Ni-Electrocatalytic Decarboxylative Arylation to Access Quaternary Centers

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ABSTRACT: There is an urgent need, particularly in the field of drug discovery, for general methods that will enable direct coupling of tertiary alkyl fragments to (hetero)aryl halides. This early disclosure serves this purpose by informing the community of a uniquely powerful and simple set of conditions for achieving this transformation with unparalleled generality and chemoselectivity.

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] Canonical 2e-cross coupling techniques such as Suzuki[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.[8–10] 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 has seen increasing use for rapidly appending alkyl fragments to arenes of all types (Figure 1B).[11–14] 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.[15–18] 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 only competent alkyl coupling partners involve systems that form radicals which are part of a strained ring system or stabilized by the presence of an α-heteroatom (as listed in Figure 1B).[15–18] In this initial disclosure, a step towards solving this issue is presented by building upon the Ag-functionalized electrode Ni-electrocatalytic method reported previously.[18] This newly invented protocol can, for example, achieve the coupling of **1a** and **2** in 45% isolated yield (along with 3% of the undesired isomer) and is general across a range of substrates that have proven challenging with all published methods to date.

Optimization studies commenced with pivalic acid-derived RAE **4** and bromopyridine **5** (Table 1). Using the electrochemical conditions previously reported,[18] 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 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 defining role as increasing the amount of phosphine could completely shut down the reaction (Table 1, entry 3). Eventually it was recognized that 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 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 a full equiv. of $AgNO_3$ was added (Table 1, entry 8). Of the many additives that were screened, simple pyridine (1.0 equiv., Table 1, entry 11) had a profound impact in both the conversion and robustness of the process (perhaps due to enhanced homogeneity of the reaction solution).[10] Aside from this substrate, the pyridine effect could be quite profound (especially on regular arenes) in enhancing conversion.

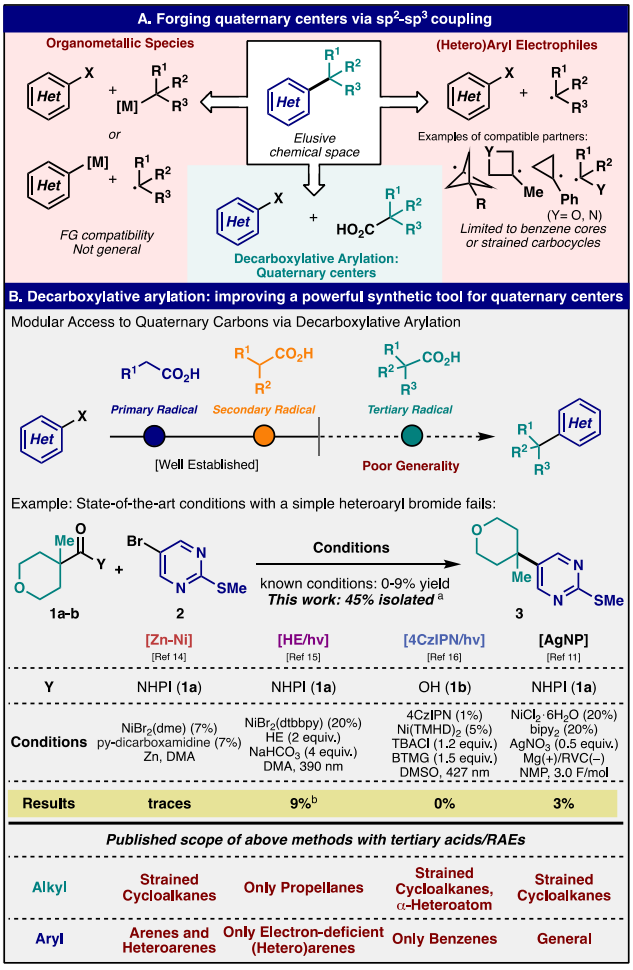
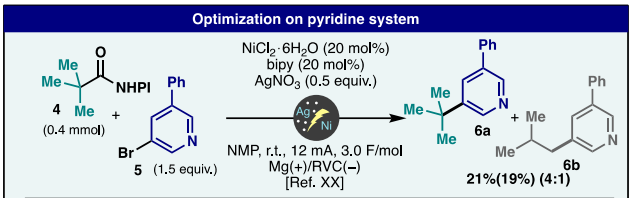


Figure 1. (A) General approaches for the synthesis of quaternary centers with sp^2-sp^3 coupling. (B) State of the art in the decarboxylative arylation of tertiary acids. [a]Desired product formed along with 3% of the undesired isomer (isomeric distribution 16:1, determined *via* NMR). [b]Desired product formed along with 8% of the undesired isomer (isomeric distribution 1:1, determined *via* NMR).

Numerous pyridine derivatives were subsequently screened (for example Table 1, entries 12 and 13) but none were superior to pyridine itself. In the final optimized conditions, the amount of BINAP could be reduced to 5 mol% along with 25 mol % Ni (Table 1, entry 14 and 15). Basic control studies confirmed the essential nature of the Ni, Ag, BINAP, and pyridine additives as well as electricity (Table 1, entries 16-20). The final set of conditions are as practically trivial to setup as our previous disclosure (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.

Historically, the synthesis of such targets has been retrosynthetically tackled using one of three approaches: 1. Direct Minisci or Friedel-Crafts alkylation,[19–21] 2. Building the quaternary center off of an electron deficient (hetero)arene,[22–25] and 3. Building the heteroaromatic ring starting with the pre-installed quaternary center.[26,27] With regards to the first category, the clear limitation is that the alkylation event can only occur at the innately activated position.[19] Thus, in Table 2, only a small fraction of substrates could be envisioned as possibly accessible using such a method (**10**, **18**, **49**). 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)[22,23] from a carbonyl (aldehyde or ester) following for example Pd-catalyzed enolate arylation or Rh-catalyzed hydroarylation.[28,29] The third category is the most difficult sequence as only certain types of molecules can be accessed this way.

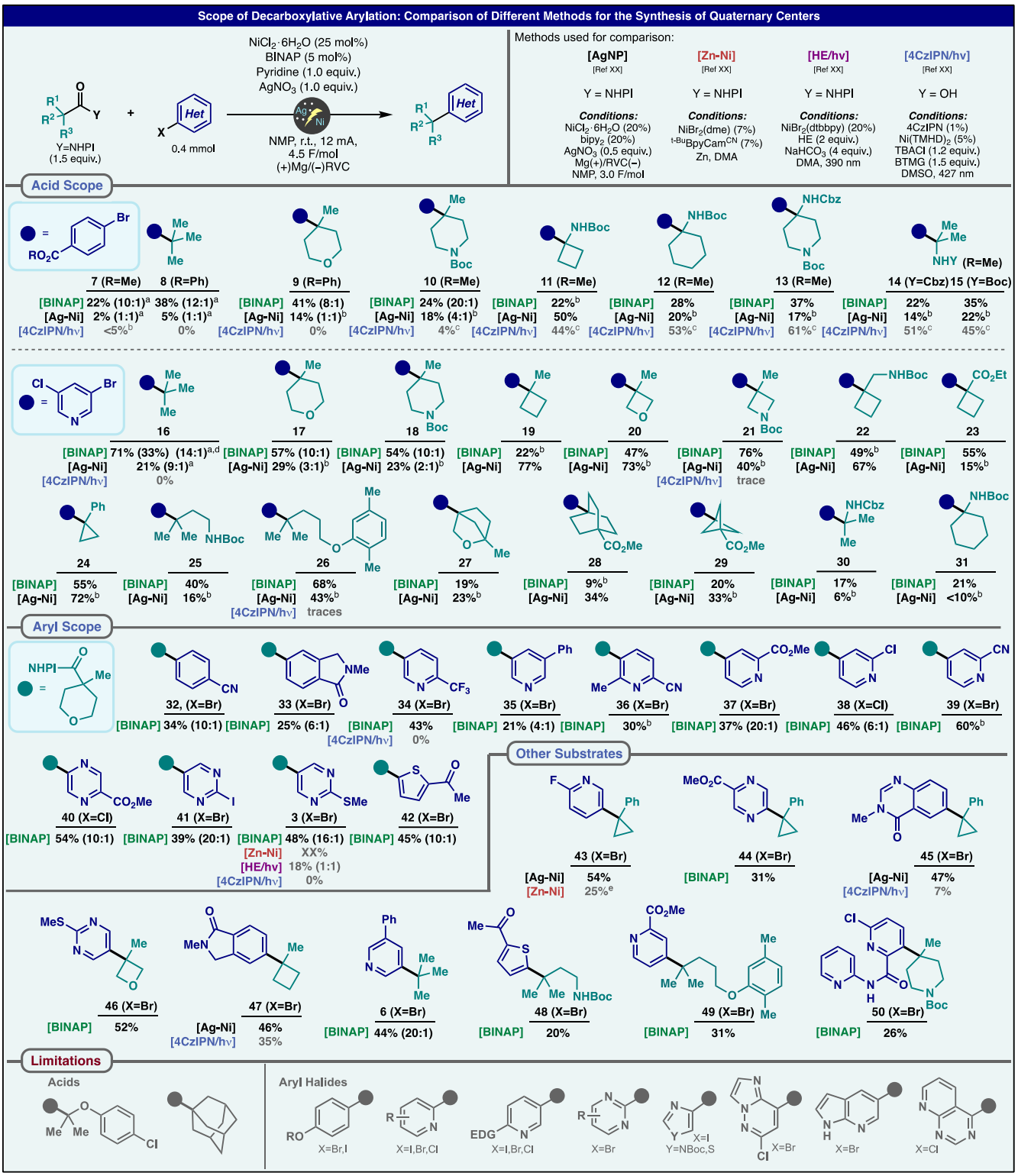
Table 1. Optimization of synthesis of quaternary centers via electrochemical decarboxylative arylation.



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%)	<5%	ca. 20:1
	Electrochemical parameter screening		
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		
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		
14	$NiCl_2·6H_2O$ (25 mol%) (*S*)-BINAP (25 mol%) Py (1.0 equiv.)	49%	>20:1
15	**$NiCl_26H_2O$ (25 mol%) (*S*)-BINAP (5 mol%) Py (1.0 equiv.)**	**49% (44%)**	**>20:1**
	Controls		
16	No Nickel	0%	-
17	No $AgNO_3$	traces	-
18	In presence of Mg (+) but no electricity	0%	-
19	No BINAP	21%	5:1
20	No Pyridine	47%	5:1

Indeed, none of the compounds in Table 1 can be accessed with such logic as one is generally restricted to heteroarenes that can be easily constructed from carbonyl or alkyne appendages.[26,27] 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**.[30] 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**.[31] Finally, if an ester is desired at the quaternary carbon, Hartwig's small-ring arylation disclosure could be very effective (**23**).[32] *At this point in time there is no known general method that can access all of the types of structures outlined in Table 2 aside from the present disclosure*

Table 2. Scope of decarboxylative arylation



[a]GC yield obtained with 1,3,5-trimethoxybenzene as internal standard. [b]NMR yield obtained with 1,3,5-trimethoxybenzene or nitromethane as internal standard. [c]From Ref. 16. [d]Volatile compound. [e]From Ref. 14

The BINAP/Py-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 Table 2. 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).[17]

Three photochemical reports show that tertiary alkyl radicals precursors can be cross-coupled with aryl halides, and $Ni(TMHD)_2$ complex is the only effective catalyst in those three

photochemical reports.[16,17,31] 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.[33] In contrast, the electrochemical method presented in this report overcomes these limitations, as exemplified by compounds **16**, **21**, and **26**. Furthermore, a vast collection of (hetero)aryl halides can be employed as suitable coupling partners (Table 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 THP- and piperidine-bearing substrates relative to either our previous reported conditions or other reported methods (employing alkyl bromides). 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. As testament to this fact, this coupling has contributed to active drug discovery campaigns, enabling the rapid modular generation of quaternary centers. For instance, substrates **3** and **34**. The reaction appears to be quite general across a range of coupling partners as documented with the synthesis of molecules **43**-**50**. The mildly reductive nature of the reaction tolerates numerous functional groups such as esters, ketones, amides, nitriles, ethers, Boc/Cbz groups, aryl halides, aryl thioethers, cyclopropanes, oxetanes, and azetidines. Substrates bearing an ortho-substituent on the arene, such as **36** and **50**, are also accessible. In terms of limitations, 2-halo pyridines and pyrimidines are unreactive. This can be exploited in the case of **41** 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 particular 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.

This early disclosure serves to aid the community in what is a rapidly developing area in the hopes that these conditions will provide immediate relief to practitioners in search of a rapid access to valuable aryl-alkyl linkages that were, in many cases, either difficult or impossible to directly access. Specific enabling applications, scalability (in flow and batch), and insight into mechanistic basis for the BINAP/pyridine-enabled improvement will be reported in a subsequent report.

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G.L., P.N. and Á.P. contributed equally. The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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