A general alkene aminoarylation enabled by N-centered radical reactivity of sulfinamides

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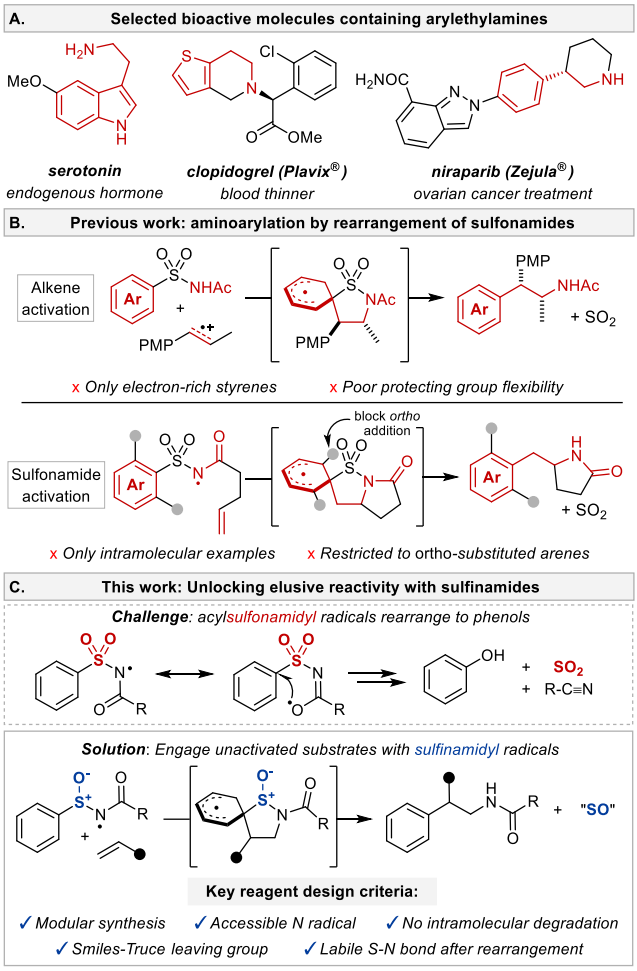
Abstract: We disclose an intermolecular 1,2-aminoarylation of alkenes using aryl sulfinamide reagents as bifunctional amine and arene donors. This reaction features excellent regio- and diastereoselectivity on a variety of activated and unactivated substrates. Using a weakly oxidizing photoredox catalyst, a sulfinamidyl radical is generated under mild conditions and adds to an alkene to form a new C–N bond. A desulfinylative Smiles-Truce rearrangement follows to form a new C–C bond. In this manner, biologically active arylethylamines and valuable building blocks can be rapidly assembled from abundant alkene feedstocks. Additionally, we demonstrate that chiral information from the sulfinamide can be transferred *via* rearrangement to a new carbon stereocenter in the product, thus advancing development of traceless asymmetric alkene difunctionalization methodologies.

Introduction: In 1900, the first isolation of epinephrine from bovine adrenal glands and its demonstration as a potent vasopressor was a landmark achievement in the budding field of pharmacology.[1] Over a century later, the intricate functions of arylethylamines remain the foci of intense study.[2] Endogenous arylethylamines including dopamine and serotonin underlie the neurochemistry of emotion, memory, and addiction.[3-5] Drugs with incorporated arylethylamine connectivity have been developed to treat heart disease[6] and cancer[7] (**Scheme 1A**) among numerous other indications. The arene and ethylene portions bear several potential sites of substitution that can act as synthetic handles to tune the molecule's metabolic and pharmacokinetic profile. Therefore, a modular method to prepare this pharmacophore would provide an enabling tool in discovery chemistry.

Contemporary advances in catalysis have unlocked new approaches for multi-component arylethylamine assembly.[8-13] Despite sustained efforts in developing arylethylamine syntheses from alkenes, most methods require either conjugated activating groups,[14-17] directing groups,[18-20] intramolecular substrate designs,[21-26] or introduction of the nitrogen atom in a higher oxidation state.[27] Therefore, a general alkene aminoarylation strategy remains an unmet need.



Scheme 1. **A**: Sample of arylethylamine-containing compounds with known bioactivity. B: Summary of our group's previous advances in aminoarylation C: Depiction of undesired sulfonamidyl radical reactivity and design of sulfinamide aminoarylation disclosed in this work.

Our group's own contributions to this area exploit a 1,4-aryl migration known as the Smiles-Truce rearrangement (**Scheme 1B**). It is defined as an intramolecular aromatic *ipso* substitution of a heteroatom leaving group by a carbon nucleophile.[28] This exchange of easily formed bonds to arenes with more valuable C–C bonds is an attractive operation which has spurred a resurgence in method development.[29-32]

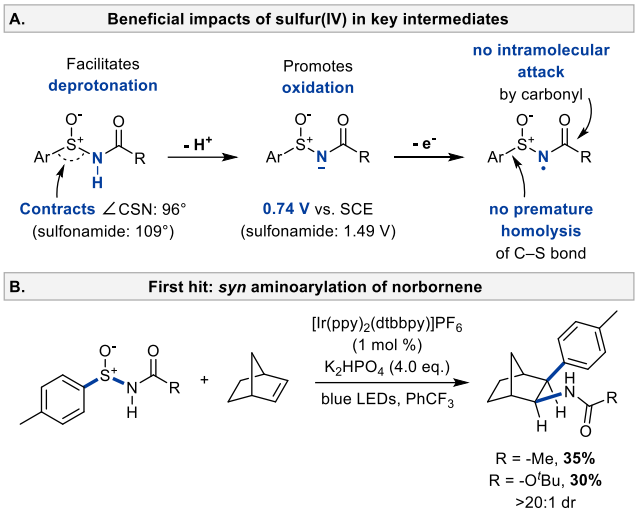
Early contributions to the radical aryl migration literature[33-35] inspired us to develop an intermolecular alkene aminoarylation with sulfonamides as bifunctional aryl and amine sources.[36, 37] Trapping of the sulfonamide nitrogen atom by the radical cation of an electron-rich styrene triggers a desulfonylative aryl migration to give the difunctionalization product. The limited alkene scope led us to explore an umpolung approach wherein the C–N bond forms between an unactivated alkene and an electrophilic N-centered

radical (NCR), allowing the Smiles-Truce rearrangement to proceed as before. In an intramolecular model system, we discovered that competing *ortho* addition and dearomatization predominates to give tricyclic dihydrobenzosultams.[38] Only when the *ortho* positions are occupied to block this dearomatization does the expected rearrangement occur to give the desired lactams.[39]

Although our NCR strategy allowed us to translate the Smiles-Truce rearrangement to aminoarylation of unactivated alkenes, competitive side reactions limited the chemistry to an intramolecular manifold with secondary restrictions on arene substitution. One such side reaction remained the primary barrier to productive intermolecular reactivity: an *intramolecular* degradation—itself a Smiles rearrangement—of the key N-acylsulfonamidyl radical to its corresponding phenol instead of its intermolecular union with an alkene (**Scheme 1C**).[40, 41] We hypothesized that by lowering the oxidation state of the sulfur atom from S(VI) to S(IV), we would attenuate its activity as a leaving group and inhibit the unwanted rearrangement. The resulting change to the sulfur atom's molecular geometry was also expected to contract the C–S–N bond angle,[42] thereby favoring the *ipso* cyclization step of the envisioned aryl migration.

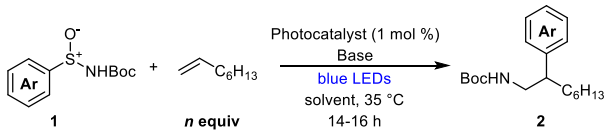
Some support for our hypothesis emerged when the Nevado laboratory reported sulfinamides as competent leaving groups in Smiles-Truce rearrangements.[43] In this asymmetric expansion of prior work,[44-47] radical conjugate addition to enantiopure *N*-arylsulfinyl acrylamides leads to enantioselective production of α-arylacetamides. We anticipated that NCRs of N-acyl sulfinamides might participate in an unprecedented intermolecular C–N bond formation which was inaccessible to their sulfonamide congeners. In support of this idea, Greaney and coworkers have demonstrated a polar Smiles rearrangement that proceeds with sulfinamide leaving groups while the sulfonamide analogs remain unreactive.[48]

Literature reports of sulfinamide NCRs are scarce and are mostly comprised of electron paramagnetic resonance spectroscopy studies. One route to their production is by hydrogen atom abstraction from sulfinamide N–H bonds.[49, 50] Another route is by radical addition to the sulfur atom of N-sulfinyl alkylamines (e.g. R–N=S=O).[51] Prior to the work disclosed herein, the only involvements in preparative organic synthesis by these intermediates were reported by Qin et. al. They implemented photoredox catalysis to generate *S*-alkyl *N*-benzoylsulfinamidyl radicals from N-H bonds; however, these NCRs underwent fast β-scission such that only the alkyl radical fragment was involved in further transformations.[52, 53]

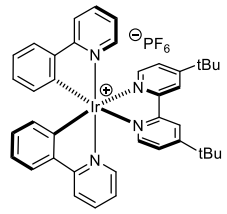


Scheme 2. **A**. Design principles of aryl sulfinamides that suppress decomposition and enable successful intermolecular aminoarylation. **B.** Initial success using norbornene.

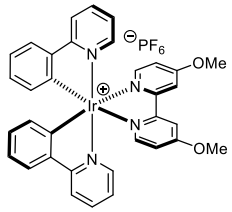
Results and discussion: We suspected that *S*-aryl *N*-acyl sulfinamides could undergo sequential proton loss-electron transfer (SPLET) to arrive at the key NCR.[54] This species was expected to resist β-scission owing to the thermodynamically challenging formation of an aryl radical. To probe this hypothesis, we conducted cyclic voltammetry experiments on a deprotonated acyl sulfinamide and measured its oxidation potential to be strikingly low at 0.74 V vs. SCE—approximately the same as *N*,*N*-dimethylaniline. (**Scheme 2A**).[55] Comparison with the analogous sulfonamide anion reveals a dramatic 0.75 V decrease in oxidation potential conferred by the sulfinyl group. This result suggested to us that even weakly oxidizing photocatalysts could provide the desired sulfinamidyl NCR. Therefore, we acetylated the commercially available *para*-tolyl sulfinamide and subjected it to modified literature conditions in the presence of norbornene (**Scheme 2B**).[52] We were excited to successfully isolate the aminoarylation product in 35% yield as a single diastereomer, which we would later assign as the *syn exo* isomer via X-ray crystallographic analysis of a related compound (**2t**, vide infra). The Boc-protected sulfinamide was also amenable to the transformation, giving 30% isolated yield of the more easily diversifiable aminoarylation product under identical conditions.



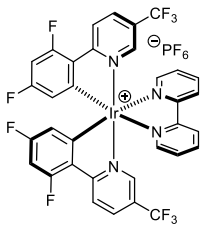
entry	Arene substitution	*n*	Photocat.	Base (equiv)	Solvent	Yield (%)
1	4-F	4	Ir-1	K_3PO_4 (3.0)	0.05 M $PhCF_3$	5
2	4-F	4	Ir-1	K_3PO_4 (0.8)	0.05 M $PhCF_3$	31
3	4-F	4	Ir-1	K_3PO_4 (0.8)	0.1 M $PhCF_3$	43
4	4-F	4	Ir-1	K_3PO_4 (0.5)	0.1 M $PhCF_3$	27
5	4-F	2	Ir-1	K_3PO_4 (0.5)	0.1 M $PhCF_3$	21
6	4-F	2	Ir-1	K_3PO_4 (0.5)	0.15 M $PhCF_3$	28
7	4-F	4	Ir-1	K_3PO_4 (0.5)	0.1 M 2,2,2-TFE	0
8	4-F	4	Ir-1	K_3PO_4 (0.5)	0.1 M DCE	34
9	4-F	4	Ir-1	$KHCO_3$ (1.0)	0.1 M $PhCF_3$	<5
10	4-F	4	Ir-1	KO*t*-Bu (0.8)	0.1 M $PhCF_3$	17
11	4-F	4	Ir-1	DBU (3.0)	0.1 M $PhCF_3$	0
12	4-F	4	Ir-2	K_3PO_4 (0.8)	0.1 M $PhCF_3$	23
13	4-F	4	Ir-3	K_3PO_4 (0.8)	0.1 M $PhCF_3$	9
14	4-F	4	4-CzIPN	K_3PO_4 (0.8)	0.1 M $PhCF_3$	14
15	4-F	4	Ir-1	K_3PO_4 (0.8)	0.1 M 1:1 DCE/H_2O	50
16	3-F	4	Ir-1	K_3PO_4 (0.8)	0.1 M 1:1 DCE/H_2O	60
17	3-F	4	Ir-1	K_3PO_4 (1.5)	0.1 M 1:1 DCE/H_2O	72
18	3-F	4	Ir-1	K_3PO_4 (3.0)	0.1 M 1:1 DCE/H_2O	76
19	3-F	3	Ir-1	K_3PO_4 (3.0)	0.2 M 1:5 DCE/H_2O	70
20	3-F	**5**	**Ir-1**	**K_3PO_4 (3.0)**	**0.2 M 1:5 DCE/H_2O**	**89**
21	3-F	5	Ir-1	--	0.2 M 1:5 DCE/H_2O	0
22	3-F	5	--	K_3PO_4 (3.0)	0.2 M 1:5 DCE/H_2O	0



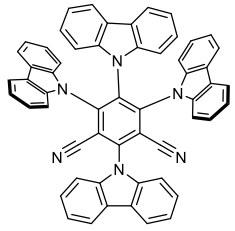
Ir-1



Ir-2



Ir-3



4-CzIPN

Table 1. Selected optimization trials (see SI for complete details). All reactions were conducted on 0.1 mmol scale. Assay yields were determined by ^{19}F NMR integration relative to 1.0 equiv. of 4-fluorobromobenzene as an internal standard. Stated concentrations are calculated with respect to sulfinamide and include total volume of aqueous and organic solvent where applicable.

These initial hits led us to perform reaction optimization with *N*-Boc 4-fluorobenzenesulfinamide, allowing use of the fluorine atom to calculate assay yields through ^{19}F NMR spectroscopy. We also changed the substrate to 1-octene due to concern that activation of the π-system in norbornene *via* ring strain was delivering anomalously high yields. Key excerpts of the optimization process are displayed in **Table 1**. Under the heterogeneous conditions employed early in the screening process, it appeared that

both superstoichiometric base loading and substoichiometric loading (below 0.8 equiv.) led to lower yields with no clear relationship to the reaction concentration (entries 1–6). Polar protic solvents were ineffective, but 1,2-dichloroethane (DCE) was found to be superior to trifluorotoluene (entries 7–8). However, to allow direct comparison with previous trials, trifluorotoluene was retained as the solvent during the base and photocatalyst screens. Weaker inorganic bases were ineffective, as were stronger organic bases (entries 9-11). Other iridium photocatalysts (entries 12-13) and organic photocatalysts (entry 14) also gave lower yields. We suspected that the insolubility of K_3PO_4 in organic solvents was a source of irreproducibility between trials; upon including water as a cosolvent, yield increased slightly (entry 15). When the sulfinamide was changed to the 3-fluoro derivative, yield increased further (entry 16). Subsequent adjustment of base loading and alkene equivalents in DCE/water mixtures (entries 17-19) led us to identify the optimal conditions represented in entry 20. We believe that when the base is fully dissolved under these biphasic conditions, we can increase the concentration of reactants in the organic phase without insoluble material hindering light penetration or mixing. Control experiments excluding either base or photocatalyst indicate that both reagents are necessary (entries 21–22). Crucially, the reaction also succeeds with the alkene as the limiting reagent under otherwise unmodified conditions (see synthesis of compound **2w** in **Table 3**).

Next, we evaluated generality of the reaction with respect to the sulfinamide using 1-octene as the benchmark substrate (**Table 2**). All sulfinamides were prepared in 1-3 steps without chromatography from their most advanced commercially available precursors (see SI). Relatively minor deviations in yield were observed across a series of electronically disparate sulfinamides (**2a-2i**). Although the iridium photocatalyst used in this transformation is a potent reductant in its reduced state,[56] neither aryl bromide **2d** nor aryl iodide **2e** underwent any observable dehalogenation. Mono-*ortho* substitution of the arene was accommodated without issue (**2j**, **2k**); however, bis-*ortho*-substitution in **1*l*** and extended conjugation in **1m** both led to diminished yields of the corresponding arylethylamines. Heteroarenes were also competent migrating groups; 2-thienyl and 3-pyridyl sulfinamides both gave good yields of the difunctionalization

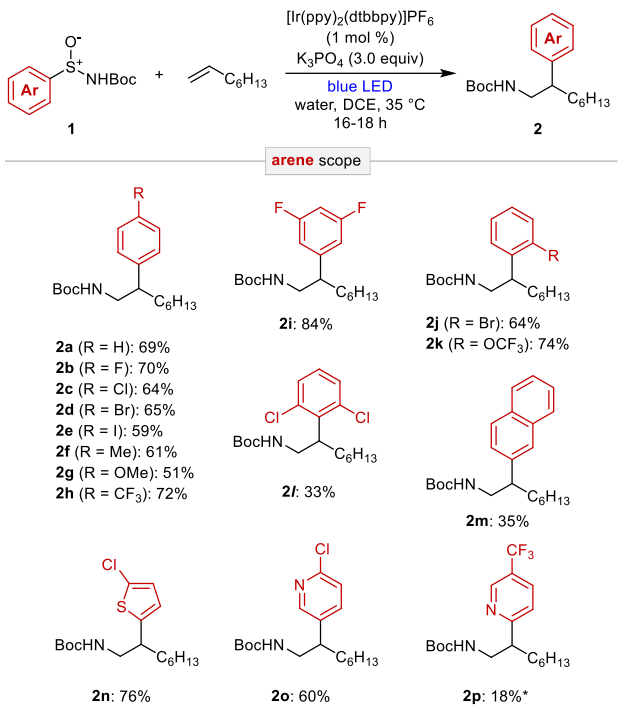


Table 2. Scope of aryl sulfinamides in the aminoarylation of 5.0 equiv. 1-octene. Reactions were conducted on 0.2 mmol scale. * = Reaction run under anhydrous conditions (see SI for details).

products **2n** and **2o**. 2-Pyridyl sulfinamide **1p** was less stable—even under anhydrous conditions—resulting in 18% yield of **2p**.

We then explored the scope of the reaction with respect to the alkene (**Table 3**). Alkyl bromides were tolerated in the synthesis of **2q** and **2r** without appreciable sulfinamide alkylation. By contrast, aminoarylation of an aziridine-containing substrate led to low yield of **2s** due to competitive nucleophilic ring opening with a sulfinamide nucleophile. 1,1-Dialkyl alkenes were well-tolerated and enabled construction of new quaternary carbon centers in products **2u**, **2v**, and **2w**. High facial selectivity is observed in the syntheses of norbornene-derived compound **2t** and of β-pinene-derived compound **2w**, which are both formed as single isomers. Compound **2x** was prepared directly from an unprotected allylic alcohol in good yield and differs from the marketed antidepressant venlafaxine only at the nitrogen atom. Likewise, the arylated γ-aminobutyric ester **2y** produced from tert-butyl-3-butenoate can be converted to the marketed muscle relaxant baclofen by simultaneous acidic deprotection of the N-Boc and tert-butyl ester moieties. Importantly, the β,γ-unsaturation in this substrate did not undergo base-assisted isomerization to the conjugated enoate ester under these conditions. Aryl-substituted alkenes were also

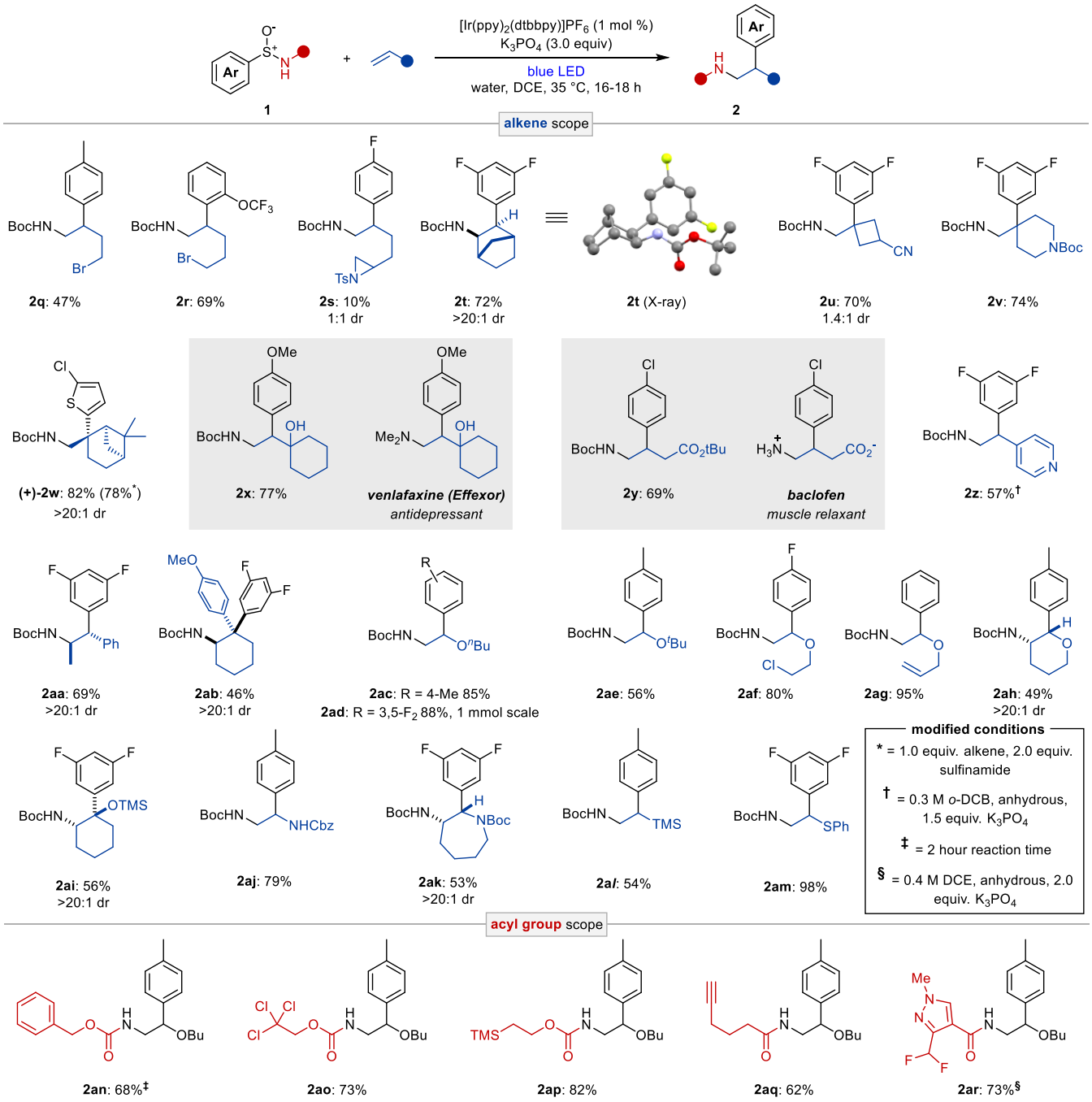


Table 3. Scope of alkenes and nitrogen protecting groups in aminoarylation using sulfinamides already benchmarked against 1-octene. Reactions were conducted on 0.2 mmol scale with 4-5 equiv. of the alkene in 0.2 mL DCE and 1.0 mL 0.6 M aqueous K_3PO_4 unless otherwise noted.

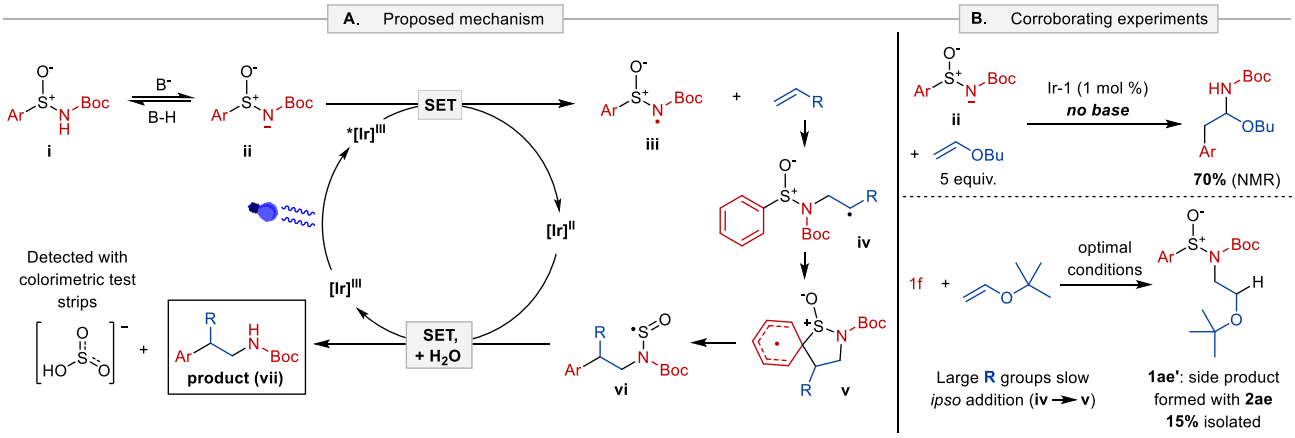
competent aminoarylation substrates as demonstrated in the syntheses of **2z**–**2ab**. Because 4-vinylpyridine is miscible with water, synthesis of **2z** was conducted under anhydrous conditions to prevent the substrate from partitioning between phases. High diastereoselectivity was observed in reactions of

both acyclic (**2aa**) and cyclic disubstituted styrenes (**2ab**) in good agreement with observations from our previous work.[36]

Electron-rich alkenes are also excellent reaction partners for this chemistry due to their improved polarity matching with electron-deficient NCRs.[57] Notably, despite their low oxidation potentials, vinyl ethers were not competent substrates in our alkene radical cation aminoarylation.[36] Using our sulfinamide reagents, however, *n*-butyl vinyl ether was converted to the protected ethanolamine **2ac** in high yield and maintained this performance in a five-fold scale-up with another sulfinamide to produce **2ad**. In scaling the reaction, we were also able to decrease the catalyst loading to 0.3 mol %. Hindered *tert*-butyl vinyl ether underwent aminoarylation to give **2ae** in moderate yield. Aminoarylation of functionalized vinyl ethers gave products **2af** and **2ag** in good yield with reactive sites for downstream diversification. Compound **2ag** originating from allyl vinyl ether underlines a pronounced chemoselectivity of the aminoarylation, which clearly favors more electron-rich alkenes in the presence of less activated ones. To conclude our survey of vinyl ethers, we found both 3,4-dihydropyran and a cyclohexanone-derived silyl enol ether to be competent substrates in the syntheses of tetrahydropyran **2ah** and TMS-protected cyclohexanol **2ai**, respectively. Enecarbamates, like vinyl ethers, were optimally suited for aminoarylation. Benzyl vinylcarbamate smoothly converted to the orthogonally protected ethylenediamine **2aj** while a protected tetrahydroazepine gave azepane **2ak**. Other heteroatom substituents were accommodated as well: vinyl trimethylsilane gave the silyl arylethylamine **2al** in moderate yield, and phenyl vinyl sulfide gave thioether **2am** in excellent yield without S-oxidation. Overall, the generality of this aminoarylation platform with respect to the alkene is a distinguishing factor that confers access to diverse chemical space.

We identified the acyl substituent of the sulfinamide nitrogen atom as a third point of diversification, as it would allow rapid synthesis of arylethylamines with other protecting groups. We were pleased to find that the Cbz-, Troc-, and 2-trimethylsilylethoxycarbonyl- (Teoc-) protected sulfinamides retained their reactivities in the aminoarylation of *n*-butyl vinyl ether to garner compounds **2an**–**2ap**. Since these three carbamates cleave under conditions distinct from one another, this methodology lends meaningful control to the user regarding protecting group selection. A pendent alkyne was not reactive with the NCR in **1t**, allowing synthesis of **2aq** in good yield. Furthermore, if one particular amide is desired in the product and only diversity about the arene or ethylene linker is of interest, it would be expedient to affix this amide to the sulfinamide prior to the aminoarylation. To prove this idea is viable in our system with

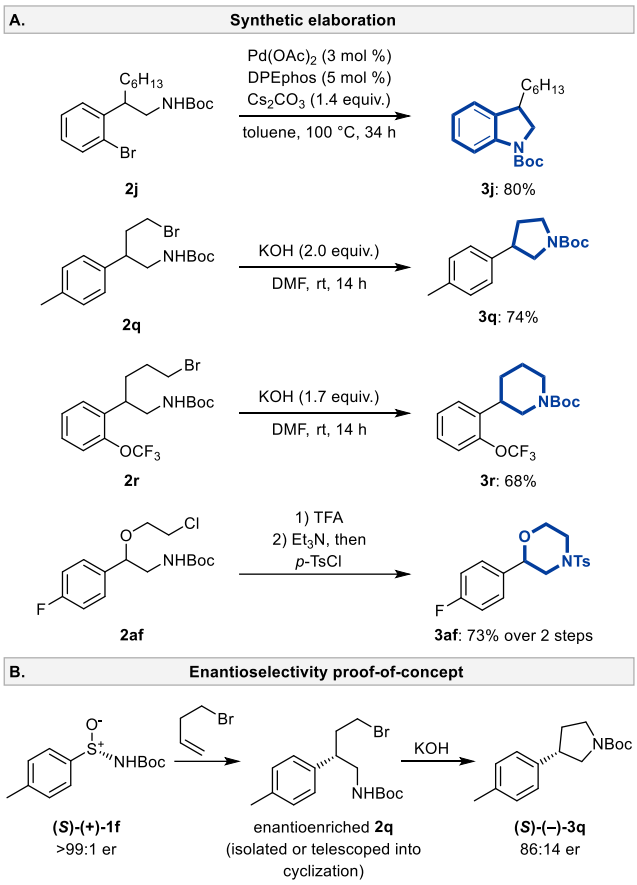
drug-like fragments, we synthesized *N*-sulfinyl difluoromethyl pyrazole **1u** from the commercially available carboxylic acid, facilitating direct preparation of the pyrazole carboxamide product **2ar**.



Scheme 3. **A.** Proposed mechanism of the aminoarylation involving oxidative NCR generation, alkene addition, radical Smiles-Truce rearrangement, and reductive N-desulfinylation. **B.** Experiments supporting intermediacy of anion **ii** (top) and radical **iv** (bottom).

To validate our SPLET hypothesis, we first conducted Stern-Volmer luminescence quenching studies using sulfinamide **1n** as the analyte and observed no quenching of the photocatalyst's excited state (see SI). This result provides evidence against electron transfer between the protonated sulfinamide and the excited photocatalyst. On the basis of the anion CV data, we propose the SPLET mechanism depicted in **Scheme 3A** wherein sulfinamide **i** is first deprotonated to anion **ii**. Oxidation of **ii** by the photocatalyst yields sulfinamidyl radical **iii**, which adds to an alkene to give radical adduct **iv**. As extra evidence for the deprotonation step, the anion **ii** synthesized for CV studies was found to react in the aminoarylation *without* base (**Scheme 3B**, top). Bulky alkene substituents can slow the ensuing Smiles-Truce rearrangement of adduct **iv** enough to permit reduction by the reduced photocatalyst, as exemplified in the isolation of hydroamination product **1ae'** from the reaction of *tert*-butyl vinyl ether (**Scheme 3B**, bottom). Otherwise, Smiles-Truce rearrangement follows from radical **iv**, likely through a dearomatized spirocyclic intermediate such as **v**. Rearomatization-driven C–S bond homolysis grants N-sulfinyl radical **vi**, which may undergo reductive cleavage by the reduced photocatalyst to give SO and the deprotonated form of the arylethylamine. Protonation delivers the final product, while a known disproportionation of SO can ensue to give SO_2 and S_2O.[58] Alternatively, radical **vi** may be subject to reduction and attack by water prior to cleavage of the S–N bond, such that free SO gas does not form. In either case, the basic aqueous reaction conditions are expected to convert SO_2 to bisulfite (HSO_3^-). This ion was detected in the

aqueous phase of the reaction using commercially available colorimetric test strips. A control experiment excluding alkene tested negative for bisulfite by the same analysis. This result supports the hypothesis that sulfur dioxide is formed indirectly *via* sulfinamide degradation following Smiles-Truce rearrangement.



Scheme 4. **A**. Transformations of aminoarylation products to obtain arylated heterocycles. **B**. Preliminary result demonstrating chirality transfer from sulfur to carbon during aryl migration.

To emphasize the utility of this aminoarylation as a tool for constructing valuable building blocks, we elaborated a selection of arylethylamine products to saturated *aza*-heterocycles (**Scheme 4A**). The *ortho* bromo substituent in **2j** served as a functional handle in an intramolecular palladium-catalyzed C–N coupling to synthesize indoline **3j**. Alkyl bromides **2q** and **2r** were cyclized to the pyrrolidine **3q** and piperidine **3r**, respectively. Alkyl chloride **2af** did not cyclize under the same conditions, requiring instead a telescoped Boc deprotection and cyclization of the free amine. *In situ* tosylation was chosen to aid isolation of 2-arylmorpholine **3af**.

Lastly, we anticipated that chirality at sulfur could transfer to new carbon stereocenters in the arylethylamine products in accord with literature precedent.[43] To evaluate the asymmetric variant of this methodology, **(*S*)-(+)-1f** was synthesized and employed in the aminoarylation of 4-bromo-1-butene. The enantioenriched product **2q** was then cyclized to afford **(*S*)-(–)-3q** in 86:14 er as determined by chiral supercritical fluid chromatography (**Scheme 4B**). Absolute configuration was assigned retroactively by derivatization of **3q** to a known compound and comparison of its specific rotation to the literature value.[59] This encouraging result is the starting point for further refinement and understanding of the factors dictating enantioselectivity in this transformation.

Conclusion: We have solved a formidable challenge in alkene carboamination by channeling the underexplored reactivity of sulfinamidyl radicals towards a cascade alkene addition/Smiles-Truce rearrangement. This innovation was informed by our prior work, wherein we attempted to use sulfonamides for the same purpose but were met with undesired side reactions. This redesigned approach simultaneously averts these side reactions and introduces opportunities for asymmetric arylethylamine synthesis. We believe this method fully harnesses the power of radical aryl migration and advances the broader field of alkene difunctionalization in a new dimension.

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Notes

The authors declare no competing financial interests.

Acknowledgment

Research reported in this publication was supported by the National Institute of General Medical Sciences of the National Institutes of Health under award number R35GM144286. The authors thank the University of Michigan for additional funding, and Dr. Jeff W. Kampf for collecting and analyzing X-ray crystallography data.

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