Nickel-Electrocatalytic Decarboxylative Arylation to Access Quaternary Centers

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Abstract: There is a pressing need, particularly in the field of drug discovery, for general methods that will enable direct coupling of tertiary alkyl fragments to (hetero)aryl halides. Herein a uniquely powerful and simple set of conditions for achieving this transformation with unparalleled generality and chemoselectivity is disclosed. This new protocol is placed in context with other recently reported methods, applied to simplify the routes of known bioactive building blocks molecules, and scaled up in both batch and flow. The role of pyridine additive as well as the mechanism of this reaction are interrogated through Cyclic Voltammetry studies, titration experiments, control reactions with Ni(0) and Ni(II)-complexes, and ligand optimization data. Those studies indicate that the formation of a BINAPNi(0) is minimized and the formation of an active pyridine-stabilized Ni(I) species is sustained during the reaction. Our preliminary mechanistic studies ruled out the involvement of Ni(0) species in this electrochemical cross-coupling, which is mediated by Ni(I) species via a Ni(I)-Ni(II)-Ni(III)-Ni(I) catalytic cycle.

Introduction

Modern pharmacophore designs are testing the limits of known chemistry such that newly emerging radical cross-coupling techniques are seeing increasing attention in drug discovery.[1] For example, the coupling of complex sp^3-hybridized tertiary carbons to (hetero)arenes to generate quaternary centers was rarely, if ever, employed a decade ago (Figure 1A).[2] In this context, canonical $2e^-$-cross-coupling techniques such as Suzuki-Miyaura[3] and Kumada[4-5] reactions suffer from low yields and/or poor chemoselectivity in addition to arduous preparation of organometallic reagents making them unreliable for modern

medicinal chemistry campaigns.[6-7] Cross-electrophile type couplings are known in such contexts and due to their radical nature are amongst the most useful for this purpose.[8-11] That said, there is a large demand for new methods that can take readily available tertiary synthons and couple them directly to complex heteroaryl halides. Decarboxylative cross-coupling (DCC) has seen increasing use for rapidly appending alkyl fragments to arenes of all types (Figure 1B).[12-15] Whereas the scope of such couplings is broad when primary and secondary acids and their redox-active esters (RAEs) are employed, extending that reactivity to tertiary acids has been a vexing problem.[16-19] For instance, the simple coupling of RAE/acid **1a-b** with pyrimidine **2** fails under the most modern of conditions (chemical, photochemical, electrochemical), delivering at most 9% yield. Although the published scope of these methods generally tolerates numerous types of arenes, the competent alkyl coupling partners mostly involve systems that form radicals that are part of a strained ring system or stabilized by the presence of an α-heteroatom (as listed in Figure 1B).[16-19] In this Article, a solution to this issue is presented by building upon the Ag-functionalized electrode Ni-electrocatalytic method reported previously.[19] This newly invented protocol can, for example, achieve the coupling of **1a** and **2** in 45% isolated yield (along with 3% of the undesired positional isomer) and is general across a range of substrates that have proven challenging with all published methods to date. It can be utilized to dramatically simplify the way such molecules have been previously prepared and is amenable to scale-up in both batch and flow settings.

Results and Discussion

Decarboxylative Arylation of Tertiary Acids: Development

Optimization studies commenced with pivalic acid-derived RAE **4** and bromopyridine **5** (Table 1). Using the electrochemical conditions previously reported,[19] a 19% isolated yield of an inseparable 4:1 mixture of isomers was obtained wherein the desired *t*-butyl pyridine **6a** was the major product. Isomer **6b** presumably arises from a Ni-mediated migratory isomerization process.[6, 8] Thus, both the conversion and isomeric distribution made this reaction synthetically unworkable. Reasoning that the ancillary ligand screening may have the biggest impact in improving the isomeric distribution it was chosen as the first parameter for optimization. Dozens of ligand scaffolds were screened (see SI for a summary), and it was discovered that phosphines such as PCy_3 could indeed deliver almost exclusively the desired *t*-butyl isomer (Table 1, entry 2). The precise ratio of ligand to Ni also appeared to play a decisive role as increasing the amount of phosphine could completely shut down the reaction (Table 1, entry 3). Eventually it was recognized that (*S*)-BINAP was singularly successful in delivering superior conversion along with a synthetically useful 18:1 isomeric ratio (Table 1, entry 6). Despite screening numerous other bisphosphines, none were superior to (*S*)-BINAP and mostly gave low conversion (albeit with high isomeric distributions, Table 1, entry 7).

Next, various electrochemical parameters were explored (Table 1, entries 8-10) and the only meaningful improvement occurred when 1 equiv. of $AgNO_3$ was added (Table 1, entry 8). Of the many additives that were screened, simple pyridine proved to be the more effective (1.0 equiv., Table 1, entry 11). Interestingly, the use of pyridine as an additive has a profound impact on the cross-coupling and conversion (~5% without pyridine) of non-pyridyl aryl bromides (*vide infra*) suggesting that compound **5** may have served a dual role being the electrophilic coupling partner and an additive.[10]

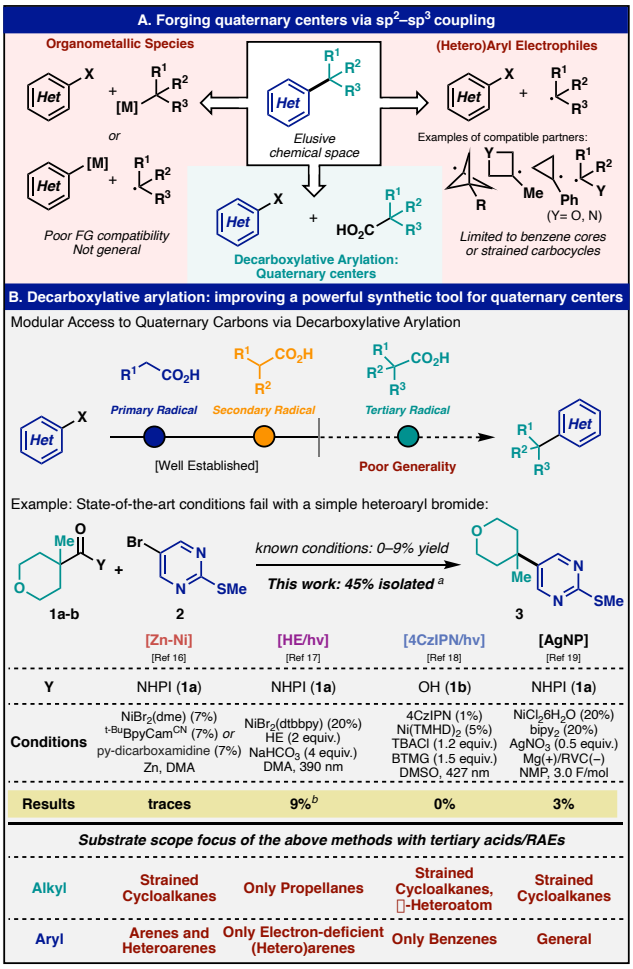


Figure 1. (A) General approaches for the synthesis of quaternary centers with sp^2–sp^3 coupling. (B) State-of-the-art in the decarboxylative arylation of tertiary acids. [a]Desired product formed along with 3% of the undesired isomer (isomeric distribution 16:1, determined *via* ^{1}H NMR). [b]Desired product formed along with 8% of the undesired isomer (isomeric distribution 1:1, determined *via* ^{1}H NMR). HE = Hantzsch Ester; NHPI = N-hydroxyphtalimide. NMP = *N*-Methyl-2-pyrrolidone.

Numerous pyridine derivatives were subsequently screened as additives (for example Table 1, entries 12 and 13), but none were superior to pyridine. In the final optimized conditions, the amount of (*S*)-BINAP could be reduced to 5 mol% along with 25 mol% Ni (Table 1, entry 14 and 15; see SI for a discussion on side products). Basic control studies confirmed the essential nature of the Ni, Ag, (*S*)-BINAP, and pyridine additives as well as electricity

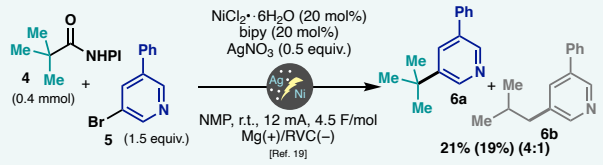
(Table 1, entries 16-20). As with our previous disclosure,[19] the final conditions are practically trivial to setup (dump and stir) with no precautions taken to remove air or moisture. Setup time for these reactions is rate-limited by how quickly the practitioner can weigh out starting materials and most of the reactions are complete within four hours.

Decarboxylative Arylation of Tertiary Acids: Scope

Historically, the synthesis of tertiary-substituted arene targets has been tackled by using one of three approaches: 1. Direct Minisci or Friedel–Crafts alkylation,[20-22] 2. Building the quaternary center off of an electron deficient (hetero)arene,[23-26] and 3. Building the heteroaromatic ring starting with the pre-installed quaternary center.[27-28] With regards to the first category, the clear limitation is that the alkylation event can only occur at the innately activated position.[20] Thus, in **Figure 2**, only a small fraction of substrates could be envisioned as possibly accessible using such a method. The second category almost always involves a laborious route relying on the proper placement of electron-deficient substituents to enable sequential enolate-type alkylation. For instance, compounds similar to **12**, **17**, **19** and **21** were prepared through a multistep sequence wherein the methyl or amino group was derived (after exhaustive reduction or Curtius rearrangement)[23-24] from a carbonyl (aldehyde or ester) following, for example, Pd-catalyzed enolate arylation or Rh-catalyzed hydroarylation.[29-30] The third category is the most difficult sequence as only certain types of molecules can be accessed this way.

Table 1. Optimization of synthesis of quaternary centers via electrochemical decarboxylative arylation. [a]GC yield obtained with 1,3,5-trimethoxybenzene as internal standard. [b]Isomeric ratio determined *via* GC.

Optimization on heteroaryl system



Entry	Modification	Yield (%)[a]	6a:6b[b]
	Ligand screening		
1	Terpy (20 mol%)	traces	-
2	PCy_3 (20 mol%)	11%	20:1
3	PCy_3 (40 mol%)	0%	-
4	P(*o*-Tol)$_3$ (20 mol%)	20%	4:1
5	P(Napht)$_3$ (20 mol%)	28%	4:1
6	**(*S*)-BINAP (20 mol%)**	**33%**	**18:1**
7	other bisphosphine ligands (20 mol%) [see SI]	<5%	ca. 20:1
	Electrochemical parameter screening (from Entry 6)		
8	**$AgNO_3$ (1.0 equiv.), RAE 1.5 equiv.**	**39%**	**17:1**
9	Zn, Al anode	traces	-
10	Graphite cathode	21%	18:1
	Additive Screening (from Entry 8)		
11	**Pyridine (1.0 equiv.)**	**44%**	**20:1**
12	Methyl Isonicotinate (1.0 equiv.)	19%	>20:1
13	2,6-Lutidine (1.0 equiv.)	0%	-
	Final Conditions (from Entry 11)		
14	$NiCl_2 \cdot 6H_2O$ (25 mol%) (*S*)-BINAP (25 mol%) Py (1.0 equiv.)	49%	>20:1
15	**$NiCl_2 \cdot 6H_2O$ (25 mol%) (*S*)-BINAP (5 mol%) Py (1.0 equiv.)**	**49% (44%)**	**>20:1**
	Controls (from Entry 15)		
16	No Nickel	0%	-
17	No $AgNO_3$	traces	-
18	In presence of Mg(+) but no electricity	0%	-
19	No (*S*)-BINAP	21%	5:1
20	No Pyridine	47%	5:1

Indeed, none of the compounds in **Figure 2** can be accessed with such logic as one is generally restricted to heteroarenes that can be easily constructed from carbonyl or alkyne appendages, leading to a non-modular strategy.[27-28] Aside from the bespoke methods outlined above, cross-couplings to access such structures must be evaluated on a case-by-case basis. For example, Shenvi's powerful hydroarylation approach can access certain scaffolds such as **9**, **10**, and **20**.[31] If the alkyl bromide is available, Sevov and Gong's cross-electrophile couplings are potentially useful options for compounds such as **7**, **8** and **9**.[8-9] If the alkyl amine is available, deaminative cross-couplings might be of use for compounds such as **8**, **9**, and **10**.[32] Finally, if an ester is desired at the quaternary carbon, Hartwig's small-ring arylation disclosure could be very effective (**23**).[33]

The BINAP/Pyridine-enabled Ni-electrocatalytic conditions described in Table 1 were applied across a range of arenes and redox active esters to access all of the structures outlined in **Figure 2**.[34] In order to place these results in the proper context, comparisons to the original Ag/Ni conditions are shown in addition to recent photochemical conditions that were optimized for hindered couplings (9 out of 52 arylations in that study formed quaternary centers with the remainder being fully substituted centers with an adjacent heteroatom),[18] and other chemical and photochemical methods.

Three photochemical reports show that tertiary alkyl radical precursors can be cross-coupled with aryl halides, and $Ni(TMHD)_2$ complex is the only effective catalyst in those three photochemical reports. [17-18, 32] While effective at promoting the formation of quaternary centers, a noticeable drawback of $Ni(TMHD)_2$ complex in those cross-couplings is its incompatibility with ligating substrates such as bromopyridine and other simple (hetero)aryl halides; doping experiments showed that pyridine and other heterocycles inhibit the active Ni-species in related cross-coupling reactions.[35] In contrast, the electrochemical method presented in this report overcomes these limitations, as exemplified by compounds **16**, **21**, and **27**. Furthermore, a vast collection of (hetero)aryl halides can be employed as suitable coupling partners (**Figure 2**).

In terms of RAE scope, alkyl groups that are prone to isomerization (i.e., not bearing a stabilizing α-heteroatom), bridgehead, strained, and α-heteroatom containing systems can all be employed. One striking finding relative to other aryl–alkyl couplings of any kind is the low levels of isomerization observed in the cross coupling of tertiary cyclic substrates relative to our previous reported conditions and to other reported methods (employing alkyl bromides).[10, 36] For the aryl scope, a broad range of aryl and heteroaryl partners are competent in this coupling to deliver synthetically useful quantities of product. While the yields in some cases may be modest (ca. 20% yield) there are currently no other viable options for such direct couplings. The reaction appears to be quite general across a range of coupling partners as documented with the synthesis of molecules **45**–**52**. The mildly reductive nature of the reaction tolerates numerous functional groups, such as esters, ketones, amides, nitriles, ethers, Boc/Cbz protecting groups, aryl halides, aryl thioethers, cyclopropanes, oxetanes, and azetidines. Products bearing an *ortho*-substituent on the arene, such as **37** and **52**, are also accessible. In terms of limitations, 2-halo pyridines and 2-halo pyrimidines are unreactive. This can be exploited in the case of

43 wherein the seemingly highly reactive C–I bond remains intact and thus available for canonical cross-coupling chemistry. Electron-rich arenes are also not efficient coupling partners. Finally, if a specific heterocycle is particularly prone to Minisci-type reactivity, it can compete with or override the desired coupling (see SI). A transparent disclosure of what we currently know regarding the limitations of this method is outlined in the SI.

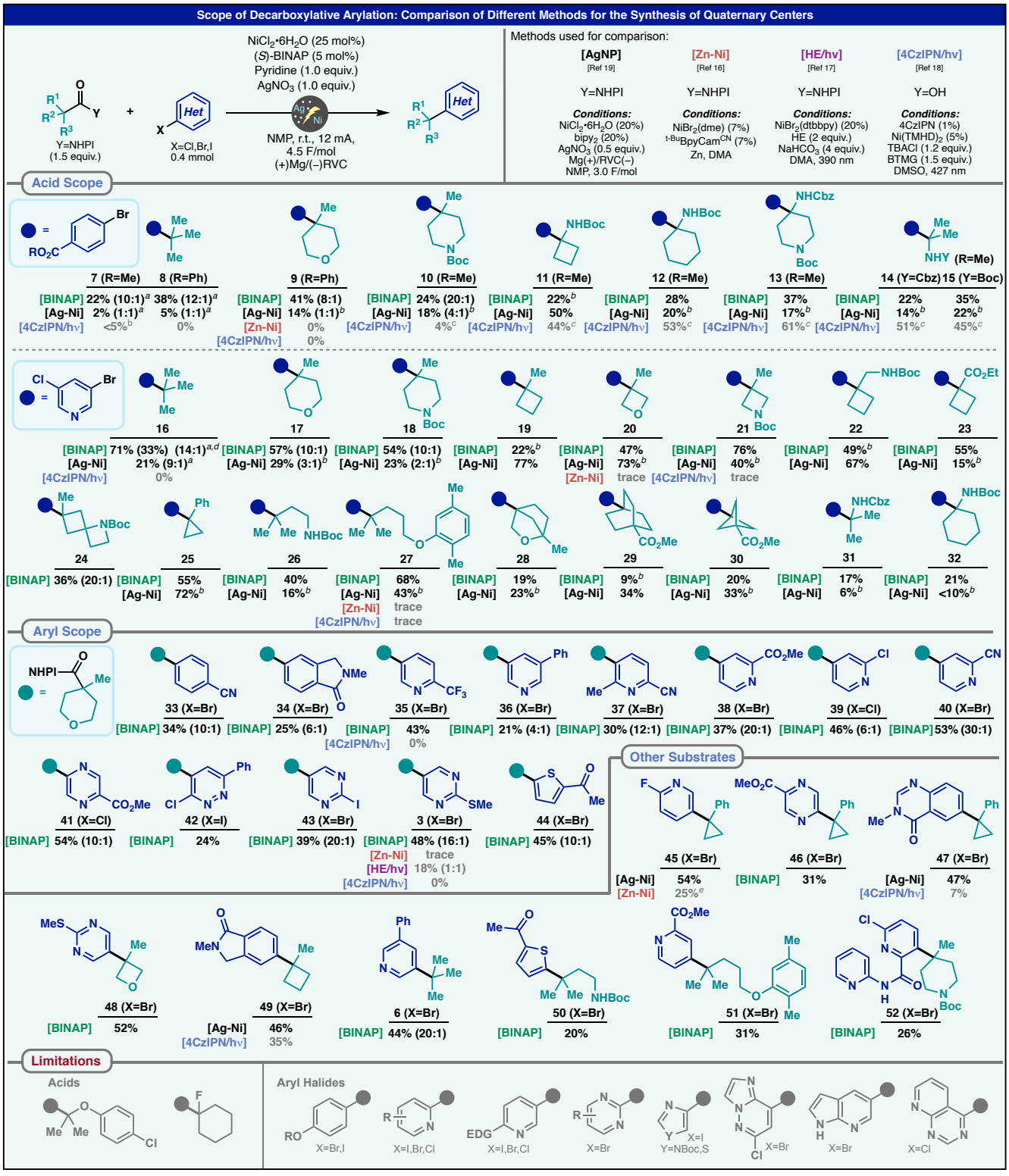


Figure 2. Scope of decarboxylative arylation (in case no regioisomeric ratio is shown, only one isomer was observed). [a]GC yield obtained with 1,3,5-trimethoxybenzene as internal standard. [b] ^{1}H NMR yield obtained with 1,3,5-trimethoxybenzene or nitromethane as internal standard. [c]From Ref. 16. [d]Volatile compound. [e]From Ref. 16.

Decarboxylative Arylation of Tertiary Acids: Applications and Scale-up

As mentioned above, access to structures of the type described herein has historically been extremely challenging. To be sure, prior routes require multiple steps often beleaguered with numerous concession steps, cryogenic temperatures, and pyrophoric reagents. **Figure 3** illustrates four examples of this challenge by drawing directly from the medicinal chemistry patent literature where quaternary-linked pyridine scaffolds were synthesized. Thus, HPK1-inhibitor intermediate **53** was prepared in an 8 step process (ca. 2% overall yield, 4 column purifications) wherein the piperidine ring system was annulated onto a pendent acyl group.[37] In contrast, decarboxylative arylation on RAE **54** followed by Pd-catalyzed amidation led to the same product in 2 steps (29 % overall yield). Kinase inhibitor intermediates **55** and **57** were previously prepared in 4 steps (30.7 and 7.5% yield, respectively with 3-4 column purifications).[38-39] The same structures could be accessed in a single-step using readily available building blocks **56** and **1a** in 66% and 38% isolated yields, respectively. Finally, an intermediate of use in antiviral research (**58**) was previously accessed in a 4-step process (10.4% overall yield, 4 column purifications) that could now be accessed easily in a single step (73% isolated yield) from **54** and **59**.[40] While the aforementioned route comparisons demonstrate how the decarboxylative arylation protocol can be used to dramatically simplify access to such structures, the ability to rapidly explore SAR beyond simple methyl substitution at the quaternary center should find broad utility.

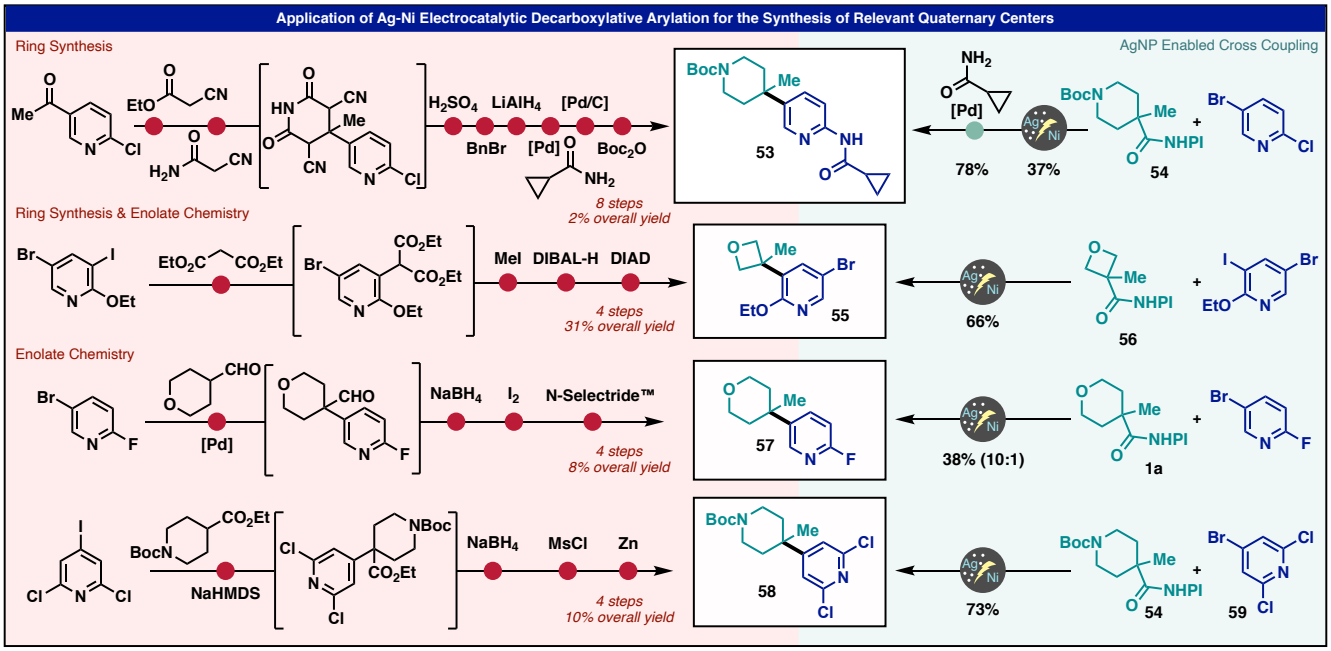


Figure 3. Strategic application of the AgNP (silver nanoparticles) electrocatalytic synthesis of quaternary centers (isomeric distribution determined *via* ^{1}H NMR, in case no regioisomeric ratio is shown, only one isomer was observed).

In terms of scalability **Figure 4** documents how the current reaction protocol can be adapted to gram and decagram scale using batch and flow reactor setups. Pyrimidine **3** could be accessed on a gram-scale in batch without precaution to remove air or moisture, and the reaction was complete within 4 hours (48% isolated yield, identical to the ca. 100 mg scale). Pyridine **27** could be synthesized on decagram scale using a simple and inexpensive recirculating flow setup similar to that previously reported.[19] Again, no onerous precautions were taken to set up this reaction. When a premade RAE was employed a similar yield to the small scale run was observed (59% isolated yield). An *in situ* preparation of the RAE could be employed resulting in a lower yield of product (similar result to smaller scale, see SI for further discussion).

Decarboxylative Arylation of Tertiary Acids: Mechanistic studies

A rigorous dive into the precise mechanistic intricacies of this new protocol is beyond the scope of this report. However, several experiments were performed to support the hypothesized high-level mechanistic picture that is outlined in **Figure 5A**. The basic elementary mechanistic steps are postulated to be as follows: 1. Deposition of Ag nanoparticles (AgNP) onto the cathode as extensively studied previously,[41] 2. Ligation of the Ni(II)-species with pyridine and (*S*)-BINAP (equilibrium),[8, 42] 3. Reduction of Ni(II)X_2 to Ni(I)X, 4. Trapping of the radical derived from the RAE (formed at the cathode or from a Ni(I) species), 5. Cathodic reduction of the Ni(II)(alkyl) complex to a Ni(I)(alkyl) species. Prior to reduction of the Ni(II)(alkyl) complex, the isomeric byproduct can be formed through a sequence involving β-hydride elimination,

and migratory insertion,[43] 6. Oxidative addition of the Ni(I)(alkyl) into the aryl halide, and 7. Reductive elimination to form the quaternary center or the isomeric product. Although a concerted oxidative addition is commonly proposed, a stepwise oxidative addition process cannot be ruled out at this time.[44]

In support of the above, three diagnostic studies were performed (panels I-III). The optimum ratio of pyridine to Ni-complex was assessed by carrying out several reactions, with varying amounts of pyridine and a fixed amount of (*S*)-BINAP-Ni(II) complex (**Figure 5B**, panel I). An optimum ratio of between 3–4 equivalents of pyridine relative to the Ni(II) complex was observed. When more equivalents of pyridine were added to the reaction, a lower yield was observed, indicating that the over-complexation of pyridine with Ni may lead to catalyst deactivation. In order to rationalize the role that pyridine plays in the cross-coupling, cyclic voltammetry (CV) experiments were conducted with varying amounts of pyridine (**Figure 5B**, panel II). The CV of (BINAP)$NiCl_2$ did not show any relevant redox activity.[45] However, the titration of 1–4 equivalents of pyridine resulted in the development of a new irreversible reduction peak at -1.3 V. The intensity of this new reduction peak increases with increasing the amount of pyridine. This peak has been assigned to Ni(I) species by Amatore and his collaborators in their studies of electrochemical reduction of bidentate-phosphine ligated $NiCl_2$ complexes.[46-47] Therefore, we hypothesize in the presence of pyridine, the formation of a (BINAP)Ni(0) is minimized, and active pyridine-stabilized Ni(I) species are sustained during the reaction. Along the same line, the enhanced efficiency of the cross-coupling at a higher $NiCl_2$ loading relative to (*S*)-BINAP (5:1 ratio, **Table 1**), may be necessary to maintain an increased concentration of active Ni(I) species.

BINAP also appears to play a critical role in promoting the desired quaternary-center forming path over the β-hydride elimination pathway, while the use of bipyridine ligand gave a 1:1 ratio of **8a:8b** (**Figure 5B**, panel III). Bipyridine-type ligands are known to enhance chain-walking in favor of the isomerization pathway.[48-49] Other mono- and bidentate phosphines, including PPh_3 and dppp, were inferior to BINAP (see panel III and SI).

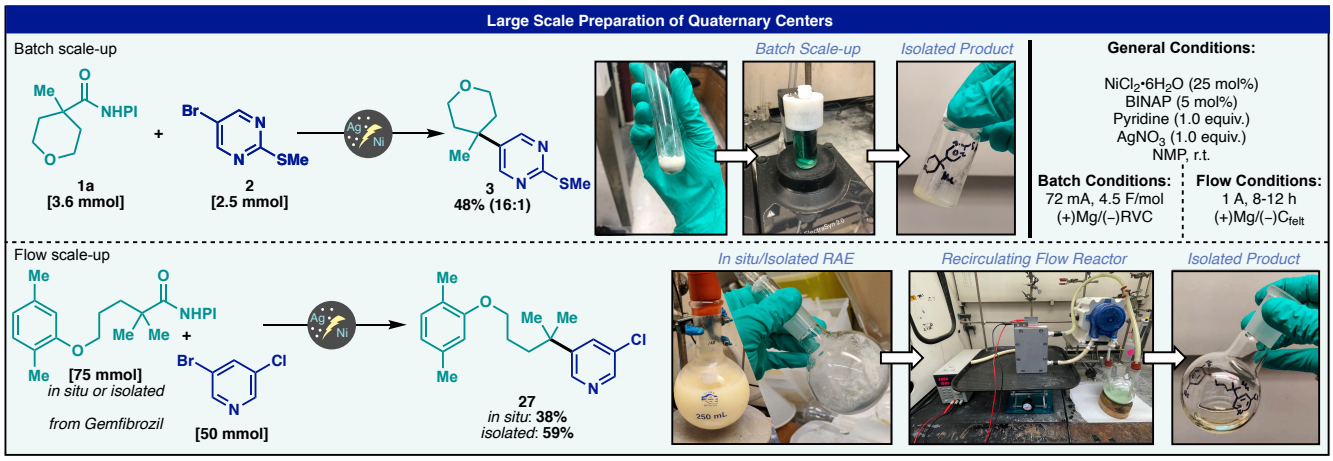
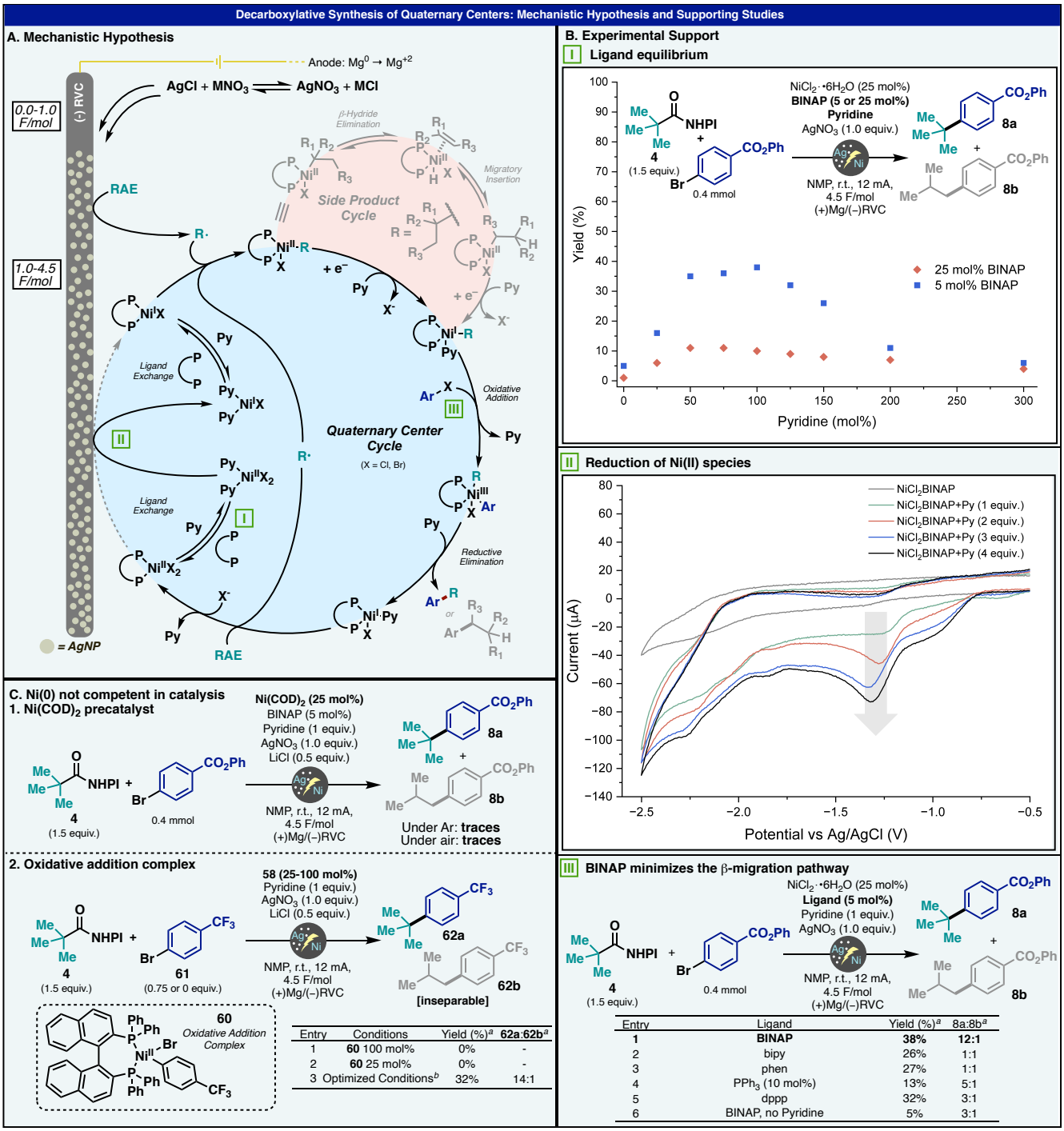


Figure 4. Scale-up of the AgNP electrocatalytic synthesis of quaternary centers (isomeric distribution determined *via* ^{1}H NMR).

Finally, other Ni-catalyzed reactions presented in previous reports on quaternary center synthesis suggest that a Ni(0) pathway can be operative when a chemical reductant is employed.[36] To probe this possibility, several experiments were conducted (**Figure 5C**). First, a possible involvement of Ni(0) species in this cross-coupling was evaluated. When $Ni(COD)_2$ was employed as precatalyst in the reaction, only traces of product were observed under inert conditions and under air, indicating that Ni(0) does not mediate this cross-coupling.[36] To further support this assertion, a set of experiments were carried out with a preformed oxidative addition complex **60**.[50] Two different reactions employing a catalytic or stoichiometric amount of complex **60** failed to produce the desired product **62**. As a control, the same reaction when conducted with the standard conditions provided **62** in 32% yield as a mixture of the isomers **62a** and **62b**. Overall, the experiments outlined in **Figure 5** do not support the involvement of Ni(0) species (see SI for further discussions and more experiments on Ni(0)), but rather suggest that this electrochemical cross-coupling is mediated by Ni(I) species *via* a Ni(I)-Ni(II)-Ni(III)-Ni(I) catalytic cycle.



Entry	Conditions	Yield (%)[a]	62a:62b[a]
1	**60** 100 mol%	0%	-
2	**60** 25 mol%	0%	-
3	Optimized Conditions[b]	32%	14:1

Entry	Ligand	Yield (%)[a]	8a:8b[a]
1	**BINAP**	**38%**	**12:1**
2	bipy	26%	1:1
3	phen	27%	1:1
4	PPh_3 (10 mol%)	13%	5:1
5	dppp	32%	3:1
6	BINAP, no Pyridine	5%	3:1

Figure 5. (A) Proposed reaction mechanism. (B) Experimental support. I. Ligand equilibrium effect. II. Cyclic voltammetry analysis of the effect of Pyridine on the $NiCl_2$BINAP complex (CV conducted in NMP as solvent, Bu_4NBF_4 0.1 M electrolyte, 0.01 M substrate, Ag/AgCl reference electrode, glassy carbon disk as working electrode, platinum as counter electrode). III. Effect of ligand on the product distribution. [a]Yields and isomeric ratio reported as GC yield obtained with 1,3,5-trimethoxybenzene as internal standard. [b]Optimized conditions from Table 1, Entry 15.

Conclusion

This Article provides a simple new protocol for the preparation of valuable aryl–alkyl linkages that were, in many cases, either difficult or impossible to directly access. Multiple enabling applications are disclosed that can dramatically reduce step-count to such structures. The reaction can be reliably scaled in both flow and batch settings. Finally, CV studies, titration experiments, control studies with Ni(0) and Ni(II)-complexes, and ligand optimization data offer insights into the role of the BINAP/pyridine-system in enabling the challenge formation of all-carbon quaternary centers with high isomeric ratio. Given the immediate uptake of this method by the industrial co-authors of this study, broad utility of this electrochemical cross coupling is anticipated.

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Keywords: Electrochemistry • Cross-Coupling • Quaternary Centers • Arylation • Decarboxylative

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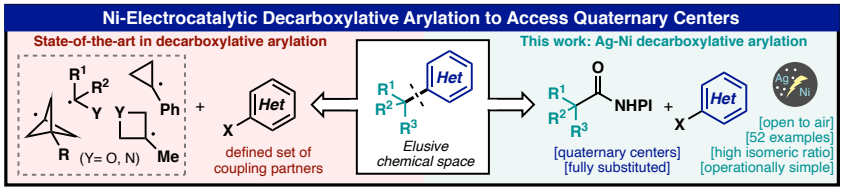

There is a pressing need for general, direct couplings of tertiary alkyl fragments to (hetero)aryl halides. Herein a uniquely powerful and simple set of conditions with unparalleled generality and regioselectivity is disclosed. This new protocol is compared to other recently reported methods, applied to simplify the routes of known building blocks, and scaled up in both batch and flow. Finally, preliminary mechanistic studies were carried out.

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