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A chemoselective electrochemical birch carboxylation of pyridines†

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Nucleophilic addition to pyridiniums, metal-catalyzed hydrogenation, and cycloadditions constitute a valuable toolbox of modern pyridine dearomatization strategies. Though, in recent years, there have been notable improvements and variations of the canonical Birch reduction to address its notorious safety hazards and poor chemoselectivity, it remains an unexplored mode of reactivity for controlled pyridine

dearomatization. Here, we report a simple and safe protocol for the electrochemical Birch carboxylation of pyridines utilizing a sustainable approach and CO₂ as a green C1 building block. This reaction is highly selective for pyridine reduction in the presence of several functional groups incompatible with the canonical Birch reduction and enables direct access to decorated piperidine scaffolds.

Green foundation

1. Our chemistry addresses many of the safety issues associated with the canonical Birch while also using CO₂, a sustainable C1 building block, as an electrophilic trap. CO₂ valorization is an important modern area of research in advancing sustainable synthetic methods and our work contributes a unique example to this.
2. Our reaction aligns with many fundamental principles of green chemistry including waste prevention, atom efficiency, less hazardous reaction design, and reagent renewability. When placed in contrast with the canonical Birch, our reaction is clearly a much greener alternative that also enables new reactivity.
3. Our work could be made greener by developing greener downstream chemistry for derivatizing the dihydropyridine products that we make using our electrochemical Birch carboxylation.

Pyridine and piperidine were the two most common heterocycles found in FDA approved drugs of the past decade.¹ Due to their growing popularity in drug discovery, pyridine dearomatization has become an area of intense research in synthetic chemistry for enabling direct access to piperidine cores and their related precursors.² Classical dearomatization strategies such as the Birch reduction³ and metal-catalyzed hydrogenation⁴ pose obvious safety concerns (*i.e.*, pyrophoric reagents and cryogenic liquid ammonia) and offer poor chemoselectivity, thus limiting their broader deployment in complex settings.^{3,4} Another classical approach, nucleophilic addition to activated pyridines, while powerful, requires the use of stoichiometric electrophilic activators that are inherently incompatible with substrates containing additional nucleophilic sites and can proceed with poor regioselectivity.^{2a} In recent years, innovative advances in both pyridine activation/nucleophilic addition chemistry^{2,5} and catalytic hydrogenation⁶ have improved upon many of these aforementioned shortcomings. Dearomative cycloadditions of pyridines have contributed towards providing more elaborative piperidine frameworks.⁷

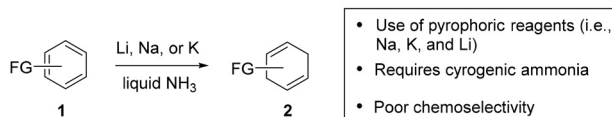
In its traditional form, the Birch reduction employs pyrophoric alkali metals (*i.e.* Na, K, and Li), with cryogenic liquid ammonia, to generate solvated electrons for arene reduction leading to the formation of a carbanion that is subsequently trapped with either a judiciously chosen proton source or carbon-based electrophile (see Scheme 1A).⁸ While the strong reduction potential of solvated electrons (~ -3.3 V vs. SCE)^{9a} allows for dearomatization to occur, this also renders the Birch reduction poorly chemoselective in the presence of functional

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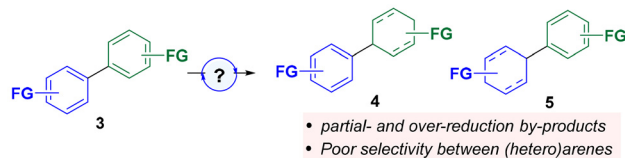
† Electronic supplementary information (ESI) available. See DOI: <https://doi.org/10.1039/d4gc05976j>



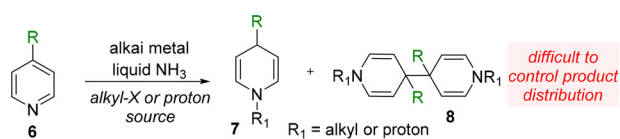
A. Classical Birch Reduction (1944)



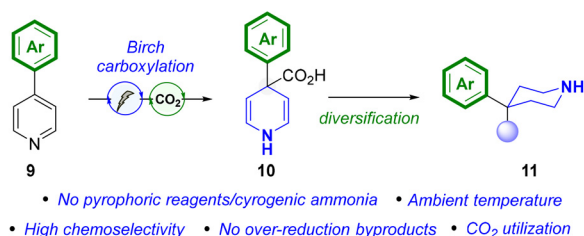
B. Selectivity Challenges in (Hetero)arene Saturation



C. Birch Reduction of Pyridine (1975)



D. This work: Electrochemical Birch Carboxylation of Pyridines



Scheme 1 A–C) Challenges with the classical Birch reduction; (D) our approach towards pyridine dearomatization.

groups with higher reduction potentials (e.g., alkenes, esters, ketones, heteroarenes, etc.).^{9f} Despite its long-standing use in synthetic chemistry, only recently have new methods emerged to address the safety hazards and chemoselectivity issues associated with the Birch reduction.⁹ Baran and co-workers disclosed an electrochemical Birch-type reduction of heteroarenes and electron-deficient arenes where they used rapid-alternating polarity (RAP) to control chemoselectivity.^{9f} Photochemical variants, like Baran's electrochemical approach, avoid the use of cryogenic ammonia and pyrophoric metals.^{9b,c} Though these advances undoubtedly represent substantial improvements over the canonical Birch reduction, there still remain many unsolved challenges. For instance, recent approaches only have demonstrated compatibility with proton electrophiles as Birch alkylations remain unexplored in this modern context. Further, even among these many noted improvements, there is an absence of literature on pyridine Birch reductions. In fact, the scarce examples of classical Birch reduction of pyridines (6) show that it is difficult to control selectivity as both dimerization products (8) and *N*-alkylation (7) complicate the product distribution (Scheme 1C).³

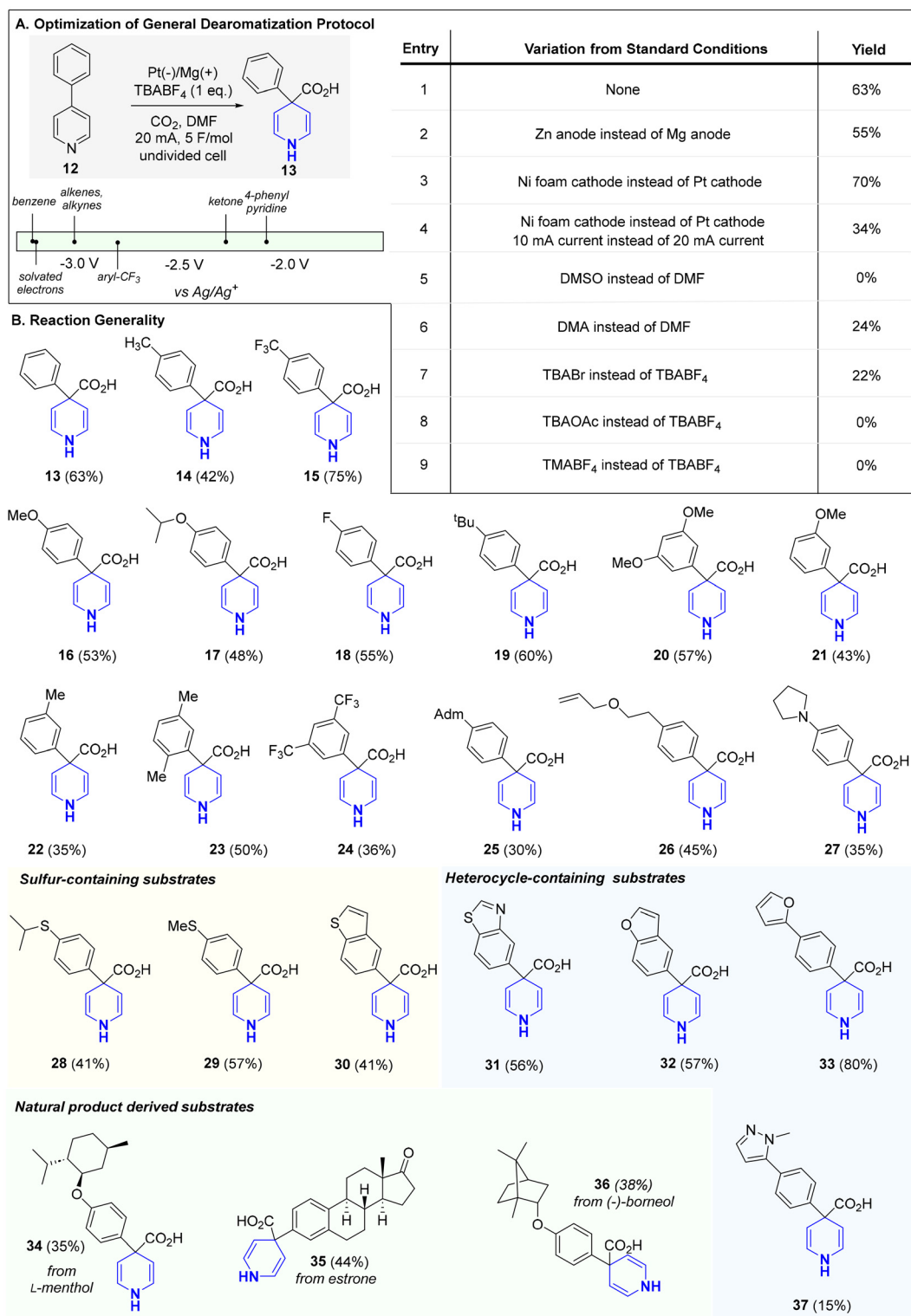
In this article, we report a mild and selective electrochemical Birch carboxylation of pyridines. This protocol enables exclusive partial reduction of pyridine in the presence of (hetero)aromatics and other functional groups typically incompatible with the canonical Birch reduction (and other

modes of dearomatization) while employing CO₂, a sustainable C1 building block, as an electrophilic trap. The deployment of CO₂ as an electrophilic trap in Birch reductions overall remains unexplored despite environmental and economic factors motivating its utilization. Since classical Birch alkylations of pyridines are complicated by competitive *N*-alkylation, CO₂ represents the ideal electrophilic trap as undesired *N*-carboxylation is entropically disfavoured and reversible. Our approach provides a greener method for pyridine dearomatization by eliminating the need for stoichiometric activators and reductants, which lead to unnecessary waste generation, while also minimizing the safety risks commonly associated with conventional dearomatization strategies.

The selective reduction of one aromatic system in the presence of another remains a common challenge in dearomatization chemistry. As reported by Doyle, pyridine, owing to its increased aromatic character compared to other heteroarenes, is notably difficult to reduce chemoselectively in this setting (see Scheme 1B).⁴ With this in mind, we choose 4-phenyl pyridine (12; −2.15 V vs. SCE)¹⁰ as our study substrate for exploring electrochemical Birch/carboxylations. While only rare examples exist of selective Birch reductions in biaryl systems of any kind,¹¹ we posited that, under controlled electroreducing conditions, the pyridine fragment in the 4-phenyl pyridine would undergo selective reduction due to the increased stabilization of the formed radical anion intermediate (i.e., benzylic radical and nitrogen anion).¹² We proceeded to examine several parameters including electrolyte, solvent, temperature, and electrode material (see ESI† for full optimization details) to effect the desired Birch carboxylation. Strikingly, in an undivided cell, employing a platinum cathode and magnesium anode in DMF at ambient temperature, (entry 1) we obtained 1,4-dihydropyridine (DHP, 13) in 63% yield. Attempts to use greener solvents in place of DMF such as MeCN were unsuccessful.¹³ Under these conditions (entry 1), no phenyl reduction was observed and carboxylation occurred exclusively at C4. The regioselectivity observed here is analogous to what would be expected from a canonical Birch reduction. Running the reaction at lower or higher temperatures, as well as with other electrode combinations, afforded little product. Other electrolytes (e.g., TBABr, TBAOAc, and TMABF₄) performed poorly as replacements for TBABF₄. However, the magnesium anode could be replaced with zinc with only a modest decrease in yield (entry 2). Though it was later found that replacing the platinum cathode with a nickel foam cathode led to a modest improvement in yield (entry 3), this condition did not translate to other substrates (<20%). As such, subsequent substrate evaluation was carried out with the conditions depicted in entry 1, which proved to be scalable up to 500 mg.

The reaction's generality is shown in Scheme 2. Bi- and triaryl pyridines were all reduced, with complete chemoselectivity and regioselectivity, to their corresponding 1,4-DHPs. Unlike the classical Birch reduction, which for biaryl systems can lead to unpredictable mixtures of reduced products, no (hetero)





Scheme 2 Optimization table and substrate scope. Reaction conditions: TBABF₄ (1 eq.) and 4-aryl-pyridine in DMF (0.10 M) in a 5 mL ElectroSyn vial with a Pt cathode and an Mg anode. CO₂ was bubbled into the reaction mixture as it was electrolyzed at 20 mA for 5 F mol⁻¹. Adm = adamantyl.

arene reduction nor dimerization products were observed in our reaction.^{3,11} Furthermore, the simplicity, avoidance of expensive additives (*i.e.*, 4',4'-di-*tert*-butylbiphenyl (DBB),

15-crown-5, and TPPA (tri(pyrrrolidin-1-yl))),^{9g} and safety of our protocol provides an attractive solution for pyridine Birch reduction. Unsurprisingly, electron-neutral and electron-rich



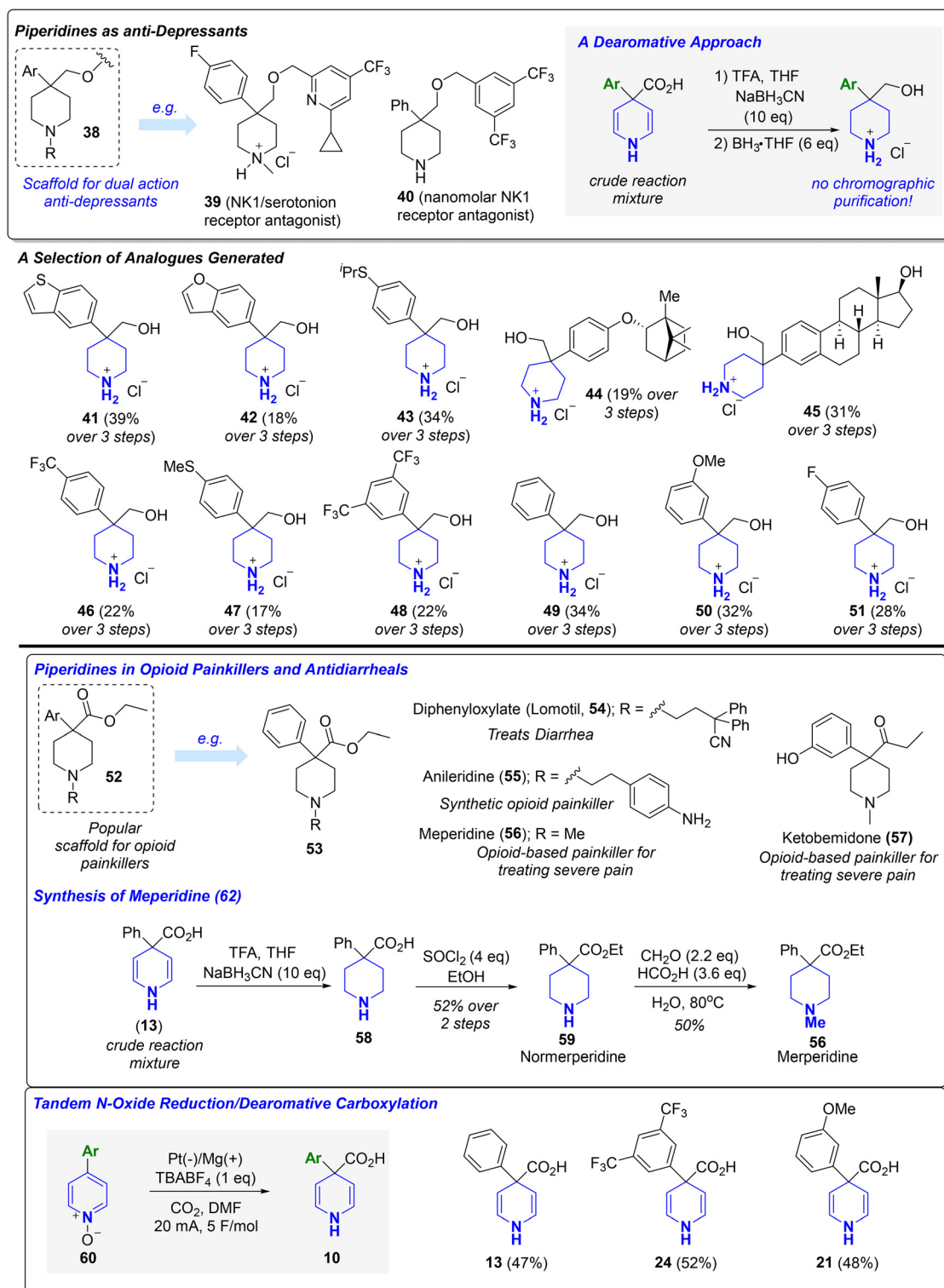
arenes were all well-tolerated as these systems require lower reduction potentials (more negative). Even electron-deficient arenes and heteroarenes (**30–33**, **37**), all of which have relatively higher reduction potentials (more positive), were not reduced under our mild conditions. Heteroarenes, in particular, are notoriously incompatible or reactive under canonical Birch reduction and other modes of pyridine dearomatization (*i.e.*, metal-catalyzed hydrogenation). For instance, canonical Birch reduction can lead to the fragmentation of furan and thiophene rings.^{9f,14} Having achieved orthogonal pyridine reduction *versus* other (hetero)aromatics, we proceeded to assess other functional groups known to pose compatibility issues with the canonical Birch reduction. Our milder conditions enabled broad functional group tolerance to aryl trifluoromethyls (**15**, **24**), aryl fluoride (**18**), ketone (**35**), and alkene (**26**). As noted by Glorius, in metal catalyzed hydrogenation, sulfur-containing motifs, which are widely prevalent in Nature and drug discovery, often lead to catalyst poisoning thus limiting the use of hydrogenation-based dearomatization strategies with sulfur-containing molecules.¹⁵ This drawback has inspired considerable effort in search of sulfur-resistant hydrogenation catalysts. However, for pyridine dearomatization our protocol provides a convenient, alternative solution to this problem as sulfur-containing motifs, including thioethers (**28**, **29**), benzothiophene (**30**), and benzothiazole (**31**) were all tolerated in our reaction. In recent years, late-stage saturation (LSS), a concept aimed at converting aromatics into their saturated counterparts in complex molecules, has shown promise as a powerful tool for improving a drug candidate's physicochemical properties.^{6c,d} Towards this goal, natural product-derived substrates were readily converted into their corresponding 1,4-DHP analogues (**34**, **35**, and **36**). Notably, the estrone-derived substrate highlights the vastly improved chemoselectivity of our reaction over the canonical Birch reduction as neither the arene nor ketone were reduced. Overall, this process aligns with many foundational principles of green chemistry including waste prevention, atom efficiency, less hazardous reaction design, and reagent renewability.¹⁶ In fact, standard green chemistry metrics further support this assertion; the atom economy (AE %) and carbon efficiency (CE %) of this reaction were determined to be 93–96% and 100%, respectively, for all substrates. Further, the products can be used in subsequent steps as crude materials or after simple recrystallization, reducing waste and enhancing efficiency. By avoiding chromatographic purification, which generates significant solvent and silica waste, the process achieves a lower *E*-factor, improving sustainability.¹⁷

1,4-DHPs are widely utilized in catalysis and as building blocks for piperidine synthesis.¹⁸ As such, we sought to provide examples of useful downstream chemistry for making popular piperidine frameworks using the 1,4-DHPs generated from our Birch carboxylation. 4,4-disubstituted piperidines are privileged scaffolds found in a plethora of FDA-approved drugs (*e.g.*, haloperidol, loperamide, traxoprodil, *etc.*) and investigational therapeutics.¹⁹ Our protocol allows for streamlined access to 4,4-disubstituted piperidines from their corres-

ponding biaryl frameworks. Bristol Myers Squibb (BMS) previously identified **38** and analogues thereof (*e.g.* **39** and **40**) as nanomolar dual NK1/serotonin receptor antagonists for treating depression.^{19b,c} Towards making the piperidine core, the crude reaction mixtures obtained from the electrochemical Birch carboxylation were treated with sodium cyanoborohydride and TFA, followed by moderate heating with borane-THF, to afford several analogues (**41–51**) of the central piperidine fragment in a convenient sequence that avoids chromatographic purification and requires only a single purification *via* recrystallization from diethyl ether after the final step. A selection of the products are shown in Scheme 3 (see ESI† for many more additional examples). 4-aryl-4-carbonyl piperidines (*e.g.* **52–57**) constitute an important subclass of opioid-based painkillers and antiarrhythmals.^{19d,e} After once again treating the crude reaction mixture obtained from Birch carboxylation with sodium cyanoborohydride, the resulting product (**58**) was then esterified and methylated to deliver merperidine (**56**), a clinically approved opioid used for treating severe pain.^{19d} Overall, these examples highlight how the electrochemical Birch carboxylation can be deployed as a tool in drug discovery for directly accessing derivatives with increased three-dimensional character from their respective planar analogues. Finally, we considered opportunities to pair our Birch carboxylation with other reductive reactions in a tandem process. Pyridine *N*-oxides not only represent a subclass of pyridine-containing therapeutics but are also common synthetic intermediates used to alter pyridine reactivity in electrophilic and nucleophilic aromatic substitutions. We showed, without any changes to the reaction conditions, that a tandem electrochemical *N*-oxide reduction/Birch carboxylation enables the streamlined conversion of pyridine *N*-oxides (**60**) into their corresponding 1,4-DHPs.

Lastly, we sought to provide a mechanistic rationale for the exclusive C4 selectivity observed in the Birch carboxylation. While we presumed that this dearomative carboxylation occurred through an electrochemical Birch-type mechanism (pathway 1), we considered a Minisci-like radical addition (pathway 2) as a possible alternative. As shown in Scheme 4, pathway 1 proposes a Birch-type reduction of the pyridine (**12**) to the radical anion (**61**). The generated benzylic radical is stabilized through electron delocalization into the arene substituent, thus lowering the barrier towards dearomatization. This hypothesis is supported by the fact that 4-methylpyridine, which would lead to the formation of a less stabilized radical, failed to undergo dearomative carboxylation under our conditions. The negative charge of the radical anion sits predominantly on the nitrogen leading to its trapping with CO₂. Subsequent cathodic reduction of the benzylic radical (**62**) and trapping with CO₂ affords **63** where the carbamic acid moiety readily undergoes decarboxylation to deliver the product **13**. The alternative Pathway 2, on the other hand, involves a Minisci-type addition of CO₂ radical anion after either activation of the pyridine ring *via* coordination to either CO₂ or Mg²⁺ cation (see **64** in Scheme 4). However, this pathway fails to rationalize the exclusive C4 selectivity that we observe.



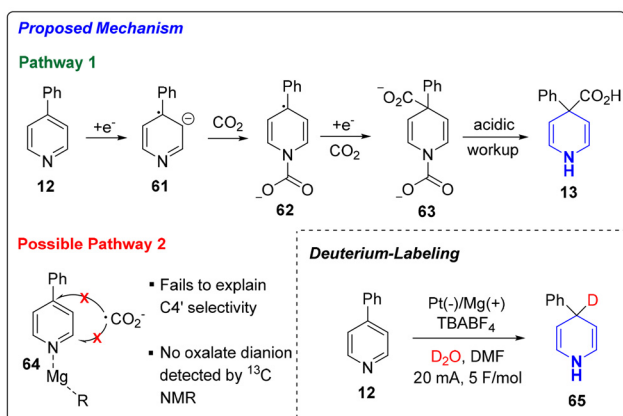


Scheme 3 Utility of electrochemical Birch carboxylation for synthesis of popular piperidine scaffolds.

Furthermore, no oxalate dianion, which is associated with CO₂ radical anion dimerization, was detected by ¹³C NMR. To confirm the presence of the benzylic anion proposed in pathway 1, we ran the reaction with D₂O and observed C4'

deuteration (**65**, 76% deuterium incorporation). As such, mechanistic evidence strongly supports pathway 1 (Birch reduction) as being the operative mode of dearomative carboxylation.





Scheme 4 Proposed mechanism.

Conclusions

In summary, we have developed an operationally simple, electrochemical Birch carboxylation of pyridines. This process is additive free, utilizes CO_2 as a green C1 building block, and is compatible with a range of functional groups not tolerated in the classical Birch reduction and other dearomatization strategies (*i.e.*, metal-catalyzed hydrogenation). Ultimately, these mild conditions address the well-known safety hazards of the canonical Birch to provide a new avenue for directly transforming pyridines into their corresponding piperidine analogues.

Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

The authors declare that there are no conflicts interests.

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