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Electrochemical Decarboxylative *N*-Alkylation of Heterocycles

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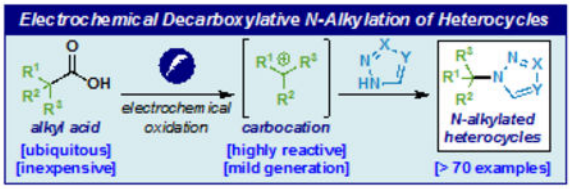
Abstract

An operationally simple method to employ non-activated carboxylic acids as alkylating agents in *N*-alkylation of heterocycles is reported through an electrochemically driven anodic decarboxylative process. A wide substrate scope across a range of heterocycles is demonstrated along with a series of applications that significantly reduce the step-count required to access such medicinally relevant structures.

Graphical Abstract



A recent analysis of the reactions conducted by modern medicinal chemists revealed that C–N alkylation, not surprisingly, represents a significant percentage of reactions conducted on a yearly basis.[1] Within this class of transformation, the alkylation of unsaturated *N*-heterocycles is a popular tactic for diversification. Numerous methods exist for to achieve this, the most popular being variants of the S_N1 or S_N2 reaction (such as Mitsunobu).[2] As the starting materials for such common reactions are alkyl halides or alcohols, the development of new entry points for this disconnection have become attractive. Carboxylic acids are perhaps even more widespread than alcohols and over the past decade numerous methods to replace the C–C bond with other valuable substituents have emerged.[3,4] Decarboxylative aminations were first reported by Barton in 1992 where his eponymous redox-active ester was converted to the corresponding amine using diazirines as radical traps.[5] Recent developments (Figure 1) include the use of intermediary NHPI-based redox active esters or I(III)-based esters in concert with Cu-based photochemical systems (with or

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Supporting Information
The Supporting Information is available free of charge on the ACS Publications website.
Additional optimization data, complete experimental procedures, characterization data, Frequently Asked Questions section and NMR spectra (PDF)

without additional photocatalysts) to achieve amine and heterocycle alkylations with broad scope.[6] Non-activated approaches that don't traverse through activated esters are less common.[7] For example, decarboxylative methods to convert stabilized acids to *N*-alkylated products were reported in 2019[7a,b] and earlier this year a photochemical *N*-alkylation of DTAD (di-*tert*-butyl azodicarboxylate) was reported and such adducts could be converted to pyrazoles after deprotection/condensation.[7c] In 2019 our group reported a simple means to prepare hindered ethers through an electrochemical decarboxylative approach wherein an electrogenerated carbocation could be intercepted with an alcohol.[8] It was hypothesized that similar conditions might also be amenable to capture with *N*-heterocycles. In this Letter we report our findings and demonstrate that a simple electrochemically driven approach analogous to ether synthesis can be employed to generate *N*-alkylated heterocycles. The reaction exhibits a broad substrate scope with regards to the heterocyclic substrate, employs a simple and scalable procedure, and can be used to simplify prior routes to such targets.

At the outset, optimization was conducted on a medicinally relevant substrate that was employed in the synthesis of a Cereblon binder, pyrazole **1** (Scheme 1A).[9] This compound was previously obtained in 6 steps starting from 4-methylpyridine wherein only 2 of those steps contribute to building skeletal bonds (C–C and C–N). Interestingly, the key C–N bond forming step relies on a single electron Mukaiyama-type reaction between an olefin and DTAD. As carboxylic acid **2** is commercial, a far more direct path to **1** would involve direct decarboxylative union with pyrazole **3** (via a 2-electron pathway this time). In its optimized manifestation, this *N*-alkylation afforded compound **1** in 52% isolated yield. Extensive optimization was conducted on this and other substrates (see SI) to arrive at this final set of conditions, some of which is summarized in Scheme 1B. Notably, both the procedure we reported for etherification and the closest electrochemical precedent only afforded low yield in this transformation (entries 1 and 2). A key departure from etherification occurred when switching the cathode material from graphite (34% yield, entry 4) to nickel. The addition of molecular sieves and collidine were essential relative to the prior e-alkylation approach (entries 5 and 6). The use of DCM, as with etherification, was also essential for the reaction (entry 7). Although lowering the amount of carboxylic acid to one or two equivalents is detrimental for the reaction (entries 8 and 9), the excess acid can be recovered if desired for valuable substrates. Finally, a screen of bases revealed that collidine was optimum (e.g. DBU afforded lower yield, entry 10). Variables such as electrolyte and concentration are discussed further in the SI but had only negligible effect on the reaction.

With an optimized set of conditions in hand, the scope of this transformation was explored as illustrated in Scheme 2. In addition to the ester moiety, a variety of functional groups were tolerated such as those sensitive to hydrolytic (cyano, **43** and **46**), oxidative (BPin, **9** and **50**), reductive (nitro, **48**), and acidic conditions (acetal, Boc-protected amines, **30**, **31**, **33**, **35**, and **36**). Aryl halides (F, Cl, Br, and I, **10**, **13**, **17**, **27**, **49** and **50**) and fluoroalkyl substituents were also unharmed in this reaction (**11**, **25**, **47**, and **67**). To our knowledge this represents the first use of non-stabilized/non-bridged tertiary acids in a direct decarboxylative *N*-alkylation process (**4**, **6** and **7**). With regards to the scope of heterocycles, aside from pyrazoles, (benzo)triazoles (**40** and **41**), tetrazoles (**42**), imidazoles (**43**), 1,2,4-triazoles (**53** and **54**), indazoles (**56** and **57**), xanthones (**58**), oxazolidinones (**59** and **69**), γ-

lactams (**60**), succinimides (**61**), pyridones (**62**), 2-aminopyrimidines (**63**), and oxindoles (**65**) could all be employed. The operationally simple protocol (setup in ca. 5–10 minutes) could be conducted on a commercial potentiostat without exclusion of air and was amenable to scale up (**8**, 69% yield on 1 mmol scale) without significant diminishment in yield. In cases where the reaction only proceeds to a modest extent (for example cyclobutane **22** and **23**), the remaining pyrazole substrate (limiting reagent) can be recovered.

Aside from the highlighted application in Scheme 1A (pyrazole **1**), a small selection of additional known compounds were targeted such as pyrazoles **70**-**72** (Scheme 3A).[10–12] Hemi-aminals **70** and **71** could be accessed in high yield in one simple step versus multistep procedures used in the past. Finally, the *tert*-butylated pyrazole **72** could be accessed in a single step (although in low yield due to an extended reaction time needed with pivalic acid).

Mechanistically we hypothesize that a cationic intermediate is formed after decarboxylation analogous to etherification (Scheme 3B). To lend evidence for this hypothesis, acids **73** and **75** were exposed to the standard conditions and the resulting products **74** and **76** formed as a result of cationic rearrangement. The limitations of this reaction are thus linked to this mechanistic requirement in that the carboxylic acid donor must be able to generate a reasonably long-lived carbocation following decarboxylation. A full summary of failed substrates is listed in the SI to aid the practitioner.

To conclude, a useful method for the direct decarboxylative *N*-alkylation of heterocycles has been developed. This direct anodic electrochemical process exhibits a wide substrate scope with regards to the carboxylic acid (stabilized and non-stabilized) and heterocycle. As such, application to the synthesis of valuable medicinal and agrochemicals can be foreseen.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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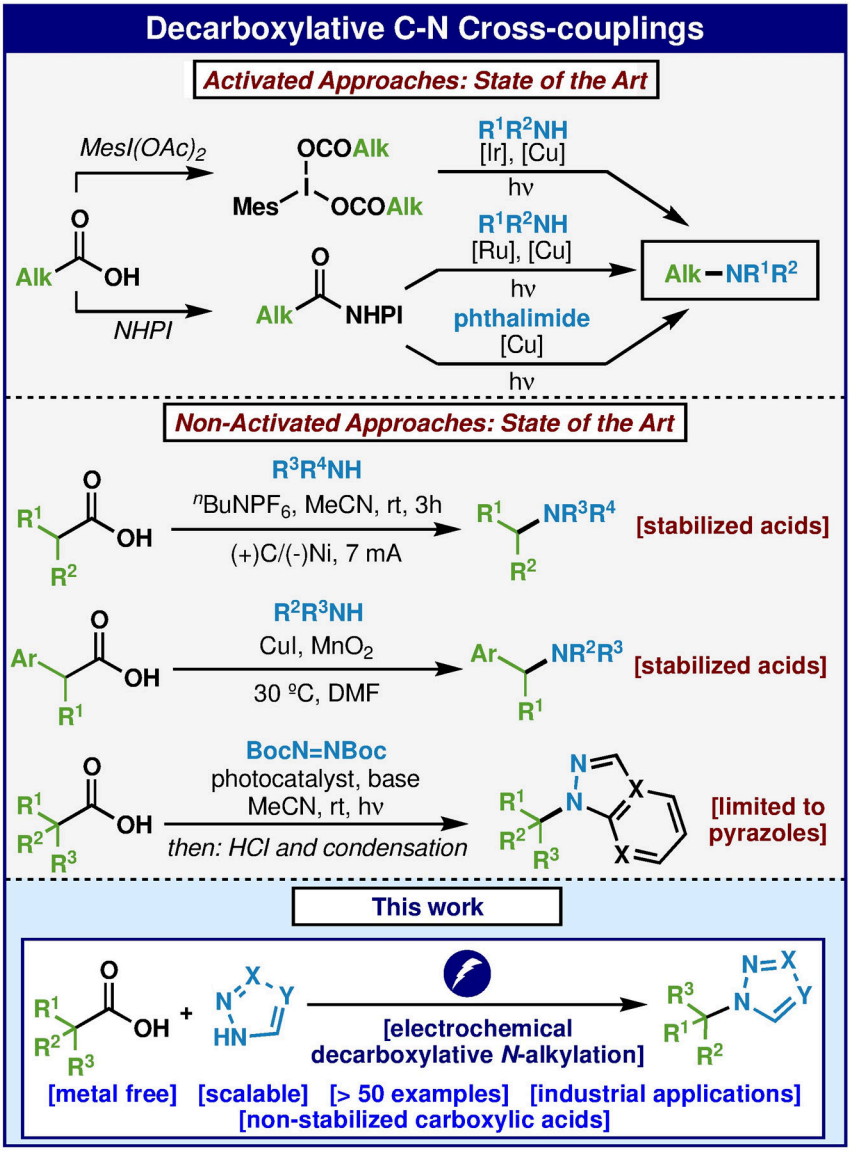
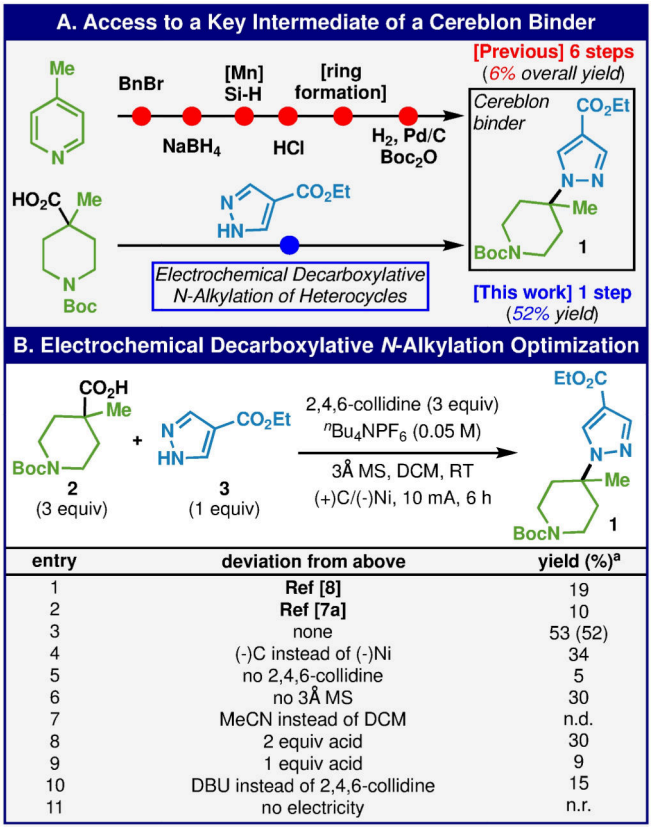


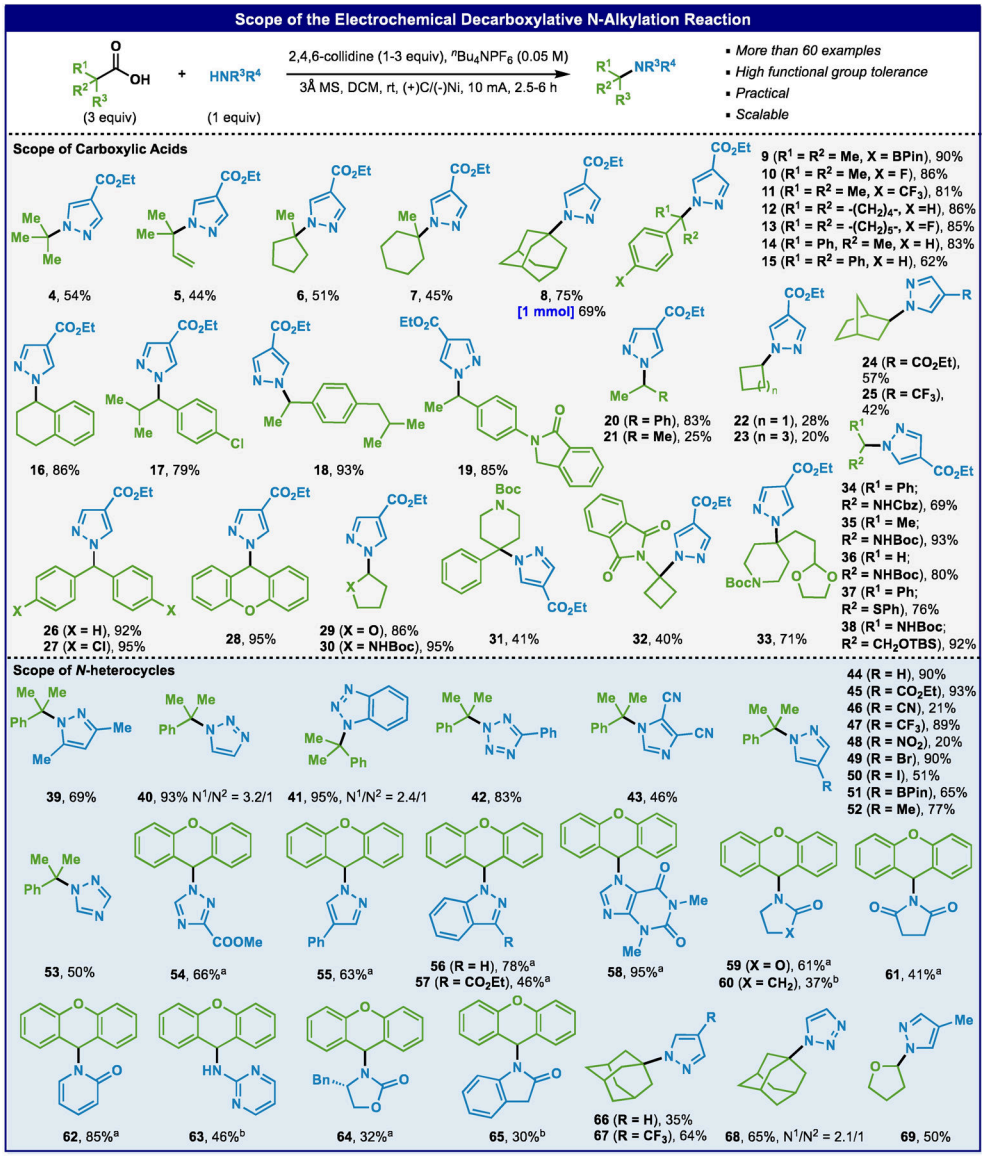
FIGURE 1.
Decarboxylative C-N cross-couplings.



entry	deviation from above	yield (%)[a]
1	**Ref [8]**	19
2	**Ref [7a]**	10
3	none	53 (52)
4	(-)C instead of (-)Ni	34
5	no 2,4,6-collidine	5
6	no 3Å MS	30
7	MeCN instead of DCM	n.d.
8	2 equiv acid	30
9	1 equiv acid	9
10	DBU instead of 2,4,6-collidine	15
11	no electricity	n.r.

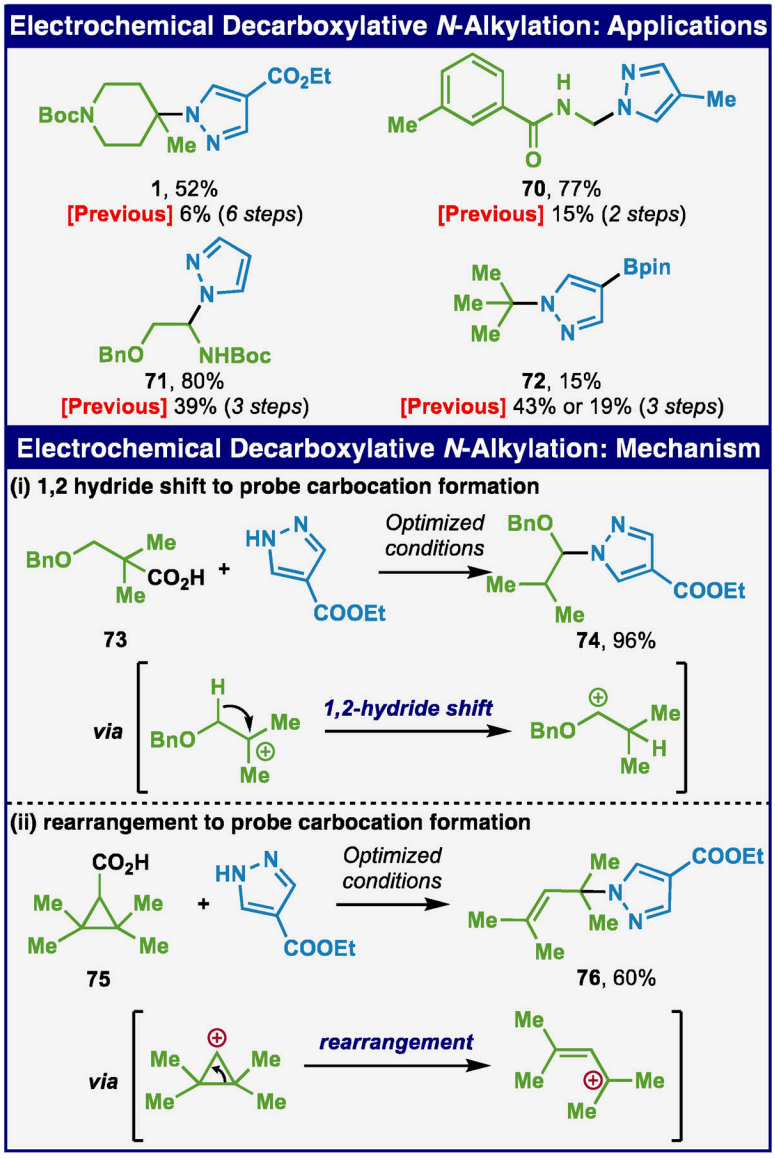
SCHEME 1.

(A) Access to a key intermediate of a Cereblon binder. (B) Optimization of the electrochemical decarboxylative *N*-alkylation of heterocycles. [a] Isolated yield.



SCHEME 2.

Scope of the electrochemical decarboxylative *N*-alkylation of heterocycles. [a]2 equivalent of acid instead of 3. [b]3 equivalent of *N*-heterocycle and 1 equivalent of acid.



SCHEME 3.

(A) Applications. (B) Mechanistic investigation.