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ARTICLE

Primary vs. Secondary Alkylpyridinium Salts: A Comparison under Electrochemical and Chemical Reduction Conditions

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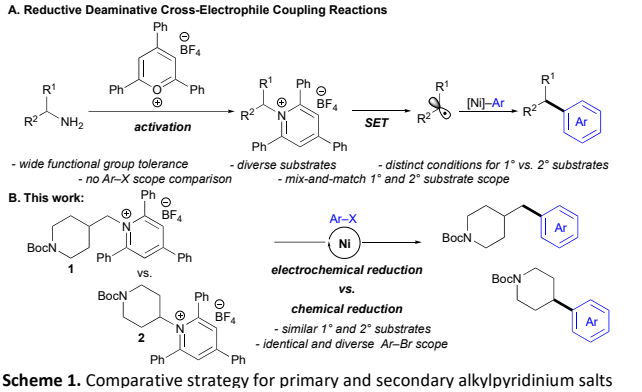
This report details a systematic comparison of the scope of aryl bromides in nickel-catalyzed, reductive cross-electrophile couplings of primary vs. secondary alkylpyridinium salts using both electrochemical and chemical reductants. Facilitated by the use of high-throughput experimentation (HTE) techniques, 37 aryl bromides, including 13 complex, drug-like examples, were investigated. By using primary and secondary substrates differing only by one methylene, we observed that the trends in ArBr scope are similar between the primary and secondary alkylpyridinium salts, although distinctions were observed in isolated cases. In addition, the electrochemical conditions compared favorably to those using chemical reductants, especially among the more complex, drug-like aryl halides.

Introduction

Reductive cross-electrophile couplings are a powerful synthetic approach for the formation of C(sp^3)–C(sp^2) bonds, offering broader functional group tolerance than their redox-neutral counterparts.[1,2] These types of methods were originally developed with manganese (Mn^0) or tetrakis(dimethylamino)ethylene (TDAE) reductants.[3,4,5] More recently, electrochemical conditions have been investigated to replace chemical reductants with an inherently more tunable approach.[6] Electroreductive couplings have been developed for alkyl halides, NHPI esters,[7] and very recently Katritzky pyridinium salts.[8] In these investigations, the reaction outcomes using electrochemical conditions are often compared to those using chemical reductants, with electrochemistry often providing complementary or improved results. However, a "mix and match" approach is often applied in scope studies, making systematic comparisons of the differences (or similarities) between scope for primary (1°) vs. secondary (2°) vs. tertiary (3°) alkyl substrates difficult. Importantly, the rates of oxidative addition of the aryl bromide and the alkyl electrophile activation must be matched for productive catalysis. Hence it is difficult to predict apriori whether the trends in ArBr scope would be the same for various alkyl classes.

The ubiquity and diversity of alkyl amines in the inventories of pharmaceutical companies and the ease of activating them as Katritzky pyridinium salts makes deaminative couplings particularly useful in the context of medicinal chemistry applications. Our previous report demonstrated dramatic differences in the optimal reaction conditions for 1° vs. 2° alkylpyridinium salts. This result is consistent with previous reactions of alkylpyridinium salts (Scheme 1A).[5] The difference in stability of 1° vs. 2° alkyl radicals impacts both the rate and reversibility of C–N bond cleavage,[9] and different conditions are often required to achieve adequate yields using these two classes of substrates across a wide range of reaction types. In reductive couplings, this difference is exacerbated because the alkylpyridiniums may be directly reduced by the reductant, instead of by single electron transfer (SET) with the Ni catalyst, leading to an imbalance in the rate of alkyl radical formation and the rate of ArBr oxidative addition. Because of these differences in the reactivity between 1° and 2° alkylpyridinium salts, it was unclear if they would have complementary or distinct trends in their ArBr scope, making it challenging to extrapolate ArBr scope studies from one alkylpyridinium class to another.

Herein, we report a systematic comparison of nickel-catalyzed reductive cross-electrophile couplings of primary and secondary



Scheme 1. Comparative strategy for primary and secondary alkylpyridinium salts

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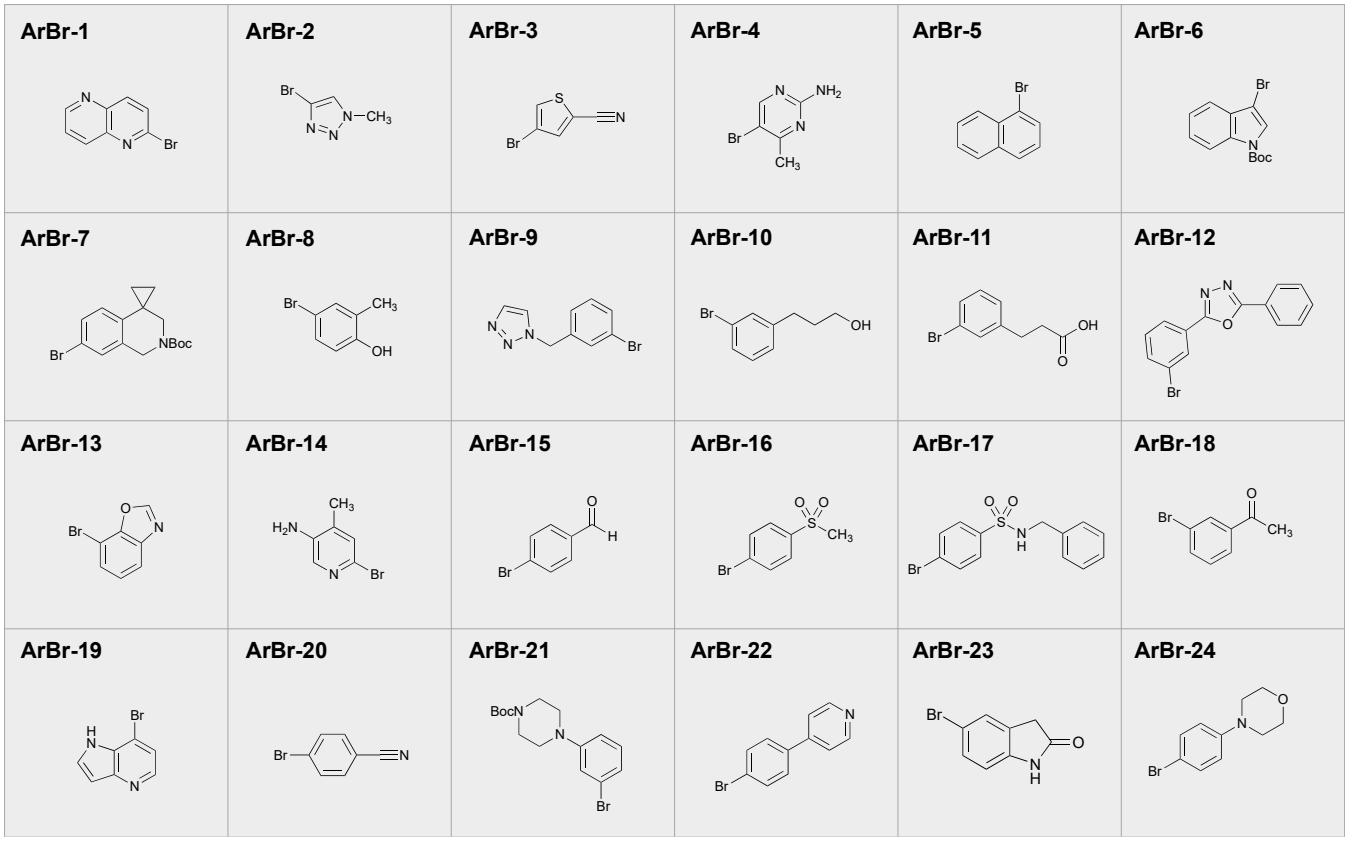


Figure 1. Structure of 24 aryl bromides used for scope studies

alkylpyridinium salts with a diverse set of aryl bromides (Scheme 1B). This study builds upon our recent report on electrochemical reductive coupling of alkyl pyridiniums with aryl halides.[8a] We now uncover relative reactivity trends between primary and secondary alkyl pyridinium substrates, where the primary and secondary substrates differ only by one methylene, making systematic comparison appropriate (Scheme 1B). Investigations were done using three distinct reaction conditions:- 1) electrochemical reduction, 2) Mn^0 as a heterogeneous reductant and 3) TDAE as a homogeneous reductant. Facilitated by the use of high-throughput experimentation (HTE) techniques, including use of the recently developed HTe-Chem reactor,[10] 24 aryl bromides were investigated, along with 13 informer halides, which are complex, drug-like aryl halides from the chemistry informer library pioneered by researchers at Merck & Co., Inc., Rahway, NJ, USA.[11] We found that the trends in ArBr scope are fairly consistent between the primary and secondary alkylpyridinium salt, although distinctions were observed in isolated cases. In addition, the electrochemical conditions compared favorably to those using chemical reductants, especially among the more complex informer halides. The translatability of ArBr scope between 1° and 2° alkyl pyridiniums will be particularly useful in the context of medicinal chemistry where predictability of the reaction scope is crucial to provide confidence for applications of cross-couplings using precious drug-discovery program intermediates.

Results and Discussion

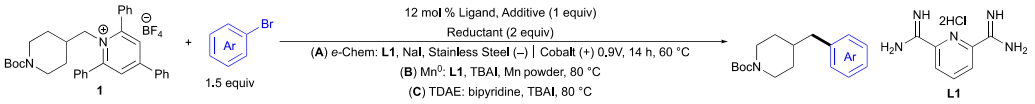
Investigations with 24 Diverse Aryl Bromides

We selected primary alkylpyridinium **1** and secondary alkylpyridinium **2** as our model substrates (Scheme 1B). Importantly, these substrates differ only by the addition of a methylene, making their results comparable. In addition, they provide mass-active products to facilitate LC/MS analysis of the crude reaction mixtures from the HTE experiments. Aryl bromides **ArBr-1** – **ArBr-24** were chosen as coupling partners, because they resulted in a wide range of product LC area percents (LCAPs) when used in our previously reported electroreductive coupling of a primary alkylpyridinium salt (Figure 1).[8a]

To determine suitable conditions for primary alkylpyridinium salt **1**, we initially evaluated conditions from the literature (Scheme 2A). Our previously published electrochemical conditions [$NiBr_2$(DME), pyridine-2,6-bis(carboximidamide) dihydrochloride (**L1**) as ligand, NaI as electrolyte, with a cobalt sacrificial anode and stainless-steel cathode at 60 °C][8a] provided satisfactory product LCAPs. Conditions using Mn^0 and TDAE were chosen based on our previous report of reductive couplings of lysine-derived pyridinium salts.[5f]

The results of these HTE campaigns using 1° alkylpyridinium substrate **1** are depicted in Scheme 2A. The electrochemical conditions compared favorably to the reactions using both chemical reductants (Mn and TDAE), with all three sets of conditions providing

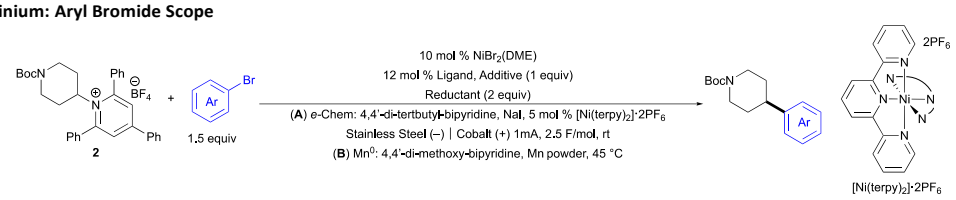
A. Primary Alkylpyridinium: Aryl Bromide Scope



Lowest LCAP — Highest LCAP

ArBr	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	Average
e-Chem Condition A	0	2	2	4	9	11	8	19	17	21	22	21	19	18	29	22	25	32	36	31	36	47	38	41	21
Mn Condition B	16	4	3	14	9	27	6	24	16	17	4	18	16	27	29	16	22	20	45	22	31	34	37	36	21
TDAE Condition C	2	3	20	24	47	15	8	10	26	14	1	37	22	33	44	37	44	45	23	36	19	61	13	16	25

B. Secondary Alkylpyridinium: Aryl Bromide Scope



ArBr	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	Average
e-Chem Condition A	4	0	23	5	30	7	21	10	3	11	2	12	22	4	24	17	26	29	4	28	13	13	28	23	15
Mn Condition B	3	0	16	3	16	7	1	1	1	2	1	13	4	4	27	21	23	15	11	31	4	2	2	3	9

Scheme 2. Primary and secondary aryl bromide scope results. Percentages reflect product LCAPs that are the average of multiple runs (see Supporting Inofrmation). Formation of triphenylpyridine was not considered for LCAP determinations. (**A**) Primary substrate coupling conditions: (a) ***e*-Chem = 1** (35 µmol, 1 equiv), ArBr (52.5 µmol, 1.5 equiv), $NiBr_2$(DME) (10 mol %), pyridine-2,6-bis(carboximidamide) dihydrochloride (12 mol %), NaI (1 equiv), DMA [0.1 M], 0.9V, 60 °C, 14 h. (b) **Mn = 1** (10 µmol, 1 equiv), ArBr (15 µmol, 1.5 equiv), $NiBr_2$(DME) (10 mol %), pyridine-2,6-bis(carboximidamide) dihydrochloride (12 mol %), Mn^0 (2 equiv), TBAI (1 equiv), DMA [0.1 M], 80 °C, 24 h. (c) **TDAE = 1** (10 µmol, 1 equiv), ArBr (15 µmol, 1.5 equiv), $NiBr_2$(DME) (10 mol %), bipyridine (12 mol %), TDAE (2 equiv), TBAI (1 equiv), DMA [0.1 M], 80 °C, 24 h. (**B**) Secondary substrate coupling conditions: (a) ***e*-Chem** = **2** (35 µmol, 1 equiv), ArBr (52.5 µmol, 1.5 equiv), $NiBr_2$(DME) (10 mol %), 4,4'-di-*tert*-butyl-bipyridine (12 mol %), $[Ni(terpy)_2]\cdot 2PF_6$ (5 mol%), NaI (1 equiv), DMA [0.1 M], 1mA constant current, 30V maximum 2.5 F/mol, rt. (b) **Mn = 2** (10 µmol, 1 equiv), ArBr (15 µmol, 1.5 equiv), $NiBr_2$(DME) (10 mol %), 4,4'-di-methoxy-bipyridine (14 mol %), Mn^0 (2 equiv), NMP [0.1 M], 45 °C, 24 h.

approximately the same average product LCAP across the 24 ArBr's. The scope of ArBr's for all three sets of conditions roughly follows similar trends. However, consistent with our previous reports, the TDAE conditions are often low-yielding for substrates with protic functional groups, such as **ArBr-8**, **ArBr-11**, and **ArBr-23**. Interestingly, the use of Mn^0 conditions with **ArBr-11** also gave low LCAP, yet these conditions generally tolerate other protic functional groups.

For the secondary alkylpyridinium salt **2**, we used electrochemical conditions that were optimal in our previous work (Scheme 2B).[8a] The use of electrochemical mediator $[Ni(terpy)_2]\cdot 2PF_6$ was shown to be beneficial for the cross-coupling of secondary alkylpyridiniums and alkyl halides. The anode (Co) and the cathode (stainless steel) were the same as those used for the primary alkylpyridinium salt couplings. The Mn^0 conditions were inspired by work done by Martin and coworkers, where secondary alkylpyridinium salts were the prime focus.[5a] Because no conditions using TDAE as a reductant have been previously reported for secondary pyridiniums, we evaluated several possible conditions (see Supporting Information); however, average LCAP was generally poor (< 3%). Because optimal reaction conditions have not yet been developed with this substrate class, comparison of the results using TDAE was deprioritized for this study.

Analogous to the results with primary alkyl pyridiniums (Scheme 2A), the electrochemical conditions compare favorably with the chemical reductant for reactions with the 2° pyridinium **2**, with an average LCAP of 15% vs. 9% for Mn^0. Unlike the 1° pyridiniums, aryl bromides bearing protic functional groups afford low product LCAPs under both conditions (**ArBr-8**, **ArBr-10**, and **ArBr-11**). Interestingly, however, **ArBr-3** and **ArBr-5** afford higher product LCAPs than analogous reactions with 1° alkylpyridinium **1** using both the electrochemical and Mn^0 conditions. We spectulate that this change in scope between 1° and 2° alkylpyridiniums may be due to the faster and more irreversible formation of the 2° alkyl radical, which requires in turn a faster oxidative addition of the ArBr. Thus, electron-rich aryl bromides (e.g., **ArBr-8**, **ArBr-10**, and **ArBr-11**) fail with alkylpyridnium **2**.

Investigations with Informer Halides

Encouraged by the scope with the 24 ArBr's detailed above, we also investigated the coupling of both 1° and 2° alkylpyridinium salts with informer halides to assess the efficacy of these methods in the context of complex, drug-like substrates (Figure 2).[11] Because we focused this study on ArBr scope, the informer aryl iodides (**X14** and **X15**) and chlorides (**X16**, **X17**, and **X18**) were left out of this study. We investigated the scope across the remaining 13 informer halides with alkylpyridinium substrate **1** under the three sets of conditions (electrochemical, Mn^0, and TDAE) and **2** under electrochemical and Mn^0 conditions.

Results for the cross-coupling of 1° alkylpyridinium **1** with informer halides **X1**-**X13** are shown in Scheme 3A. The average LCAPs were 12%, 10%, and 15% for the electrochemical, Mn^0, and TDAE conditions, respectively.

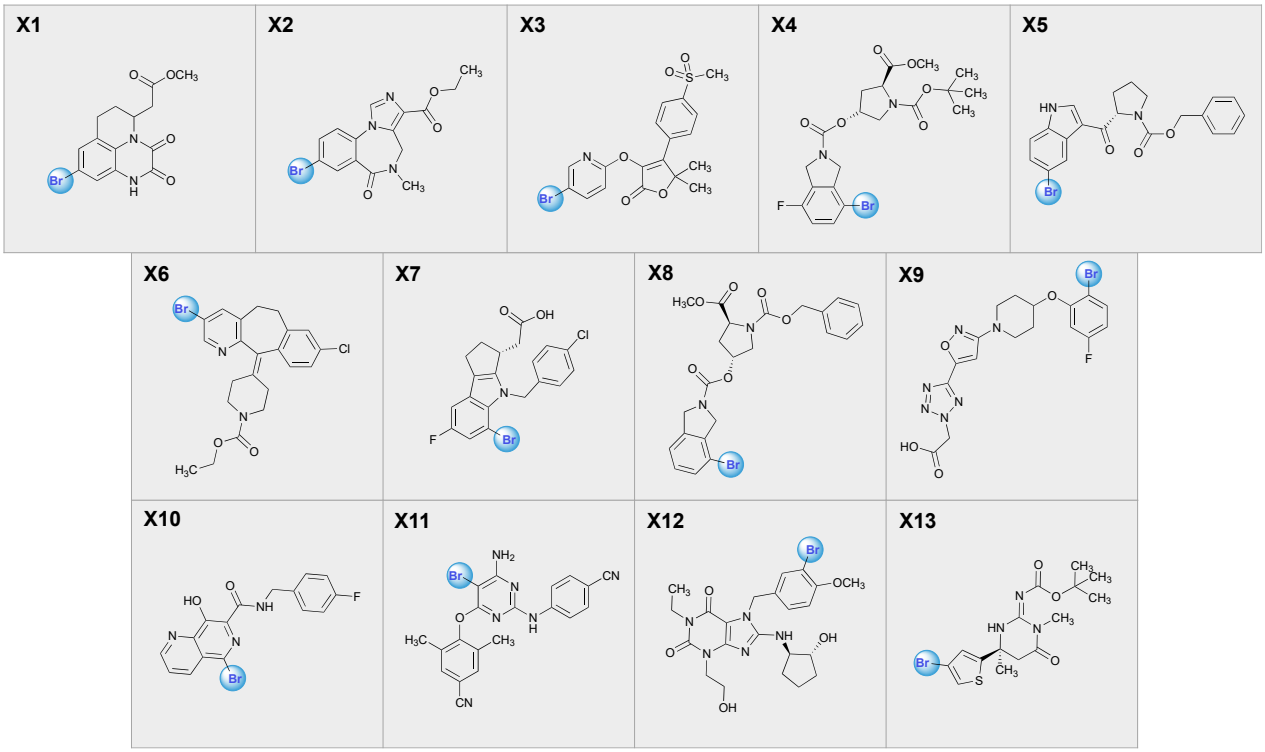
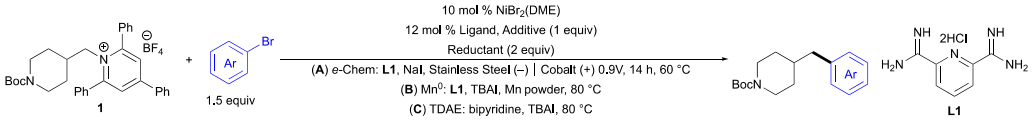


Figure 2. Structure of informer halides

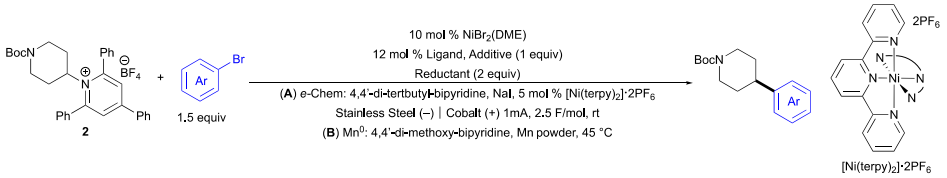
A. Primary Informer Halide Scope



Lowest LCAP Highest LCAP

Informer	1	2	3	4	5	6	7	8	9	10	11	12	13	Average
e-Chem Condition A	35	20	0	2	33	29	0	4	1	0	0	12	21	12
Mn Condition B	27	28	10	3	19	30	0	6	0	1	1	6	5	10
TDAE Condition C	0	67	15	12	3	56	0	15	0	0	0	25	2	15

B. Secondary Informer Halide Scope



Informer	1	2	3	4	5	6	7	8	9	10	11	12	13	Average
e-Chem Condition A	12	23	4	6	20	18	0	8	27	0	0	19	15	12
Mn Condition B	3	13	5	0	1	17	0	3	15	1	3	3	4	5

Scheme 3. Primary and secondary informer halide scope results. Percentages reflect product LCAPs that are the average of multiple runs (see Supporting Inofrmation). Formation of triphenylpyridine was not considered for LCAP determinations. (**A**) Primary substrate coupling conditions: (a) ***e*-Chem = 1** (35 µmol, 1 equiv), ArBr (52.5 µmol, 1.5 equiv), $NiBr_2$(DME) (10 mol %), pyridine-2,6-bis(carboximidamide) dihydrochloride (12 mol %), NaI (1 equiv), DMA [0.1 M], 0.9V, 60 °C, 14 h. (b) **Mn = 1** (10 µmol, 1 equiv), ArBr (15 µmol, 1.5 equiv), $NiBr_2$(DME) (10 mol %), pyridine-2,6-bis(carboximidamide) dihydrochloride (12 mol %), Mn^0 (2 equiv), TBAI (1 equiv), DMA [0.1 M], 80 °C, 24 h. (c) **TDAE = 1** (10 µmol, 1 equiv), ArBr (15 µmol, 1.5 equiv), $NiBr_2$•DME (10 mol %), bipyridine (12 mol %), TDAE (2 equiv), TBAI (1 equiv), DMA [0.1 M], 80 °C, 24 h. (**B**) Secondary substrate coupling conditions: (a) ***e*-Chem** = **2** (35 µmol, 1 equiv), ArBr (52.5 µmol, 1.5 equiv), $NiBr_2$(DME) (10 mol %), 4,4'-di-*tert*-butyl-bipyridine (12 mol %), $[Ni(terpy)_2]\cdot 2PF_6$ (5 mol%), NaI (1 equiv), DMA [0.1 M], 1mA constant current, 30V maximum 2.5 F/mol, rt. (b) **Mn = 2** (10 µmol, 1 equiv), ArBr (15 µmol, 1.5 equiv), $NiBr_2$(DME) (10 mol %), 4,4'-di-methoxy-bipyridine (14 mol %), Mn^0 (2 equiv), NMP [0.1 M], 45 °C, 24 h.

For all three sets of conditions, the scope was similar. An apparent limitation for the electrochemical conditions are pyridyl and fluorine

containing partners **X3**, **X4, X7 and X9-11**, although it should be noted that simpler 3-bromo-5-phenylpyridine was successfully employed in our previous report and that the complexity of the informers makes such generalizations difficult.[8a]

As shown in Scheme 3B, the couplings with 2° alkylpyridinium **2** was more challenging with average LCAPs of 12%, and 5% for electrochemical and Mn^0 conditions, respectively. Here, electrochemical conditions provided the broadest scope, with 6 informer halides leading to LCAPs ≥15%.

Conclusions

In summary, this report describes a systematic comparison of the cross-electrophile couplings of two, nearly identical 1° and 2° alkylpyridinium salts under three different modes of reduction. The use of HTE techniques facilitated the cross-couplings and analysis of reactions using 24 diverse aryl bromides and 13 complex informer halides using electrochemical (using a sacrificial cobalt anode and stainless-steel cathode), and non-electrochemical conditions (using Mn^0 and TDAE). Overall, the electrochemical conditions compare favorably with conditions using chemical reductants. In addition, and perhaps most importantly, the trends in ArBr scope were in general similar between the 1° and 2° alkylpyridinium salts, showing that one can extrapolate successes with one pyridinium class to the other with a reasonable level of confidence. This knowledge will be useful for chemists employing electrochemical deaminative couplings in pharmaceutical discovery and other synthetic endeavors. It strengthens the confidence that methods developed with chemical reductants can be translated to electroreductive approaches, and that the scope of newly developed electroreductive deaminative methods is likely to be similar to those developed with Mn^0. Perhaps even more importantly, this study provides future researchers with the knowledge that the scope of ArBr's is likely to be similar between 1° and 2° alkylpyridinium salts, facilitating the use of electrochemical deaminative cross-couplings broadly in parallel medicinal chemistry campaigns.

Experimental

General procedure for HT*e*-Chem Experiments. In a nitrogen-filled glovebox, to 1-mL vials (secured in a 24-well aluminum block) equipped with 5 x 2 mm PTFE-covered magnetic stir bars was added pyridinium (175 µL, 0.2 M solution in DMA, 35 µM, 1 equiv), aryl bromide (105 µL, 0.5 M solution in DMA, 52.5 µM, 1.5 equiv), NaI (50 µL, 0.7 M solution in DMA, 35 µM, 1 equiv), and pre-complexed $NiBr_2$·DME catalyst/ligand mixture (23.3 µL, 0.15 M solution in DMA, 3.5 µM, 10 mol %) sequentially. The electrodes were inserted, and the HT*e*-Chem reaction block was assembled inside the glovebox. The reactor was then connected to the external power supply inside the glovebox and heated to the appropriate temperature on an IKA stir plate. Upon reaching the desired temperature, the reactions were electrolyzed. For constant voltage mode (V = 0.9V) for 14h (overnight). For constant current mode (I = 1 mA, 2.5 F/mol). After electrolysis, the HT*e*-Chem reactor was allowed to cool to rt (if applicable), taken outside of the glovebox, and disassembled. A 5 µL aliquot of the crude reaction mixture was taken and diluted in 400 µL of DMSO for UPLC-MS analysis.

Preparation of Nickel Stock Solutions for HT*e*-Chem Experiments. In a nitrogen-filled glovebox, a 4-mL vial (equipped with a stir bar) was charged with $NiBr_2$·DME catalyst (238.50 µmol) and appropriate ligand (1.2 equiv regarding Ni) and DMA (1341.65 µL) was added to prepare the final 0.15 M stock solution. The mixtures were stirred for ~20 minutes (resulting in a slurry) before dosing into the reaction vials. The slurry was continually stirred at 1000 rpm while dosing.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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