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Catalytic intramolecular aminoarylation of unactivated alkenes with aryl sulfonamides†

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Arylethylamines are abundant motifs in myriad natural products and pharmaceuticals, so efficient methods to synthesize them are valuable in drug discovery. In this work, we disclose an intramolecular alkene aminoarylation cascade that exploits the electrophilicity of a nitrogen-centered radical to form a C–N bond, then repurposes the nitrogen atom's sulfonyl activating group as a traceless linker to form a subsequent C–C bond. This photoredox catalysis protocol enables the preparation of densely substituted arylethylamines from commercially abundant aryl sulfonamides and unactivated alkenes under mild conditions. Reaction optimization, scope, mechanism, and synthetic applications are discussed.

Introduction

The arylethylamine pharmacophore is conserved across a range of biologically active natural products and drugs, particularly in molecules that act on the central nervous system (Fig. 1A, left).¹ Conventional preparations of arylethylamines rely on linear, stoichiometric transformations to forge key C–C and C–N bonds.² Such routes lack the combinatorial flexibility favored in early-stage medicinal chemistry campaigns and they restrict the accessible substitution patterns of the ethylene linker fragment. Substituents on the linker can drastically alter the molecule's lipophilicity, conformation, and elimination half-life.^{3,4} Modular preparations of complex arylethylamines from commercially available or easily synthesized substrates are therefore highly valuable, and considerable efforts have focused on this need (Fig. 1A, right).

Recently, Murphy, Barrett, and coworkers published a method for arylethylamine synthesis by palladium-catalyzed $\text{Csp}^3\text{--Csp}^3$ cross-coupling of (chloromethyl)aryl electrophiles and aminomethyltrifluoroborate salts.⁵ A diverse library of compounds could be quickly produced in this manner; however, no products bearing linker substituents were reported. An alternative and succinct disconnection of an arylethylamine could be the difunctionalization of an alkene to incorporate (1) the C–N bond, (2) the aryl– Csp^3 bond, or (3) both bonds at once. The first case describes anti-Markovnikov hydroamination of a styrene, and many methods exist to accomplish this transformation effectively with the aid of photoredox, lanthanide, or transition metal catalysts.^{6–9} The second case necessitates anti-Markovnikov hydroarylation of an enamine, which was only

recently reported in good yields by Jui and coworkers.¹⁰ The third case entails aminoarylation of an unactivated alkene and is, in principle, the most modular of the three difunctionalization strategies. Because the substrate is decoupled from both the arene and the nitrogen atom, simple alkenes can be converted to arylethylamines in one step. Our interests in complex molecule synthesis by radical methods led us to question whether aminoarylation could be achieved with nitrogen-centered radicals. Such electrophilic intermediates can be accessed readily through photoredox catalysis.^{11,12} We perceived the advances by Knowles and coworkers in catalytic N-centered radical generation as particularly enabling towards our goal.^{13,14} Formal homolysis of N–H bonds *via* multiple-site concerted proton-electron transfer (MS-CPET) permits useful reactivity of N-centered radicals without the need for harsh oxidants or strong bases.¹⁵ If the N–H bond is sufficiently acidic, stepwise deprotonation/oxidation sequences can also give N-centered radicals under mild conditions.¹⁶

We first considered the state of the art in unactivated alkene aminoarylation to inform our reaction design. Palladium-catalyzed alkene aminoarylation was explored extensively by Wolfe and coworkers in the preparation of saturated nitrogen heterocycles.^{17,18} The Chemler and Antonchik groups have put forth copper-catalyzed¹⁹ and metal-free²⁰ approaches to intramolecular carboamination. Engle and coworkers employed directing groups to orchestrate palladium- and nickel-catalyzed intermolecular aminoarylations of β,γ -unsaturated enamides and of homoallylic alcohols, respectively.^{21,22} The Molander and Leonori laboratories merged photoredox- and transition metal catalysis by trapping amidyl radical cyclization intermediates with nickel to accomplish C–C cross-coupling.^{23,24} Gaunt and coworkers achieved a three-component copper-catalyzed alkene azidoarylation using diaryliodonium triflates as aryl radical precursors.²⁵ We envisioned a desulfonylative 1,4-aryl migration (Smiles–Truce rearrangement) as an unconventional

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Fig. 1 (A) Selected biologically active molecules containing arylethylamines and recent catalytic disconnections. (B) Summary of our group's prior work on aminoarylation through alkene radical cations. (C) Abstract depiction of aminoarylation cascade in the present work and challenges that were overcome.

disconnection of the C–C bond that could be induced by an N-centered sulfonamidyl radical addition to an alkene. Aryl migrations have become increasingly accessible to synthetic chemists as modern photochemical techniques have matured.^{26–28} In this case, the migration would grant entry to the arylethylamine scaffold from inexpensive sulfonamides.^{29,30} Mechanistically, this distinct cascade would not require a cross-coupling catalyst and may grant access to sterically congested products that are challenging to prepare through transition metal-mediated methods. Although Molander's approach to aminoarylation initiates by an N-centered radical cyclization from an N–H bond, the MS-CPET method chosen to generate the radical necessitates N-aryl amide precursors. Oxidative cleavage of the auxiliary arene in the product is therefore necessary to provide the free lactam. By contrast, the designed desulfonylative aryl migration in this work would function as an *in situ* deprotection of the nitrogen atom.

We previously reported an alkene aminoarylation that proceeded through alkene radical cation intermediates.³¹ These electrophilic species successfully coupled with sulfonamides, leading to a Smiles–Truce rearrangement that delivered the desired arylethylamine (Fig. 1B). However, only electron-rich, 1,2-disubstituted styrenes gave good yields. This restriction was attributed to the low oxidation potentials of the activated alkenes (1.28 V vs. SCE in CH₃CN for *trans*-anethole) and the higher propensity of monosubstituted styrene radical cations to oligomerize.^{32,33} We expected our N-centered radical approach to circumvent this limitation as well, based on strong literature precedent describing anti-Markovnikov sulfonamidyl radical additions to unactivated alkenes.^{19,34–39} However, Smiles–Truce rearrangements following such radical additions have only been reported to occur by Deagostino and Liu in specially designed γ,δ -unsaturated arylsulfonyl hydrazones as applied to the synthesis of tetrahydropyridazines.^{40,41}

We hypothesized that a second electron-withdrawing group on the nitrogen atom could convert the sulfonamide into a better leaving group. This modification would also prevent a reactive free amine from forming after *N*-desulfonylation, and it would further increase the acidity of the N-H bond ($pK_a \approx 5$) such that stepwise N-centered radical generation could be feasible.⁴² However, intermolecular addition of *N*-acylsulfonamidyl radicals to unactivated alkenes was not observed. 1,4-Aryl migration to the carbonyl oxygen instead gave desulfonylated phenols.^{43,44} To avert this undesired Smiles rearrangement, we synthesized *N*-acylsulfonamides bearing tethered alkenes that would rapidly trap the N-centered radical in a 5-*exo-trig* cyclization. Desulfonylative aryl migration to the incipient alkyl radical would then provide the desired arylethylamine (Fig. 2, right).

Results and discussion

Our initial efforts to develop this reaction revealed that instances of the substrates with only *meta* or *para* substitution would selectively undergo dearomative addition of the alkyl radical *ortho* to the sulfonyl group, followed by radical-polar crossover and protonation to garner 1,4-cyclohexadiene-fused sultams (Fig. 2, left).⁴⁵ We reasoned that substituents in the *ortho* positions could inhibit the dearomative cyclization. Thus, when 2,6-difluorobenzenesulfonyl enamide **1d** was exposed to the dearomatization conditions from our previous work, the Smiles–Truce rearrangement occurred instead to give lactam **2d** in 45% isolated yield. Notably, the new quaternary center in **2d** is difficult to assemble through comparable transition metal-catalyzed methods.^{23,24,46} Compound **1d** was therefore chosen as a model substrate for optimization, and key observations from this process are highlighted in Table 1.

Although ^tBuOH was beneficial for the dearomative cyclization as part of a binary solvent mixture with PhCF₃, yield of **2d** improved when ^tBuOH was excluded (entry 2). The strong oxidizing properties of Ir-1 were crucial; less oxidizing iridium photocatalysts such as Ir-2 and Ir-3 gave reduced yields. At ambient temperature, CH₃CN was found to give the highest yield of **2d** among all solvents evaluated (entry 4). However, at 60 °C, the yield decreased in CH₃CN but improved further in PhCF₃ (entries 7 and 8). We initially deemed tetrabutylammonium dibutylphosphate (NBu₄PO₂(OⁿBu)₂) a suitable base, but

it required several days to dry fully once prepared and was inconvenient to handle under ambient atmosphere due to its marked hygroscopicity. To allow a simpler reaction set-up, we sought alternative bases (entries 9–13). Ultimately, we identified potassium *p*-chlorobenzoate as a free-flowing powder that gave satisfactory yields of **2d** despite its low solubility in PhCF₃. Although isolated yields were slightly lower in larger vials (entry 14), the increased volume was necessary to conduct the reaction on a scale greater than 0.1 mmol. In this work, we opted to report the substrate scope on a 0.2 mmol scale. Control experiments excluding photocatalyst or light failed to generate detectable quantities of **2d**, while only trace product was observed in the absence of a base (entries 15–17).

After identifying optimal conditions, the arene scope of the reaction was demonstrated on a variety of electron-neutral and electron-deficient mono- and bis-*ortho*-substituted benzene derivatives, as well as on a selection of heteroaromatic sulfonamides (Fig. 3). *ortho*-Halogenated arenes—many of which would be incompatible with palladium or nickel catalysts—and *ortho*-trifluoromethylated arenes were generally well-tolerated (**2a–2k**). (*E*)-Styrenyl sulfonamide **1l** underwent a vinylogous Smiles–Truce rearrangement and alkene isomerization to give the aminoalkenylation product **2l** as a 4 : 1 mixture of *Z/E* isomers. Heterocycles including pyridine (**2m**), furan (**2n**), thiophene (**2o–2q**), and thiazole (**2r**) could all undergo migration as well in modest to good yields. 2-Substituted thiophene **1o** gave a 9 : 1 mixture of lactam **2o** with the 3-substituted thiophene regioisomer **2o'** arising from a C3-addition/ β -elimination sequence (see ESI†).⁴⁷ In the presence of an *ortho* ester substituent (**1s**), the amidyl anion liberated upon desulfonylation displaced the alkoxide to produce the tricyclic imide **2s**. Next, we surveyed the scope of amenable alkenes. Mono-substituted (**2t**), disubstituted (**2u–2z**), trisubstituted (**2aa–2ad**), and tetrasubstituted (**2ae**) alkenes were all successfully functionalized, producing lactams with diverse carbon skeletons. The more electron-deficient trichlorophenyl ring in compound **1z** was necessary to promote successful migration to the inherently less nucleophilic benzylic radical intermediate.

Seemingly minor manipulations of the alkene tether in **1ad** could greatly alter the reaction: when the tether was homologated and *gem*-dimethyl substitution was incorporated alpha to the carbonyl, the ensuing 6-*exo* trig cyclization triggered the migration of a 4-trifluoromethylphenyl ring lacking *ortho*

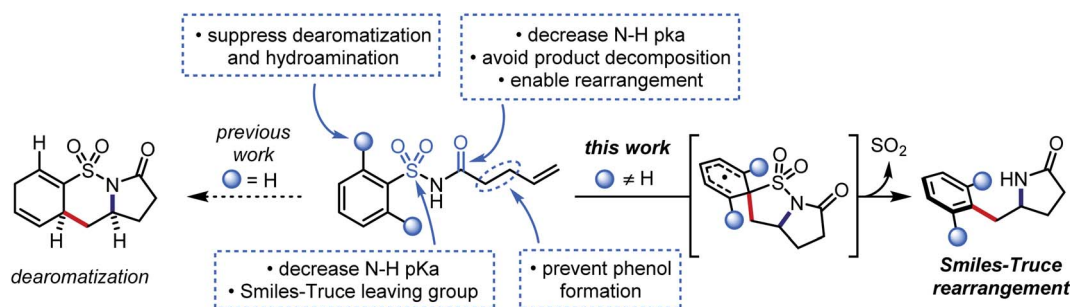
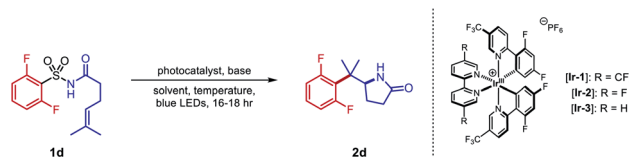


Fig. 2 Structural features of the aminoarylation substrates that favor Smiles–Truce rearrangement and disfavor undesired side reactions.

Table 1 Selected optimization trials (see ESI for complete details). All reactions were conducted on 0.1 mmol scale. All reactions were irradiated in vials with 10 mm external diameter unless otherwise noted. Yields were determined by ^{19}F NMR integration relative to 1.0 equiv. 4-fluoro-bromobenzene as an internal standard



Entry	Photocatalyst	Base	Solvent	Temp. (°C)	Yield (%)
1	Ir-1	$\text{NBu}_4\text{PO}_2(\text{O}^n\text{Bu})_2$	1 : 1 PhCF_3 / $^t\text{BuOH}$ (0.05 M)	35	45 ^a
2	Ir-1	$\text{NBu}_4\text{PO}_2(\text{O}^n\text{Bu})_2$	PhCF_3 (0.05 M)	35	68
3	Ir-1	$\text{NBu}_4\text{PO}_2(\text{O}^n\text{Bu})_2$	PhCF_3 (0.1 M)	35	39
4	Ir-1	$\text{NBu}_4\text{PO}_2(\text{O}^n\text{Bu})_2$	CH_3CN (0.05 M)	35	70
5	Ir-2	$\text{NBu}_4\text{PO}_2(\text{O}^n\text{Bu})_2$	CH_3CN (0.05 M)	35	44
6	Ir-3	$\text{NBu}_4\text{PO}_2(\text{O}^n\text{Bu})_2$	CH_3CN (0.05 M)	35	43
7	Ir-1	$\text{NBu}_4\text{PO}_2(\text{O}^n\text{Bu})_2$	CH_3CN (0.05 M)	60	63
8	Ir-1	$\text{NBu}_4\text{PO}_2(\text{O}^n\text{Bu})_2$	PhCF_3 (0.05 M)	60	74
9	Ir-1	NBu_4OBz	PhCF_3 (0.05 M)	60	67
10	Ir-1	KOBz	PhCF_3 (0.05 M)	60	71
11	Ir-1	$p\text{-OMeC}_6\text{H}_4\text{CO}_2\text{Na}$	PhCF_3 (0.05 M)	60	45
12	Ir-1	$p\text{-OMeC}_6\text{H}_4\text{CO}_2\text{K}$	PhCF_3 (0.05 M)	60	77
13	Ir-1	$p\text{-ClC}_6\text{H}_4\text{CO}_2\text{K}$	PhCF_3 (0.05 M)	60	78 (72 ^a)
14 ^b	Ir-1	$p\text{-ClC}_6\text{H}_4\text{CO}_2\text{K}$	PhCF_3 (0.05 M)	60	70 (64^a)
15	None	$p\text{-ClC}_6\text{H}_4\text{CO}_2\text{K}$	PhCF_3 (0.05 M)	60	0
16	Ir-1	None	PhCF_3 (0.05 M)	60	<5%
17	Ir-1 (no light)	$p\text{-ClC}_6\text{H}_4\text{CO}_2\text{K}$	PhCF_3 (0.05 M)	60	0

^a Asterisks (*) denote isolated yields. ^b Reaction conducted in a 17 mm diameter vial.

substitution. This result was surprising because the same arene in our previous work on dearomative cyclization was not observed to undergo rearrangement.⁴⁵ We believe that the Thorpe–Ingold effect in this substrate accelerates 6-*exo*-trig ring closure, and that the resultant alkyl radical is oriented closer to the *ipso* carbon of the sulfonamide than to the *ortho* carbons. This intriguing divergence invites further study of the impact that conformational biases may exert on the course of the reaction.

Certain limitations also became clear as we interrogated the scope of the reaction. Benzothiazole substrate **1ag** degraded to benzothiazolone **1ag'** through the aforementioned desulfonylative arene oxygenation, which may be faster than sulfonamidyl radical cyclization in heterocycles with high migratory aptitudes.⁴⁸ Electron-donating *ortho* substituents on the sulfonamide prohibited the desired aryl transfer. Consequently, hydrogen atom transfer (HAT) or reduction of the alkyl radical following 5-*exo* cyclization led to undesired hydroamination side products.

Compounds **1u–1z** bearing 1,2-disubstituted olefins underwent aminoarylation with varying diastereoselectivities. The major diastereomer of product **2u** (8 : 1 dr) was isolated and its relative configuration was elucidated through X-ray crystallographic analysis. A possible model to rationalize the observed stereoselectivity is provided in Fig. 4A. Following 5-*exo* cyclization, a bond rotation positions the larger alkene substituent to

minimize steric interaction with the newly formed lactam. When the alkene was substituted with larger groups, compounds **2v**, **2w**, and **2z** were isolated as single diastereomers. In the aminoarylation of *N*-aroyl sulfonamide **1x** (1 : 1 *E/Z*), the sp^2 -hybridized carbon atoms at the lactam/arene ring fusion possess an attenuated steric influence on the methyl group. Therefore, diminished diastereoselectivity (3 : 1 dr) was observed in the isomer distribution of **2x**.

We then investigated the mechanism of N-centered radical generation. We considered three possibilities: (1) oxidation of benzoate by the photocatalyst, followed by HAT from the N–H bond of **1** to the resulting benzoyloxy radical; (2) oxidative MS-CPET involving the photocatalyst and a hydrogen-bonded substrate–benzoate complex, or (3) deprotonation of **1** by benzoate and subsequent oxidation of the *N*-acylsulfonamidyl anion. The first proposal seemed unlikely based on observations from the reaction optimization. Specifically, use of potassium *o*-methylbenzoate as the base gave 55% yield of product **2d**, even though the benzoyloxy radical derived from this compound undergoes 1,5 HAT that would likely outcompete intermolecular HAT in the dilute reaction conditions.⁴⁹ Use of pyridine, with an oxidation potential (2.2 V vs. SCE in CH_3CN) well beyond that of the excited state of Ir-1 (1.68 V vs. SCE in CH_3CN), still resulted in 12% yield of **2d**.^{50,51} The second proposal was evaluated and rejected in our previous work based on Stern–Volmer luminescence quenching experiments, which



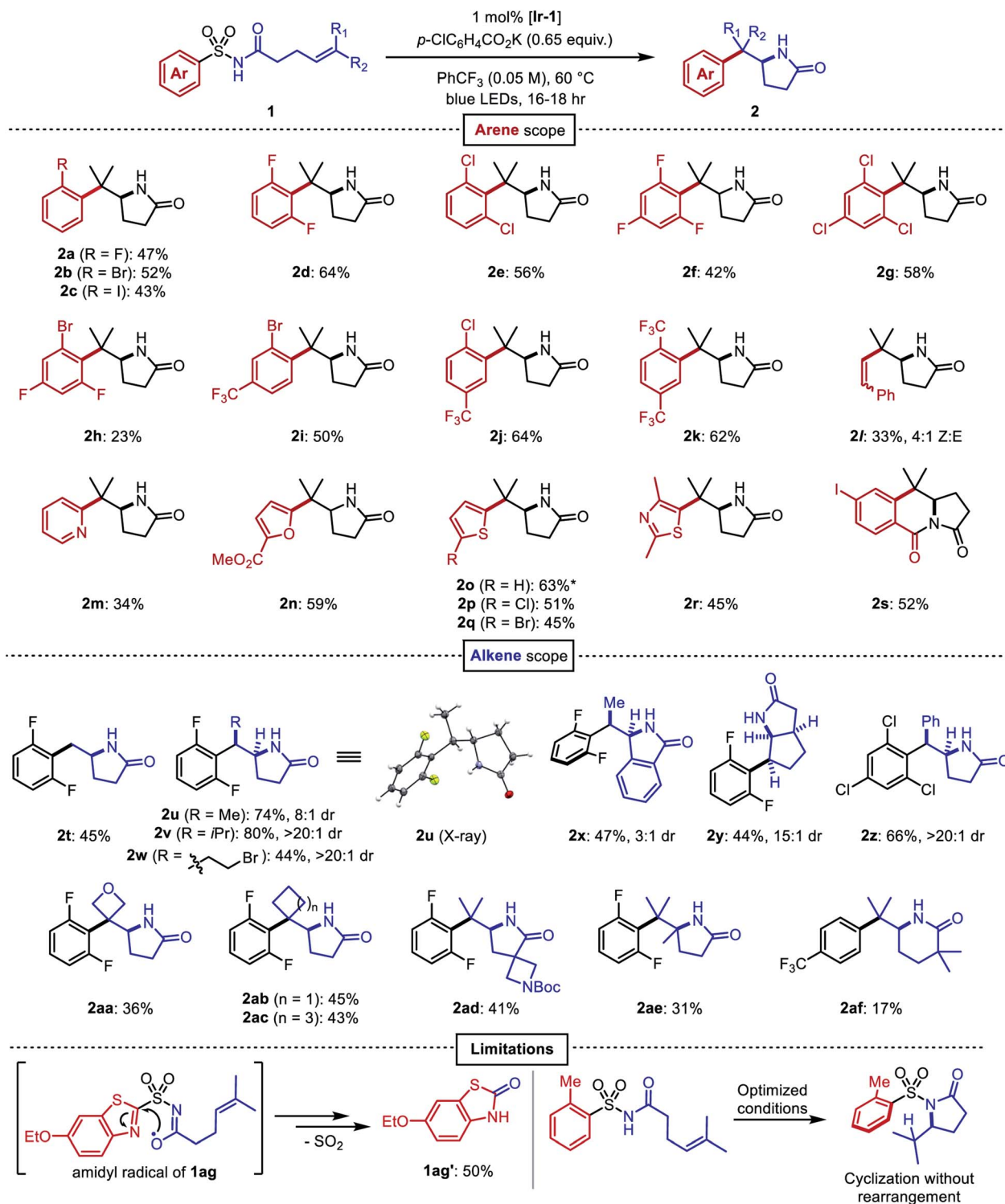


Fig. 3 Scope of the aminoarylation. All reactions performed on 0.2 mmol scale. All yields are from isolation. *Isolated as 9 : 1 mixture with regioisomeric product **2o'**, see ESI†.

indicated that tetrabutylammonium dibutylphosphate and *N*-acylsulfonamides do not form more easily oxidizable complexes in CH₂Cl₂ solution.⁴⁵ The base and the solvent examined in the quenching studies differ from those employed in our optimized aminoarylation conditions, but both can be substituted

successfully with only moderate yield reduction (see ESI†). To assess the third proposal, a 3 : 7 mixture of K⁺[**1d**[−]] and **1j** was subjected to the optimized conditions without added base. In this case, full consumption of both compounds and good yields of their respective products **2d** and **2j** was observed (Fig. 4B).



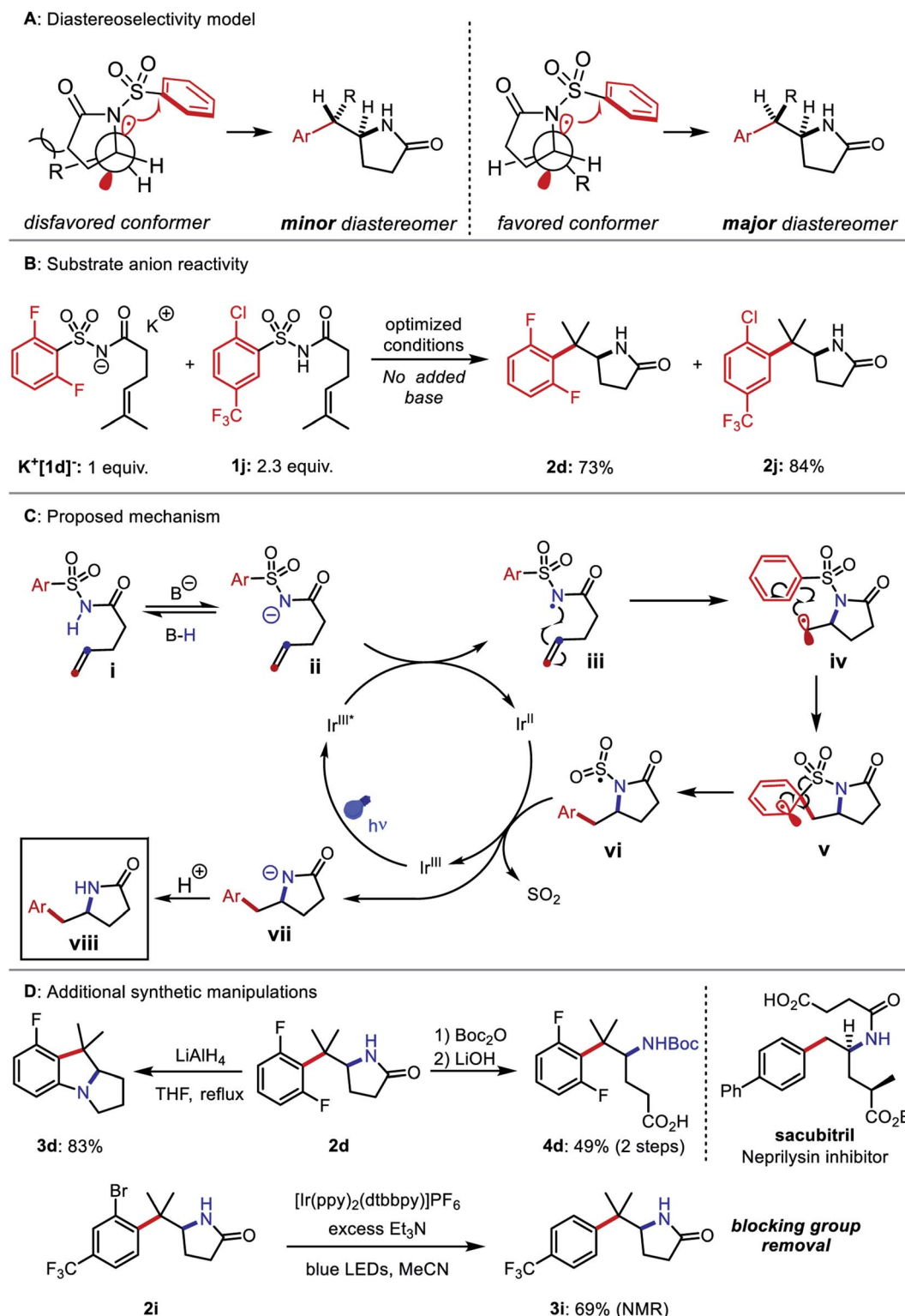


Fig. 4 (A) Newman projections depicting disfavored and favored conformers of the *N*-sulfonyl lactam and stereochemical outcomes of C–C bond formation. (B) Experiment establishing reactivity and catalytic turnover of deprotonated *N*-acylsulfonamides. Yields determined by ¹⁹F NMR integration relative to 4-fluorobromobenzene internal standard. (C) Mechanistic proposal of the aminoarylation. (D) Further reactions of aminoarylation products including reductive cyclization, lactam hydrolysis, and photochemical removal of an *ortho* substituent.

These data suggest a stepwise deprotonation-oxidation as the operative mechanism by which the *N*-centered radical forms. The data also imply that some reaction intermediate can

deprotonate the starting material. Based on these findings, we posit a mechanism for the reaction detailed in Fig. 4C: The photoexcited iridium catalyst Ir^{III}* oxidizes the deprotonated *N*-

acylsulfonamide **ii** to the N-centered radical **iii**. The C–N bond is then formed *via* 5-*exo-trig* cyclization and the resultant alkyl radical **iv** adds to the arene to yield dearomatized spirocycle **v**. Elimination of the sulfonyl group from **v** restores the aromatic system and gives the N-sulfonyl radical **vi**. Desulfonylation from **vi** and reduction by Ir^{II} restores the ground state of the photocatalyst and produces amidyl anion **vii**. The anion irreversibly deprotonates either the benzoic acid or another equivalent of **i** to furnish the product **viii**.

Finally, we performed additional diversification of the aminoarylation products that either leveraged the *ortho* substituents as functional handles to build additional complexity or converted the structures to molecules resembling other biologically active compounds (Fig. 4D). Reaction of **2d** with LiAlH₄ gave benzopyrrolizidine **3d** through a sequential lactam reduction and S_NAr of fluoride. A Boc protection/hydrolysis sequence yielded 3-(arylmethyl)-3-aminobutyric acid **4d**, which mimics the carbon skeleton of the neprilysin inhibitor sacubitril. Using a strongly reducing photocatalyst⁵² and an amine reductant, we carried out the hydrodehalogenation of aryl bromide **2i**, thus rendering the bromine atom a traceless blocking group in the synthesis of *ortho*-unsubstituted aryethylamine **3i**.

Conclusion

In summary, we have developed a unique alkene aminoarylation that affords products containing privileged aryethylamine connectivity. The method is compatible with a broad selection of unactivated alkenes and is orthogonal to existing cross-coupling methods. We engineered the substrates to curb unproductive pathways *en route* to a Smiles–Truce rearrangement prompted by C–N bond construction from an N-centered radical. The substrates are easily synthesized from commercially abundant building blocks and the reaction set-up is performed under ambient atmosphere using conveniently handled reagents. The strategy disclosed herein will inform future efforts to revisit the recalcitrant intermolecular variant of this chemistry. This work is a testament to the complexity-building capabilities of N-centered radicals and the cascade reactivities that they can unleash when properly controlled.

Data availability

The X-ray crystal structure of compound **2u** is available free of charge from the Cambridge Crystallographic Data Centre under deposition number 2045499.

Author contributions

EAN and RCM conceived the project with direction from CRJS. EAN and RCM performed the initial reaction discovery and optimization. EAN performed mechanistic studies as well as synthesis and characterization of all new compounds. EAN prepared the manuscript with input from RCM and CRJS.

Conflicts of interest

There are no conflicts to declare.

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