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Direct Aryl C–H Amination using Primary Amines via Organic Photoredox Catalysis

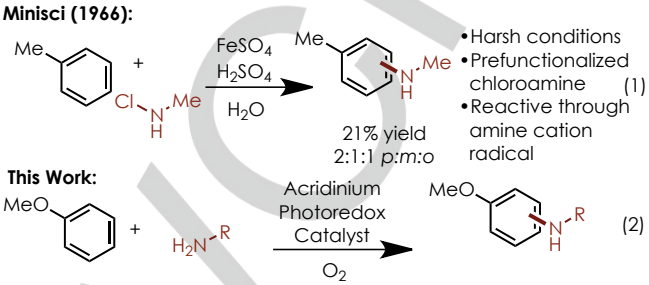
Kaila A. Margrey, Alison Levens, and David A. Nicewicz*

Abstract: The direct catalytic C–H amination of arenes is a powerful synthetic strategy with useful applications in pharmaceuticals, agrochemicals, and materials chemistry. Despite the advances in catalytic arene C–H functionalization, the use of aliphatic amine coupling partners is limited. Herein, we demonstrate the construction of aryl C–N bonds to primary amines via a direct C–H functionalization using an acridinium photoredox catalyst under an aerobic atmosphere. A wide variety of primary amines, including amino acids and more complex amines, are competent coupling partners. Various electron-rich aromatics and heteroaromatics are useful scaffolds in this reaction, as are complex, biologically active arenes. We also describe the ability to functionalize arenes that are not oxidized by an acridinium catalyst, such as benzene and toluene, supporting a reactive amine cation radical intermediate.

The construction of aryl C–N bonds is of particular importance due to their prevalence in natural products, pharmaceuticals, agrochemicals, and materials.[1,2] Strategies for the direct functionalization of carbon-hydrogen (C–H) bonds have garnered much attention due to the ability to streamline complex molecule synthesis in an atom-economical manner.[3–5] Specifically, aromatic C–H functionalization bypasses the need for employing a pre-oxidized arene coupling partner required for conventional cross-couplings.

While several methodologies have been developed for arene C–H amination,[6–8] nitrogen coupling partners are generally limited to electron-poor species, such as amides and imides.[9–12] Significant challenges exist for aromatic C–N couplings using aliphatic amines, since many strategies for functionalization of these substrates involve C–C bond construction adjacent to nitrogen.[13–16] Accordingly, C–H amination of arenes with aliphatic amines has been demonstrated only in select examples (Scheme 1).[17] To achieve C–N bond formation, the use of strongly acidic media and prefunctionalized chloroamines, which suffer from limited stability, are often required (eq. 1).[18,19] To address these shortcomings, we hoped to develop a direct aryl C–H amination with aliphatic amines using a mild catalytic system.

Previously, our laboratory reported a method for direct C–H amination of arenes and heteroarenes with nitrogen-containing heterocycles and ammonia surrogates, circumventing the need for pre-oxidized coupling partners.[20] This reaction features a high degree of site selectivity, with monosubstituted arenes favoring functionalization in the *para* position. This approach exploits an acridinium photoredox catalyst capable of oxidizing arenes through single electron transfer (SET) to generate the corresponding cation radicals, which then act as electrophilic intermediates for nitrogenous nucleophiles.



Scheme 1. Arene C–H amination with aliphatic nitrogen coupling partners

In designing a strategy to construct aryl C–N bonds using aliphatic amines via photoredox catalysis (eq. 2), it is noteworthy that both aliphatic amines and electron-rich arenes can be oxidized by the acridinium photocatalyst to the corresponding cation radicals (See Supporting Information, Table S1).[21] To examine whether aryl amination could occur using aliphatic amines, irradiation (455 nm LEDs) of an arene and an amino acid ester hydrochloride salt in the presence of acridinium photocatalyst **Me_2-Mes-Acr+** in a mixture of 1,2-dichloroethane (DCE) and pH 8 phosphate buffer afforded the aminated arene products (Figure 1). A wide variety of amino acid ester hydrochloride salts participated in the reaction, providing access to *N*-arylated amino acids under mild conditions. When anisole was used as the arene coupling partner, the *ortho* isomer was favored in all cases in moderate to excellent yields (**1a**–**14a**), complimentary to the aryl amination previously reported by our laboratory. The regioselectivity could be reversed by employing *tert*-butyldimethylsilyl (TBS) phenyl ether as the arene, favoring the formation of the *para* isomer (**1b**–**14b**). In addition to amino acids bearing hydrocarbon side chains, the reaction tolerated additional functionality, with protected serine and threonine, *N*-Boc lysine, and glutamic and aspartic acid esters all reacting smoothly. Furthermore, amination products derived from isoleucine and threonine (**6a/b** and **11a/b**) formed as single diastereomers, as observed by ^{1}H NMR analysis, indicating that amino acids do not epimerize during the reaction. Fourteen amino acids were shown as coupling partners, highlighting the generality of this approach.

Applying these conditions to other commercially available amines, the pH 8 buffer could be omitted when using the free base instead of the hydrochloride salt (**15**–**26**). The use of linear aliphatic amines afforded products **16a** and **16b** in good yields, despite the presence of a methylene adjacent to the nitrogen, which is prone to oxidative degradation. Halogenated amine coupling partners also provided the aminated products **17a** and **17b** in moderate yield. Allylamine afforded moderate to high yields of **18a** and **18b**, and benzylamine derivatives were also competent (**19** and **20**). Enantiopure (*S*)-α-methylbenzylamine did not racemize over the course of the reaction, indicating that even chiral benzylic amines retain stereochemical fidelity throughout the transformation. This reaction was performed on 2.5 mmol scale using a flow apparatus, affording the desired product in 61% yield. Amines bearing increased steric bulk also participated in the reaction, however in diminished yield, with *tert*-butylamine providing aniline **21** in 34% yield.

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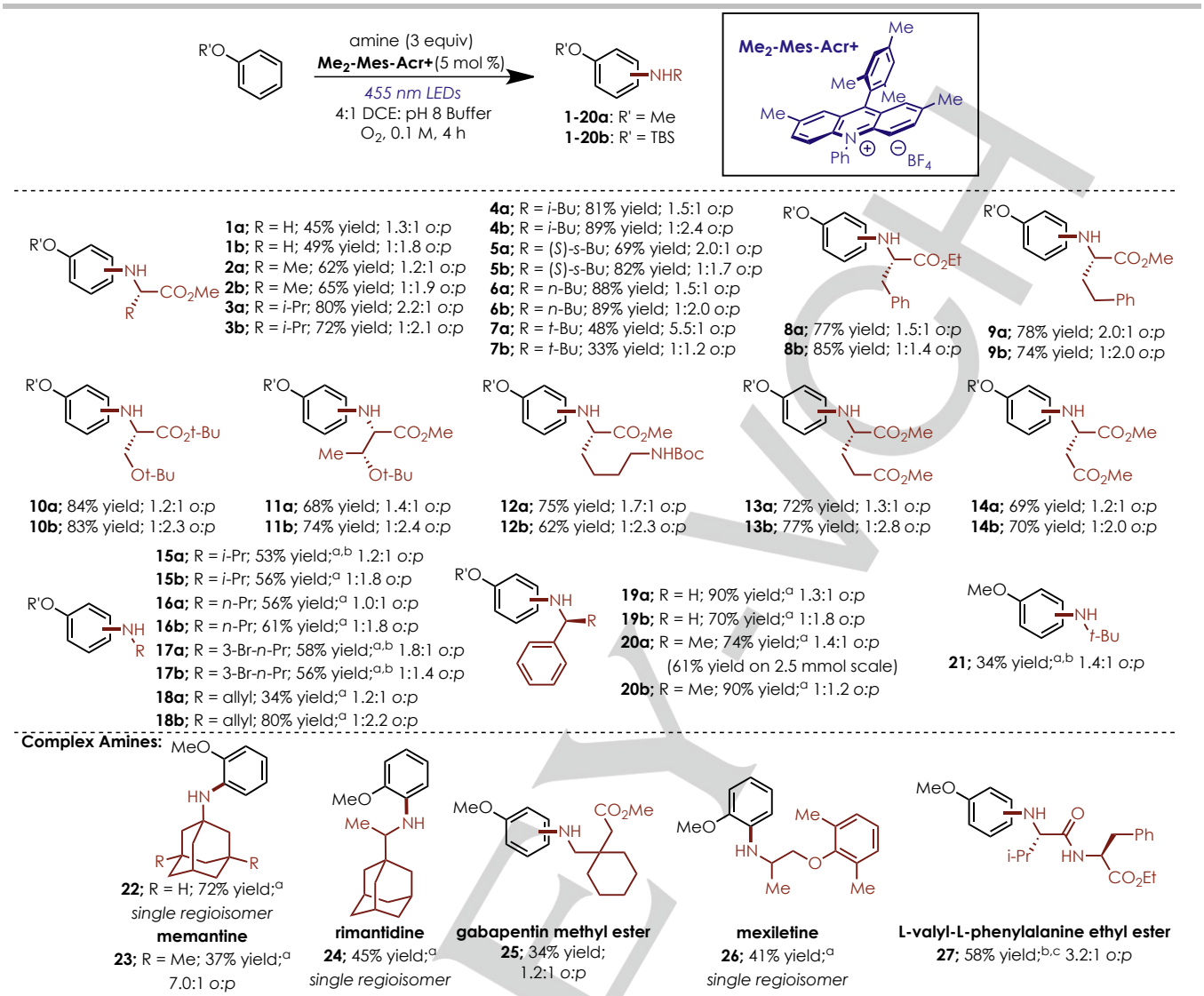

Figure 1. Products of C–H amination illustrating amine scope. Ratios refer to *ortho*:*para* (*o*:*p*) selectivity for the given adduct. Reactions were run in 4:1 DCE and pH 8 phosphate buffer at 0.1 M concentration with respect to the arene limiting reagent. [a] Reaction run in DCE at 0.1 M concentration with respect to the arene limiting reagent [b] ^{1}H NMR yield of adduct [c] Reaction run in DCE at 0.1 M concentration with respect to the arene limiting reagent for 14 h.

The use of more highly substituted amines was demonstrated with the addition of adamantylamine and memantine, anti-Parkinson and anti-Alzheimer pharmaceuticals, respectively, affording **22** and **23** in modest to good yields and high *ortho* selectivities with anisole.[22] Furthermore, the antiviral rimantidine[23] produced aminated arene **24** as a single regioisomer in 45% yield. Gabapentin methyl ester, a pharmaceutical used to treat seizures,[24] afforded aryl amine **25** in 34% yield, while anti-arrhythmic pharmaceutical mexiletine[25] provided **26** in 41% yield as a single regioisomer. The coupling of L-valyl-L-phenylalanine ethyl ester with anisole in 58% yield (**27**) highlights the application of this methodology to peptidic compounds.

With a wide variety of primary amines shown as competent coupling partners, the arene scope was explored using valine methyl ester hydrochloride as the amine component (Figure 2). As discussed above, the regioselectivity of the amination could be altered by changing the substituent on the phenolic ether. Exposure of aliphatic (-Me, -Et, -*t*-Bu) and silyl protected (-TES, -TBS, -TBDPS) phenolic ethers to the reaction conditions demonstrated that increased steric demand leads to higher amounts of the *para* adduct (**3a/b, 28–31**). Diphenyl ether, diphenyl sulfide, and biphenyl underwent amination in modest to good yields, also showing a preference for formation of the *para* isomer (**32–34**). Furthermore, halogens were tolerated on the arene to afford **35–38**, using modified reaction conditions that employ substoichiometric TEMPO as an additive, similarly to our prior work.[20] For these substrates, the major product resulted from addition *ortho* to the methoxy substituent. Importantly, the presence of a halogen in these products allows for subsequent derivatization through cross-coupling reactions, highlighting the utility of the present methodology in the synthesis of complex benzenoids. 4-Alkyl substituents were also tolerated, with amination of 4-isopropyl anisole proceeding in 43% yield (**39**) in

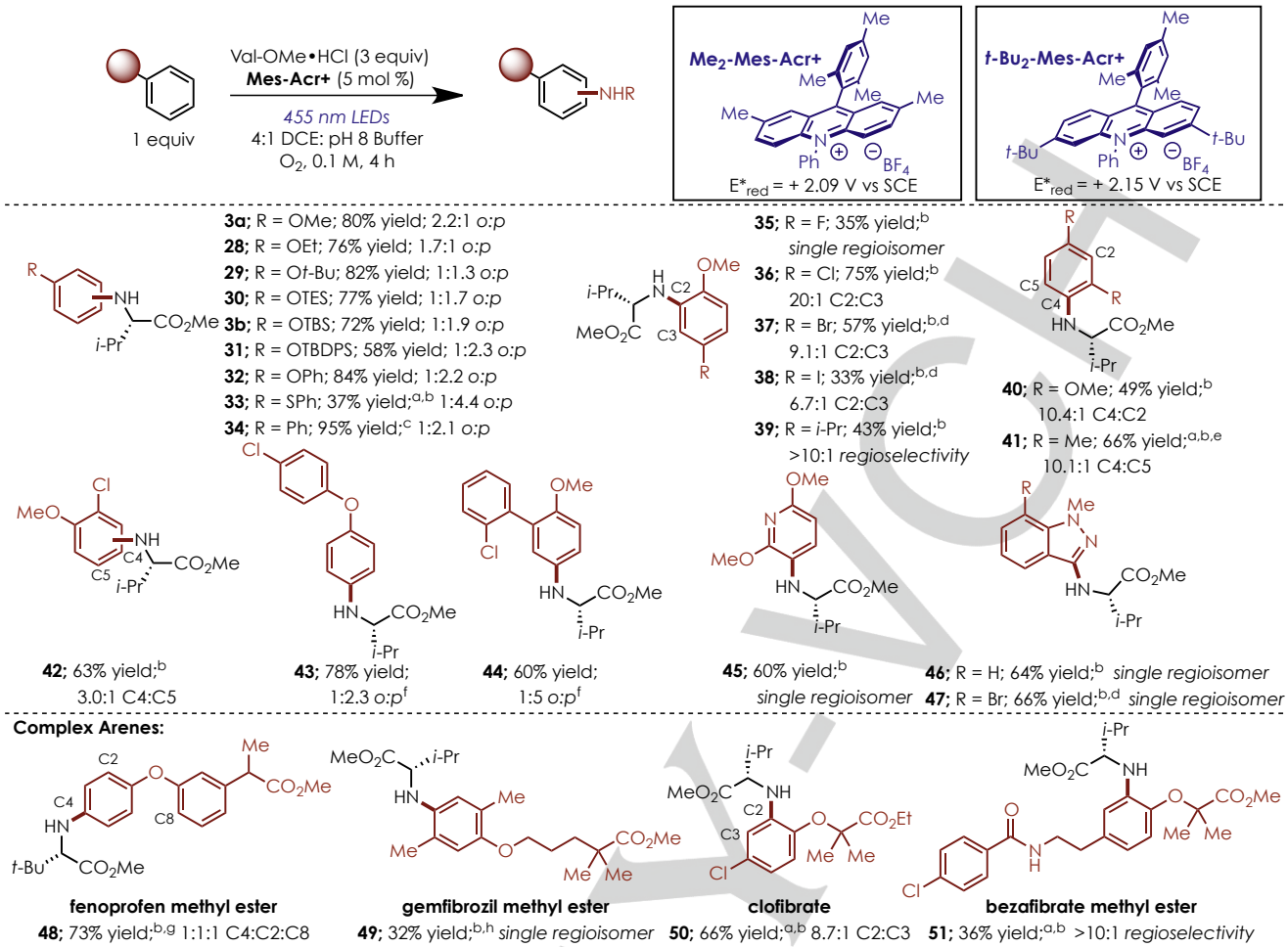

Figure 2. Product of C–H amination illustrating arene scope. Ratios refer to *ortho:para* (*o:p*) selectivity for the given isomer unless otherwise specified. Reactions were run using **Me_2-Mes-Acr+** in 4:1 DCE and pH 8 phosphate buffer at 0.1 M concentration with respect to the arene limiting reagent. [a] ^{1}H NMR yield of adduct [b] Reactions run with 40 mol% TEMPO and 5 mol% ***t*-Bu_2-Mes-Acr+** for 15–26 h. [c] Reaction run for 13 h [d] Reactions were run in 4:1 trifluorotoluene and pH 8 phosphate buffer [e] 10 equiv of *meta*-xylene was used with limiting amine [f] *o:p* ratio determined after isolation [g] Reaction was run with 3 equiv of *tert*-leucine methyl ester hydrochloride [h] 5 equiv of amine used

high selectivity for the C2 isomer. Additionally, 1,3-disubstituted benzenes reacted well, with 1,3-dimethoxybenzene and *meta*-xylene providing aminated products **40** and **41** in moderate to good yields and excellent regioselectivity. 1,2-Disubstituted arenes such as 2-chloroanisole also participated in the amination, leading to product **42** in 63% yield. More complex substrates bearing an additional aryl ring afforded anilines **43** and **44** in good yields, with functionalization only occurring on the more electron-rich ring. Heterocycles also served as efficient arene coupling partners, with 2,6-dimethoxypyridine and *N*-methylindazole providing **45** and **46**, respectively, as single regioisomers in good yields. Moreover, amination of halogenated heterocycles such as 7-bromo-*N*-methylindazole afforded a single regioisomer (**47**) in good yield.

To highlight the derivatization of complex arenes using this methodology, fenoprofen, a non-steroidal anti-inflammatory drug, was subjected to amination with *tert*-leucine methyl ester, affording **48** in 73% yield. Gemfibrozil, a lipid-lowering drug,[26] also participated in the amination reaction, with valine methyl ester, to give **49** as a single regioisomer in 32% yield. Clofibrate and bezafibrate methyl ester, pharmaceuticals that are also used to lower LDL cholesterol,[27] were both functionalized in moderate yields and good selectivity (**50** and **51**), further illustrating the utility for late stage pharmaceutical derivatization.

In our previous work on arene functionalization, we exploited electrophilic arene cation radicals generated by SET to the acridinium photoredox catalyst. Since the present system allows the primary amine to be oxidized to the amine cation radical, we questioned whether arenes with oxidation potentials above the reduction potential of the excited state acridinium could undergo amination. Under slightly modified reaction conditions, benzene ($E_{1/2}^{ox}$ = +2.75 V vs. SCE) afforded aniline **52** in 40% yield, indicating a pathway for C–H amination not accessible through an arene cation radical generated by the acridinium catalyst (Figure 3). Toluene ($E_{1/2}^{ox}$ = +2.42 V vs. SCE) also underwent amination, affording **53** as a mixture of regioisomers in 50% combined yield.

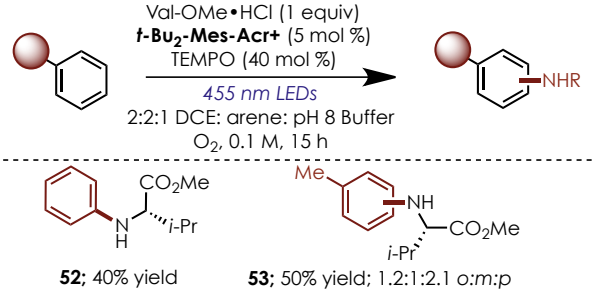

Figure 3. Amination of benzene and toluene. Reactions were run in 2:2:1 DCE, arene, and pH 8 phosphate buffer at 0.1 M concentration with respect to the amine limiting reagent.

Based on these experiments, we hypothesized that for benzene and toluene, the reaction can proceed through an amine cation radical intermediate. The reaction begins with excitation of **Mes-Acr+** with 455 nm LEDs to **Mes-Acr+*** (Figure 4). The excited state of the catalyst oxidizes the amine to the cation radical, generating **Mes-Acr•**. The addition of the arene forms a cyclohexadienyl radical intermediate that can be rearomatized using molecular oxygen as originally proposed by Fukuzumi.[28] However, since several arenes in Figure 2 possess similar oxidation potentials to those of the amine coupling partner, an arene cation radical could also account for the observed reactivity.[20] As determined by Stern-Volmer fluorescence quenching analysis (see Supporting Information, Figure S1), amines and electron-rich arenes both quench the acridinium excited state, but insufficiently electron-rich arenes such as toluene do not. Based on these results, insufficiently electron-rich arenes such toluene cannot undergo amination through an arene cation radical and instead react via an amine cation radical pathway. For electron-rich arenes, neither reactive intermediate can be excluded since both the amine and the arene quench the acridinium excited state.

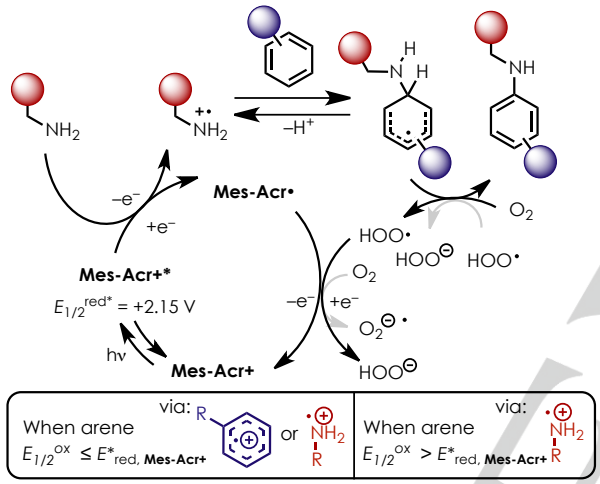

Figure 4. Proposed mechanism for direct C–H amination with primary amines via photoredox catalysis.

In conclusion, we have developed a direct aryl C–H amination via photoredox catalysis using primary amines. Further work will be required to extend this protocol to secondary amines. This methodology is mild and compatible with a variety of functional groups on both the arene and the amine, and enables extension of the arene coupling partners to non-activated aromatics such as benzene.

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Keywords: organocatalysis · photoredox catalysis · synthesis

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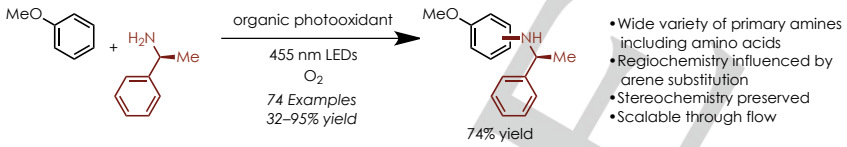

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