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Electrochemically Enabled, Ni-Catalyzed Amination

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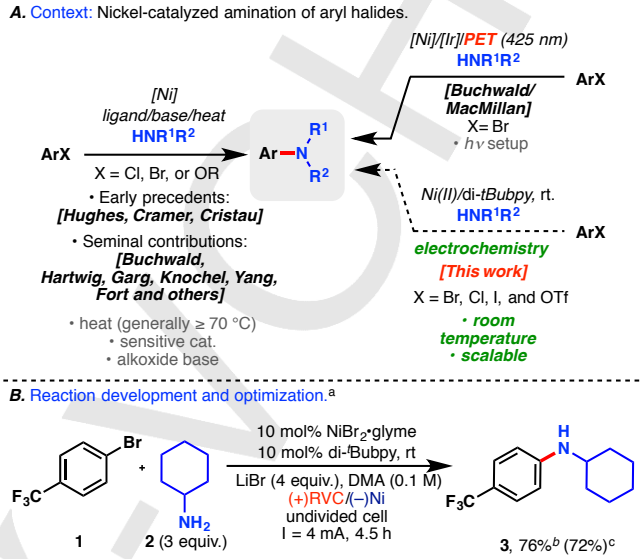
Abstract: Along with amide bond formation, Suzuki cross-coupling, and reductive amination, the Buchwald-Hartwig-Ullmann type amination of aryl halides stands as one of the most employed reactions in modern medicinal chemistry. This Communication demonstrates the potential of utilizing electrochemistry to provide a complementary avenue to access such critical bonds using an inexpensive nickel catalyst under mild conditions. Of note is the scalability, functional group tolerance, rapid rate, and the ability to employ a variety of aryl donors (Ar–Cl, Ar–Br, Ar–I, Ar–OTf), amine types (primary and secondary), and even alternative X-H donors (alcohols and amides).

Despite its short history of merely several decades, palladium catalyzed amination of aryl halides has emerged rapidly as one of the most widely utilized reactions in modern organic chemistry.[1] In fact, a recent study ranks the venerable Buchwald-Hartwig amination amongst one of the 20 most frequently used reactions in medicinal chemistry in 2014.[2] Similarly, the copper catalyzed Ullmann coupling has also been a regular tool in medicinal chemists' armamentorium.[3] Unequivocally, the formation of aryl C–N bonds is of paramount importance in drug discovery. The first example of nickel mediated C–N coupling dates back to the 1950s using $NiCl_2$ at 200 °C;[4,5] subsequent efforts by Cramer[6(a)] and Cristau[6(b)] broadened the scope of similar reactions—nevertheless, the harsh conditions still precluded broad adoption (Figure 1A). It was not until 1997 when Buchwald's seminal efforts spawned strong interests in utilizing nickel (0) ligand complexes to catalyze the cross-coupling reactions between aryl halides and amines.[7] Over the years, efficient protocols have been developed by the groups of Buchwald,[8(a)] Hartwig,[8(b)] Garg,[8(c)] Knochel,[8(d)] Yang,[8(e)] Fort,[8(f)] and others.[8(g)-(j)] Nickel's inexpensive nature and its high reactivity toward less reactive electrophiles such as aryl chlorides offers an alternative approach to palladium and copper catalysis. Nevertheless, these efforts are plagued by several drawbacks, including the use of air-sensitive Ni(0) catalysts, the need for high temperatures, and the necessity of alkoxide bases. While elegant Ni(II) pre-catalysts and *in situ* methods of catalyst generation have been devised to address the first problem,[8] the other issues remain largely unresolved. In 2016, Buchwald, MacMillan, and co-workers reported a photochemically assisted C–N cross-coupling via nickel catalysis wherein the photoinduced electron transfer between an iridium sensitizer and nickel catalysts allows readily available Ni(II) salts to serve as catalysts under milder conditions.[9]



entry	Deviation from above	Yield%[b]
1	Graphite, Al, or steel cathode	17–34
2	Zn sacrificial anode instead of RVC	7[d]
3	8 mA, 2 h	22
4	2 mA, 8 h	32
5	No electricity	0
6	15 min. electrolysis	5
7	No ligand	0
8	No Ni cat.	0
9	LiCl instead of LiBr	35
10	Pyridine (2.0 eq) as an additve	75
11	DABCO (2.0 eq) as an additive	48
12	Reaction under air	42

[a] 0.2 mmol. [b] Yield determined by gas chromatography (GC). [c] Isolated yield in "()". [d] Complete consumption of starting material; formation of biaryl.

Figure 1. (A) Background and historical context of Ni-based aryl amination methods. (B) Invention and optimization of Ni-catalyzed amination. Abbreviations: RVC = reticulated vitreous carbon; di-^{t}Bubpy = 4,4'-di-*tert*-butyl-2,2'-bipyridine; DMA = N, N'-dimethylacetamide.

These studies spanning two decades point to two critical challenges to achieve nickel-catalyzed amination of aryl halides namely the generation of a reactive low valent nickel catalyst and the C–N bond-forming process via reductive elimination. The former often entails the reduction of a Ni(II) species[10] while the latter may be promoted by the intermediacy of a high valent nickel species accessible via oxidation[11,12]—the ability to access Ni complexes of various oxidation states in the same pot is thus crucial. Electrochemistry represents the most direct and controllable means of redox manipulation—each electrochemical process seamlessly combines concurrent anodic oxidations with cathodic reductions.[13] As such, it was surmised that various oxidation states of nickel complexes could co-exist in harmony under electrolytic conditions. This realization, coupled with the innate scalability, sustainability, and tunability of electrochemistry,[14] prompted the investigation of electrochemically promoted cross-coupling reactions under nickel catalysis.[15]

In this Communication, an electrochemical method to achieve the cross-coupling between aryl halides and alkyl amines at

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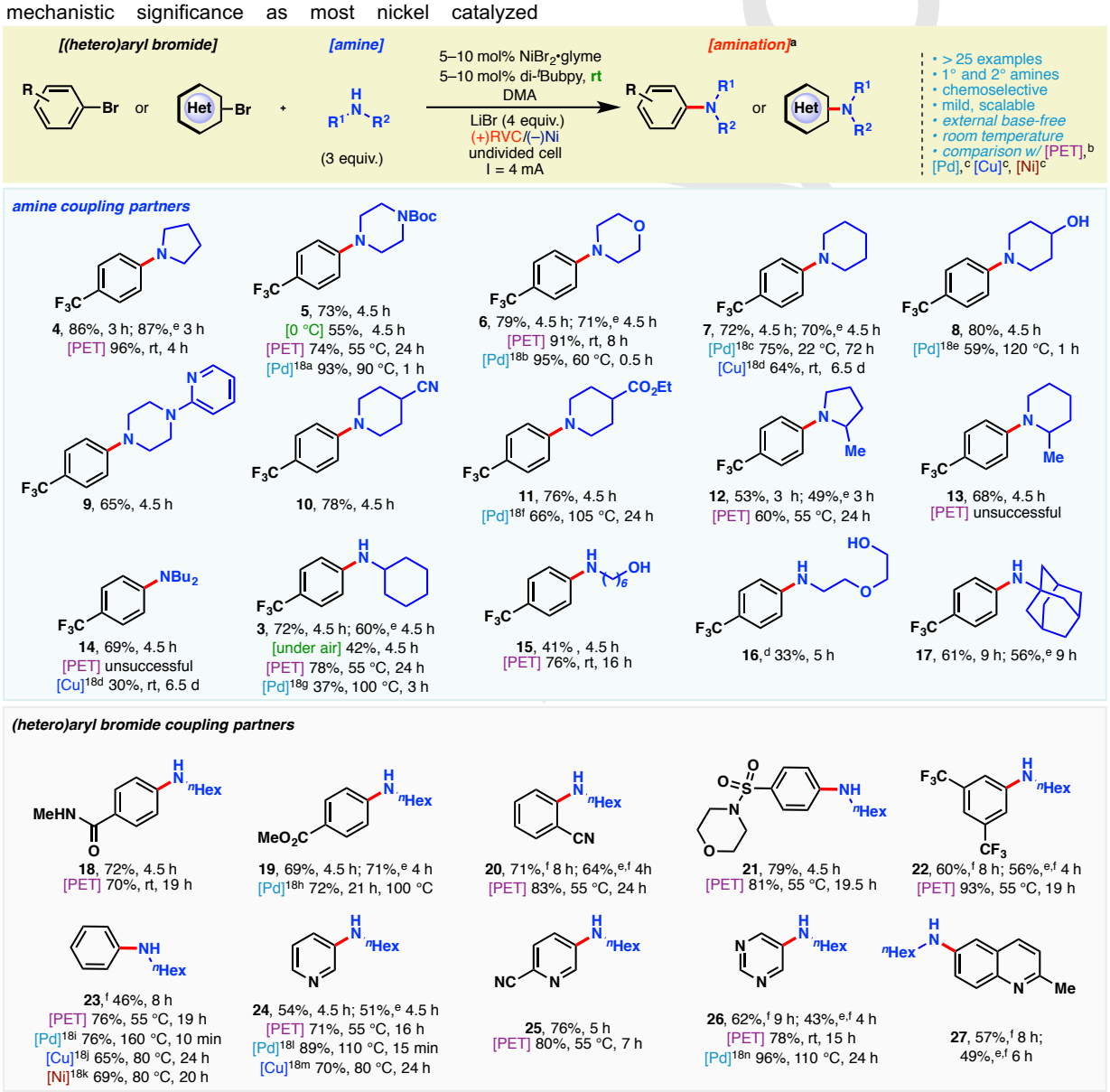
room temperature and in the absence of an external base is presented. The scope of this electrolytic protocol encompasses aryl bromides, chlorides, triflates, and iodides. Additionally, alcohols and amides can also serve as nucleophiles.

Figure 1B provides the optimal conditions alongside an abbreviated picture of reaction optimization on the coupling of aryl bromide **1** with cyclohexylamine (**2**). The use of expensive electrode materials was avoided at the outset of the study—the highest yield was obtained with an RVC anode and a nickel foam cathode. Coupling products were still observed with alternative cathode materials such as graphite, aluminum, and stainless steel, albeit in diminished yields (entry 1, Figure 1B). The use of a zinc sacrificial anode exerted deleterious effects on the reaction (entry 2)—homocoupling of the aryl halide ensued instead. This result has mechanistic significance as most nickel catalyzed electrochemical coupling of aryl halides utilize sacrificial anodes to prevent the competitive oxidation of low-valent nickel catalysts and to avoid the need for a divided cell.[15] Thus, the intermediacy of high valent nickel species appears to be essential.[16,17] As mentioned above, such concurrent oxidation/reduction cycles are ideally suited for electrochemistry. A current of 4 mA was optimal on 0.2 mmol scales. Adjusting the current (while maintaining the total amount of electron passage constant) lowered the yields of coupling products (entries 3 and 4). Unsurprisingly, no coupling products were observed in the absence of an electric current (entry 5). Reducing the duration of electrolysis (the overall reaction time is still 4.5 h), too, had detrimental effects (entry 6)—thus, electricity does not merely initiate a chain reaction.



Scheme 1. Scope of the electrochemically enabled Ni-catalyzed amination of aryl bromides. *a*) Standard reaction conditions: aryl bromide (1.0 equiv.), amine (3.0 equiv.), $NiBr_2$•glyme (10 mol%), di-^{t}Bubpy (10 mol%), DMA (0.1 M), LiBr (4 equiv.), RVC anode, Ni cathode, constant current (I = 4 mA for 0.2 mmol scale), rt. *b*) Based on results reported in reference 9(a). *c)* Based on specified references for each substrate (footnote 18). *d)* I = 8 mA for 0.2 mmol scale. *e)* Using $NiBr_2$•glyme (5 mol%), di-^{t}Bubpy (5 mol%). *f)* I = 2 mA for 0.2 mmol scale.

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The inexpensive combination of $NiBr_2$•glyme and a bipyridyl ligand provides the most effective catalyst system for the transformation—on substrate **1**, the omission of either component led to no product formation (entries 7 and 8). The choice of electrolyte has a significant impact on the reaction outcome as well—the use of LiCl instead of LiBr led to a significant drop in yield (entry 9). The addition of external bases is unnecessary. In fact, the presence of pyridine had little influence on the yield (entry 10), whereas the use of DABCO had deleterious effects (entry 11). Although optimal results are obtained when the reaction was set up under a protective atmosphere of argon, rigorous deoxygenation is unnecessary. The coupling product was afforded in 42% yield even under air (entry 12). Overall, C–N coupling is accomplished under galvanostatic (constant current) conditions in a simple undivided cell at room temperature generally within five hours.

With the optimized conditions in hand, the scope of the reaction was probed next. Medicinally privileged cyclic secondary amines such as pyrrolidine, piperazine derivatives, morpholine, and piperidine have all proven to be viable substrates, affording **4**–**7** in good yields. Amines containing hydroxyl, pyridinyl, cyano, and ester substituents (see **8**–**11**) have also been successfully coupled with **1**, underscoring the functional group compatibility of the reaction. Cyclic amines bearing an additional α-substituent (*e.g.*, 2-methyl-pyrrolidine and 2-methyl-piperidine) can be used in the reaction as well, as is evidenced through the formation of **12** and **13**. Notably, the attempted coupling of 2-methyl-piperidine (to furnish **13**) under PET was unsuccessful. Additionally, cross-couplings using acyclic secondary amines have been demonstrated. Although dibutylamine is not a competent coupling partner under PET, it was found to react via this electrolytic system, affording **14** in 69% yield. Aside from cyclohexylamine (see **3**), other primary amines can also be coupled with aryl bromides—these include ethylene-glycol derived 2-(2-aminoethoxy)ethanol (see **16**). It is of note that the ability to rapidly incorporate poly-PEG motifs into small molecule pharmaceuticals has recently gained importance due to exploding interest in PROTACs, where a poly-PEG chain often links a target binding motif with an E3 ligase recognition motif.[19]

This reaction also showcased a broad scope with respect to the aryl bromide electrophiles. Various electron-withdrawing functional groups were tolerated, such as amide (**18**), ester (**19**), nitrile (**20**, **25**), and sulfonamide (**21**). Couplings with heteroaryl bromides derived from pyridine, pyrimidine, and quinoline have also been successful (see **24**–**27**). In addition, unsubstituted bromobenzene can be employed as a coupling partner (see **23**).

Across a number of substrates, coupling products were afforded in comparable yields to those obtained under photochemical, palladium-catalyzed, copper-catalyzed, and nickel catalyzed (thermal) conditions. The amount of the catalyst/ligand can be reduced to 5 mol%—12 of the substrates were furnished in similar yields under these conditions. In fact, **4** and **19** were afforded in higher yields with lower catalyst loading. The use of electrochemistry enables C–N coupling at ambient conditions. **5** could even be synthesized at 0 °C (55%, 4.5 h) with this technology.

Electrochemical amination can facilitate many applications in organic synthesis (Scheme 2). For instance, this reaction may be utilized to derivatize amine motifs in bioactive molecules. Electrochemcial *N*-arylation has been achieved on amoxapine and paroxetine, affording **28** and **29** respectively (Scheme 2A). In each case, the amine was used as the limiting reagent (3–5 equiv. of aryl bromide; 2 equiv. of DBU was added), highlighting the applicability of this method to complex and possibly precious amine starting materials. It is also noteworthy that the aryl chloride motif in amoxapine was left unscathed after the coupling.

The scalability of this reaction has also been demonstrated through the cross-coupling of **1** and *N*-Boc-piperazine on a 23-gram scale (Scheme 2B). Aniline product **5** was afforded in 66% yield. Moreover, this large-scale electrolysis was complete within 7 h, attesting to the high reaction rate and practicality.

Aside from aryl bromides, other aryl (pseudo)halides can also serve as coupling partners under electrochemical conditions. For example, cross-coupling of aryl chlorides have been successfully achieved under room temperature, affording **4**–**6** in good yields with no changes to the standard reaction conditions in Scheme 1. Additionally, the coupling using aryl triflates and aryl iodides is also possible under the standard conditions, as shown by the preparations of **4** and **30** respectively (Scheme 2C).

This versatile system may be adapted for the coupling between aryl halides and other nucleophilic species (Scheme 2D). For example, the coupling of an aryl bromide with a primary alcohol has been demonstrated; **31** was afforded in a moderate yield with the addition of a base (DBU). Inclusion of an external base also allowed pyrrolidinone to serve as the nucleophile in this electrochemically facilitated cross-coupling, **32** was furnished in 55% yield.

From a practical vantage point, this robust reaction does not require rigorous deoxygenation procedures (a simple air/argon exchange usually suffices, see SI for details). Admittedly, as with other electrochemical reactions under constant current conditions fluctuations in applied potential as a result of varying cell resistance stemming from variabilities in setups may undermine the yield of the coupling. This can be circumvented through the use of additional electrolyte. As shown in Figure 1, the choice of electrode materials also exerted a substantial impact on the reaction. Nevertheless, preliminary results indicate that readily available graphite plates and stainless steel rods can serve as anode and cathode materials. With regards to substrate scope, the current conditions are not compatible with anilines. Under the present system, the use of 3 equiv. of amine is optimal when the aryl halide is the limiting reagent (for the synthesis of **3**, the use 1.5 equiv. of amine led to 41% GC yield instead of 76%, see SI).

To summarize, nickel catalyzed coupling between aryl (pseudo)halides and aliphatic amines has been enabled at room temperature, in the absence of an external base, through a simple and inexpensive experimental setup (constant current, undivided cell) using electrochemistry. The scalability and practicality of this protocol, which utilizes inexpensive catalysts and electrode materials, is not surprising as this is often the case in electrochemistry.[14(a)] The utility of reaction has already been field-tested in both process (Asymchem) and medicinal chemistry (Pfizer) settings.

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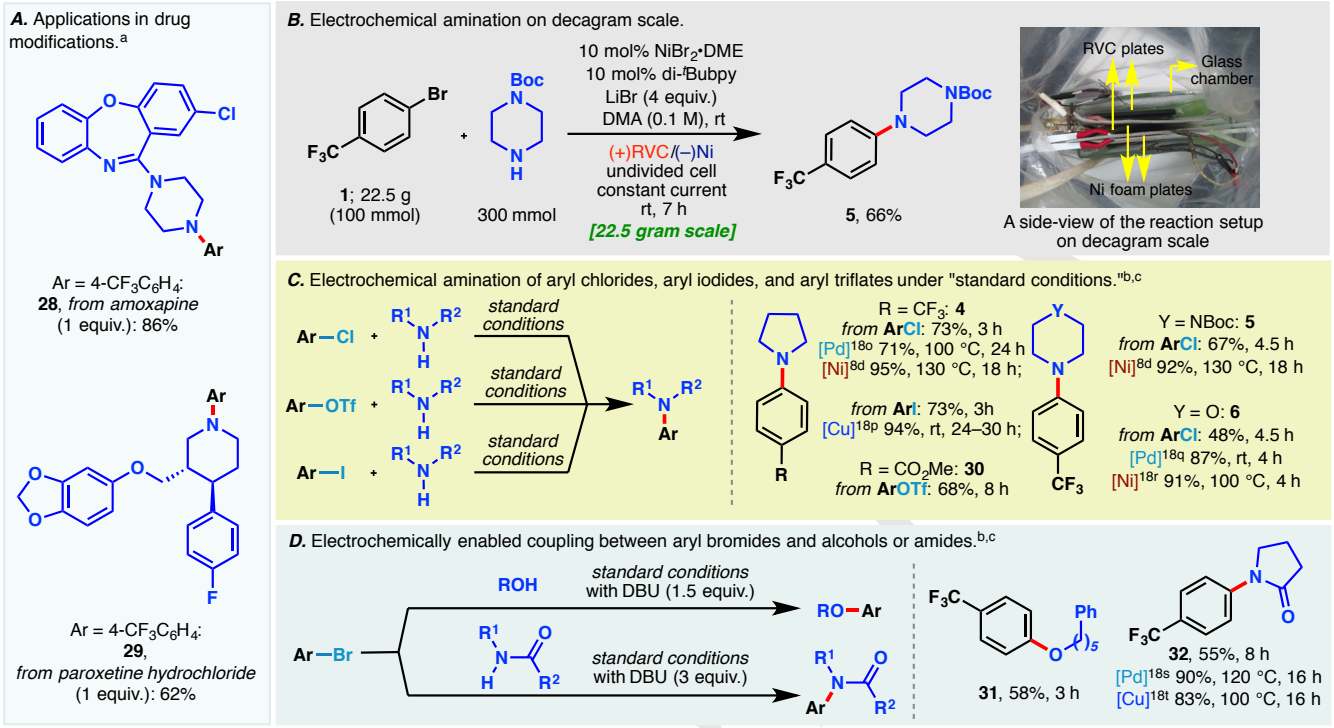

Scheme 2. Applications and extensions of the electrochemically enabled amination reaction to achieve (A) drug modifications, (B) decagram scale C–N coupling, (C) amination of aryl chlorides/triflates/iodides, (D) cross-coupling using alcohols and amides as nucleophiles. *a*) Reaction conditions: aryl bromide (3.0–5.0 equiv.), amine (1.0 equiv.), $NiBr_2$•glyme (10 mol%), di-^{t}Bubpy (10 mol%), DBU (2.0 equiv.), DMA (0.08 M), LiBr (4.8 equiv.), RVC anode, Ni cathode, constant current (I = 4 mA for 0.167 mmol scale), rt (See SI for experimental details). *b*) experimental procedures adapted from the standard conditions with modifications indicated. For details, see SI. *c)* Comparisons based on specified references for each substrate (footnote 18 and reference 8d).

This work represents a rare example where anodic and cathodic processes are reconciled to synergistically generate reactive catalyst species in different oxidation states—a sacrificial electrode is thus not involved.[20] From a holistic standpoint, this study is reminiscent of Moeller's electrochemically assisted Heck reaction using simple unmodified electrodes[21]—a pioneering contribution that has largely been overlooked by the community. Little's work on electroreductive coupling provides another instructive example where electrochemistry opens up new dimensions in nickel catalysis.[22] Taken together, electrochemical strategies to facilitate challenging cross-coupling reactions in a simple and sustainable fashion represent an exciting area whose full potential is yet to be realized.[23]

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Keywords: nickel catalysis • electrochemistry • amination • cross-coupling • arylation

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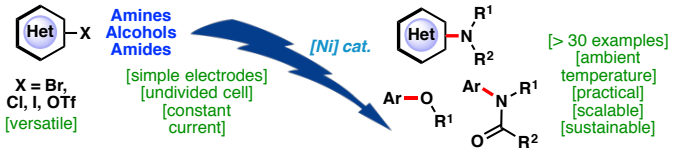

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Electrochemically Enabled, Ni-Catalyzed Amination

Amination, electrified: Arguably one of the most important types of bonds, the C–N bond can now be forged under Ni-catalysis with the aid of electrochemistry. Broad scope, scalability, sustainability, mildness, and rapid reaction rates are some highlights of this interesting new reaction.