Catalytic Oxidative Benzylation of Amines Enabled by Direct Ionic Decarboxylation

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Abstract Decarboxylative C(sp^3)–N substitution reactions are an emerging class of amination protocols that avoid the preparation of sensitive alkyl (pseudo)halides, improving process efficiency and scope. However, stoichiometric activation of the carboxylic acid with high molecular weight reagents is necessary to induce a radical decarboxylation required for coupling. We demonstrate an approach in which aryl acetic acids undergo ionic decarboxylation to enable the direct benzylation of nitrogen nucleophiles via oxidative Cu-catalysis. The reaction proceeds from native carboxylic acids at room temperature, is compatible with protic, electrophilic, and other potentially complicating functionality, allowing the direct functionalization of complex amines.

The strategic formation of C(sp^3)–N bonds is of paramount importance for the synthesis of functional molecules.[1] The benzylic amine fragment is a particularly significant unit found in a diverse array of pharmaceuticals and clinical cand-dates, including Imatinib, Abemaciclib, Lacosamide, Clopidogrel, among many others.[2] Substitution between a nitrogen nucleophile and a benzylic (pseudo)halide and reductive amination of carbonyl compounds are standard approaches to benzylic amines. These textbook reactions are widely used in drug discovery, comprising nearly 10% of all transformations reported in synthetic medicinal chemistry journals in 2008,[3] with increase in use reported in 2014.[4] Alkyl electrophiles used to generate benzylic amines can be tedious to prepare and exhibit modest stability. Selective nucleophilic substitution of these species can be complicated by the presence of other protic or electrophilic groups, limiting utility in the synthesis of complex targets. Thus, the development mechanistically distinct synthetic methods that use alternative N-benzylating reagents stand to directly impact the preparation of complex nitrogen-containing molecules.[6–8]

Decarboxylative C(sp^3)–N coupling strategies using readily available, bench-stable carboxylic acids can increase versatility in complex amine synthesis the synthesis by circumventing the need for electrophilic N-alkylating reagents. Decarboxylative N-alkylation processes that proceed via C–carboxyl homolysis to form carbon-centered radicals have been reported (**Fig 1a, path I**).[9] These indirect methods require the stoichiometric modification of the carboxylic acid with high molecular weight activators like N-hydroxyphthalimide (NHPI)[9b,9c] or hypervalent iodine reagents (**A*** in **Fig 1**),[9a, 9d, 9e] hampering process step economy and overall reaction efficiency. Decarboxylation must be paired with a selective amination step in order to avoid non-productive quenching of the radical intermediate. In these cases, intermolecular coupling is restricted to poorly nucleophilic substrates (imide,[9b] anilines,[9c, 9e] sulfonamides,[9d, 9e] N-heterocycles[9e]). A mechanistically distinct, but unknown, amination approach involves the direct ionic decarboxylation and trapping of native carboxylic acids, which would bypass stoichiometric carboxylate activation and streamline alkyl amine synthesis (**Fig. 1a, path II**). Control over the generation of the nucleophilic intermediate in tandem with an appropriate catalyst/oxidant system would allow for selective amination in the presence of other reactive functionality. We describe such an approach herein using electron-poor aryl acetic acids as selective N-benzylating reagents (**Fig. 1b**).[10] This method leverages ionic decarboxylation to enable the controlled generation of benzylic nucleophiles, where Cu serve to both mediate the redox coupling steps and prevent undesirable substrate protodecarboxylation in the presence of protic nucleophiles by slowing the release of reactive intermediate.[11] The mechanistic steps of the oxidative coupling likely parallel those established for the Cu-catalyzed coupling of amines and aryl boronic acids (Chan–Evans–Lam reaction) to engender broad functional group compatability.[12, 13]

Reaction development studies culminated in conditions that allowed the decarboxylative amination of aryl acetate **1a** with piperidine to give **2a** in 92% yield using 30 mol% CuI and MnO_2 as the oxidant (**Fig. 2a**). The free acid could be used with the addition of mild base (94% yield). The cost-effective nature of MnO_2 (~$0.10/g) made

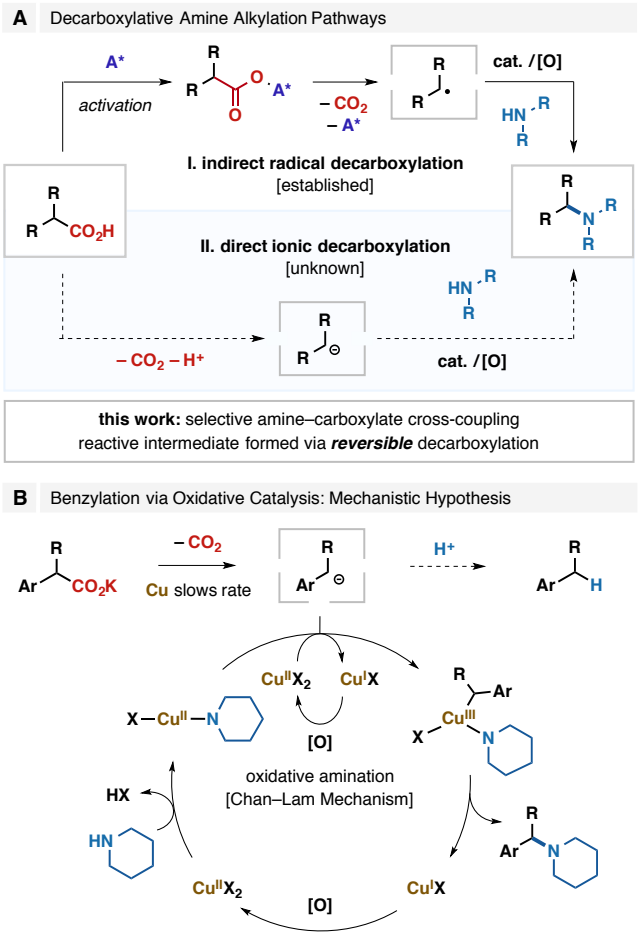

Figure 1. (**A**) Decarboxylative amination of carboxylic acids. (**B**) Mechanistic hypothesis for the direct oxidative amine benzylation by the decarboxylation of aryl acetic acids.

it an attractive oxidant, reactions conducted under air gave reasonable product yield (50%), while the use of pure O_2 gave dimerization product and effectively no cross-coupling. A number of Cu-based catalysts afforded **2a** in good yield (CuI, $Cu(OAc)_2$, $Cu(OTf)_2$). Other metal salts including Pd, Ni, Co, or Fe-species were inferior to CuI but afforded some benzylated product (see the SI for additional data). To rapidly assess functional group compatibility, a tolerance screen was conducted under the standard conditions.[14] High product yields without consumption of additive was observed in the presence of alkyl chlorides, aldehydes, alcohols, amides, sulfonamides, olefins, and basic N-heterocycles (**Fig 2a**). Chemoselectivity for coupling at the benzylic carboxylate unit was observed in the presence of aryl or primary alkyl carboxylic acids (terminal alkynes were not tolerated, see the SI).

The generality of the benzylation process was explored with other classes of nucleophiles (**Fig 2b**). Secondary or primary alkyl amines and NaN_3 were alkylated in good yields (**2a**–**2c**, 57–98%) under the standard conditions, with ~10% product generated in the absence of catalytic CuI. The amine scope of compliments radical decarboxylative aminations that require less-nucleophilic substrates.[9] Sulfinates, thiolates, and malonate underwent benzylation in good to excellent yields (**2e**–**2g**, 61–90%), but did not require Cu catalysts. Unlike amine-based nucleophiles which can be coupled to a range of electron-poor aryl acetates (Fig 4), sulfur and malonate nucleophiles provide synthetically useful yields only with nitro-activated partners. Aniline and phenol were resistant to benzylation (<2% yield).

Decarboxylation is a key step in the reaction pathway; Cu enhances the stability of the aryl acetate substrates, preventing undesirable protodecarboxylation. Under the conditions in **Fig 2a**, the remaining aryl acetate mass

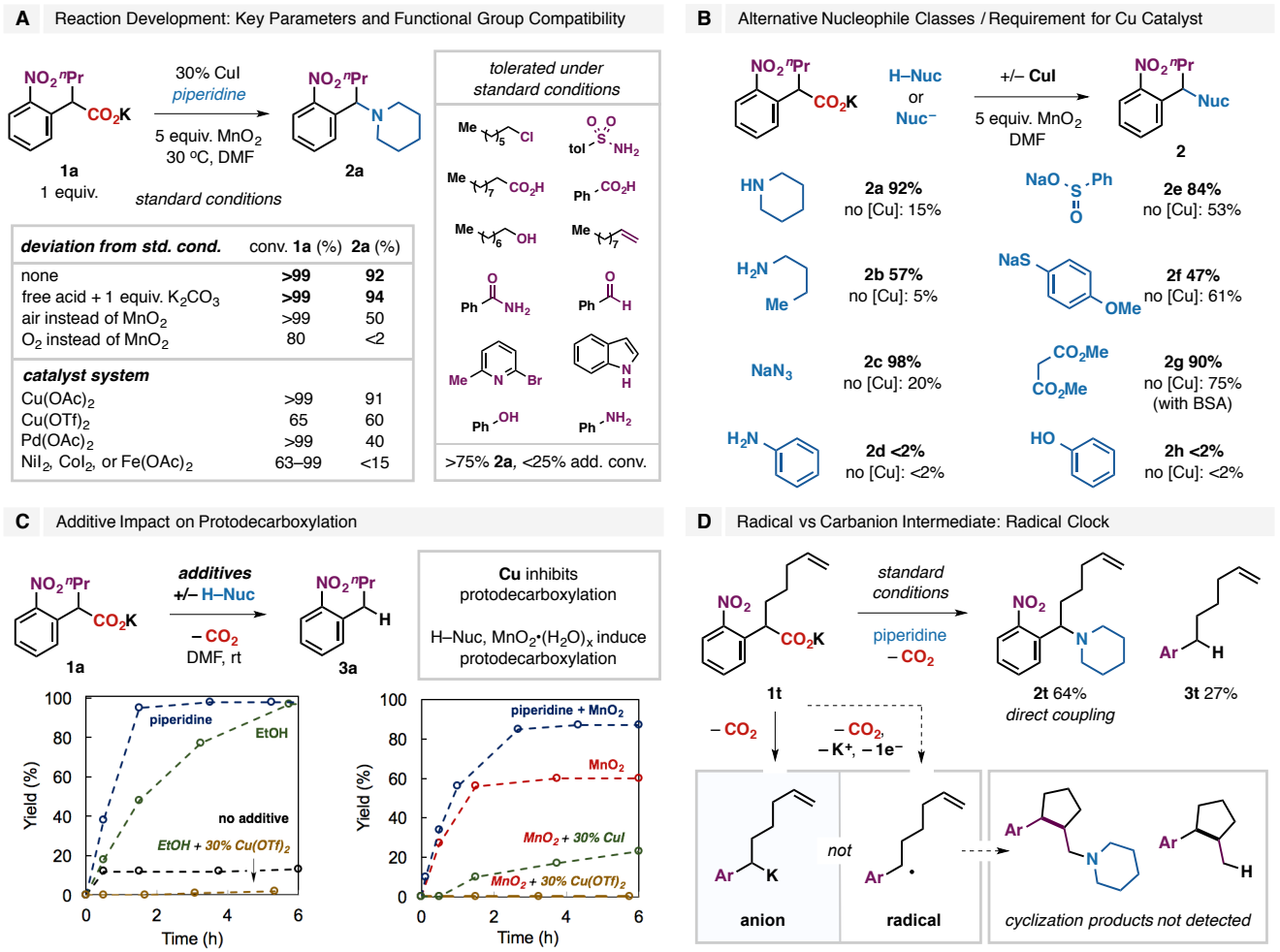

Figure 2. (**A**) Reaction development and functional group compatibility. (**B**) Nucleophile classes for oxidative benzylation (**C**) Impact of protic nucleophiles and additives on protodecarboxylation (**D**) Direct coupling of alkene-tethered aryl acetate. See SI for full details.

balance is alkylated arene **3a** (~5%). Acid **1a** is stable in DMF, however the addition of protic nucleophiles (piperidine or EtOH), led to rapid generation of **3a**, as does activated MnO_2 which is partially hydrated (**Fig 2c**). Catalytic amounts of Cu salts suppress protodecarboxylation in the presence of both protic nucleophiles (EtOH) and MnO_2, in agreement with past studies that showed Cu(aryl acetate)$_2$ species are slower to decarboxylate than the corresponding alkali metal salts.[10b] The nature of the decarboxylation step was explored by subjecting an olefin-tethered aryl acetate substrate (**1t**) to the standard conditions (**Fig 2c**). Only direct amine coupling product was observed (**2t**, 64% yield) along with proto-decarboxylated material (**3t** 27% yield). Radical cyclization products were not observed, likely excluding the intermediacy of a benzylic radical formed by homolytic decarboxylation of a carboxyl radical or oxidation of a benzylic anion.[15] Substrate **1a** was also found to add to aldehyde electrophiles to generate homobenzylic alcohols in the absence of catalyst or oxidant to further support the generation of a nucleophilic benzyl intermediate (>80% yield with PhCHO, see SI for details).[16]

Mechanistic controls further support a pathway in which decarboxylation occurs prior to C–N bond formation via a Chan–Evans–Lam-type cycle (**Fig 3**). Both ester substrate **4a** and amino carboxylate **4b** do not generate product under the standard conditions and are recovered in high yield. These observations rule out a dienolate carbonyl α-amination pathway (see the SI for details).[17,10a] Consistent with a direct oxidative amination mechanism,

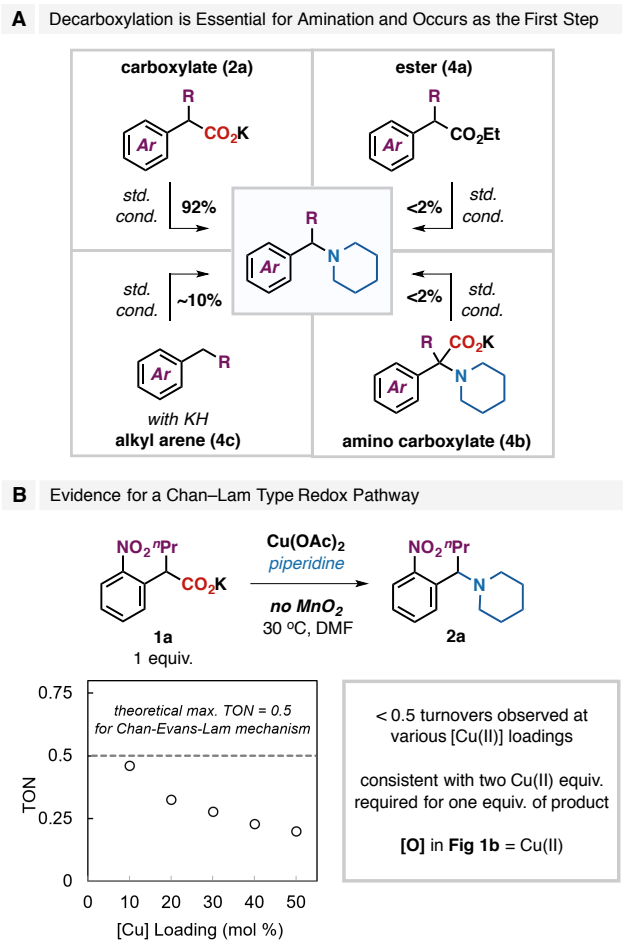

Figure 3. (**A**) Viability of alternative substrates or intermediates (**B**) Product yields under varying Cu(II) loadings. Ar = 2- or 4-$NO_2C_6H_4$, R = H, Me, or *n*-Pr.

stoichiometric deprotonation of the ethyl-substituted nitroarene **4c** with KH under standard conditions provided the amination product in low, but observable yield (~10%, **Fig 3a**). Decomposition of the putative benzyl nucleophile intermediate is observed under these conditions, highlighting the importance of a controlled release of organometallic species to achieve efficient cross-coupling. Various loadings of $Cu(OAc)_2$ deliver product with less than 0.5 turnover number (TON) in the absence of an external oxidant. (**Fig. 3b**). This is consistent with two equivalents of Cu(II) being required to form one equivalent of product, analogous to the Chan-Evans-Lam mechanism.[13] Under catalytic conditions MnO_2 or O_2 likely serve to re-oxidize the Cu(I) generated in the bond forming process.[18]

With an understanding of mechanism and functional group compatibility, the scope of the reaction was explored (**Fig. 4**). Cyclic or acyclic secondary amines derivatives provided the corresponding benzylic amines in good to excellent yields. Selective N-benzylation was achieved in the presence of other heteroatom-containing functionality including other protected or unprotected amines (**5d**–**5f, 5h**), alcohols (**5g**), 1°/2° amides (**5i**, **5j**), and sulfur-containing heterocycles (**5c**, **5k**). N-benzylation in the presence of an electrophilic aldehyde (**5m**) was achieved, complementing reductive amination protocols. Primary amines could be benzylated, albeit in lowered yields (**5r**–**5u,** 52–57%) Bis-alkylation was not observed in these cases which facilitated easy isolation. Marketed amine drug molecules bearing sensitive functionality including aryl fluorides and chlorides, functionalized N- and S-heterocycles and a tetrasubstituted olefin, were alkylated in good yields (Paroxetine, Debenzyldonepezil, Desloratadine, Crizotinib Fasudil, and Duloxetine; **5v**-**5aa**).

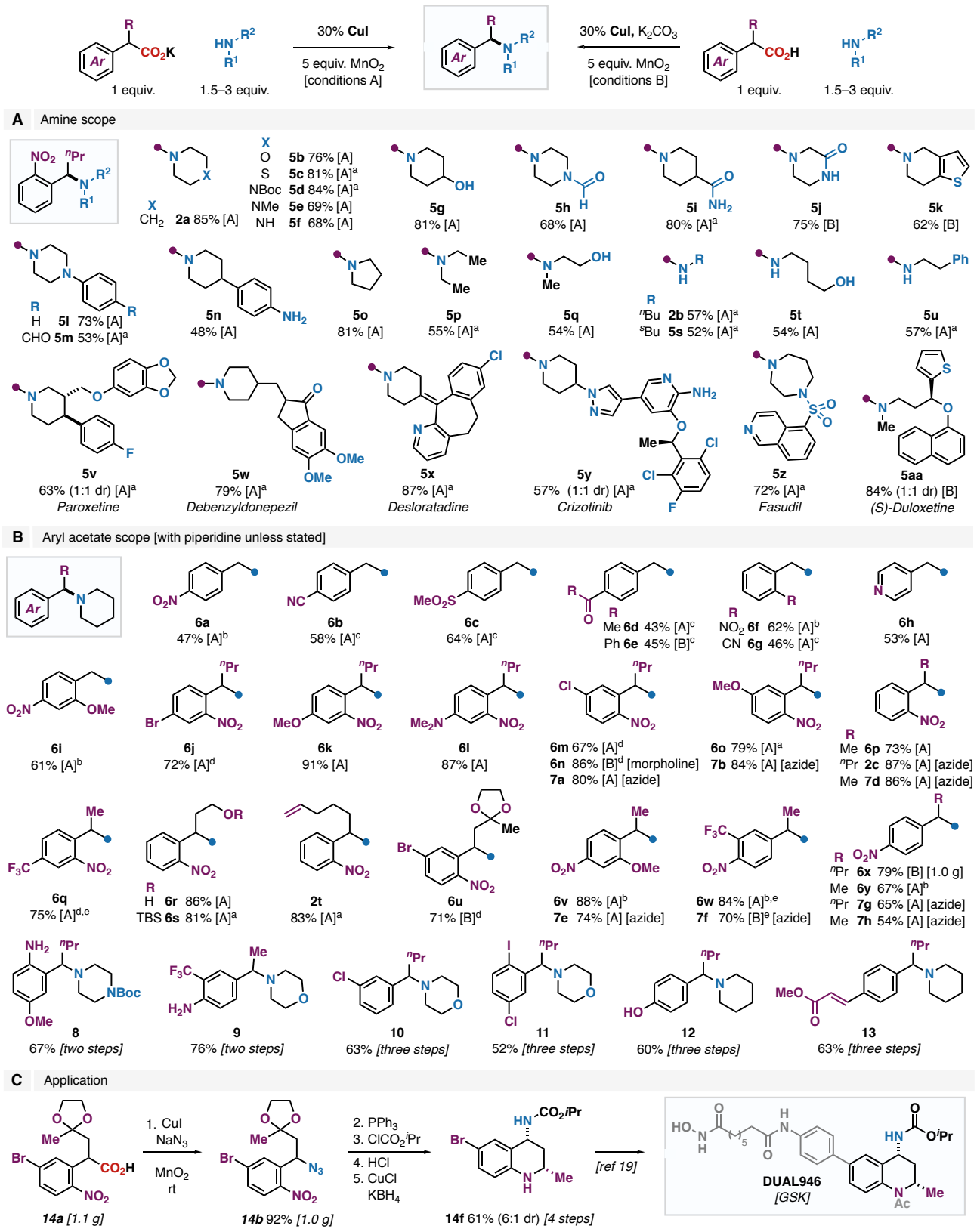

Figure 4. Scope and application. Unless noted, yields are of isolated material; [a] with 25 mol% Zn(OAc)2, [b] Cu(OAc)2 instead of CuI, [c] CuBr2 instead of CuI, [d] with 1 equiv. Zn(OAc)2, [e] 1:1 DCE/DMF. See SI for details and less successful example.

The scope of aryl acetic acid partner was investigated using piperidine. A range of electron-deficient aryl acetate derivatives proved suitable partners, including 4- and 2-nitro (**6a**, **6f**), 4- and 2-cyano (**6b, 6g**), 4-sulfonyl (**6c**), 4-acetyl (**6d**), 4-benzoyl (**6e**) and 4-pyridyl (**6h**) derivatives. Substituents on the aryl acetic acid partner were well tolerated, including halogens (**6j, 6m, 6u**) or trifluoromethyl (**6q**) groups and electron-donating methoxy (**6i, 6k, 6o**) or dimethylamino (**6l**) groups. Successful benzylation was achieved using aryl acetic acids bearing other sensitive functionality such as free or silyl-protected alcohols (**6r, 6s**), a terminal olefin **2t**), and a ketal (**6u**). Under the standard conditions, this protocol was extended to achieve decarboxylative azidation using NaN_3. Azidation of functionalized 2- and 4-nitrophenyl acetic acids could be achieved in moderate to excellent yields (**2c**, **7a**–**7h**). The process is currently restricted to electronically activated benzyl partners; however, a series of diverse targets could be obtained in good overall yields by simple nitro-group functionalizations, including conversions to anilines (**8, 9**). Further modifications by aromatic substitution to access products of arene deamination (**10**), iodination (**11**), hydroxylation (**12**) or Heck cross-coupling (**13**) was achieved in overall yields of 52–76%.

The formal synthesis of a family of histone deacetylase/bromodomain and extra-terminal protein (HDAC/BET) inhibitors[19] was accomplished using the decarboxylative azidation protocol, showcasing the method's potential utility in complex molecules synthesis. Decarboxylative azidation of **14a** to form **14b** was conducted on gram scale in 92% yield. Target **14b** contains differentiated amino-precursor units that can be 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 (**14f**) in 61% yield over 4 steps.

In summary, chemoselective N-benzylation of amines can be achieved directly from native carboxylic acids in the presence of protic or electrophilic groups via oxidative Cu-catalysis. The Cu-controlled ionic decarboxylation pathway enables the slow 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 compliments 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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