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Arylsulfonylacetamides as bifunctional reagents for alkene aminoarylation

Timothy M. Monos[1,†], **Rory C. McAtee**[1,†], **Corey R.J. Stephenson**[1,*]

[1]Department of Chemistry, University of Michigan, 930 North University Avenue, Ann Arbor, MI

Abstract

Alkene aminoarylation with a single, bifunctional reagent is a concise synthetic strategy. Despite the synthetic brevity of aminoarylation, combined with opportunities for stereoselective alkene functionalization, few methodologies have deviated from an intramolecular aminometallation-arylation reaction design. To contrast this paradigm, we report a protocol utilizing photoredox catalysis for the aminoarylation of electron-rich alkenes with arylsulfonylacetamides. This process is understood to operate through chemo- and regioselective alkene radical cation trapping with nucleophilic arylsulfonylacetamides, wherein a subsequent Smiles-Truce reaction transfers a variety of aryl groups in high diastereoselectivity. As this process is driven by visible light, employs readily-available starting materials, and demonstrates convergent synthesis, it is well-suited to impact a variety of synthetic endeavors.

One Sentence Summary:

Photoredox catalysis activates arylsulfonylacetamides to provide both the arene and amine for alkene difunctionalization.

The arylethylamine motif is conserved in dopamine, serotonin, and many opioid receptor drugs responsible for modulating pain sensation and treating neurobehavioral disorders (Figure 1A) (1,2). In light of the opioid epidemic, the climate surrounding opioid pain medications is conflicted. It is noteworthy that frontline medications treating opioid addiction contain such arylethylamine substructures (naltrexone and buprenorphine) (3–5). With this rationale, continued drug development in the arylethylamine chemical space is necessary for general hit-to-lead exploration and the discovery of new and safer medicines. Conventional methods to synthesize arylethylamines employ multi-step homologation and reductive amination sequences. Alternatively, alkene aminoarylation, particularly of anethole and other biomass-derived alkenes, allows for direct access to this medicinally desirable functionality. Development of methodologies to rapidly construct two new bonds (C−C

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*Correspondence to: crjsteph@umich.edu.
†These authors contributed equally.

Author contributions: TMM and RCM performed the experiments; TMM, RCM and CRJS designed the experiments; TMM, RCM, and CRJS wrote the manuscript.

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and C–N) in a single operation from feedstock chemicals can improve and expedite the discovery of new arylethylamine-based small molecule therapeutics.

Alkene aminoarylation has been demonstrated with palladium (6,7), copper (8–10), nickel (11,12), and gold (13), in which alkenes are activated by the transition metal to facilitate a stereoselective amine cyclization, followed by a two-electron metal-mediated arylation event (Figure 1B). The metals used in these aminoarylation platforms control stereoselectivity and activate the alkene for reactivity, while suppressing proto-demetallation or β-hydride elimination pathways that hinder desired C–C bond formation. Amides and amines are more nucleophilic than the alkene coupling partner; thus, elevated temperatures are often necessary to facilitate ligand substitution to unite the reactants in the initial amination event (14). Despite robust investigation, these methods are generally limited by the need for directing groups and intramolecular reaction designs which restrict the products to pyrrolidine and piperidine structures. Recently transformations effecting intermolecular aminoarylation and carboamination have been accomplished in which the alkene is decoupled from the arylation and amination reagents. In one case, Lin and Liu demonstrated an enantioselective copper(I) catalyzed aminoarylation of vinyl arenes relying upon pre-oxidized sulfonamide reactants (*N-fluoro-N-methylbenzenesulfonamide*) (Figure 1B) (9). Separately, Rovis and Piou demonstrated an intermolecular carboamination using *N*-enoxyphthalimides and Rh(III) catalysis (15).

Photocatalysis and radical-based chemistry has proven similarly influential in alkene difunctionalization. The simplest strategy is Meerwein aminoarylation, a Markovnikov-selective reaction that begins with the reductive generation of a radical from a suitable precursor (arene diazonium salt or diaryliodonium salt) followed by radical-polar crossover and carbocation trapping with acetonitrile solvent (16). These reactions are regioselective, but devoid of stereoselectivity. Photocatalytic *anti*-Markovnikov selective alkene hydro- and carboamination reactions have been recently demonstrated by both Knowles (17–21) and Nicewicz (22–24). These approaches represent contrasting C–N bond formation strategies, while employing a common catalytic cycle. Knowles et. al. has demonstrated both aminium radical cation and amidyl radical generation for the addition to olefins. In both cases, nitrogen centered radicals couple with π-systems to generate β-amino radicals that are rapidly trapped with a H-atom transfer reagent. Successful H-atom transfer reagents are minimally nucleophilic to prevent thiol-ene reactivity. Nitrogen radical based chemistry is particularly challenging as both alkene addition and allylic H-atom abstraction are kinetically competitive processes (25), thus excesses of the alkene component or intramolecular amino-cyclization is often necessary for success. Additionally, amine and amide oxidation generates a more reactive, but no more nucleophilic nitrogen atom. In contrast, Nicewicz et. al. has targeted alkene single electron oxidation, a similarly rapid process to amide or amine oxidation. This approach benefits from converting the alkene to a more electrophilic species in solution, necessitating lower equivalents of the nitrogen nucleophile to conduct alkene difunctionalization.

To contrast the widely investigated field of transition metal-mediated aminoarylation and build upon the successes of photocatalytic alkene difunctionalization chemistry, we were inspired by the possibility of a radical Smiles-Truce rearrangement to provide alkene

aminoarylation products in a diastereoselective fashion. Traditionally, the Truce variant of the Smiles rearrangement is a nucleophilic aromatic substitution effected by benzylic lithiation of *ortho*-tolyl-arylsulfones (26). The rearrangement is more broadly applicable to *ipso*-substitution reactions with aryl sulfides, sulfoxides, sulfones, and amides. Pennell and Motherwell furthered the utility of this transformation by demonstrating that aryl radicals are also capable of the same arene transposition (27) (Figure 1C). Although there are numerous intramolecular examples of radical Smiles-Truce reactions (28–33), many of these reactions employ net reductive conditions, generate a stoichiometric amount of waste, and rely upon a substrate design that tethers the radical precursor to the aryl-sulfonate derivative. Realizing this intramolecular tether can be formed via *in situ* oxidation of an alkene and subsequent nucleophilic trapping with an arylsulfonylacetamide (34), we sought to design a photocatalyzed radical Smiles-Truce reaction which showcases the utility of arylsulfonylacetamides as capable reagents for both C–N and C–C bond formation in aminoarylation (Figure 1D).

A general catalytic cycle was postulated to begin with an oxidation event between a photoexcited catalyst ($*Ir^{III}$) and an alkene (I) (Figure 2A) (23,24). Single electron oxidation of the alkene would enable nucleophilic addition of an arylsulfonylacetamide (II) to afford the desired β–alkyl radical intermediate (III) (35–37). This radical is poised for regioselective cyclization onto the *ipso*-position of the appended arene to generate IV (38). Lastly, an entropically-favored desulfonylation can proceed via two plausible pathways to generate the aminoarylation product (VII): rapid radical desulfonylation from IV to generate nitrogen-centered radical V followed by catalyst turnover; or homolytic fragmentation of the C_{Ar}–S bond to furnish VI, which can turnover the catalyst and undergo desulfonylation to VII. Exploiting both the electronic activation of the sulfonylated arene unit and tunable nucleophilicity of the nitrogen motif allows for this photoredox catalysis platform to promote both the C–N and C–C bond forming events with arylsulfonylacetamides.

To realize the proposed aminoarylation reactivity, reaction optimization was first conducted with vinyl anisole (1) ($E_{p/2}$=1.6 V vs SCE) (39) and 1-naphthylsulfonylacetamide (2) (Table S1). A potent photooxidant, $[Ir(dF(CF_3ppy)_2)(5,5'\text{-}CF_3\text{-}bpy)]PF_6$ (3) ($Ir^{II/III*}$=1.68 V vs SCE in MeCN) (40) was initially selected for alkene radical cation formation (Figure 2B). Early optimization experiments lent evidence to the chemoselectivity of this reaction; excess loading of arylsulfonylacetamide and base were unnecessary (Table S1). Nearly equivalent stoichiometry between **1** and **2** afforded the highest yield for the optimization product **4**. A base screen revealed potassium acetate, benzoate, and tribasic phosphate as superior bases to the less basic potassium trifluoroacetate and potassium phosphate (mono- or di-basic). The reaction was incompatible with pyridine, or stronger alkoxide bases, as photocatalyst decomposition was observed. Reaction dilution past 0.1 M slowed the rate of product formation, while reaction concentrations greater than 0.1 M inhibited product formation. Further optimization proved that less oxidizing photocatalysts such as $[Ru(bpy)_3]Cl_2$ ($Ru^{I/II*}$ = 0.77 V vs SCE in MeCN), $[Ir(dF(CF_3ppy)_2)(dtbbpy)]PF_6$ ($Ir^{II/III*}$ = 0.89 V vs SCE in MeCN), $[Ir(ppy)_2(dtbbpy)]PF_6$ ($Ir^{II/III*}$ = 0.31 V vs SCE in MeCN) (41,47), were unable to catalyze this transformation. Employment of Fukuzumi's catalyst ($PC^{\bullet}/PC*$ = 1.88 V vs SCE in MeCN) (42) did produce **4** in 13% yield. Finally, H-atom donor additives such as

1,4-cyclohexadiene and isopropanol did not improve upon the established conditions for the optimization product **4**. Exclusion of either light or photocatalyst failed to promote aminoarylation (Table S1). With the proof-of-concept established, we identified the acyl group, among a range of amides and carbamates, as the optimal activating group for the sulfonamide reagent in this transformation (Figure 3, **4**–**7**). We reasoned that the acidity and the steric encumbrance of the sulfonamide activating group control the nucleophilicity of the arylsulfonylacetamide.

A substantial increase in aminoarylation was observed when using 1,2-disubstituted *p*-methoxyphenyl alkenes in comparison to **1** (Figure 3A). This substitution allowed us to realize the aryl transfer of several groups including 1-naphthyl (**4**–**6, 8**–**10**, **21, 22**), 2-napthyl (**11**), 3-thiophenyl (**12**, **13**), 2-thiophenyl (**14**, **15**, **18**), 2- furanyl (**16**), 8-quinolino (**17**), 2-benzothiazole (**19**), and β-styrene (**20**) all in greater than 20:1 diastereoselectivity. X-Ray crystallographic analysis of **15** was found to show a *syn*-configuration between the 5-bromothiophene and the acetamide groups supporting the stereochemical assignment. Use of cyclic (*E*)-alkenes allowed for the synthesis of cyclic arylethylamines (**23**–**26**) containing two contiguous stereocenters, one of which is quaternary (Figure 3B). Furthermore, the *cis*-diastereomer **27** can be formed when a cyclic (*Z*)-alkene is used as the oxidizable alkene substrate partner (Figure 3C). Preparation of arylethylamine **21** containing an *N*-tosyl amide showcases the chemoselective nature of this aminoarylation, while the successful isolation of **22** suggests that nucleophiles tethered to the alkene are well tolerated under the reaction conditions. The current aminoarylation conditions are not amenable to benzenesulfonylacetamides, likely due to the increased enthalpic barrier for dearomatization during the initial radical cyclization (Figure S3).

To provide mechanistic insight, several studies were carried out to understand the efficiency and high diastereoselectivity of this transformation. We hypothesized that both acyclic (*Z*)- and (*E*)-alkenes would convert to the same *trans*-aminoarylation diastereomer due to bond rotation outcompeting cyclization of intermediate III. Notably, performing the titleaminoarylation with (*Z*)-anethole afforded a nearly identical yield of **9** (72%), in comparison to (*E*)-anethole (82%), while diastereomer **9'** was not observed (Figure 4A). Reaction progress analysis by ^{1}H-NMR spectroscopy of (*Z*)-anethole aminoarylation reveals that (*E*)-anethole is generated during the reaction (Figure 4B). Based on this observation, we examined the rates of isomerization for each anethole isomer to the photostationary state (Figure 4C). This revealed a photostationary state of 1.4:1 (*Z:E*), with the initial rate of (*Z*)-anethole isomerization being much faster than (*E*)-anethole isomerization (Figure S4, S8-S10) (43). Furthermore, initial rate analysis of aminoarylation shows alkene consumption to be slower (Figure S6) than (*Z*)-anethole isomerization (Figure S8, S9). These data suggest the diastereoselectivity arises from either, but not exclusively, a kinetically favored generation of (*E*)-anethole radical cation and subsequent aminoarylation; or a thermodynamic preference of radical intermediate III to adopt an *anti*-periplanar conformation between the *para*-methoxyphenyl (PMP) and methyl substituents prior to cyclization (Figure 4D). One other competing possibility is that (*E*)-anethole radical cation reacts with **2** faster than (*Z*)-anethole radical cation. Overall, these mechanistic details

describe how the combination of a Smiles-Truce aryl transfer and radical cation chemistry can be combined into a highly diastereoconvergent alkene aminoarylation.

In conclusion, given the current availability of sulfonamide building blocks along with the ubiquity of alkenes as feedstock substrates, we view the method to be a highly enabling platform for research efforts synthesizing the arylethylamine pharmacophore diastereoselectively in a single operation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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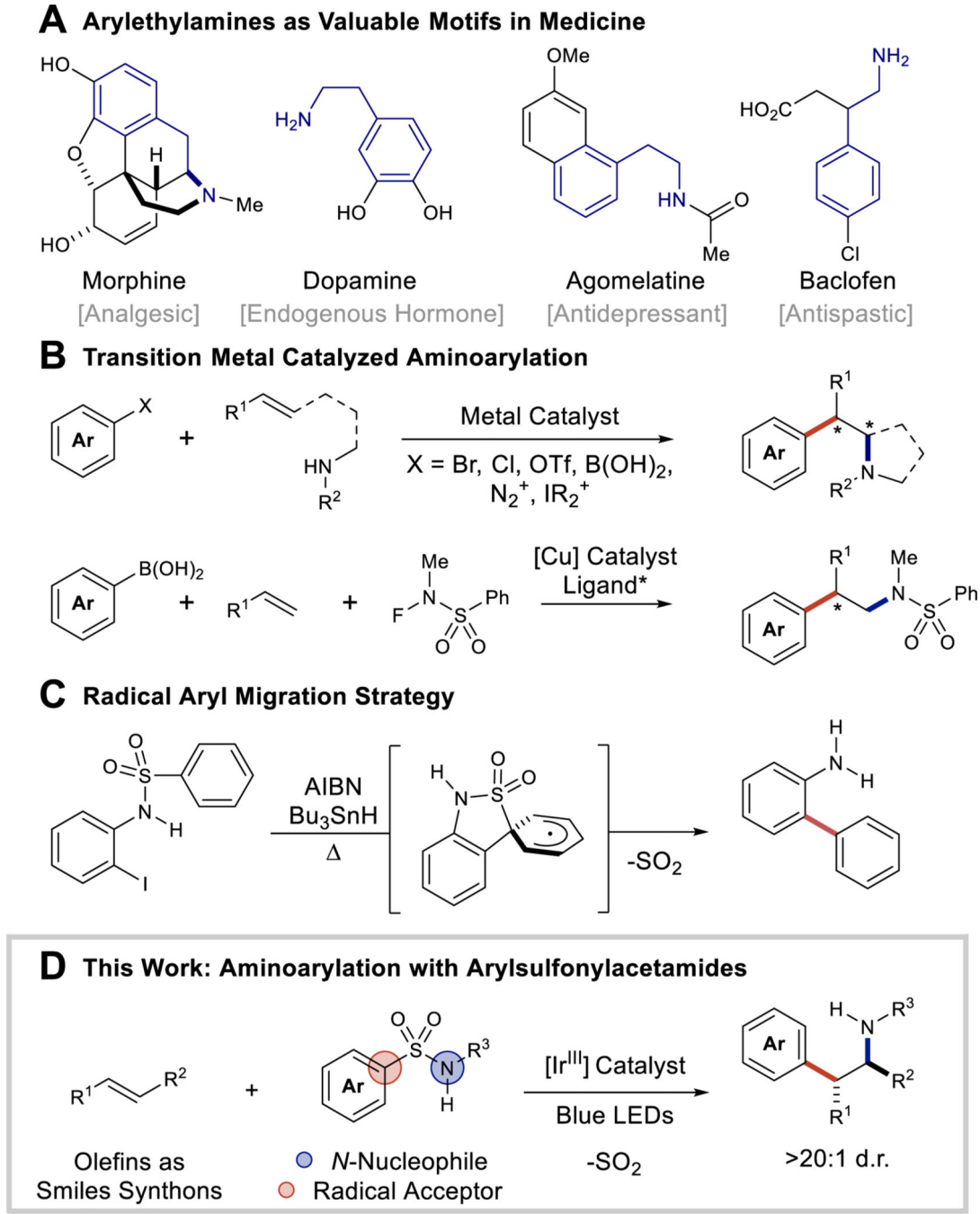

Figure 1. Strategies to access arylethylamines.

(**A**) Arylethylamines as valuable motifs. (**B**) Current approaches toward arylethylamines with transition-metal catalysis. (**C**) The Smiles-Truce rearrangement as an aryl migration strategy. (**D**) The method proposed herein. Me, methyl; Ph, phenyl; AIBN, azobisisobutyronitrile; $HSnBu_3$, tributyltin hydride.

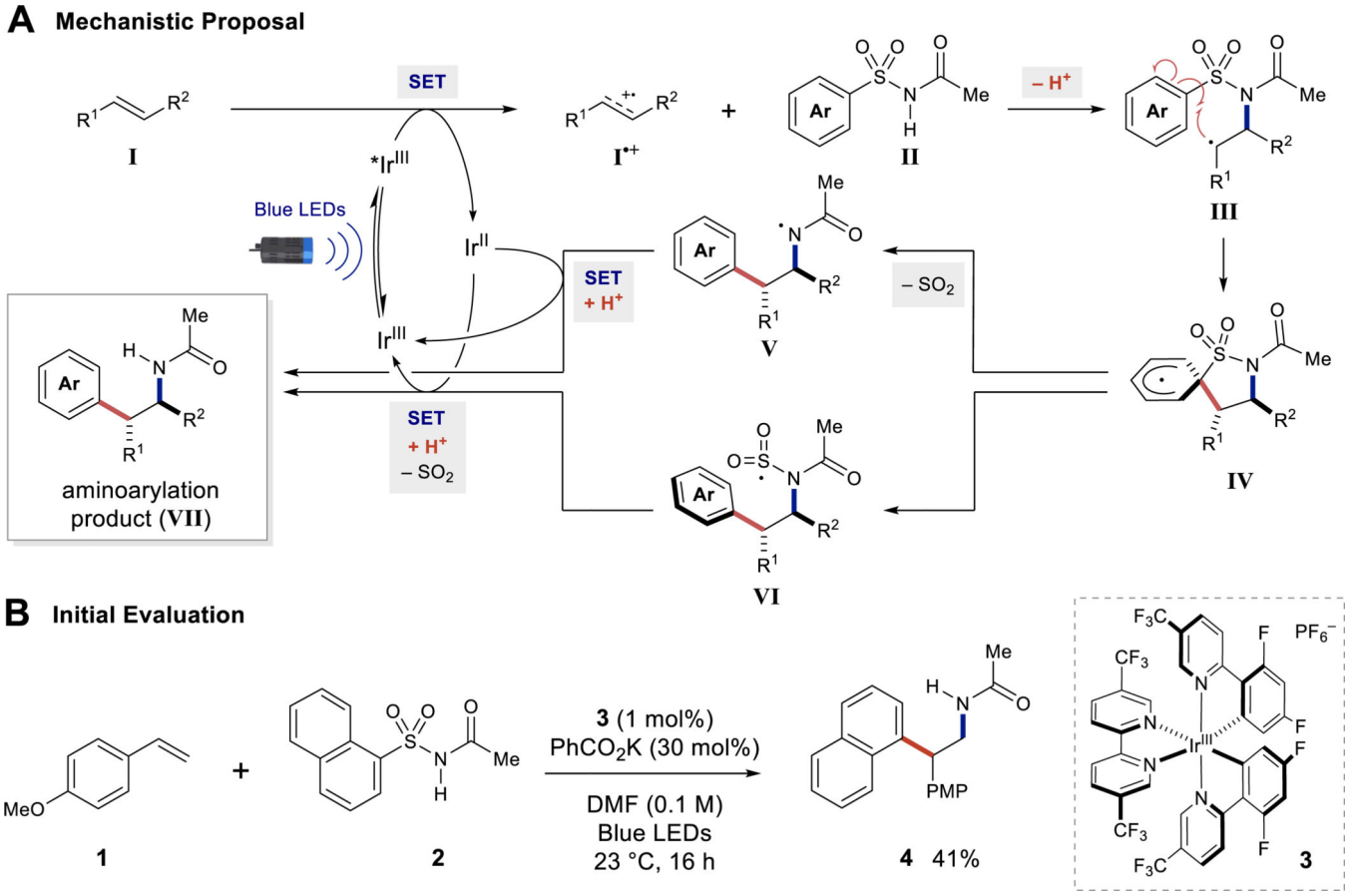

Figure 2. Proposed reaction design for aminoarylation with arylsulfonylacetamides.

(**A**) Proposed reaction mechanism. (**B**) Initial reaction evaluation. PMP, *p*-methoxyphenyl; Me, methyl; Ph, phenyl.

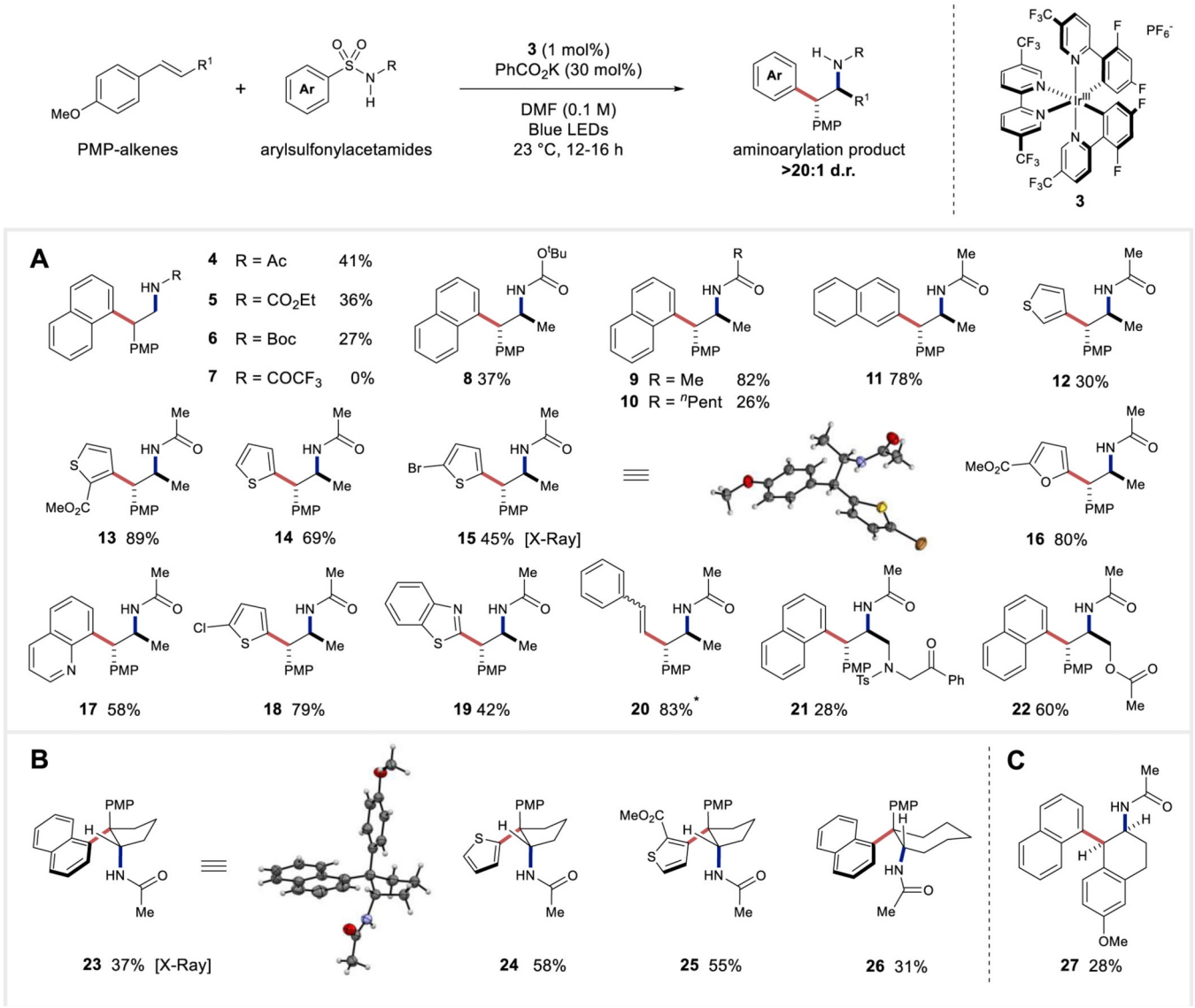

Figure 3. Exploration of substrate scope.

All yields are isolated yields. Relative configurations of products were assigned by analogy to **15** and **23**. (**A**) Evaluation of scope of aryl group. (**B**) Scope of cyclic *trans*-PMP alkenes. (**C**) Scope of a compatible cyclic *cis*-PMP alkene. PMP, *p*-methoxyphenyl; Ac, acetyl; Boc, *tert*-butyloxycarbonyl; Me, methyl. ^{n}Pen, pentyl; Ph, phenyl, Ts, tosyl. *2:1 mixture of E/Z alkene diastereomers.

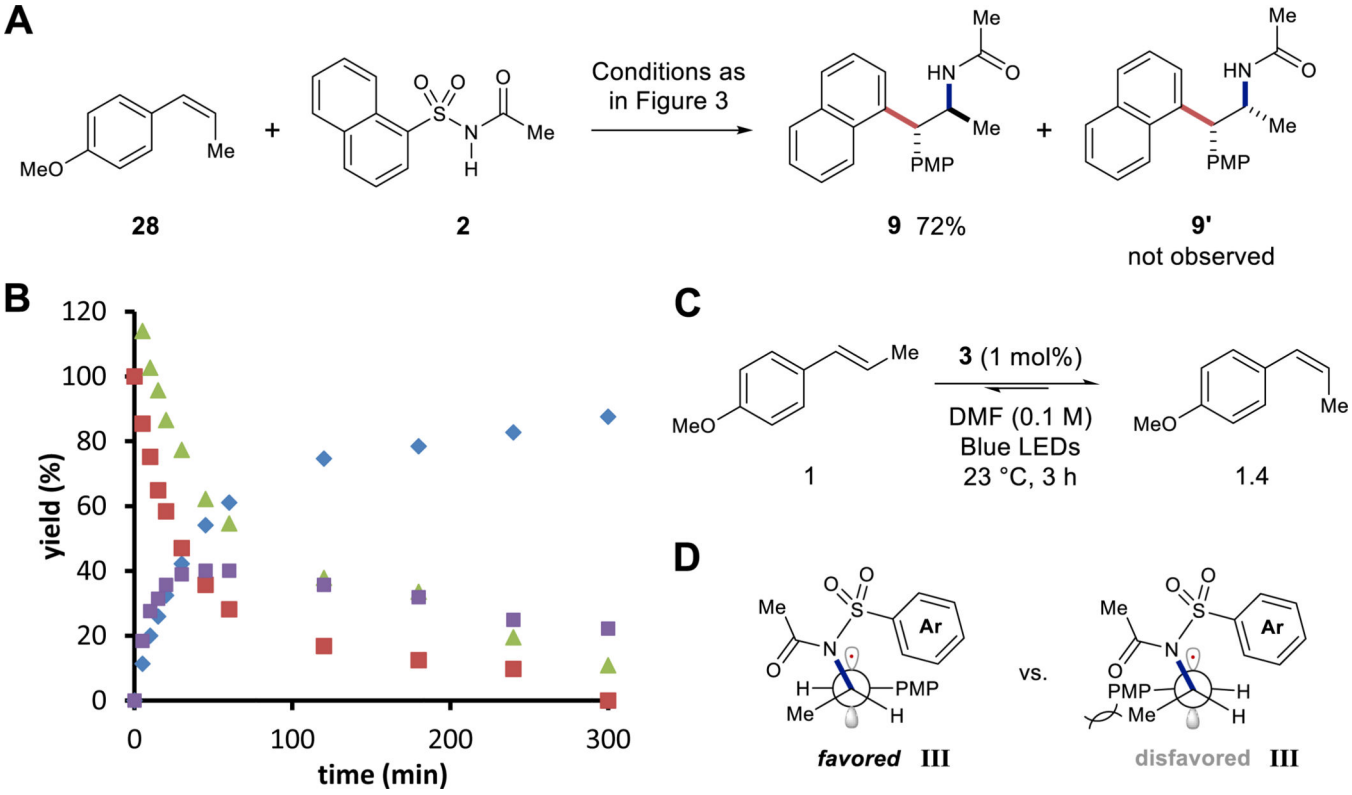

Figure 4. Experiments to probe reaction mechanism.

(**A**) Aminoarylation with *(Z)*-anethole (28). (**B**) Tracking reaction progress for aminoarylation with *(Z)*-anethole (28) (▲ = **2**, ■ = *(Z)*-anethole, ♦ = **9**, ■ = *(E)*-anethole). (**C**) Determination of the photostationary state for anethole isomers catalyzed by **3**. (**D**) Favored and disfavored conformations for intermediate III.