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Direct Catalytic Decarboxylative Amination of Aryl Acetic Acids

Duanyang Kong, Patrick J. Moon, Odey Bsharat, and Rylan J. Lundgren*[a]

Abstract: *The decarboxylative coupling of a carboxylic acid with an amine nucleophile provides an alternative to the substitution of traditional organohalide coupling partners. Benzoic and alkynyl acids may be directly aminated via oxidative catalysis. By contrast, methods for intermolecular alkyl carboxylic acid to amine conversion, including amidate rearrangements and photoredox-promoted approaches, require stoichiometric activation of the acid unit to generate isocyanate or radical intermediates. We report a process for the direct chemoselective decarboxylative amination of electron-poor arylacetates via oxidative Cu catalysis. The reaction proceeds at (or near) room temperature, uses native carboxylic acid starting materials, and is compatible with protic, electrophilic, and other potentially complicating functionality. Mechanistic studies support a pathway in which ionic decarboxylation of the acid generates a benzylic nucleophile which is aminated in a Chan-Evans-Lam type process.*

Introduction

Carboxylic acids are a widely available, structurally diverse class of molecules. The decarboxylative conversion of acids into other functional groups is a valuable approach in synthetic chemistry.[1] Owing to the importance of amines in a range of applied fields, effort has been placed on realizing decarboxylative amination processes[2] that complement C–N bond forming reactions such as substitutions of organohalides[3] and activated alcohols[3] and reductive amination of carbonyls.[4]

Cu-catalyzed direct oxidative amination under conditions similar to that of the Chan-Evans-Lam reaction[5] has been established for both C(sp)- and C(sp^2)-carboxylates.[6] These processes are complementary to substitution of alkynyl and aryl (pseudo)halide electrophiles.[7] Electron-poor benzoic acids undergo decarboxylation and coupling with several classes of nitrogen nucleophiles at elevated temperatures (140–170 °C) (Figure 1A). Both weakly nucleophilic NH-partners[6a, 6b] and simple alkyl amines have been demonstrated; however simple alkyl amines require dual Pd/Cu catalysis.[6c] Cu-catalyzed C(sp)–N decarboxylative alkynylation has been limited to weakly nucleophilic NH partners (carbamates, lactams, indoles, sulfoximines).[8]

For C(sp^3)-carboxylate amination, reports are limited to decarboxylative condensation processes that ultimately generate C(sp^2)–N units in arylquinazolines,[9] or intramolecular decarboxylative aminations that require picolyl amine directing groups.[10] Existing methods for intermolecular decarboxylative cross-coupling of carboxylic acids and NH-nucleophiles to generate C(sp^3)–N bonds require stoichiometric activation of the acid. These approaches include Curtius-type rearrangements[11] and photoredox-mediated coupling of N-hydroxyphthalimide esters[12] and iodonium carboxylates[13] (Figure 1B). The isocyanate intermediates generated in Curtius-type rearrangements[11a] may be incompatible with nucleophilic functional groups, and photoredox-mediated processes are limited to weakly nucleophilic substrates like imides,[12a] anilines,[12b, 13a] sulfonamides,[13] and select N-heterocycles.[13a]

We have described a family of reactions that use electron-poor arylacetates as benzylic nucleophile surrogates in transition metal catalyzed cross-couplings.[14] Compared to the use organometallic benzylating reagents, these reactions enable coupling under mild conditions while tolerating functional groups that would be incompatible with highly basic species. We became interested in expanding this approach to the development of a Chan-Evans-Lam type decarboxylative coupling of unmodified C(sp^3)-carboxylic acids with alkyl amine partners (Figure 2A).[15] This process would complement existing Cu-catalyzed oxidative coupling reactions of alkyl boronic acid derivatives with anilines or amides that use peroxide-based oxidants[16] or decarboxylative halogenation/substitution procedures of β-carboxy acids.[17]

Our mechanistic hypothesis was based on the established individual elementary steps similar to the Chan-Evans-Lam reaction (Figure 2B).[5b, 5c] The key step involves the generation of a benzyl anion by ionic decarboxylation.[14] The capture of this species by a Cu-catalyst could form a Cu(amido)(benzyl) complex

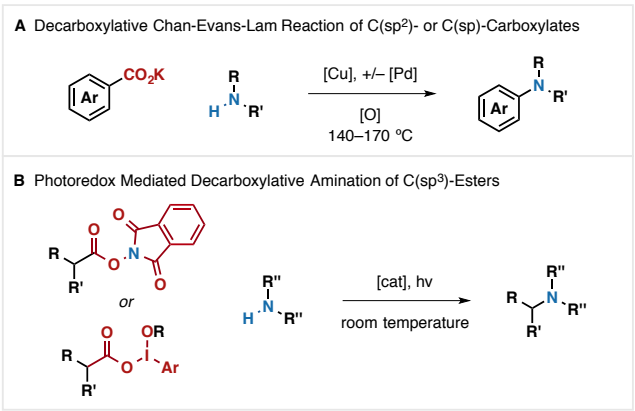

Figure 1. Methods for the catalytic intermolecular amination of carboxylic acid derived groups to form C(sp^3)–N bonds.

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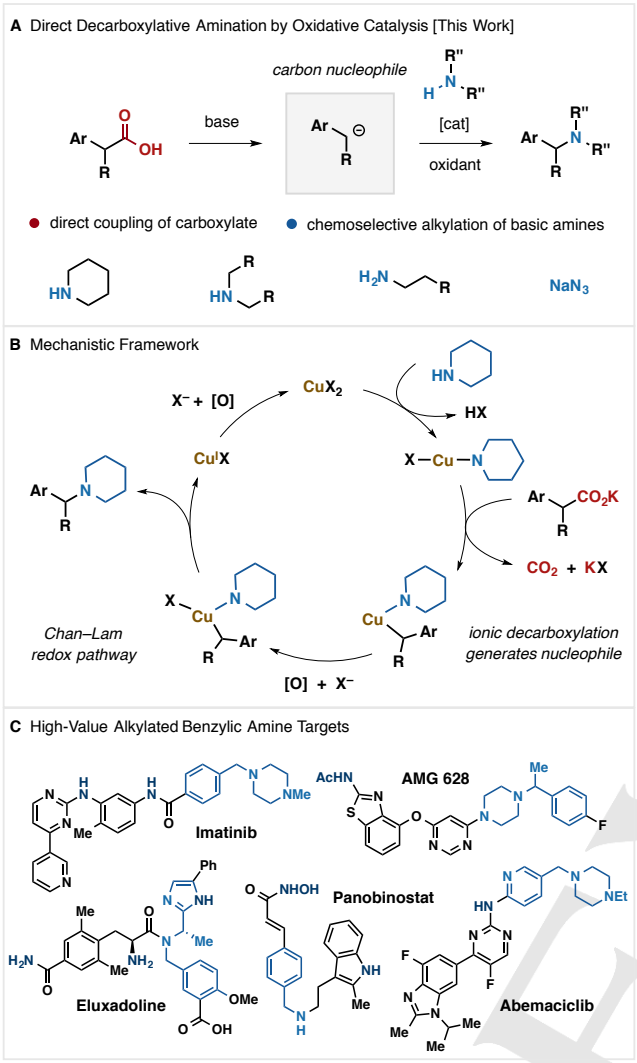

Figure 2. Overview of the process developed, mechanistic hypothesis, and molecules that contain alkylated benzylic amine units.

which could undergo disproportionation to Cu(III) and subsequent reductive elimination to generate a benzylic amine product.[5],[16b] A terminal oxidant would regenerate active Cu(II) species.[5] Given the mild reaction conditions and exceptional functional group compatibility of mechanistically related Cu-catalyzed C(sp^2)–N oxidative aminations of aryl boron nucleophiles, a process following this path should have the opportunity to share similar characteristics and potentially be of value in generating polyfunctionalized benzylic amines (Figure 2C).

Results and Discussion

We selected piperidine as a target amine nucleophile for catalytic oxidative benzylation due to the inability of established photoredox methods to engage this class of substrate.[17] Carboxylate **1** underwent direct decarboxylative amination promoted by CuI/MnO_2 mixtures under operationally simple conditions to give the benzylic amine product **2** in 92% yield (Figure 3A). The free acid could be used instead of the K-carboxylate by adding K_2CO_3 with no change in efficiency (94% yield). Ambient air is a suitable oxidant (50% yield of **2**); however, MnO_2 resulted in higher yield and is inexpensive (~$0.10/g). Use of pure O_2 atmosphere provided effectively no product. Peroxide, persulfate, or other metal-based oxidants were less productive. Pd-, Ni-, Co-, and Fe-based catalysts afforded non-zero yields but were inferior to a range of simple Cu-salts such as CuI, $Cu(OAc)_2$, $Cu(OTf)_2$.[18] Amination under halide-free conditions rule out a halogenation/substitution pathway. The reaction proceeds best in polar, aprotic solvents, the use of DMSO, DMA, or NMP also resulted in good yields of **2** (61–83%). In cases where product yields are modest, the remaining mass balance is largely protodecarboxylated material.

The mild decarboxylative amination conditions and efficient reactivity enable exceptional chemoselectivity, which was rapidly evaluated by a functional group compatibility screen (see SI for complete details).[18] Protic nucleophiles including NH-heterocycles, anilines, NH-amides, sulfonamides, phenols,

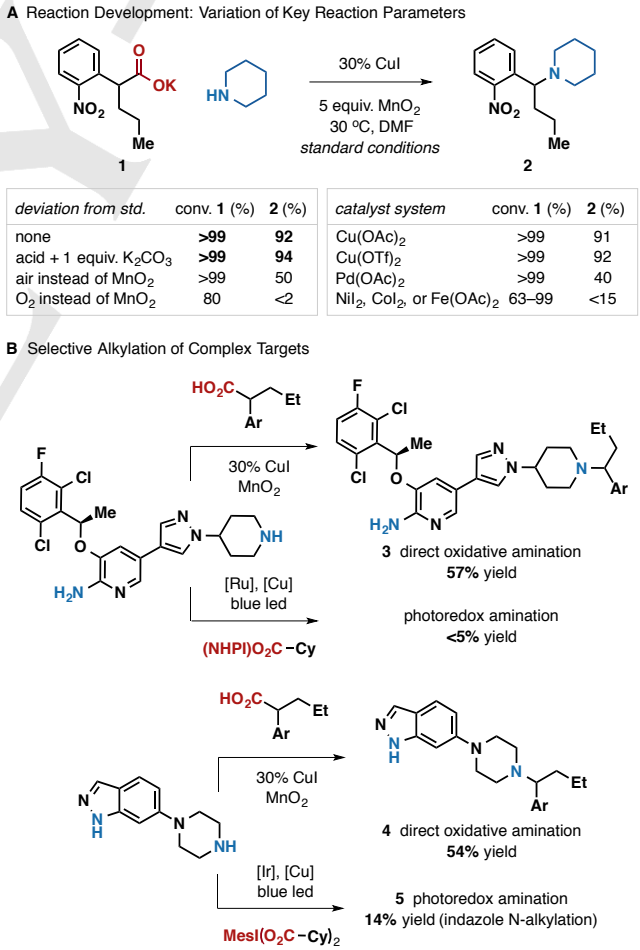

Figure 3. Key reaction parameters and application in chemoselective amine alkylation. Conversions and yields determined by calibrated ^{1}H NMR spectroscopy using an internal standard. Ar = 2-$NO_2C_6H_4$. See the SI for complete details.

alcohols and other carboxylic acids were tolerated, with the standard reaction giving >75% of product **2** and <20% consumption of the additive in competition studies. Despite the likelihood of a benzylic nucleophile being generated as an intermediate (see below), electrophilic groups are preserved, including alkyl and aryl halides, boron Lewis acids, aldehydes, and Michael acceptors.[17b]

The chemoselectivity of the decarboxylative amination was demonstrated in the late-stage benzylation of complex targets (Figure 3B). Under the standard conditions the alkylation of Crizotinib occurs exclusively at the piperidyl NH over the aminopyridine unit (**3**, 57% yield). Benzylation of an aminoindazole substrate occurs exclusively at the secondary amine position to generate **4** (54% yield). Photoredox methods fail to deliver reasonable yields of decarboxylative alkylation products under the host of conditions examined and when C–N bond formation does occur it is predominantly at the less nucleophilic NH position.[18c]

Under the optimized conditions, a host of alkyl amine nucleophiles and electron-poor aryl acetic acids can be decarboxylatively cross-coupled (Figure 4). Both cyclic and acyclic secondary amines in addition to primary amines undergo benzylation in moderate to excellent yields (**2**, **6**–**25**). Included are examples of amines featuring unprotected alcohol groups (**11**, **21** **24**), various potentially reactive amide or aniline groups (**12**–**14**, **16**), and electrophilic or potentially oxidizable groups (**15**, **18**). When primary amine substrates were used, bis-alkylation was not observed enabling facile isolation of the alkylated products (**22**–**25**). Marketed amine-containing drug molecules bearing sensitive functionality including aryl fluorides and chlorides, functionalized N- and S-heterocycles and a tetrasubstituted olefin could be alkylated in good yields (Paroxetine, Debenzyldonepezil, Desloratadine, Crizotinib, Fasudil, and Duloxetine; **3**, **26**–**30**). In some cases, the addition of $Zn(OAc)_2$ was found to be useful to suppress undesirable protodecarboxylation. The supporting information section contains details on less successful N–H partners (very bulky amines, anilines, amides; see Figure S5) and reactions with C-, and S-based nucleophiles (malonates, aryl sulfides, sulfinates; see Figure S6).

A diversity of electron-deficient aryl acetates proved suitable partners for amination, including 4- and 2-nitro (**31**, **36**), 4- and 2-cyano (**32**, **37**), 4-sulfonyl (**33**), 4-acetyl (**34**), and 4-pyridyl (**35**) derivatives (Figure 4). Substituents on the aryl acetic acid partner were well tolerated, including halogens (**39**, **43**) or trifluoromethyl groups (**49**) and electron-donating methoxy (**40**, **44**, **45**) or dimethylamino (**41**) groups. Successful benzylation was achieved using aryl acetic acids bearing other sensitive functionality such as free or silyl-protected alcohols (**38**, **47**), olefins, and acetals (see below). The process is currently restricted to electronically activated benzylic partners that form a stabilized anion; however, a varied series of targets could be obtained in good overall yields by simple nitro-group functionalizations. Conversion to anilines (**50**, **51**) and further modifications by facile aromatic substitution gives access to products of arene deamination (**52**), iodination (**53**), hydroxylation (**54**) or Heck cross-coupling (**55**) in overall yields of 52–76%.

The scope and functional group compatibility studies described above illustrate strengths and limitations of a decarboxylative Chan-Evans-Lam approach to C(sp^3)-amination. In comparison to substitution reactions of alkyl halides or reductive aminations of carbonyls, two of the top ten most used reactions in medicinal chemistry,[20] the decarboxylative process is currently restricted to coupling electron-poor arylacetates and alkyl amines. Our standard conditions enable C–N bond formation in the presence of typically reactive alkyl halide, ketone, and aldehyde functional groups. Arylacetates can be constructed using arene substrates via alkylation processes (SnAr, cross-coupling, oxidative alkylation),[21] contrasting methods for benzylic electrophile synthesis that involve C–H or benzyl alcohol halogenation. In this light, while not a general solution for benzylic amine synthesis, decarboxylative amination can serve as a complementary strategy where high chemoselectivity for an alkyl amine nucleophile is required.

Showcasing the method's potential utility in complex molecule synthesis, the formal synthesis of a family of histone deacetylase/bromodomain/extra-terminal protein (HDAC/BET) inhibitors[22] was accomplished using a decarboxylative azidation protocol (Figure 5). NaN_3 could be used as an easily reducible ammonia surrogate to access primary amines in high yield[20] Decarboxylative azidation of **56** to form **57** was conducted on gram scale (1 gram of product) in 92% yield. Target **57** contains differentiated amino-precursor units that were chemoselectively reduced and acylated to yield the key amino tetrahydroquinoline pharmacophore. Azide reduction and carbamate installation, acetal deprotection, and one-pot nitro-group reduction/diastereoselective reductive amination afforded the advanced intermediate of DUAL946 (**58**) in 61% yield over 4 steps.

In order to investigate the possibility of decarboxylation by C–CO_2 homolysis to generate a radical intermediate,[23] alkene functionalized substrate **59** was subjected to the standard Cu-catalyzed conditions. Only direct amination (**60**, 64% yield) and protodecarboxylation (**61**, 27%) were observed. In contrast to photoredox-mediated pathways involving alkyl radical intermediates,[9],[10] no cyclized products were obtained (Figure 6A).

Mechanistic studies support a pathway in which the acid substrate undergoes an ionic decarboxylation to generate a carbanion intermediate. In the absence of Cu and oxidant, the combination of protic additives piperidine or ethanol and

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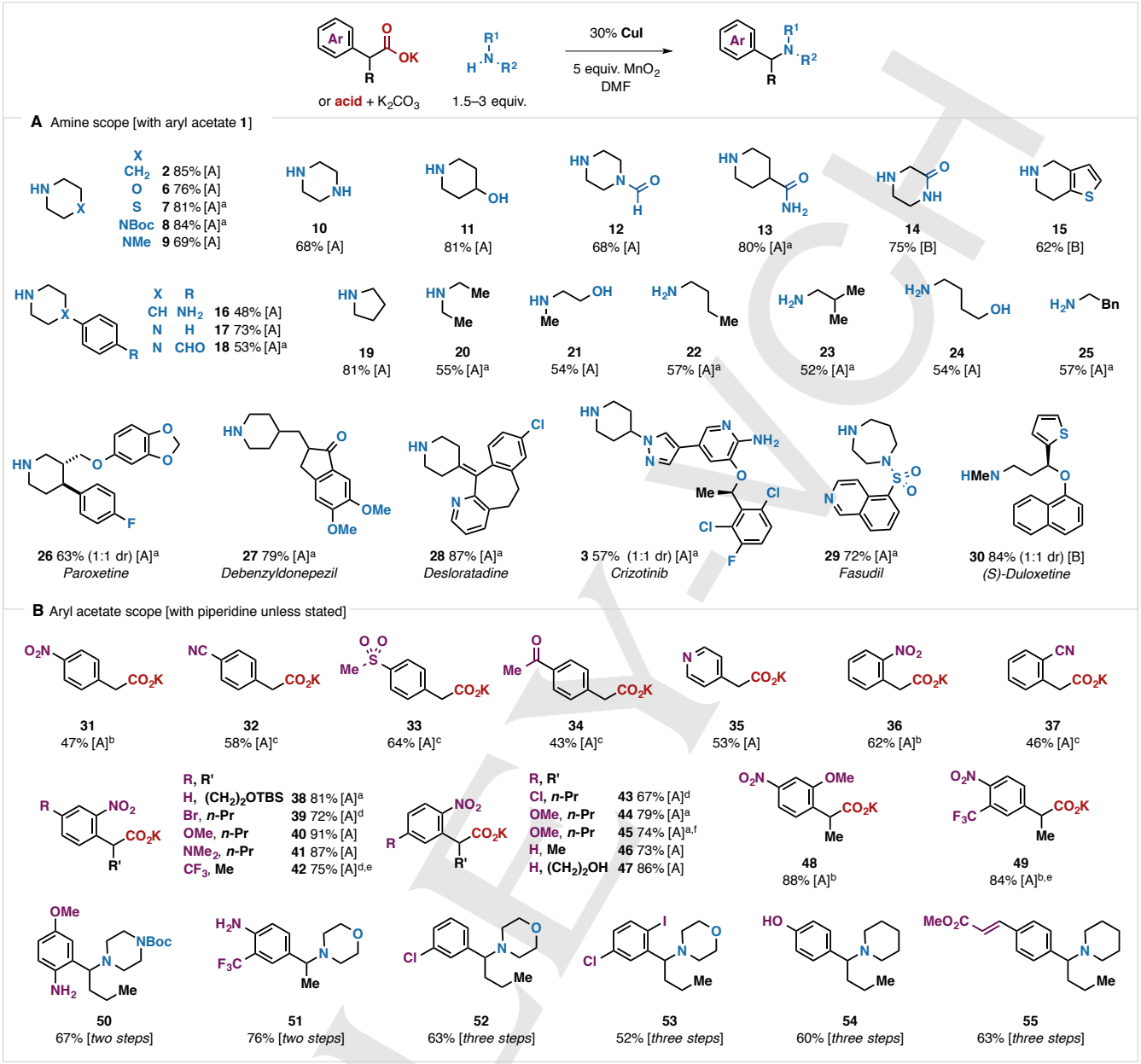

Figure 4. Scope of direct decarboxylative amination of aryl acetic acids. Yields are of isolated material under the standard conditions from Figure 2. Condition [A]: procedure with potassium aryl acetate, Condition [B]: Using aryl acetic acid and K_2CO_3, [a] 1.5 equiv. amine, 25 mol% $Zn(OAc)_2$, ^{1}H NMR yield, [b] $Cu(OAc)_2$ instead of CuI, [c] $CuBr_2$ instead of CuI, [d] 1 equiv. $Zn(OAc)_2$, [e] 1:1 DCE/DMF, [f] Using 1-Boc-piperazine. See SI for experimental details and less successful examples.

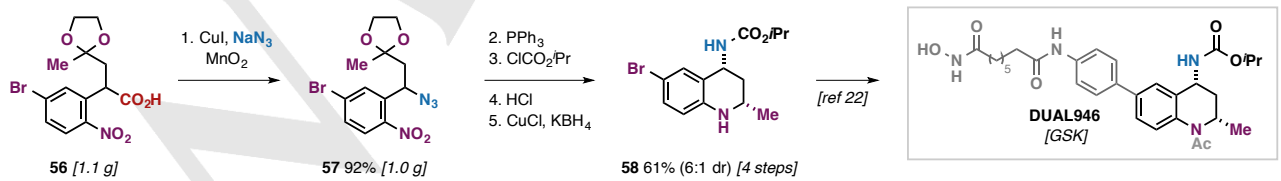

Figure 5. Decarboxylative azidation and application toward the preparation of DUAL946 intermediate. See the supporting information for details and additional scope examples using NaN_3.

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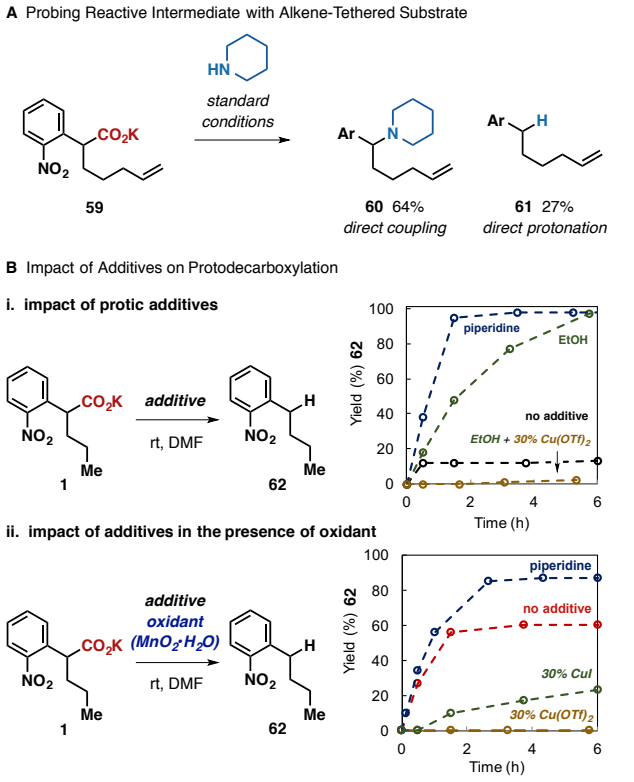

Figure 6. Mechanistic investigations into the nature of reactive intermediate generated upon decarboxylation.

carboxylate **1** in DMF resulted in only protodecarboxylation product **62** (Figure 6B–i). The trapping of the putative nucleophilic intermediate with aldehyde electrophiles is also possible under the standard conditions in the absence of catalyst and oxidant.[18d] Protodecarboxylation of **1** in the presence of ethanol (a non-productive nucleophile) is suppressed when $Cu(OTf)_2$ is added, and **1** is largely recovered after quenching.

When **1** and the terminal oxidant, partially hydrated MnO_2, were combined in DMF with piperidine or ethanol, protodecarboxylation is the dominant pathway. The addition of piperidine resulted in only ~10% of amination product product **2** and nearly 90% protonated product **62** (Figure 6B–ii). When CuI or $Cu(OTf)_2$ is added to a mixture of **1**, ethanol, and hydrated MnO_2, protodecarboxylation is suppressed. These studies help confirm MnO_2 alone is not capable of productively oxidizing the substrate or intermediates generated from it; instead the water that accompanies activated MnO_2 quenches the carbanion without the presence of a Cu catalyst. Cu slows the rate of decarboxylation, we speculate that ionic decarboxylation is driven by the formation of a charge-separated ion pair in polar aprotic solvents, which is in agreement with past observations.[14b] Dimerization products are not observed under the standard conditions and the control reactions described above, further suggesting a benzylic radical is not generated in the process.[25]

Support for ionic decarboxylation of the acid substrate as the first step in a Chan-Evans-Lam redox pathway was obtained

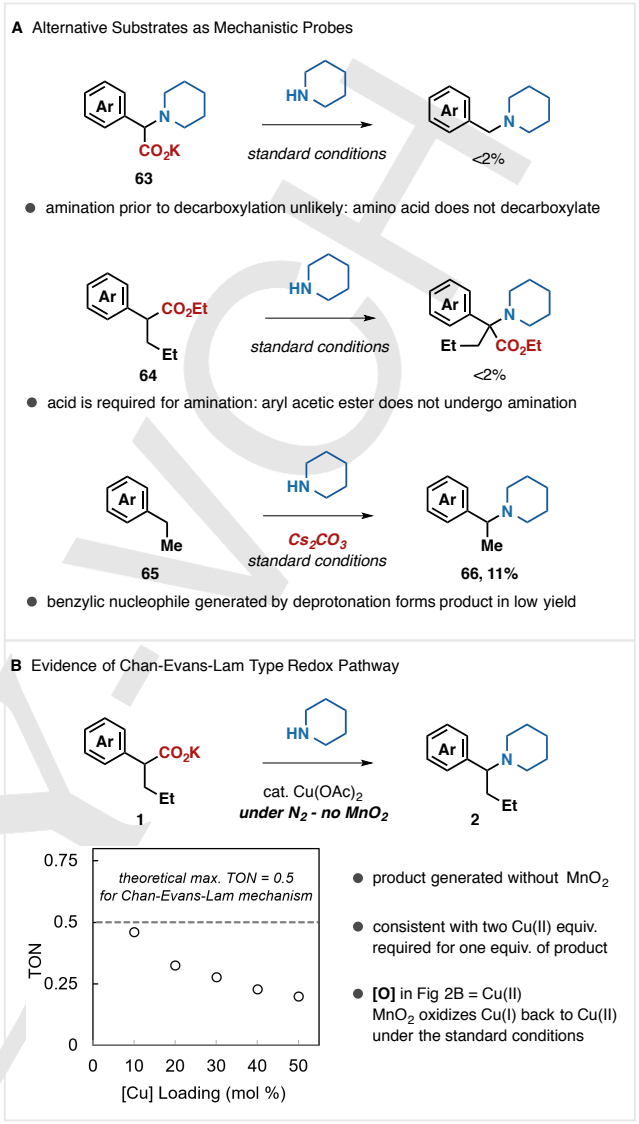

Figure 7. A) Use of alternative substrates support mechanism in which aryl acetate decarboxylation occurs prior to amination. B) Reaction stoichiometry in Cu(II) reflects a Chan-Lam type disproportionation redox pathway. Ar = 2-NO_2-C_6H_4 or 4-NO_2-C_6H_4. See the SI for complete details.

through subjecting alternative substrates and potential reaction intermediates to the standard reaction conditions (Figure 7A). Neither α-aryl amino acetate **63** nor α-aryl ester substrate **64** undergoes decarboxylation under the standard conditions to form benzyl amine product. These observations rule out an oxidative carbonyl α-amination pathway.[26] In the presence of Cs_2CO_3, alkylated nitroarene **65** provides some benzylated amine product. Decomposition of the putative benzyl nucleophile intermediate is observed under these and an array of related basic conditions, highlighting the importance of a controlled release of organometallic species via decarboxylation to achieve efficient cross-coupling. Finally, in the absence of additional oxidant, various loadings of $Cu(OAc)_2$ deliver product with less than 0.5 turnover number (Figure 7B). This observation is consistent with

two equivalents of Cu(II) being required to form one equivalent of product, analogous to the Chan-Evans-Lam type redox mechanism.

Conclusion

In summary, chemoselective N-benzylation of alkyl amines can be achieved directly from native carboxylic acids in the presence of protic or electrophilic groups via oxidative Cu-catalysis. Building on previous studies that use aryl or alkynyl acids as substrates, an ionic decarboxylation pathway enables the liberation of a benzylic nucleophile to allow for efficient oxidative trapping with basic alkyl amines, including those found in complex pharmaceuticals. The scope of reaction partners complements radical decarboxylative amination approaches. The benzylic amine products can be expediently diversified, showcasing this method's potential in complex molecule synthesis. Efforts are underway to apply this concept in the development of related chemoselective ionic decarboxylative cross-coupling reactions.

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Keywords: amination • decarboxylation • copper • chemoselectivity • oxidative coupling

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[18] a) See Figure S1 in the supporting information for additional optimization details; b) See Figures S2 and S3 in the supporting information; c) See Figure S4 for a more detailed analysis of the NH-functional group compatibility of photoredox-type decarboxylative aminations; d) Benzaldehyde can be trapped in ~80% yield, see Figure S8 for details.

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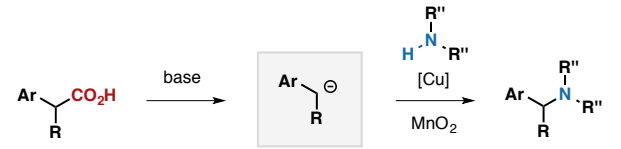

● direct coupling of carboxylate ● chemoselective alkylation of basic amines

The direct, chemoselective amination of aryl acetic acids is reported. The process enables late-stage alkylation of drug targets without interference from other protic groups or electrophiles. Mechanistic studies support the generation of a benzylic nucleophile which is aminated in Chan-Lam type redox pathway.

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Direct Catalytic Decarboxylative Amination of Aryl Acetic Acids