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A Metallaphotoredox Method for the Expansion of Benzyl SAR on Electron-Deficient Amines

Meghan D. Shea, Umar Faruk Mansoor, and Brett A. Hopkins*

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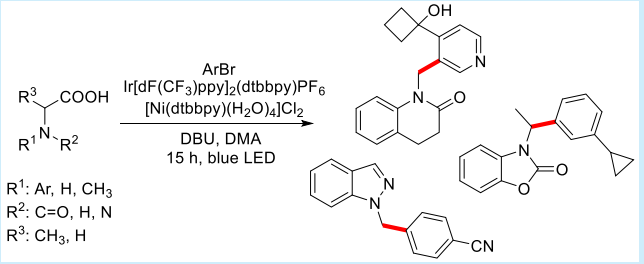
ABSTRACT: A metallaphotoredox reaction is described that allows for the efficient exploration of benzyl structure-activity relationships on electron-deficient amines. Typically, accessing a variety of benzyl groups on these substrates can be difficult due to the limited availability of the prerequisite building blocks, namely benzyl halides. However, the use of aryl bromides in this metallaphotoredox reaction allows for greater diversity in the benzyl piece. The reaction scope is discussed herein, including conditions for product scaleup using flow.



Benzyl amines are prominently featured in biologically relevant molecules, with an array of activity across various disease states.[1] Among these biologically active benzyl amines is a prominent subgroup bearing electron-deficient amines.[1] For instance, a few of the top selling pharmaceuticals possess this motif including apremilast for the treatment of plaque psoriasis,[1a] lacosamide for the treatment of seizures,[1b] and linagliptin for the treatment of diabetes (Figure 1).[1c] Due to

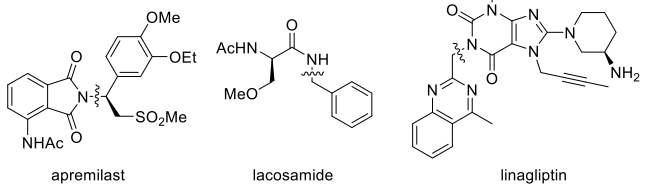
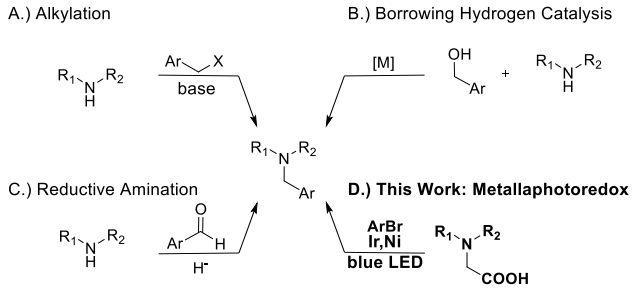


Figure 1. Pharmaceuticals containing electron-poor benzyl amines.

the prevalence of pharmacologically active electron-poor benzyl amines, synthetic methods to efficiently access diverse chemical matter in this space are highly sought after.

For an ongoing project, we were interested in exploring the benzyl amine structure−activity relationships (SAR) in a late-stage manner, employing an electron-poor amine as the coupling partner. Typically, this synthesis would be accomplished via an alkylation between a benzyl halide and an electron-deficient amine (Scheme 1A).[1c,2] However, it is difficult to achieve chemical diversity with this approach, as benzyl halides suffer from a lack of commercial availability compared to more utilized building blocks like aryl bromides. For example, in our internal collection of building blocks there are 10 times more aryl bromides than benzyl bromides.[3] Moreover, other methods for synthesizing benzyl amines using benzaldehyde or benzyl alcohol monomers (Scheme 1, B, C)

Scheme 1. Synthetic Approaches to Benzyl Amines



are usually limited to electron-rich amines.[4,5] Therefore, to efficiently explore benzyl SAR on electron poor amino groups, a synthetic method using aryl bromides would be advantageous.

Recently, multiple literature reports have noted the utility of metallaphotoredox reactions to afford new bonds between nonclassical coupling partners.[6−8] For example, the MacMillan group disclosed a metallaphotoredox reaction that yielded a C−C bond between carboxylic acids and aryl halides.[6] Since α-heteroatom bearing acids were excellent substrates in this chemistry,[6] we envisioned that this type of reaction could be well suited to access electron-deficient benzyl amines (Scheme 1 D) and that the required nitrogen linked acid starting materials could be readily synthesized from bromoacetic acid derivatives. A recent report from the Molander group disclosed the synthesis of electron-rich benzyl amines via a metal-

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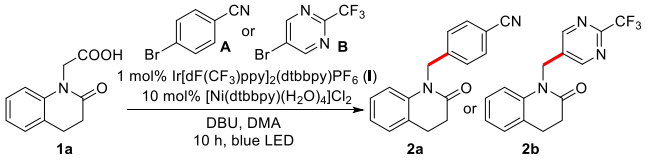
laphotoredox reaction utilizing α-silyl amines as radical precursors; however, electron-deficient amines were not suitable substrates in this transformation.[9] To our knowledge, a metallaphotoredox reaction has not been used to synthesize benzyl amines by placing an acid directly on an amine nucleophile.[9b] Herein, we disclose the scope of this method to afford diverse benzyl amine products from electron-poor amine acids and aryl bromides.

Initially, to test this proposed metallaphotoredox reaction, the electron-deficient *N*-linked acid **1a** was subjected to the reaction conditions noted in Table 1.[10] Based on similarities

Table 1. Initial Screening[a]



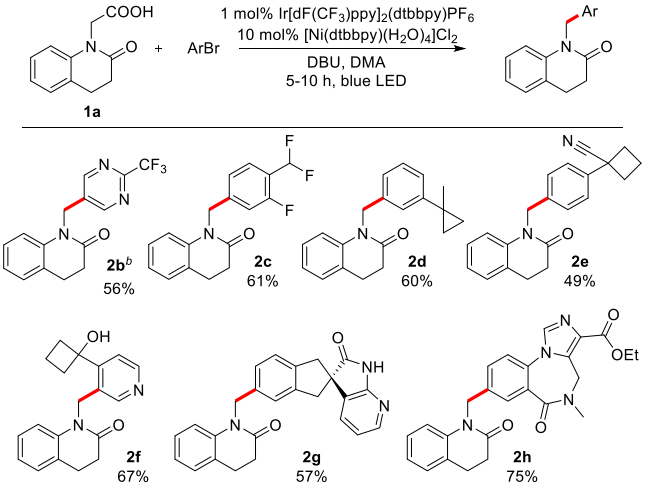
entry	change	ArBr	yield[b] (%)
1	**none**	**A**	**80, 2a**
2	$Ru(bpy)_3(PF_6)_2$	A	0, **2a**
3	4-CzIPN	A	32, **2a**
4	$Ir[dF(Me)ppy]_2(dtbbpy)PF_6$	A	54, **2a**
5	Cs_2CO_3	A	77, **2a**
6	**none**	**B**	**50, 2b**
7	Cs_2CO_3	B	24, **2b**

[a]Conditions: 1 mol % Ir catalyst, 10 mol % Ni catalyst, 1.0 equiv of ArBr, 1.5 equiv of **1a**, 1.5 equiv of base, 0.1 M in DMA, 10 h. Reactions in Table 1 were conducted in a hepatochem duo photoreactor. [b]Yields were based on ^{1}H NMR with phenanthrene as an internal standard.

between substrate **1a** and acids recently reported to undergo decarboxylative alkynylation, we envisioned that iridium catalyst **I** (Table 1) would react with acid **1a**.[11a] Utilizing **I** as the photocatalyst in this reaction afforded **2a** in 80% yield (entry 1). The less oxidizing $Ru(bpy)_3(PF_6)_2$ photocatalyst ($E_{1/2}[*Ru^{II}/Ru^{I}]$ = +0.77 vs $E_{1/2}[*Ir^{III}/Ir^{II}]$ = +1.21 for **I**), which was used for a related transformation with electron-rich substrates,[9] was not viable in this reaction, and no desired product was afforded under these conditions (entry 2).[6,9a] Changing to the slightly more oxidizing metal free photocatalyst 4-CzIPN ($E_{1/2}[*P/P^-]$ = +1.35), which has been used in other decarboxylative arylations, gave a lower yield of **2a** (entry 3).[11b] Other iridium photocatalysts (entry 4) afforded lower yields of **2a** when compared to photocatalyst **I**. Initially, Cs_2CO_3 was utilized as the base for these reactions, as it had been employed for related transformations.[6,11b] However, we found that DBU afforded higher and more consistent yields for a variety of acids and aryl halides when compared to the Cs_2CO_3 conditions (entries 1 and 6 vs entries 5 and 7).[11c] With these optimal conditions in hand, further screening on the aryl halide and acid scope was initiated.

To exemplify some of the novel SAR this reaction can deliver, aryl halides that had no commercially and/or readily available benzyl halide equivalents were employed as coupling partners in Scheme 2.[12] As noted below, this reaction affords a variety of benzyl amine products in moderate to good yields with an array of aryl bromides. For example, the reaction tolerates electron-poor aryl halides as noted in examples **2b** and **2c**, but it also works well for electron-rich aryl halides such as the methyl cyclopropyl substituted arene in example **2d**. Of

Scheme 2. Aryl Bromide Scope[a]

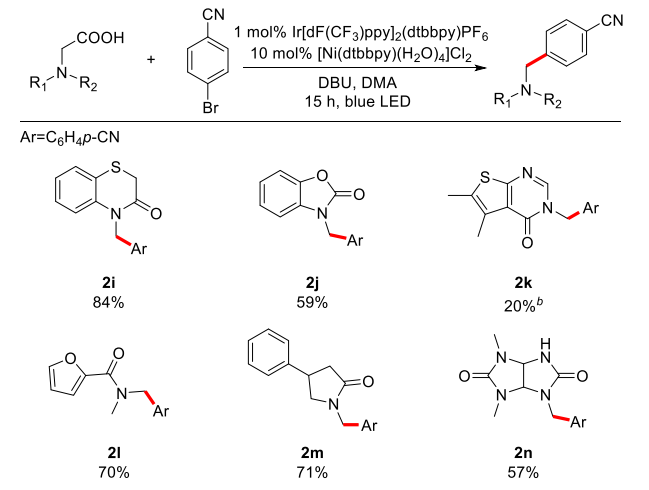


[a]Conditions: 1 mol % Ir catalyst, 10 mol % Ni catalyst, 1.0 equiv of ArBr, 1.5 equiv of **1a**, 1.5 equiv of DBU, 0.1 M in DMA, 5−10 h. [b]5% Ni catalyst used. Reactions in Scheme 2 were conducted in a PennOC/Merck photoreactor with 450 nm light.

further interest, the reaction works well in the presence of an unprotected alcohol (**2f**), which would be difficult to react selectively when using a benzyl halide. More complex aryl bromides worked in this reaction as well, and the desired products **2g** and **2h** were afforded in good yield when subjected to the conditions noted in Scheme 2.

To further test the utility of this transformation, a variety of electron-deficient *N*-linked acids were subjected to the reaction conditions. As noted in Scheme 3, aryl amide substrates like **1a** performed well in this reaction. For instance, *N*-linked acids bearing other heteroatoms in the ring such as oxygen and sulfur worked well under the reaction conditions to afford products **2i** and **2j** in good yields. A more complex aryl amide *N*-linked acid also worked, albeit in modest yield,[13] to afford compound **2k**. Expanding the scope to nonaryl amide and urea

Scheme 3. Electron-Deficient *N*-Linked Acid Scope[a]



[a]Conditions: 1 mol % Ir catalyst, 10 mol % Ni catalyst, 1.0 equiv of ArBr, 1.5 equiv of **1a**, 1.5 equiv of DBU, 0.1 M in DMA, 5−10 h. Reactions in Scheme 3 were conducted in a hepatochem duo photoreactor. [b]Reaction used 2 mol % Ir, 5 mol % Ni, and was conducted in a PennOC/Merck photoreactor.

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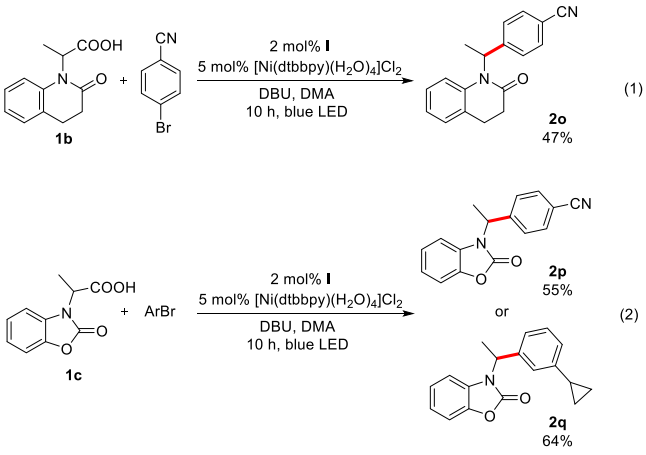
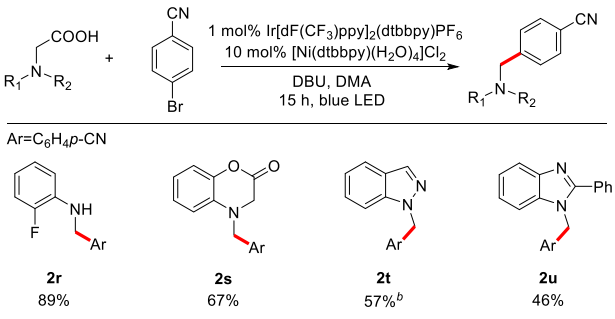
N-linked acids was fruitful as well, as exemplified by products **2l**, **2m**, and **2n**.

It was also desired to see if α-substituted *N*-linked acids would be competent coupling partners in this transformation. If so, this would be a straightforward method to access α-substituted benzyl amines, which are also important cores in biologically active compounds.[1a,14] Moreover, there is an even greater disparity in the availability of α-substituted benzyl halides when compared to aryl bromides, making this metallaphotoredox approach very attractive from an SAR perspective.[15] Gratifyingly, the α-methyl substituted acid **1b** worked under the reaction conditions to afford product **2o** in moderate yield (eq 1). Additionally, substrate **1c** was subjected to the below reaction conditions and afforded products **2p** and **2q** in good yields (eq 2).



Other electron-deficient amine groups, such as anilines and heteroaromatic amines, are also interesting classes of electron-poor amine nucleophiles. Therefore, we tested these types of electron-deficient *N*-linked acids in this coupling reaction. Initially, an aniline acid was subjected to the reaction conditions, and product **2r** was afforded in excellent yield (Scheme 4). A cyclic aniline derivative worked well under the reaction conditions too, and product **2s** was also afforded in good yield. To test the reactivity with commonly used heteroaromatic amines such as indazoles and benzimidazoles, *N*-linked acids of these amines were subjected to the reaction conditions. Products **2t** and **2u** were both afforded in moderate yields as well, showing the robustness of this catalyst system to react with a variety of electron-poor *N*-linked acid substrates.

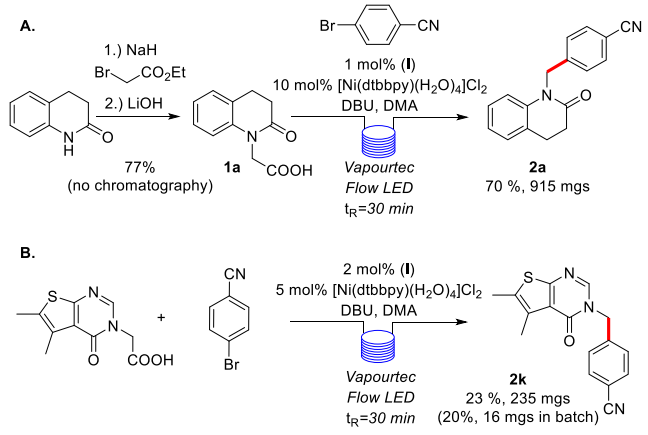
Scheme 4. Nonamide *N*-Linked Acid Scope[a]



[a]Conditions: 1 mol % Ir catalyst, 10 mol % Ni catalyst, 1.0 equiv of ArBr, 1.5 equiv of **1a**, 1.5 equiv of DBU, 0.1 M in DMA, 5−10 h. Reactions in Scheme 4 were conducted in a hepatochem duo photoreactor. [b]Reaction used 2 mol % Ir, 5 mol % Ni, and was conducted in a PennOC/Merck photoreactor.

A limitation that sometimes arises in photoredox chemistry is the scalability of the reaction.[16] This can be an even bigger issue in medicinal chemistry, as a quick scale up of hundreds of milligrams to grams of compound can be necessary for initial compound profiling. Therefore, to demonstrate the ability to scale up this reaction, we decided to test this reaction in continuous flow. To display the ease of synthesis for these substrates, **1a** was synthesized in two steps without any column chromatography needed (Scheme 5A).[17] Next, this batch of **1a** was subjected to the flow conditions noted below to afford 915 mg (70%) of the desired product **2a**. Further, to assess how the flow conditions would work for a lower yielding reaction, **2k** from Scheme 3 was also selected to test under flow conditions. As shown below in Scheme 5B, the flow reaction provided almost 15 times more of product **2k** compared to the original batch scale reaction from Scheme 3.[18]

Scheme 5. Reactions Conducted under Flow Conditions



In conclusion, an SAR-friendly metallaphotoredox reaction was devised that allows for the synthesis of benzyl amines via a coupling reaction between aryl bromides and electron-deficient *N*-linked acids. With a robust set of reaction conditions, 9 diverse aryl halides and 13 varied *N*-linked acids were shown to afford the desired benzyl amine products. Also, α-methyl substituted *N*-linked acids were revealed to be good substrates for this reaction, providing a novel late-stage method to access these difficult targets. Conditions to execute this reaction in flow were also provided, allowing for the efficient scale up of this chemistry. Moreover, this reaction has been shown to work well in a photoreactor,[19] in the library friendly hepatochem PhotoRedOX Duo photoreactor, and in the Vaportec R-series flow reactor, making it a proficient reaction for accessing both single compounds and small libraries. Lastly, with the broad scope of *N*-linked acids and aryl bromides[20] that worked well in this reaction, it is envisioned that this will be a useful method to enable efficient SAR exploration in this important class of compounds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04587.

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Experimental procedures, characterization data for all new compounds (starting material and final products), and ^{1}H and ^{13}C NMR spectra for all compounds (PDF)

AUTHOR INFORMATION

Corresponding Author

Brett A. Hopkins − *Discovery Chemistry, Merck & Co., Inc., Boston, Massachusetts 02115, United States;* orcid.org/0000-0002-5218-5065; Email: brett.hopkins@merck.com

Authors

Meghan D. Shea − *Discovery Chemistry, Merck & Co., Inc., Boston, Massachusetts 02115, United States*

Umar Faruk Mansoor − *Discovery Chemistry, Merck & Co., Inc., Boston, Massachusetts 02115, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.9b04587

Notes

The authors declare no competing financial interest.

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(10) (a) Compound **1a** is a quinolone, which is a motif found in a variety of drug products; thus it is type of motif we are interested in and a good test substrate for this reaction. See the following review: Gao, F.; Zhang, X.; Wang, T.; Xiao, J. Quinolone hybrids and their anti-cancer activities: An overview. *Eur. J. Med. Chem.* **2019**, *165*, 59−79. (b) 4-Bromobenzonitrile was used as an example aryl halide in this work as it is often used to test new metallaphotoredox reactions; see ref 9a and the following: Zuo, Z.; Cong, H.; Li, W.; Choi, J.; Fu, G. C.; MacMillan, D. W. C. Enantioselective Decarboxylative Arylation of α-Amino Acids via the Merger of Photoredox and Nickel Catalysis. *J. Am. Chem. Soc.* **2016**, *138*, 1832−1835.

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(12) All aryl bromides selected in the scope for Scheme 2 had no equivalent benzyl halide partner that was available either in our inventory or commercially available. If there was a commercially available equivalent its cost had to be 10 times greater than the aryl bromide or have a synthesis lead time greater than 12 weeks to be included in this scope.

(13) For further insight into attempts at optimizing the conditions for substrate **2k** and general commentary on approaches to optimize for difficult substrates, see the Supporting Information. For example **2k**, much of the acid (approximately half of the 1.5 equiv) was left after the reaction, but yields typically halted at just over 20%.

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(17) For more on substrate synthesis, see the Supporting Information.

(18) For more information on the flow conditions, see the Supporting Information.

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(20) See the Supporting Information for a disscussion on other aryl halide SAR.

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