Catalytic Intramolecular Aminoarylation of Unactivated Alkenes with Aryl Sulfonamides

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Abstract: 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 under mild conditions. Reaction optimization, scope, mechanism, and synthetic applications are discussed.

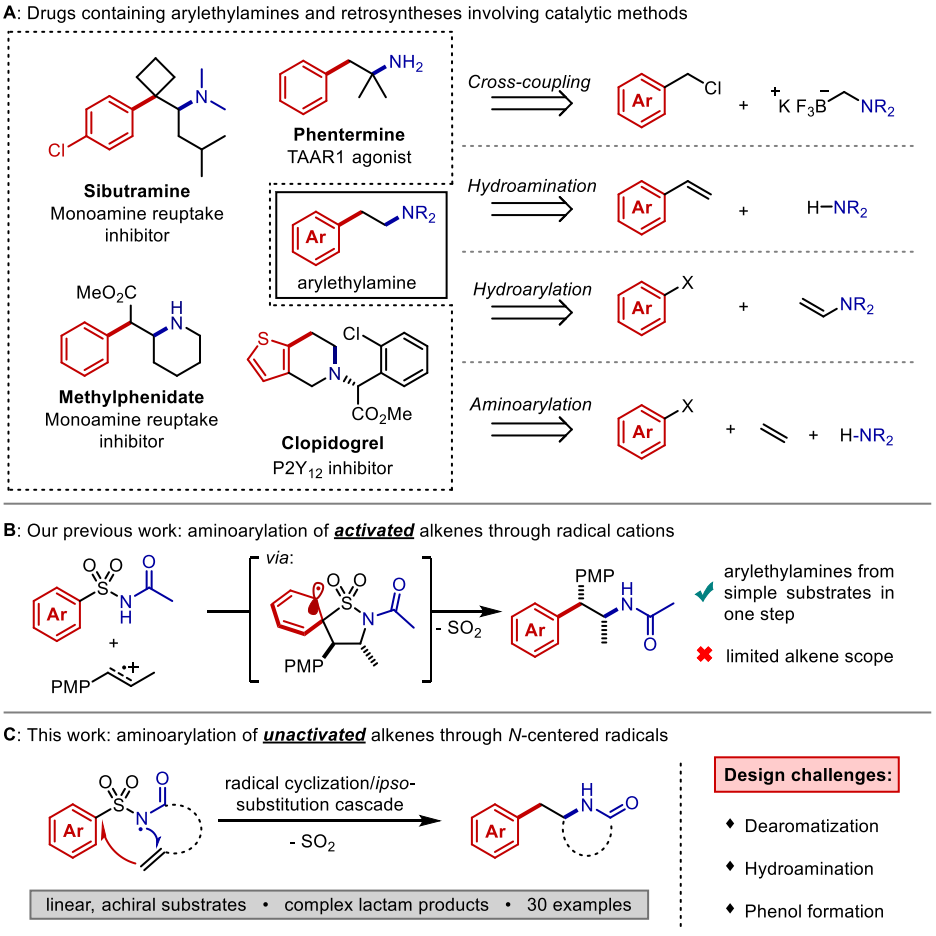


Figure 1. A: Selected biologically active molecules containing arylethylamines and recent catalytic disconnections. **B**: Summary of our group's prior work on aminoarylation through alkene radical cations. **C**: Abstract depiction of aminoarylation cascade in the present work and challenges that were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

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 (**Figure 1A**, left).[1] Conventional preparations of arylethylamines rely on linear, stoichiometric transformations to forge key C–C and C–N bonds. 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.[2,3] Modular preparations of complex arylethylamines from commercially available or easily synthesized substrates are therefore highly valuable, and considerable efforts have focused on this need (**Figure 1A**, right).

Recently, Murphy, Barrett, and coworkers published a method for arylethylamine synthesis by palladium-catalyzed Csp^3–Csp^3 cross-coupling of (chloromethyl)aryl electrophiles and aminomethyltrifluoroborate salts.[4] 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.[5-8] The second case necessitates *anti*-Markovnikov hydroarylation of an enamine, which was only recently reported in good yields by Jui and coworkers.[9] 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. We perceived the advances by Knowles and coworkers in catalytic N-centered radical generation as particularly enabling towards this goal.[10, 11] 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.[12] If the N–H bond is sufficiently acidic, stepwise deprotonation/oxidation sequences can also give N-centered radicals under mild conditions.[13]

We first considered the state of the art in unactivated alkene aminoarylation to inform our reaction design. Varied tactics exist to construct the C–N bond, but the C–C bond is typically formed *via* reductive elimination of the aryl and alkyl fragments from a high-valent transition metal complex. Palladium-catalyzed alkene aminoarylation was explored extensively by Wolfe and coworkers in the preparation of saturated nitrogen heterocycles.[14, 15] Engle and coworkers employed directing groups to orchestrate palladium- and nickel-catalyzed intermolecular aminoarylations of β,γ-unsaturated enamides and of homoallylic alcohols, respectively.[16, 17] Molander and coworkers merged photoredox- and transition metal catalysis by trapping amidyl radical cyclization intermediates with nickel to accomplish C–C cross-coupling.[18] We envisioned a desulfonylative 1,4-aryl migration (Smiles-Truce rearrangement) as an unconventional disconnection of the C–C bond that could be induced by an N-centered sulfonamidyl radical addition to an alkene. This aryl migration strategy would allow expedient entry to the arylethylamine scaffold from inexpensive sulfonamides.[19, 20] Mechanistically, this distinct cascade would not require a cross-coupling catalyst and would 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, 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.[21] These electrophilic species successfully coupled with sulfonamides, leading to a Smiles-Truce rearrangement that delivered the desired arylethylamine (**Figure 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 CH_3CN for *trans*-anethole) and the resistance of the corresponding radical cations to oligomerization.[22, 23] 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.[24-30] However, no examples of Smiles-Truce rearrangements have been demonstrated in these systems.

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 (pKa ≈ 5) such that stepwise N-centered radical generation could be feasible.[31] 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. To avert this undesired 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 (**Figure 2**, right).

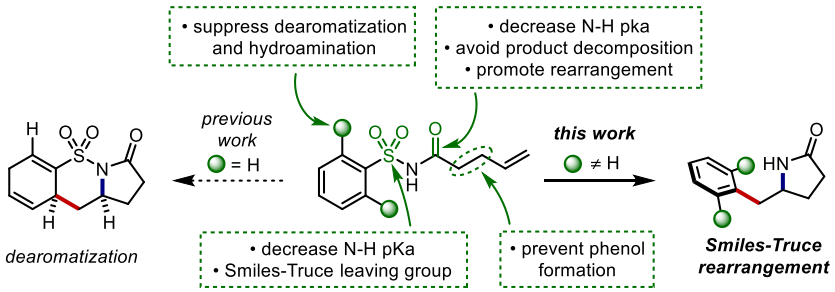
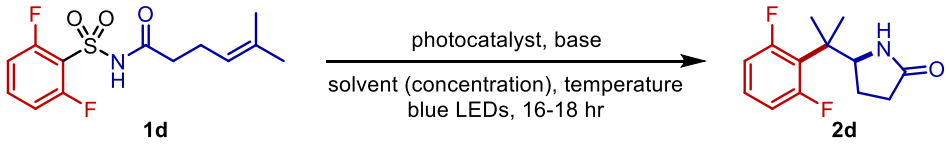
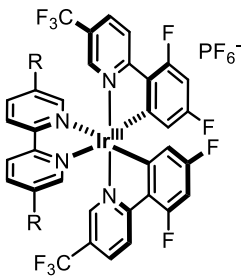


Figure 2. Structural features of the aminoarylation substrates that favor Smiles-Truce rearrangement and disfavor undesired side reactions.

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 (**Figure 2**, left).[32] We reasoned that substituents occupying the *ortho* positions could inhibit this dearomative cyclization. Thus, when 2,6-difluorobenzenesulfonyl enamide **1d** was exposed to the optimized dearomatization conditions from our previous work, the Smiles-Truce rearrangement occurred instead to give lactam **2d** in 45% isolated yield. Compound **1d** was therefore chosen as a model substrate for the ensuing reaction optimization, and key observations from this process are highlighted in Table 1.



1d **2d**



[**Ir-1**]: R = CF_3
[**Ir-2**]: R = F
[**Ir-3**]: R = H

Entry	Photocatalyst	Base	Solvent	Temp. (°C)	Yield (%)
1	Ir-1	$NBu_4PO_2(O^nBu)_2$	1:1 $PhCF_3$ / ^tBuOH (0.05 M)	35	45*
2	Ir-1	$NBu_4PO_2(O^nBu)_2$	$PhCF_3$ (0.05 M)	35	68
3	Ir-1	$NBu_4PO_2(O^nBu)_2$	$PhCF_3$ (0.1 M)	35	39
4	Ir-1	$NBu_4PO_2(O^nBu)_2$	CH_3CN (0.05 M)	35	70
5	Ir-2	$NBu_4PO_2(O^nBu)_2$	CH_3CN (0.05 M)	35	44
6	Ir-3	$NBu_4PO_2(O^nBu)_2$	CH_3CN (0.05 M)	35	43
7	Ir-1	$NBu_4PO_2(O^nBu)_2$	CH_3CN (0.05 M)	60	63
8	Ir-1	$NBu_4PO_2(O^nBu)_2$	$PhCF_3$ (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*-$OMeC_6H_4CO_2Na$	$PhCF_3$ (0.05 M)	60	45
12	Ir-1	*p*-$OMeC_6H_4CO_2K$	$PhCF_3$ (0.05 M)	60	77
13	Ir-1	*p*-$ClC_6H_4CO_2K$	$PhCF_3$ (0.05 M)	60	78 (72*)
14[a]	**Ir-1**	***p*-$ClC_6H_4CO_2K$**	**$PhCF_3$ (0.05 M)**	**60**	**70 (64*)**
15	none	*p*-$ClC_6H_4CO_2K$	$PhCF_3$ (0.05 M)	60	0
16	Ir-1	none	$PhCF_3$ (0.05 M)	60	<5%
17	Ir-1 (no light)	*p*-$ClC_6H_4CO_2K$	$PhCF_3$ (0.05 M)	60	0

Table 1. Selected optimization trials (see Supplementary Information for complete details). Reactions were conducted on a 0.1 mmol scale in vials with 10 mm external diameter unless otherwise noted. Yields were determined by ^{19}F NMR integration relative to 1.0 equiv. 4-fluorobromobenzene as an internal standard. Asterisks (*) denote isolated yields. [a]Reaction conducted in a 17 mm diameter vial.

Reaction Optimization

Although ^tBuOH was beneficial for the dearomative cyclization as part of a binary solvent mixture with $PhCF_3$, yield of **2d** improved when ^tBuOH was excluded (entry 2). The strong oxidizing properties of **Ir-1** were crucial; less oxidizing iridium photocatalysts such **Ir-2** and **Ir-3** gave reduced yields. At ambient temperature, CH_3CN was found to give the highest yield of **2d** among

all solvents evaluated (entry 4). However, at 60 °C, the yield decreased in CH_3CN but improved further in $PhCF_3$ (entries 7-8). We initially deemed tetrabutylammonium dibutylphosphate ($NBu_4PO_2(O^nBu)_2$) 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 $PhCF_3$. 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).

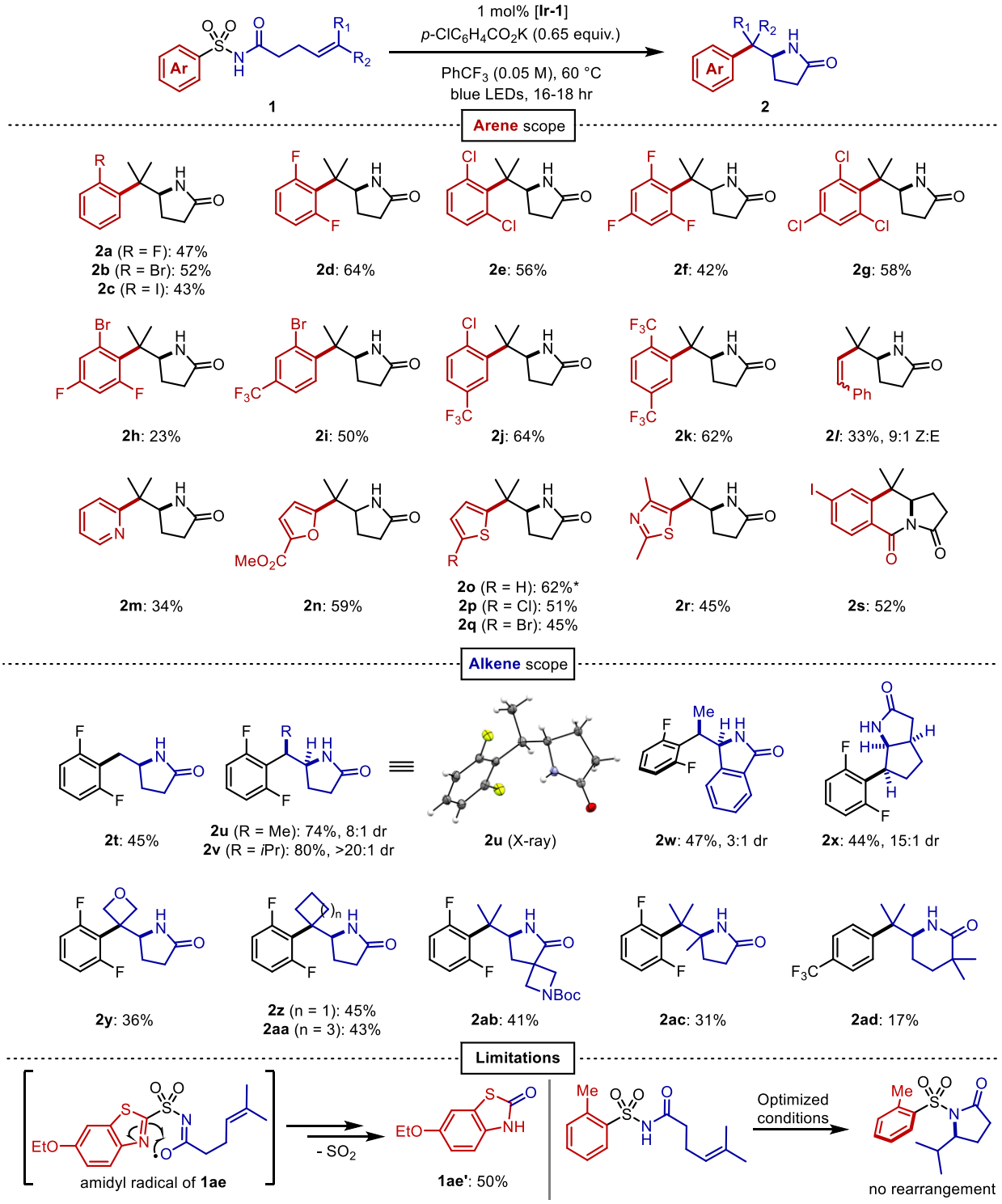


Figure 3. Scope of the aminoarylation. All reactions performed on 0.2 mmol scale. All yields are from isolation. *Isolated as 9:1 mixture with regioisomeric product **2o'**, see Supplementary Information.

Reaction scope

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 (**Figure 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 **1*l*** underwent a vinylogous Smiles-Truce rearrangement and alkene isomerization to give the aminoalkenylation product **2*l*** as a 1:9 mixture of E/Z 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-subsituted thiophene regioisomer **2o'** arising from an unexpected *cine*-substitution sequence (see Supplementary Information). 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. Monosubstituted (**2t**), disubstituted (**2u-2x**), trisubstituted (**2y-2ab**), and tetrasubstituted (**2ac**) alkenes were all successfully functionalized, producing lactams with diverse carbon skeletons. 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* substitution. This result was surprising because the same arene in our previous work on dearomative cyclization was not observed to undergo rearrangement.[32] 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 **1ae** degraded to benzothiazolone **1ae'** through the aforementioned desulfonylative arene oxygenation, which may be faster than sulfonamidyl radical cyclization in heterocycles with high migratory aptitudes.[33] 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**, **1v**, **1w**, and **1x** 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 **Figure 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 an isopropyl group (**1v**), compound **2v** was formed as a single diastereomer. In the aminoarylation of N-aroyl sulfonamide **1w** (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 **2w**.

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.[34] 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**.[35, 36] The second proposal was evaluated and rejected in our previous work based on Stern-Volmer luminescence quenching experiments, which indicated that tetrabutylammonium dibutylphosphate and N-acylsulfonamides do not form more easily oxidizable complexes in CH_2Cl_2 solution.[32] 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 Supplementary Information). To assess the third proposal, we synthesized the putative intermediate $\mathbf{K^+[1d^-]}$, a deprotonated salt of compound **1d**. When a

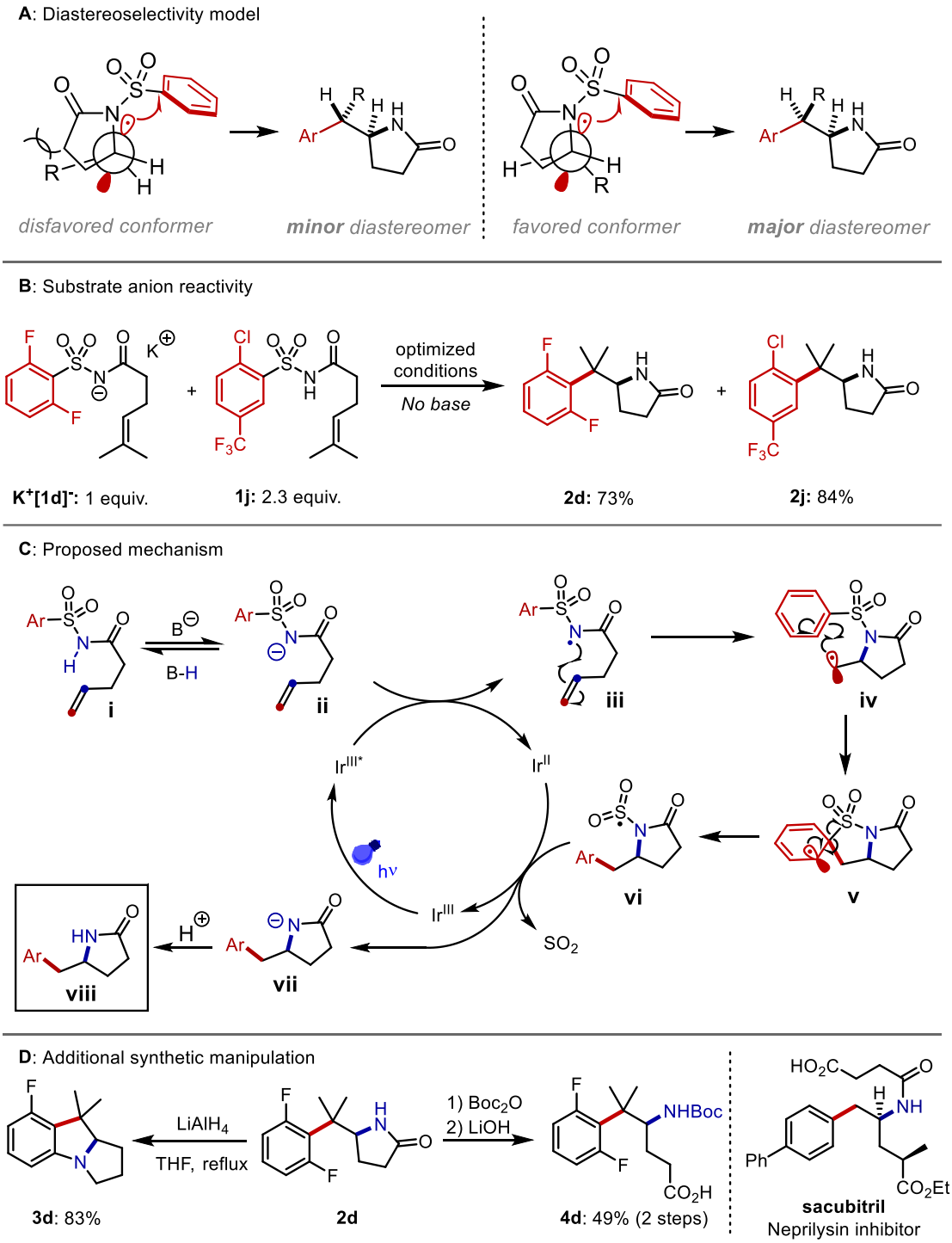


Figure 4. A: Newman projections depicting disfavored and favored conformers of the N-sulfonyl lactam and stereochemical outcomes of C–C bond formation **B**: Experiment establishing reactivity and catalytic turnover of deprotonated *N*-acylsulfonamides. Yields determined by ^{19}F NMR integration relative to 4-fluorobromobenzene internal standard. **C**: Mechanistic proposal of the aminoarylation. **D**: Further reactions of aminoarylation products.

3:7 mixture of **K$^+$[1d$^-$]** and **1j** was subjected to the optimized conditions without added base, we still observed full consumption of both compounds and good yields of their respective products

2d and **2j** (**Figure 4B**). 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 **Figure 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 (**Figure 4D**). Reaction of **2d** with $LiAlH_4$ 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.

Conclusion

In summary, we have developed a unique alkene aminoarylation that affords products containing privileged arylethylamine 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 an unprecedented 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.

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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.

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