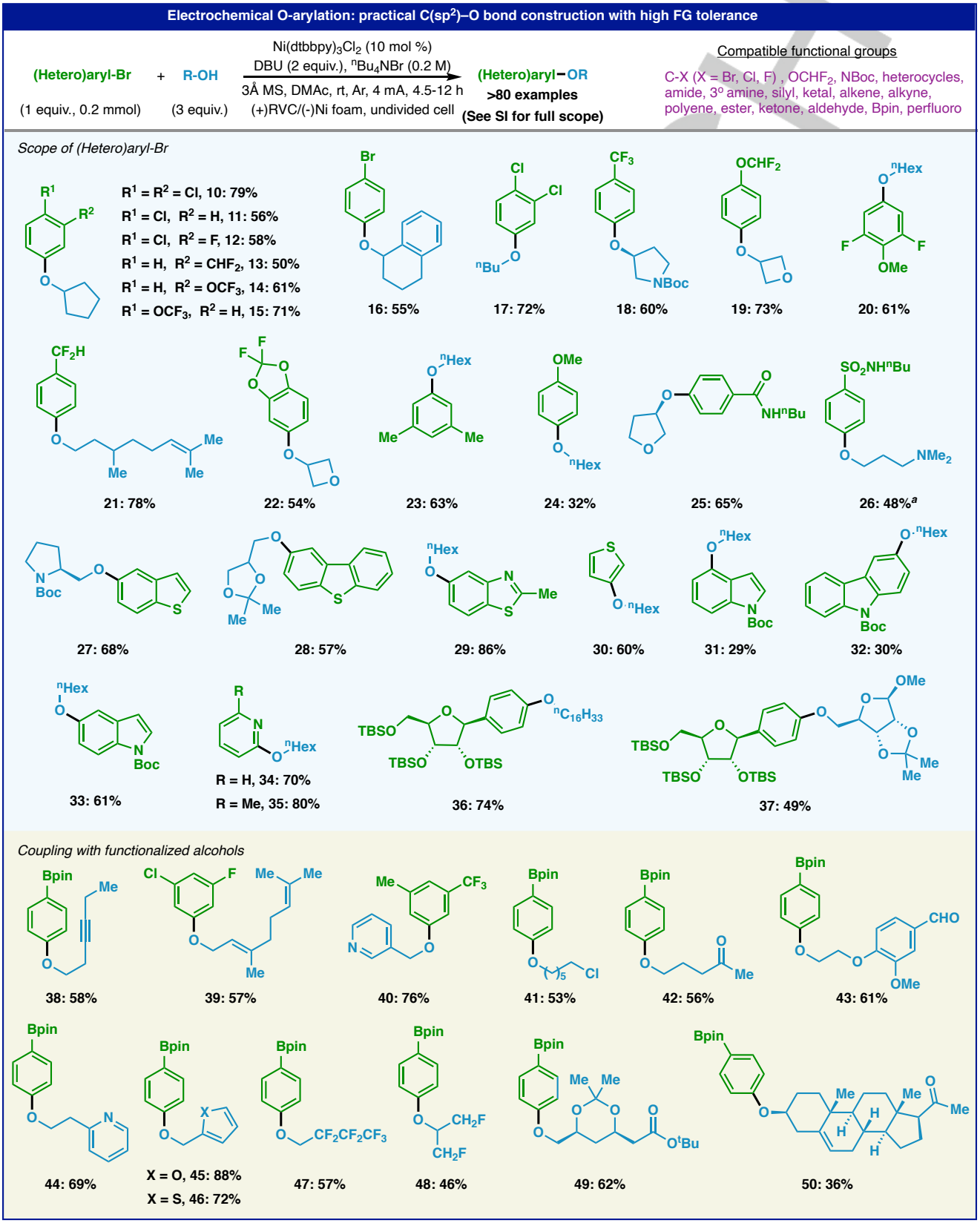

Table 1. Selected scope of aryl bromides and alcohols (See SI for the full scope). All yields are isolated yields. [a] Using 6 equiv. of alcohol.

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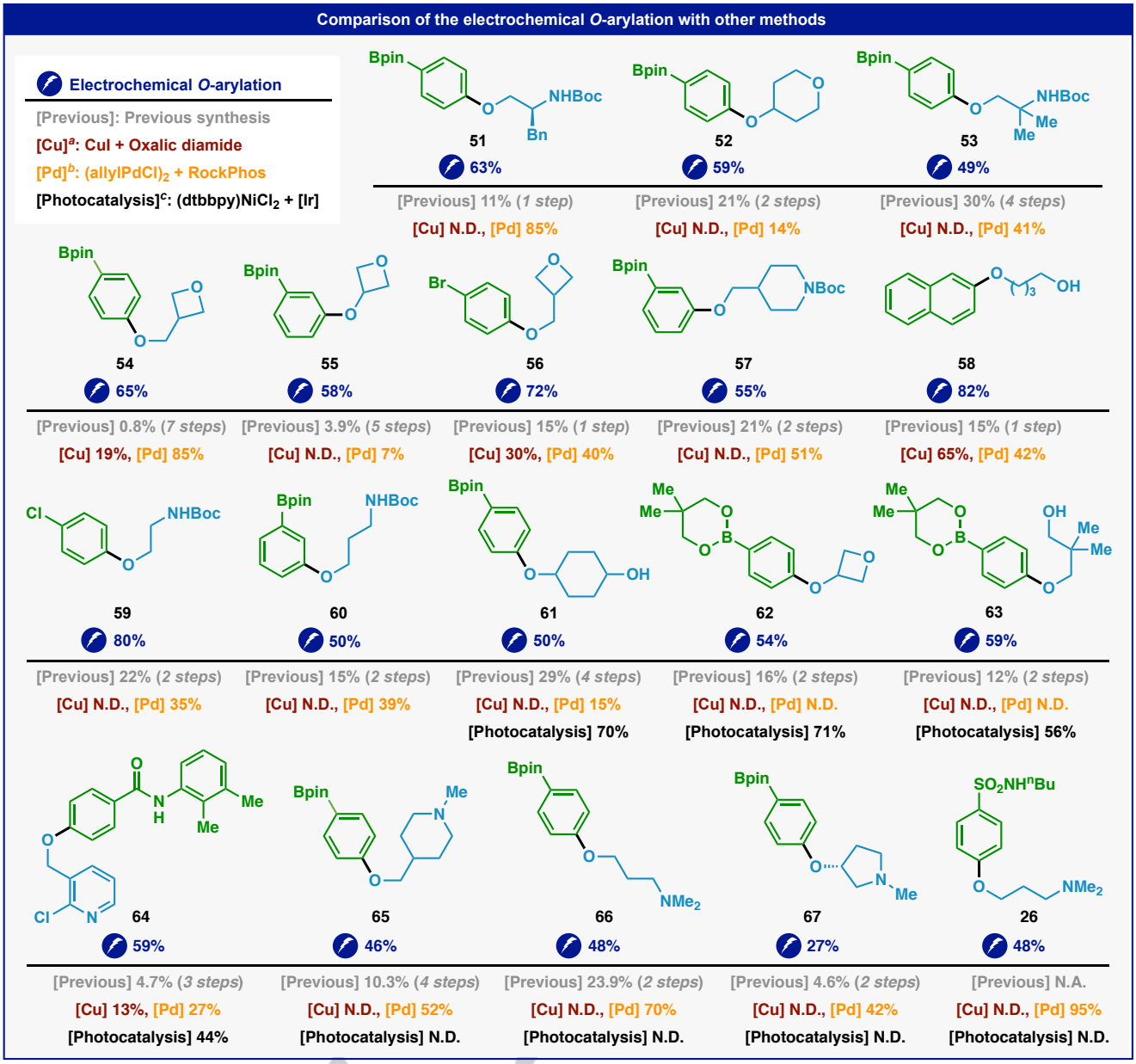

Table 2. Improved access to various compounds by electrochemical *O*-arylation. Yields under other coupling conditions are also shown. See SI for the experimental conditions for each compound. The yields of electrochemical *O*-arylation are isolated yields. [a] Ref. [9n], crude ^{1}H-NMR yields. [b] Ref. [8i], crude ^{1}H-NMR yields. [c] Ref. [11a], isolated yields.

to access such valuable intermediates, a strong reliance on S_N2 and Mitsunobu chemistry along with Miyaura borylation leads to lengthy and low yielding routes. In the case of oxetane-containing structures such as **54** and **56**, recourse to oxetane ring synthesis after ether bond formation is required (See SI for full summary of all past routes). Most notably, e-etherification succeeded in delivering ether products even with substrates on which analogous photochemical conditions did not work (**65**-**67**, **26**), demonstrating broader substrate scope that can be achieved by the electrochemical means. The unique success of e-etherification in such instances despite having mechanistic similarities to the photochemical variant might be ascribed to the more strongly oxidizing conditions that favor reoxidation of Ni(II) to Ni(III) versus tertiary amine oxidation.

In addition to superior functional group tolerance to other methods, another important advantage of the current method stems from the ease with which scale-up can be accomplished. As depicted in Figure 3, the reaction conditions can be used for batch preparation of **69,** a valuable building block for drug discovery using a commercial potentiostat from 2 mmol to 60 mmol. Most significantly, adaptation to flow carries several salient advantages as exemplified for the decagram synthesis of ether **71**. These include: (1) the use of simple inexpensive carbon felt electrodes; (2) no precautions to remove air; and (3) no need for exclusion of water using molecular sieves. As such, a 100 mmol run on aryl bromide **70** can be completed in only 16 hours to deliver 70% isolated yield of **71**. Furthermore it is possible to reduce the amount of the electrolyte to substoichiometric quantity (0.75 equiv.) if needed (See Supporting Information for details).

In conclusion, an electrochemical method for the etherification of aryl bromides has been developed that exhibits a broad substrate scope tolerating numerous sensitive functionalities. To the best of our knowledge, this work exhibits the widest substrate scope among all the related methods

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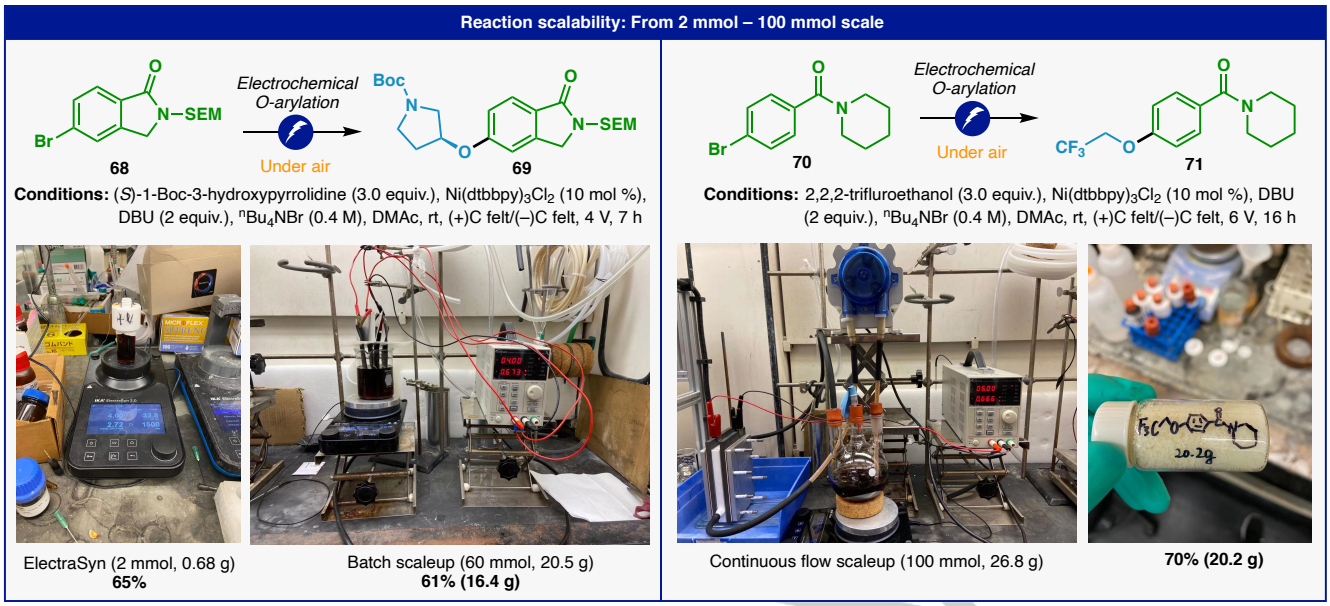

Figure 3. Electrochemical O-arylation performed on various scale from 2 mmol to 100 mmol. All yields are isolated yields.

published thus far. It offers a useful alternative to classic S_N2-based methods for ether synthesis, and represents a practical, scalable, and inexpensive gateway to such structures that does not rely on precious metal additives or complex ligands.

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Keywords: Electrochemistry • *O*-Arylation • Coupling • Nickel • Chemoselective

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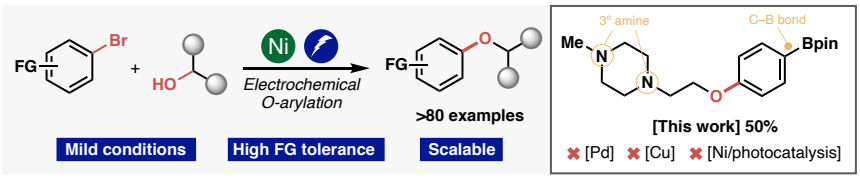

Highly chemoselective and practical *O*-arylation was achieved by electrochemically-driven nickel catalysis. This method exhibits broad substrate scope comparable to the state-of-the-art Pd, Cu and photochemically facilitated Ni catalysis. Notably, this e-etherification successfully forged ether bonds in demanding settings where other methods did not work. Combined with excellent scalability, this work represents a modular, mild, and simple ether bond formation to address the increasing demand for etherification transforms in contemporary medicinal chemistry.