

Overcoming Limitations in Decarboxylative Arylation via Ag-Ni Electrocatalysis

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ABSTRACT: A useful protocol for achieving decarboxylative cross coupling (DCC) of redox-active esters (RAE, isolated or generated in situ) and halo(hetero)arenes is reported. This pragmatically focused study employs a unique Ag-Ni electrocatalytic platform to overcome numerous limitations that have plagued this strategically powerful transformation. In its optimized form coupling partners can be combined in a surprisingly simple way: open to the air, technical grade solvents, an inexpensive ligand and Ni source, substoichiometric AgNO₃, proceeding at room temperature with a simple commercial potentiostat. Most importantly all of the results are placed into context by benchmarking with state-of-the-art methods. Applications are presented that simplify synthesis and rapidly enable access to challenging chemical space. Finally, adaptation to multiple scale regimes, ranging from parallel mg-based synthesis to decagram recirculating flow is presented.

INTRODUCTION

The use of radicals in organic synthesis has a rich history in the progression of chemical synthesis.^{1,2} In the early days, proving the very existence of radicals was an exciting area.³ Following that, their exploration in organic and organometallic chemistry led to a wellspring of useful discoveries. The classic studies of Stork,⁴ Curran,⁵ Barton,^{6,7} Zard,⁸ Minisci,^{9,10} and others¹¹⁻¹³ showed how radicals could be tamed to make useful bonds. The modern manifestation of radical retrosynthesis has the potential to transform conventional logic and enable dramatically simplified routes to seemingly trivial and structures.¹⁴ It has now been demonstrated multiple times that such logic can obviate the need for otherwise arduous multistep synthetic sequences that are wedded to polar (2 electron) disconnections.¹⁵ Polar bond analysis, a useful rubric for synthesis planning, is often plagued by a reliance on protecting group chemistry, superfluous redox fluctuations and functional group manipulations that lower the ideality of a synthetic design.¹⁶ In contrast, radical-based transformations offer new disconnection opportunities that are often far more convergent, enabling access to an expanded chemical space. This is in part due to the higher chemoselectivity of single electron processes leading

to a lower reliance on protecting groups. Such approaches have been highly impactful in the context of medicinal chemistry efforts, where expedient and modular access to a broad range of analogues is critical for exploring key biological hypotheses.¹⁷ For instance, the construction of potential drug candidates is often guided by the presence of C(sp²)-C(sp³) linkages, which are an essential motif in countless active pharmaceutical ingredients and are often a vector where SAR studies are performed with great diligence.¹⁸ Therefore, the development of synthetic methods that give access to a vast swath of chemical space by merging two accessible and benchtop-stable partners have attracted great attention. To this end, cross coupling partners such as carboxylic acids and aryl halides represent an attractive choice owing to their widespread commercial availability. For this reason, numerous radical decarboxylative cross coupling methodologies have been developed thereby opening up a more intuitive retrosynthesis of high-value targets.¹⁹⁻²¹

As an example, trivial looking unnatural amino acids like homotyrosine (Figure 1A), have historically been accessed through linear multistep syntheses using exclusively polar transformations that require careful reaction set up, preparation of organometallic reagents, multiple protecting group manipulations, and unstable intermediates that do not intuitively map onto the final target.^{22–25} Strikingly, these multistep routes, ranging from 5–10 steps, feature only one strategic bond forming step to forge a single C–C bond. Alternatively, using radical retrosynthesis, homotyrosine and other analogues could easily be traced back to glutamic acid and an appropriate aryl halide in a single step operation.

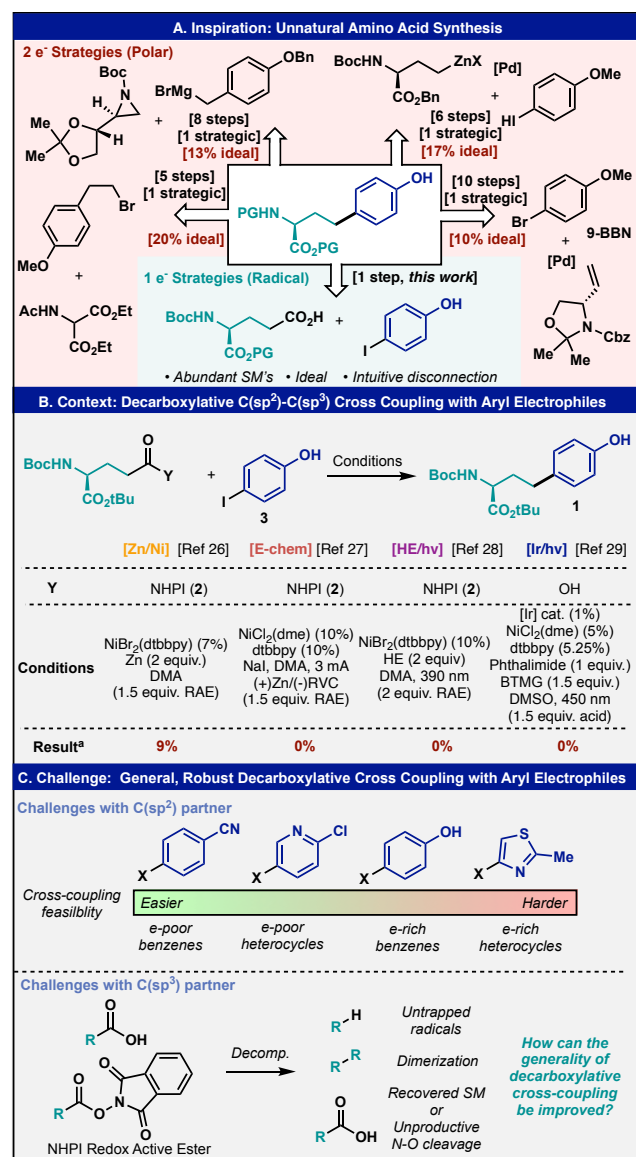


Figure 1. (A) Prior synthetic strategies guided by polar bond analysis towards homotyrosine and the proposed radical decarboxylative arylation strategy. (B) State-of-the-art DCC methods towards the synthesis of **1** failed to generate serviceable amounts of product for a deceptively simple coupling. (C) Limitations of state-of-the-art DCC with aryl electrophiles include limited scope with complex arenes and a variety of decomposition pathways of the radical precursors.

To test the viability of this strategy, numerous decarboxylative cross coupling (DCC) methods that represent the current state of the art were tested (Figure 1B). First, cross electrophile coupling using zinc as a terminal reductant delivered only 9% of **1**.²⁶ Next, an electrochemical approach was pursued but no product formation with this challenging coupling partner **3** was observed.²⁷ We next turned our attention towards photochemically enabled reactivity platforms. First, a reductive cross electrophile coupling leveraging electron donor acceptor complexes was evaluated.²⁸ In the event, no desired product was formed. Finally, an oxidative activation of the carboxylic acid was evaluated, using photoinduced-electron transfer (PET, Ir-based) and a key phthalimide additive.²⁹ However, even with this method, only no desired product was observed. At first glance, these results are surprising given the extensive body of literature around such transformations. However, upon closer examination of our desired cross coupling reaction and the surrounding literature, several key challenges were limiting the success of this coupling (Figure 1C). First, the scope of aryl electrophiles for C(sp²)-C(sp³) reductive cross coupling generally favors electron deficient arenes and heterocycles over their electron rich counterparts even without considering sensitive functionality. Second, the carboxylic acid or corresponding redox active ester, if it is not engaged in productive catalysis, is prone to several decomposition pathways. These include H-atom abstraction by transient radicals, dimerization, and in the case of redox active esters, unproductive N-O bond heterolysis resulting in recovery of the acid starting material. In extreme cases, where the reaction does not proceed, only starting materials are recovered. In this Article a practical method to overcome the limitations of decarboxylative arylation is presented. It features a wide scope amongst challenging real-world substrates, extreme operational simplicity, and a versatile scale regime from parallel screening (mg) to recirculating flow scale up (decagram). Most importantly, the results herein are presented in context with existing methods for achieving the same transformation and conducted in collaboration with a diverse array of practitioners across five different pharmaceutical partners (the typical end user of this method).

Ag-Ni ELECTROCATALYTIC DCC-ARYLATION: DEVELOPMENT

Considering the aforementioned limitations of chemical, electrochemical, and photochemical methods, our recent exploration in the area of terpene synthesis was particularly inspiring.³⁰ In that study, the unique ability of an Ag-functionalized electrode surface was exploited to enable DCC-alkenylation when chemical and electrochemical means faltered. The role of the *in situ* formed electrode bound Ag-nanoparticles was extensively studied and found to play three key roles: (1) extending catalyst lifetime, (2) preventing background decomposition of the redox active ester and most importantly (3) lowering the required overpotential which in turn greatly expanded functional group compatibility. Upon closer examination of the mass balance from the prior attempts, we had observed full consumption of the redox active ester but very little product formation alongside homocoupling byproducts. These starting points were strikingly similar to the limitations encountered in the initial exploration of Ag-functionalized electrode surfaces for

decarboxylative alkenylation. It was therefore hypothesized that for the same reasons the Ag-Ni electrocatalytic manifold may provide similar advantages in DCC-arylation.

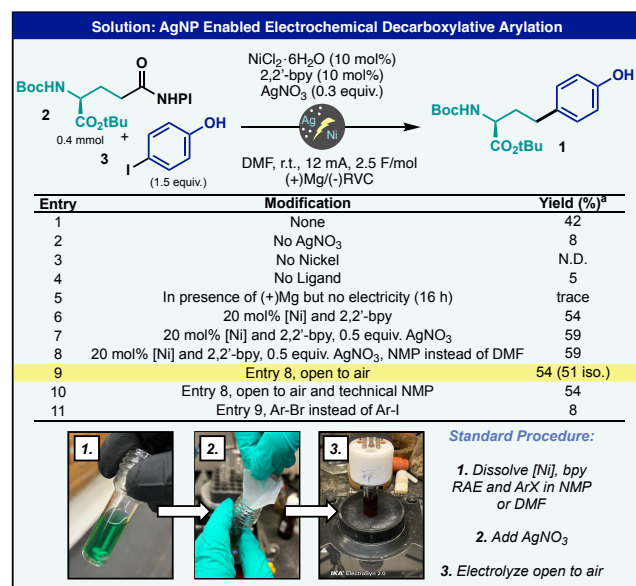


Figure 2. Development of the Ag-Ni Electrocatalytic DCC reaction. ^aYield determined by ¹H-NMR with 1,3,5-trimethoxybenzene as an internal standard.

To begin this investigation, the electrochemical coupling of redox active ester **2** with 4-iodophenol (**3**) under recently disclosed Ag-Ni electrocatalytic vinylation conditions was pursued (Figure 2). In the event, these coupling partners were combined with NiCl₂·6H₂O (10 mol %), 2,2'-bipyridine (10 mol %) and the key AgNO₃ additive (0.3 equiv.) in DMF under constant current electrolysis with a reticulated vitreous carbon (RVC) cathode and sacrificial magnesium anode (Figure 2). To our delight, the desired homotyrosine derivative was generated in 42% yield (entry 1). Importantly, the absence of AgNO₃ resulted in low yield of the desired product along with substantial amounts of decomposed RAE, thus highlighting the one of the critical roles of the Ag-functionalized electrode in mitigating background consumption of the limiting reagent (entry 2). Omission of ligand or the nickel catalyst resulted in substantially lower yields and poor reaction performance (entries 3 – 4). Additionally, the role of electricity was crucial as simply allowing the reaction mixture to stir in the presence of the magnesium electrode which in principle could act as a terminal reductant only gave trace yield of product (entry 5). Increasing the nickel and ligand loading to 20 mol % and slightly increasing the amount of silver provided a significant boost in yield to 59% (entry 6 – 7). Additionally, the reaction could be performed equally well in NMP and to our surprise could even be run open to air in the absence of any Schlenk techniques delivering the desired compound in 51% isolated yield (entry 8 – 9). Despite the slightly lower yields observed for this less rigorous setup it was selected as the preferred general conditions based on the practical advantages as it enables easy parallel synthesis set-ups and reduces preparation time for single reactions. Even technical grade NMP could be used in this cross-coupling reaction without affecting the yield thus highlighting the robust nature of this cross coupling (entry 10). Unfortunately, the corresponding aryl bromide did not couple as efficiently likely due to sluggish

oxidative addition to the highly electron rich arene (entry 11). An important point of differentiation to the developed method is the stoichiometry of the starting materials. All the previously mentioned protocols use an excess of the redox active ester while this approach uses a slight excess of the aryl halide coupling partner in the optimized conditions but can alternatively be run using excess RAE with minimal losses in yield (See SI).

In the final optimized manifestation of this protocol, the reaction was carried out as follows. First, all the reagents except AgNO₃ were added to a 5 mL ElectraSyn 2.0 vial directly. It was observed that extend stirring of the solution with AgNO₃ led to detrimental outcomes, likely due to decomposition of the in situ generated AgCl salt.³⁰ Then, NMP or DMF were added resulting in a homogeneous solution. Finally, silver nitrate was added directly as a solid and the contents were allowed to undergo constant current electrolysis at 12 mA for 2.5 F/mol (around 2.5 h). No precautions were taken to exclude water or air and all reagents were used as delivered from a commercial supplier. The catalyst (NiCl₂·6H₂O) is amongst the most inexpensive sources of Ni available (ca. \$57/mole). The ligand (2,2'-bpy) can be obtained for approximately \$1.5/gram. Finally, AgNO₃ is a benchtop stable reagent that used to be widely used in the photographic industry (ca. \$10/g). As previously reported, recycled Ag-electrodes can be employed.

EXPLORATION OF SCOPE

The generalization of the Ag-enabled DCC-arylation is outlined in Table 1. In consultation with our pharma collaborators, a vast range of functionality relevant to medicinal chemistry campaigns were curated and benchmarked against contemporaneous decarboxylative arylation methods. Selection criteria for substrates were biased towards historically challenging coupling partners and pharmacophores of high interest. A diverse array of both arene and RAE subunits were evaluated and the arenes can be segregated into four categories: (1) substituted benzenes, (2) 6-membered heterocycles, (3) five membered heterocycles, and (4) fused heterocycles. Across these four categories a variety of alkyl components were evaluated and include primary, secondary, strained tertiary, and alpha-heteroatom redox active esters.

Substituted benzenes represents the largest class of reported substrates for DCC-type couplings. Yet, numerous limitations remain, some of which are not widely advertised. For instance, electron neutral or rich arenes are often problematic. Substrates **4** and **5** are emblematic of this issue. Whereas photochemical based DCC reactions of simple carboxylate precursors to these compounds are well documented, they fail when employing anisole or toluene-based haloarenes. Although chemical activation provides serviceable yields of **4** and **5** (when using Ar-I), the current protocol proved superior. In these cases, even the corresponding aryl bromides also work whereas none of the other methods evaluated provided any product. From a strategic standpoint, the value of accessing **4** in one step is undeniable as prior routes required laborious multistep processes based on 2-electron logic.³¹ The boron-containing substrate **6** has been synthesized before using an exotic organosilicate coupling partner.³² While the current method enabled it's synthesis in reasonable yields from the aryl iodide, it outshined

other methods when using the corresponding bromide, which may be the only option a medicinal chemist has when advancing a complex chemical series. Aryl iodides that bear the acetylated *ortho* bromoaniline motif could be coupled efficiently while preferentially reacting at the aryl iodide to afford unnatural amino acid derivative **7** in 45% yield. This product represents a useful starting material for a Larock/Castro indole synthesis.³³⁻³⁵ Histidine, an amino acid bearing an oxidatively-labile imidazole motif, could be derivatized effectively affording **8** in 55% yield with 4-iodobenzonitrile and in 27% yield with the corresponding bromide. Interestingly, existing literature methods failed to deliver more than 20% of the desired product with the iodide and only gave trace product with the aryl bromide. Morpholines are an important motif in medicinal chemistry owing to their favorable physiochemical, biological, and metabolic properties.³⁶ To probe the robustness of the reaction to this valuable functional group compound **9** was accessed efficiently from the corresponding aryl iodide yet faltered with the aryl bromide. Comparatively, existing methods failed to deliver more than 10% yield with either halide.

6-Membered heterocycles such as pyridine, pyrimidine, pyrazine and pyridazine are ubiquitous in marketed therapeutics.³⁷ Despite their prevalence in this sector, their behavior in cross-coupling reactions is often hard to predict owing to the vast range of electronic properties they can adopt as well as the presence of Lewis-basic nitrogen atoms that can complicate transition metal mediated processes.³⁸ Chloropyridines **10** and **11** are emblematic of this problem. Whereas **10** was barely accessible with existing literature methods, **11** was produced far more efficiently across the board when the chlorine atom was moved from the C-3 to C-2 position. In contrast, the current DCC protocol coupled both in a highly efficient manner. Functionalized pyridines such as **12** could be accessed efficiently with strained and stabilized cyclopropyl radicals. 2-substituted pyridines are a challenging class of compounds to access through cross-coupling methods.⁴⁰ To this end, compounds **13** – **15** were selected to encompass a wide range of electronic and steric properties. Electron rich, neutral, and deficient 2-halo pyridines could be coupled in serviceable yields using the developed protocol. Importantly, existing methods, while sporadically working with the 2-iodopyridine derivatives, generally failed with the corresponding bromides, highlighting the challenges associated with this specific pyridine substitution pattern. Pyrrolidine adduct **14** has previously been prepared either through Suzuki/hydrogenation of the corresponding pyrrolidinone or via *de novo* pyrrolidine synthesis (dipolar cycloaddition), both of which are non-ideal in a medicinal chemistry setting. Substituted pyrimidines coupled efficiently as well.^{41, 42} Notably, excellent halo selectivity was observed when bromo-iodopyrimidines were employed delivering, for example, ketone bearing **16** in 44% yield. Notably, cysteine in its protected thiazoline form could be coupled with 5-iodo-2-chloropyrimidine to afford **17** in 25% yield. This coupling is noteworthy in the context of the existing methods as it bears a sulfide functional group

which can poison catalytic processes and easily engage in exogenous redox events. Unsubstituted pyrimidines perform efficiently as well as the redox active ester derived from gabapentin which could be coupled with 5-bromopyrimidine to **18** in 65% yield. A chlorine atom adjacent to a nitrogen atom in a six membered heterocycle is a versatile intermediate towards further derivatization. Additionally, such motifs are easily accessed in highly complex ring systems owing to the numerous deoxychlorination methods that map onto the products of heterocycle ring synthesis products.⁴³ Therefore, countless methods have emerged to engage them in cross coupling reactions to further extend their utility.⁴⁴⁻⁴⁶ Ester-bearing chloropyrimidine was coupled efficiently with an alkene bearing redox active ester to afford **19** in 61% yield. It is instructive to point out that pyrimidines did not perform well in zinc or electrochemically mediated reductive cross-coupling reactions unless they were activated by a neighboring electron withdrawing group (EWG). To further probe the reactivity of heteroaryl chlorides, pyrazine-containing **20** was generated in 51% yield, and pyridazine-containing **21** was accessed in 41% yield from the respective heteroaryl chlorides. In a final test of functional group compatibility for six membered heterocycles, uracil derivative **22** (ca. 1000\$/g) was targeted as there are limited protecting group options for this heterocycle rendering uracil ring synthesis as the most logical current option.⁴⁷ Despite these challenges, coupling with iodo- and bromouracil afforded **22** in 42% yield and 22% yield respectively.

5-membered heterocycles represent an important challenge in the context of radical cross-coupling methodology.⁴⁸⁻⁵⁰ Such molecules are often underrepresented in the current C(sp²)-C(sp³) radical cross-coupling literature. Given the functional group compatibility demonstrated above, several 5-membered heterocycles were targeted. Imidazole containing propellane **23** was generated from the corresponding iodo- and bromo-imidazole coupling partners in 32% yield and 16% yield respectively. SEM-protected iodo-pyrazole was coupled with a secondary acyclic homoallylic redox active ester giving **24** in 20% yield. It is important to note that all the existing methods tested for DCC transformations failed to give more than trace yield of product for these challenging cross coupling partners. Thiazoles were able to perform well in this cross-coupling platform. Beta-glycine derivative **25** was generated from the corresponding bromo- and iodo-methylthiazole. Activation of the thiazole with an electron withdrawing bromine atom significantly improved the results of the cross coupling as evidenced by **26** which formed in 49% from the corresponding bromide. Notably, excellent chemoselectivity was observed between the second bromine atom on the thiazole as well as the pendant alkyl chloride on the redox active ester fragment. Finally, the RAE derived from unprotected chenodeoxycholic acid was coupled efficiently with 3-iodothiophene to provide **27** in 58% yield. Such arylated cholic acid derivatives are usually synthesized through Minisci transformations limited to 6-membered heterocycles.^{51, 52}

A. Contextualized Scope: State-of-the-Art Comparison Across a Range of Substrates

$\text{R}^1\text{CH(R}^2\text{)C(=O)NHPi}$ + Cl/Br/I (1.5 equiv.) $\xrightarrow[\text{NMP or DMF, r.t., 12 mA, 2.5 - 4.0 F/mol (+)Mg/(-)RVC 2.5-4 h}]{\text{NiCl}_2 \cdot 6\text{H}_2\text{O (20 mol\%), 2,2'-bpy (20 mol\%), AgNO}_3 \text{ (0.5 equiv.)}}$ $\text{R}^1\text{CH(R}^2\text{)Het}$ [dump and stir] [open to air]				Substituted Benzenes																																					
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Higher order heterocycles that bear fused aromatic rings are important subclasses of arenes as well.⁵³ Unprotected indole motifs were well tolerated in this reaction as 5-iodoindole was coupled efficiently to afford **28** in 61% yield while giving a modest 33% conversion with the corresponding bromide. Quinoline, another important bicycle which is usually functionalized *via* Minisci approaches,⁵⁴ could be coupled to the free alkyne bearing RAE to give **29** in 42% yield from the iodo-quinoline and 12% from the bromide. Pyrazolopyrimidine derivative **30** was successfully accessed in 31% yield from the corresponding bromide. Prior published routes to **30** involved the coupling of an alkyl bromide in a reductive cross electrophile coupling mediated by zinc in 15% yield.⁵⁵ Finally, sulfonamide-protected azaindole-containing cyclobutanone **31** was synthesized in 34% yield with this cross-coupling protocol while only the previously reported electrochemical approach gave comparable yields.

In general, many of the known methods for achieving DCC-arylation feature complementary scope. Empirical screening is often needed to deconvolute which particular method is suitable for a particular substrate class, akin to ligand enabled Pd-based cross couplings.⁵⁶ Some methods fare well with electron-deficient arenes but not with electron-rich arenes. Similarly, certain couplings don't tolerate sensitive functional groups (e.g. free phenols, indoles, histidines, acidic heterocyclic N-H) or Lewis-basic heteroatoms. The present method appears to be a particularly general protocol for achieving such couplings in consistent and meaningful yields by leveraging the unique reactivity benefits of Ag-functionalized electrodes in Ni-electrocatalysis³⁰ (*vide infra*); however, it is not without its limitations. Throughout the course of this study heterocycles were encountered that were unreactive such as *N*-alkyl pyrazoles, trichloropyrimidines, quinazolines and other fused heterocycles. Additionally, isoxazole motifs were found to undergo reductive ring opening during the reaction and led to no desired cross coupling products. With respect to the alkyl coupling partner, [2.2.2] redox active esters failed to couple as well as adamantyl and simple tertiary radical precursors.

In real-world scenarios it may be an inconvenience to isolate and purify RAE coupling partners. In other cases, the RAE may be too hydrolytically labile to be easily isolated. Thus, an *in situ* protocol for RAE generation was developed as depicted in Table 1B. The stable RAE precursor to **32** was used as a test case for this purpose. The only major procedural difference here involved conducting activation and cross coupling steps under a balloon of Ar. This was necessary due to the empirical observation that the presence of urea byproduct (from RAE formation) rendered the reaction more air-sensitive. This is likely due to the urea's ability to complex the nickel catalyst and interfere with productive cross coupling under air. Using this modified *in situ* protocol, **32** was obtained in 62% isolated yield (75% NMR yield). Substrates **33-37**, unlike **32**, utilized RAEs that were either unstable or difficult to purify. Due to the polar nature of products **33-37**, NMR yields are also given as some material was lost during purification. RAE's bearing trifluoromethyl motifs were surprisingly hydrolytically labile. Fortunately, utilizing the *in situ* protocol, trisubstituted pyridine **33** could be accessed in 33% isolated yield (53% NMR

yield). Next, a 3-oxabicyclo[3.1.1]heptane bearing RAE could be coupled with 2-fluoro-4-bromo pyridine to afford **34** in 34% isolated yield. Sulfone bearing redox active esters were highly challenging to purify due to degradation on silica as well as coelution with coupling reagent byproducts. However, **35** was accessed efficiently in 43% isolated yield (52% NMR yield) after coupling with a densely functionalized bromoazaindole. RAE generated from amino acid derivatives and dipeptides were particularly challenging to purify when reactive residues were used but could be coupled efficiently using this protocol. Tryptophan analog **36**, bearing an unprotected indole, was accessed in 31% isolated yield (46% NMR yield). Finally, a tyrosine bearing dipeptide was engaged in successful cross coupling, delivering **37** in 40% yield (45% NMR yield) in the presence of the unprotected phenol.

APPLICATIONS TO SIMPLIFY SYNTHESIS

The broadened scope and enhanced chemoselectivity of this electrocatalytic DCC enables distinct access to structures of medicinal importance. To demonstrate this point, five case studies were chosen, four of which are derived from the literature and one of which was encountered internally by our pharma collaborators. Each of these provide unique examples of how the current protocol proved superior to both conventional and newly emerging methods. Pyridine-containing amino acid **38** has previously been accessed through a Negishi-coupling strategy from glutamic acid necessitating several FG-interconversions to access the requisite organozinc derivative.⁵⁷ In contrast, the same starting materials can be employed directly to arrive at **38** in 63% or 45% from either the pyridyl iodide or bromide, respectively. Gram quantities of both are easily accessible with the same potentiostat by simply increasing the reaction vial size and current delivered with a similar yield. Pyrazole-cyclohexanone derivative **40** was previously accessed through a very common Suzuki-hydrogenation approach.⁵⁸ This route, which is emblematic of hundreds if not thousands of examples found in the patent literature, necessitates formation of a vinyl boronate (**41**) via a vinyl triflate and subsequent Suzuki cross coupling followed by hydrogenation. In this case two protecting group steps are needed due to the presence of another ketone and three different Pd catalysts are required across three steps, adding drastically to the cost of the route. In contrast, **40** was accessed directly from a cyclohexanone bearing redox active ester (**42**) and an appropriate iodopyrazole (**43**) in 31% yield. Morpholine **44** was previously accessed through a lengthy synthetic sequence that was centered around stepwise construction of the morpholine (via **46**) onto the acid bearing pyrimidine starting material **45**.⁵⁹ Instead, **44** could be accessed from coupling of a morpholine derived redox active ester **47** (derived from the commercial acid) and 2-iodo-5-bromo pyrimidine in 28% yield thus bypassing the need for a tedious ring synthesis strategy for such compounds. Indoline **48** is an intermediate towards (R)-silodosin (RapafloTM), an FDA-approved therapeutic for the treatment of benign prostatic hyperplasia. In collaboration with Minakem, our lab previously pursued an approach towards **48** that utilized a reductive cross electrophile coupling between **49** and **50**.⁶⁰ In that initial approach, **50** must first be converted to the more reactive iodide (via Cu-catalyzed

exchange)⁶¹ prior to a Zn-mediated reductive DCC as utilizing the aryl bromide directly failed. In contrast, the newly developed protocol described herein can be used to couple the bromide directly in 37% yield without the need for the aromatic halogen exchange step. Finally, intermediate **51**, a useful scaffold for a current medicinal chemistry program was specifically targeted as its access proved elusive under a variety of known DCC conditions. Thus, DCC of RAE **52**

with pyrimidine **53** (Y = ZnX) under Negishi-like conditions failed as well as chemical and photochemical cross-electrophile strategies (Y = Br, **54**).^{28, 62} Oxidative PET-based DCC using acid **55** and pyrimidine **56** (a C2-Cl reagent was used rather than the photochemically labile SMe group) was also unsuccessful.⁶³ In contrast, the current protocol delivered 41% isolated yield of the target from **52** and **54** thereby opening the door to exploring SAR on this valuable series.

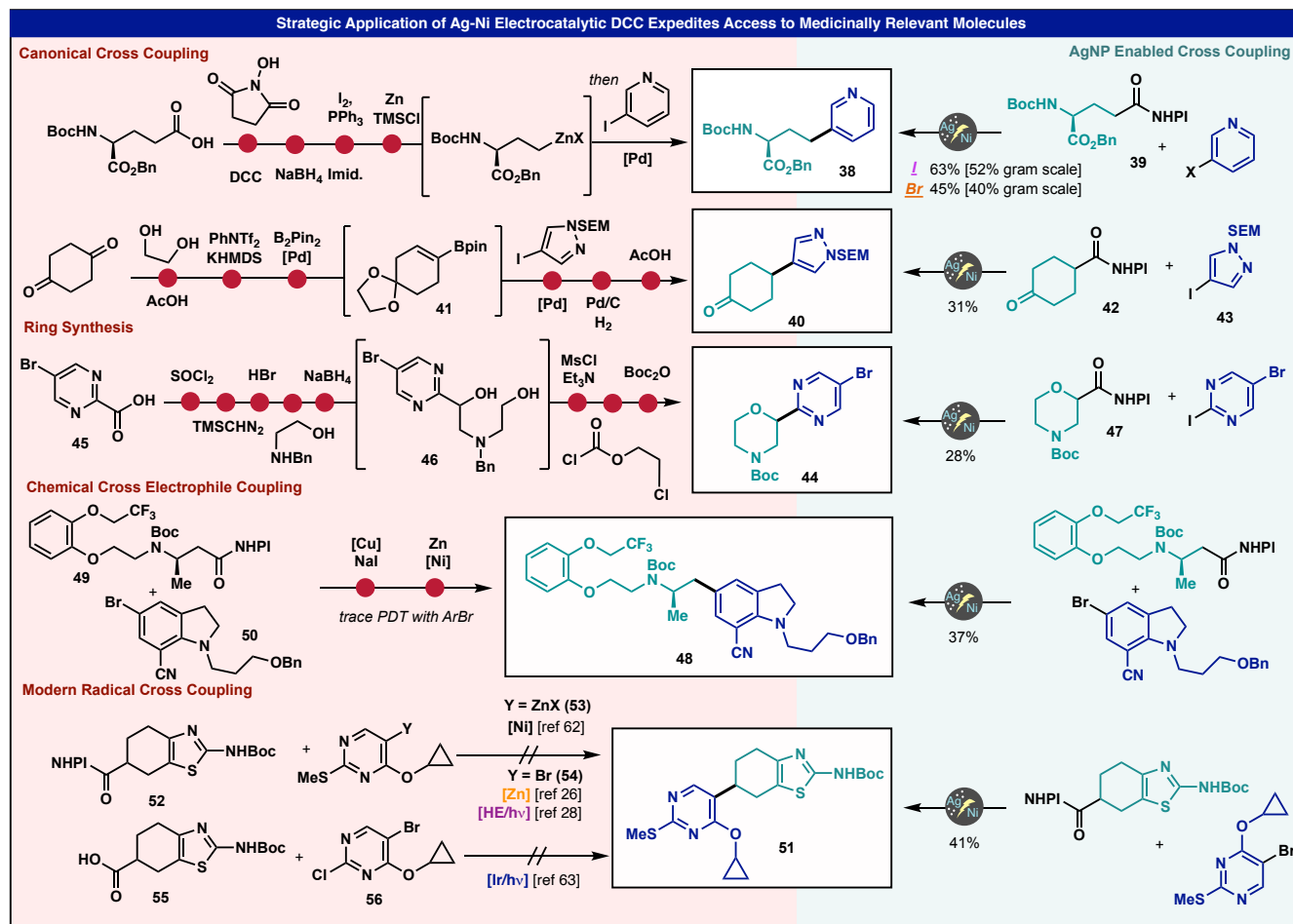


Figure 3. Strategic applications of the Ag-Ni electrocatalytic DCC to medicinally relevant motifs across a wide range of literature sources and active collaborations.

SCALE REGIMES: PARALLEL SYNTHESIS TO FLOW-BASED SCALE UP

While the aforementioned attributes of Ag-Ni based electrocatalytic DCC are attractive from the standpoint of enabling access to new chemical space, the ability to generate libraries and scale up promising structures is critical. In 2019, commercial vendors began selling standardized equipment geared towards synthetic chemists for parallel electrochemical synthesis. More recently, the Lin group in collaboration with Merck revealed another interesting approach to reaction miniaturization.⁶⁴ For this study we elected to use the commercial “E-hive” module sold by IKA that conveniently attaches to ElectraSyn 2.0 (Figure 4A). This device is capable of running 24 reactions in parallel at constant potential. It features a unique design wherein the reaction vessel is itself an electrode (stainless steel) and a small graphite rod (which is part of the cap) is the other

electrode. Either one can serve as a cathode or anode depending on the desired setting. To demonstrate the utility of such a setup for library synthesis a set of 12 arenes (screened against **55**) and 12 RAEs (screened against **56**) were selected. To replicate an actual discovery setting, we deliberately chose substrates that had not been tested before. Furthermore, the electrode materials, concentration, and current density were completely different from the standardized procedure, rendering e-hive screening an real-world robustness test for this reaction.

In practice, the above concerns proved unnecessary as the experiment was both simple and intuitive to setup and worked well largely owing to the reaction’s innate insensitivity to air, current, and excess electricity. Thus, of the 24 substrates run in parallel on this device, 20 gave detectable amounts of product by HPLC/MS analysis. The functionality present across the successful entries of this screen cover a wide range of chemical space and allowed us to test various

functional groups that were not explored in the prior scope study. With respect to the arene, several entries are worth noting. Thiazoles and benzothiazole (**57**, **66**), an anisole derivative (**58**), sulfide bearing pyrimidines (**59**), a variety of 2-substituted pyridines (**60**, **61**, **67**), the nucleobase found in remdesivir (**62**), as well as a Boc-protected aniline (**63**) and fluorobenzene (**64**) all gave detectable amounts of products. Unfortunately, aldehyde bearing azaindole (**65**) and a complex pyrazole (**68**) failed to give any detectable amounts of product. The chemical space of the redox active ester screen led to some unique discoveries of functional group compatibility. [2.2.1] bicycle (**69**), homoproline (**70**), cyclopropyl (**71**), protected hydroxyproline (**72**), monofluoromethyl (**74**), alpha-amide (**75**), pyranyl (**76**), nitrile bearing [1.1.1] propellane (**77**), neopentyl (**78**) and diols derived from tartaric acid (**80**) all gave the substituted azaindole product in this screen. However, the hindered sesquiterpene fragment derived from gibberellic acid (**73**) and the tertiary substructure (**79**) derived from clofibril acid failed to give product likely due to steric issues.

With a panel of successful couplings demonstrated on the 15–20 mg scale, validation under optimized reaction conditions was pursued (Figure 4B). Electron poor 2-bromo-3-fluoro-6-chloropyridine coupled efficiently with **55** to afford **81** in 44% isolated yield (51% NMR yield). Inverting the electronics of the pyridine and coupling with 2-bromo-5-methoxypyridine gave pyran derivative **82** in 32% yield (34% NMR yield). Adding an ortho substituent was still tolerated and **83** was accessed in 28% yield (28% NMR yield) after coupling with 2-iodo-3-methylpyridine. On the other three positions of the carousel, a series of azaindole derivatives were accessed simultaneously. Pyrrolidine bearing **84** was synthesized in 46% isolated yield (57% NMR yield). Neopentyl substituted **85** was similarly accessed in 37% isolated yield (47% NMR yield). Finally, cyclopropyl substrate **86** represented an interesting opportunity to couple strained radicals using this chemistry. While this compound was detected in the e-hive screen, it was low yielding in the preparative reaction giving **86** in only 5% isolated yield (11% NMR yield) and was found to readily decompose upon standing. Consistent with the above miniaturization in the e-hive, these couplings gave serviceable yields of product in this parallel preparative procedure.

Finally, to probe the scalability of this reaction, a 100 mmol scale synthesis of unnatural amino acids **1** and **38** was pursued utilizing recirculating flow (Figure 4C).⁶⁵ Additionally, given the inconvenience of synthesizing and isolating 100 mmol of the necessary RAE, an in situ protocol was targeted to avoid an intermediate purification step en route to multigram quantities of **1** and **38**. In practice, 100 mmol (ca. 34 g) of glutamic acid derived **87/88** was activated in THF with DIC and NHPI for 3 h. Given the empirical observation that the urea byproducts from in situ activation can hinder the performance of the reaction, a means by which to remove this byproduct was needed in order to carry out this large scale reaction open to air. Fortunately, the diisopropylurea is not completely soluble in THF and can simply be filtered off using filter paper as the RAE is being transferred to the round bottom flask containing the nickel catalyst and the iodoarene coupling partner together with lithium chloride as a supporting electrolyte. Once the addition was complete, the key silver nitrate additive was added

directly to the flask as solids. A peristaltic pump was enlisted to recirculate the reaction mixture through the reactor bearing a sacrificial magnesium plate anode and carbon felt cathode (see SI for full details and graphical guide). In the initial hour of the reaction, the reaction mixture progressed from a heterogeneous suspension of silver halide salts to a homogeneous green solution as the silver is plated within the electrode chamber on the carbon felt cathode. After electrolysis at 1 A for 12 hours, the reaction mixture was worked up following the standard protocol and **1** and **38** were accessed in 15 grams (43%) and 18 grams (49%) respectively.

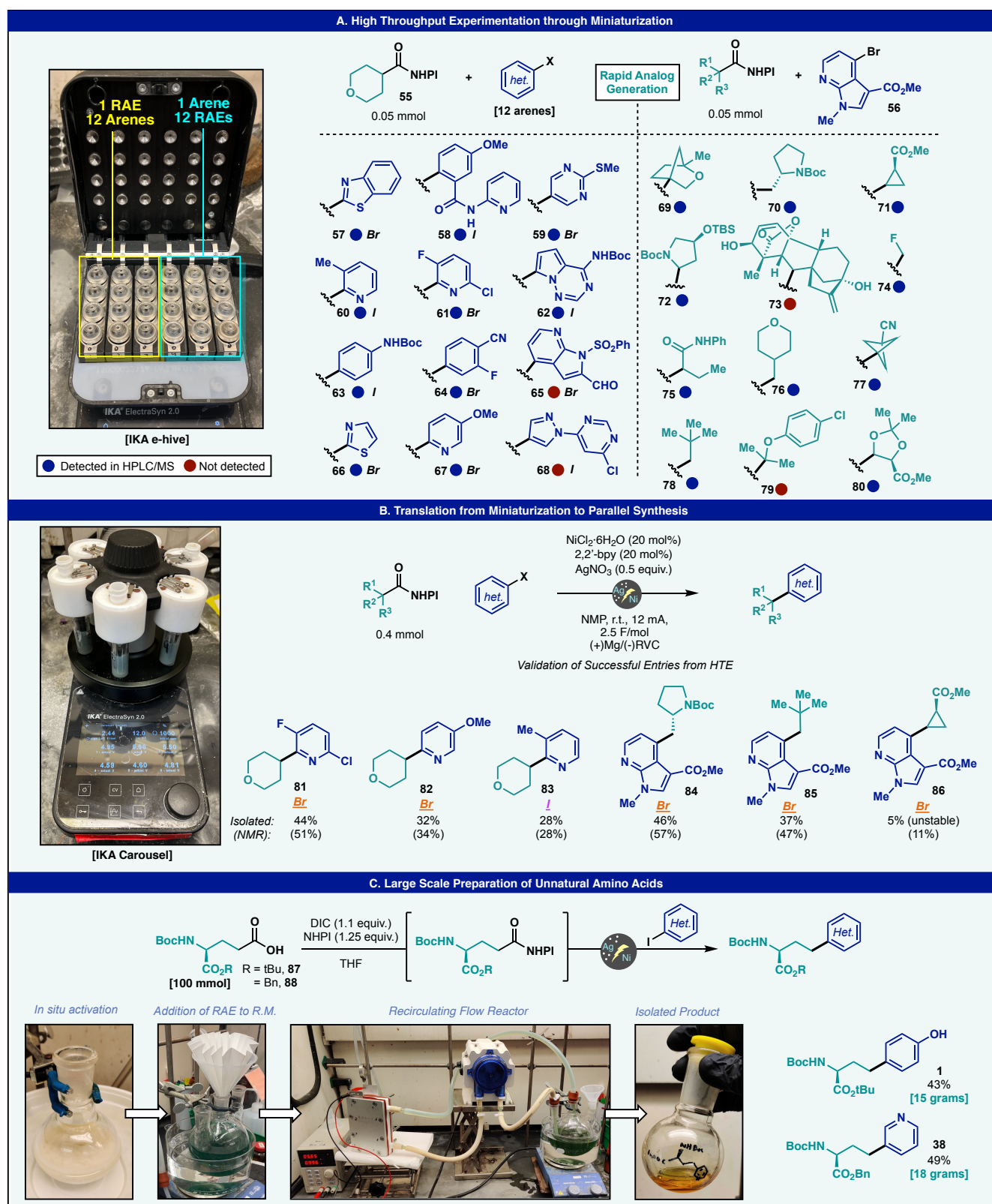
OUTLOOK AND CONCLUSION

Owing to the ubiquitous nature of carboxylic acids in nature and within the catalogs of commercial suppliers, the utilization of decarboxylative cross-coupling methods is seeing increasing use. In essence, carboxylic acids (or their RAE congeners) can be viewed as easily accessible and stable surrogates for alkyl halides (of which relatively few are available) and thus represent ideal radical synthons. The current study capitalizes on a unique observation made during the course of a terpene total synthesis campaign involving in situ deposited Ag-nanoparticles on an electrode surface.³⁰ Such functionalized electrodes were shown to dramatically improve the yield of DCC-based alkenylation in a variety of contexts. The mechanistic aspects of this phenomenon were explored in great detail and laid a groundwork for the current study. Specifically, the issues encountered in that study (low yields and chemoselectivity) were quite reminiscent of the challenges facing DCC-based arylation.

This comprehensive study, conducted in collaboration with multiple companies, addresses many of the less publicized limitations with this powerful transformation. Foremost in our view were the scope limitations apparent on both the arene and carboxylic acid-based fragments. To be sure, electron rich arenes, diverse heterocycles, and highly functionalized carboxylic acids are all highly coveted coupling partners. To vividly demonstrate this challenge, the present work benchmarks state-of-the-art conditions across the entire scope explored. Overall, the present Ag-Ni electrocatalytic protocol appears to have superior generality. In addition, it features high simplicity, robustness, and short reaction times (2.5 h). Several examples are highlighted wherein the success of these uniquely enabled reactions can have a simplifying effect on synthesis. This reaction has been extensively field-tested amongst our collaborators and works on a wide range of additional proprietary structures not depicted herein. Finally, for this reaction to have maximal impact it must be useful in real-world scale regimes. Thus, a demonstration of parallel synthesis to rapidly generate analog libraries, subsequent scale-up for more meaningful quantities, and a simple recirculating-flow setup for decagram scale and beyond are reported.

From a strategic standpoint this study adds another chapter to the growing body of literature showing that in many contexts a one-electron based retrosynthetic plan should be considered alongside more conventional polar bond analysis. It is anticipated that this work will therefore find utility in a variety of settings and contribute to the more

mainstream adoption of electrochemical tactics and radical retrosynthetic strategies.



ASSOCIATED CONTENT

Supporting Information

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. ‡These authors contributed equally.

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ABBREVIATIONS

DCC, Decarboxylative cross coupling; RAE, Redox active esters; PET, Photoinduced electron transfer; DMF, *N,N'*-dimethylformamide; NMP, *N*-methyl-2-pyrrolidone; EWG, Electron withdrawing group; SAR, Structure-activity relationship.

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