Complexity-Generating Transformations Enabled by Intramolecular Radical Migration: Alkyl–Arylation of Simple Olefins

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Abstract: A free-radical cascade approach has enabled the development of a synthetically versatile alkyl–arylation of olefins. This transformation engages an excellent range of olefins, from mono- to tetrasubstituted, without requiring directing or electronically activating groups. Further synthetic advantages, such as the facile generation of quaternary centers and the introduction of heteroaryl groups with Lewis basic nitrogen atoms, also complement transition-metal-catalyzed alkyl–arylation. Vicinal stereoarrays were generated with high levels of diastereoselectivity. The synthetic potential of this transformation was demonstrated by serving as the key step in a concise synthesis of oliceridine, a new painkiller that received FDA approval in 2020.

Carbon–carbon bond-forming reactions are central approaches for preparing valuable organic compounds such as medicines, agrochemicals, materials, and fragrances.[1] Transformations that forge multiple C–C bonds from simpler starting materials are particularly enabling for the rapid construction of complex molecular frameworks.[2] Accordingly, extensive efforts over the past few years have sought to establish a new C(sp^3)–C bond at both C(sp^2) sites in olefins in an intermolecular fashion.[3,4] These vicinal alkene difunctionalizations have proven impactful in large part because simple olefins are feedstock chemicals. Even in more complex frameworks, these groups are still ubiquitous or can easily be installed.[5]

Given the importance of aromatic moieties in bioactive compounds and the continued underrepresentation of sp^3 content in pharmaceuticals,[6] vicinal alkyl–arylations of olefins hold a privileged position among alkene difunctionalizations. In this arena, transition-metal-catalyzed conjunctive couplings between olefins, aromatic substrates, and aliphatic substrates have received the most attention.[7,8] Conjunctive couplings, however, have overwhelmingly relied on olefins bearing additional functionality to promote olefin–catalyst interactions, which inherently restricts the products that may be obtained directly from these reactions. That functionality, whether a conjugated 'activating' group or an electronically isolated directing group, is needed to overcome the poor Lewis basicity of olefins and the propensity of transition metals to promote direct aryl–alkyl coupling. This limitation has been addressed[9] by converting the alkyl partner to a free radical that can add

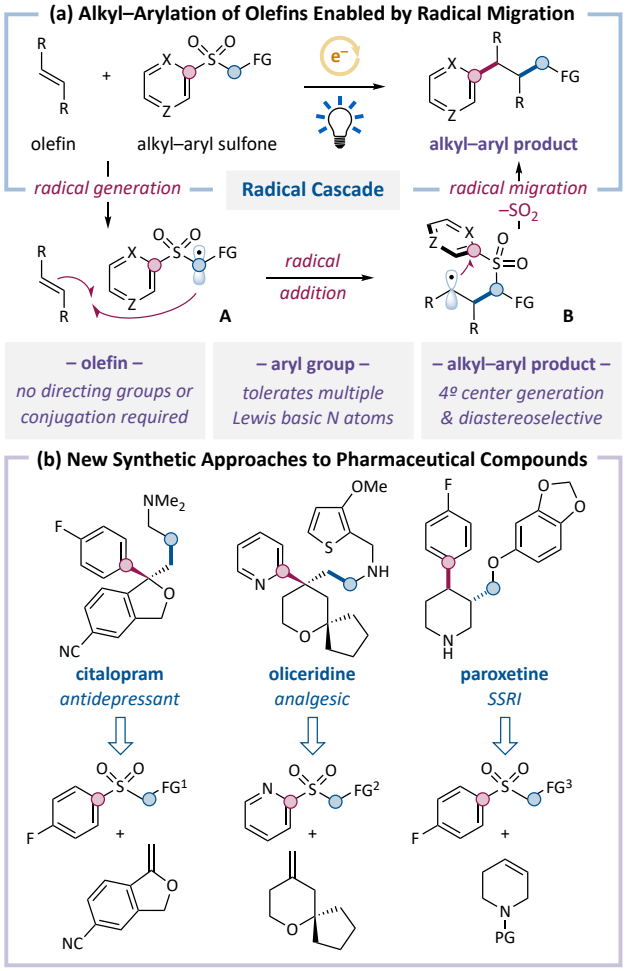


Figure 1. (a) General design and advantages of a free-radical alkyl–arylation of olefins. (b) Synthetic approaches to a selection of bioactive targets enabled by olefin alkyl–arylation.

directly to 'simple' olefins (i.e., not bearing activating or directing groups) without assistance from the metal, but this approach has only proven effective when using hindered, tertiary or electron-poor, highly fluorinated congeners to prevent[10] their direct, metal-mediated arylation.[11]

We thus hypothesized that a completely free-radical

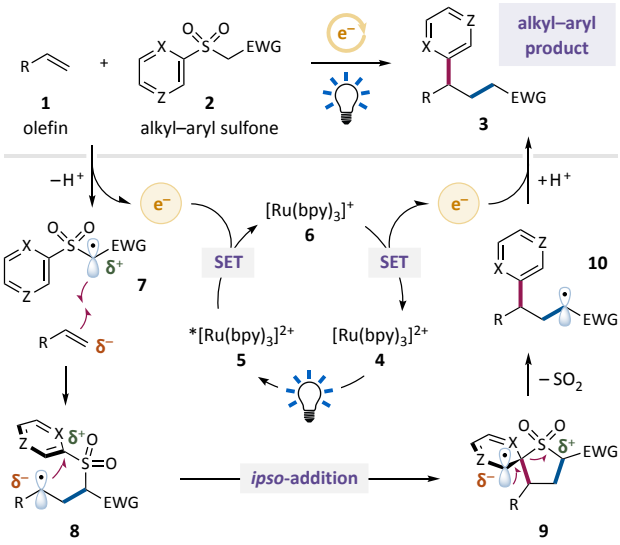


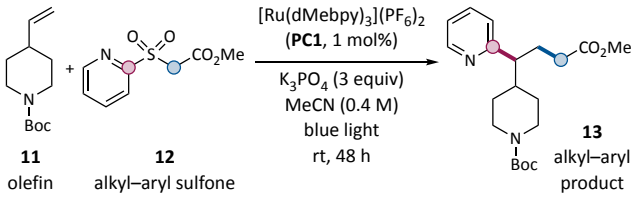
Figure 2. Mechanistic design of olefin alkyl–arylation enabled by a photoredox-catalyzed radical cascade. See text for details.

approach[12] would be well-suited to address these limitations. As shown in Figure 1a, we envisioned that simple alkyl–aryl sulfones,[13,14] straightforwardly prepared in 1–2 steps from readily available alkyl halides and aryl sulfinates or thiols, could add their alkyl and aryl groups across an olefin under photoredox activation[15] and extrude SO_2. Mechanistically, electrophilic sulfone-derived alkyl radical **A** would add to the olefin, generating the desired C(sp^3)–alkyl bond and a new alkyl radical (**B**). The latter intermediate would be well-poised for a key radical migration (radical Smiles-Truce Rearrangement) and desulfonylation to forge the C(sp^3)–aryl bond.[16,17] This approach should afford clear synthetic advantages. First, a wide scope of olefins is expected to add to electrophilic radical **A**, avoiding the need for activating or directing groups on the alkene. Second, the radical-migration-mediated arylation should accommodate biologically privileged[18] nitrogen-rich heteroaryl groups that often inhibit transition-metal catalysts. Finally, the elongated open-shell transition states involved in all steps should facilitate the generation of quaternary centers,[19] which is also challenging for transition metals, without forgoing diastereocontrol.[17c,f]

This transformation could also empower new synthetic approaches to a range of bioactive molecules, a selection of which are shown in Figure 1b. The structures depicted therein could all be retrosynthetically simplified to easily accessible olefin and sulfone precursors. The highlighted bonds would be introduced in a single step by the proposed alkyl–arylation, with standard functional-group manipulations completing the peripheral structures.

The mechanistic design for the alkyl–arylation of olefins (**1**) with alkyl–aryl sulfones (**2**) to afford product **3** is illustrated in Figure 2. Deprotonation of the acidic C–H site in alkyl–aryl sulfone **2** (pK_a = 11.4 in DMSO for $PhSO_2(COPh)CH_2$)[20] and single-electron oxidation of the resulting anion (not shown, $E_{1/2}^{red}$ [$PhSO_2(COPh)CH•$/ $PhSO_2(COPh)CH^-$] = +0.78 V vs. SCE in DMSO)[20] by an excited-state photoredox catalyst such as $Ru(bpy)_3^{2+}$ (**4**, $E_{1/2}^{red}$[$*Ru(bpy)_3^{2+}$ (**5**)/$Ru(bpy)_3^{+}$ (**6**)] = +0.77 V vs. SCE in MeCN)[21] would generate radical **7**. This radical would be highly electrophilic owing to the two adjacent electron-withdrawing groups. Addition to simple olefin **1** to form the first C–C bond and new alkyl radical **8** would therefore be polarity-matched and not require specific substituents on the alkene. Unstabilized alkyl radical **8** would then be well-poised for a [1,4]-radical migration, ultimately forging the second desired C–C bond while extruding SO_2. Importantly, both proposed steps of the radical migration would also be polarity-matched, further underpinning the reaction's projected generality. Specifically, the *ipso*-addition involving **8** would occur between the nucleophilic alkyl radical[22] and the electrophilic arylsulfonyl carbon. Resulting cyclohexadienyl radical **9** would then fragment to cleave the weak,[23] electrophilic C–S bond and restore aromaticity. Subsequent loss of SO_2 would generate electron-poor alkyl radical **10** ($E_{1/2}^{red}$ (EtCO)(Me)CH•/(EtCO)(Me)CH^-] = –0.55 V vs. SCE in DMSO), [24] which would receive one electron from the reduced, ground-state photoredox catalyst ($E_{1/2}^{red}$[$Ru(bpy)_3^{2+}$ (**4**)/$Ru(bpy)_3^{+}$ (**6**)] = –1.33 V vs. SCE in DMSO)[21] to generate an anion such as an enolate (not shown, pK_a = 27.1 in DMSO for (EtCO)(Me)CH).[24] Protonation of this anion, either from the more-acidic alkyl–aryl sulfone or the conjugate acid of an exogenous Brønsted base, would afford the desired alkyl–aryl product. Optimization studies between monosubstituted olefin **11** and alkyl–aryl sulfone **12** to afford model alkyl–aryl product **13** identified general conditions employing commercially available $[Ru(dMebpy)_3](PF_6)_2$ (**PC1**) as the photoredox catalyst under blue-light irradiation and K_3PO_4 as a Brønsted base in MeCN (Table 1). Using a fairly high

Table 1. Control Experiments for Alkyl–Arylation of Olefins.[a]

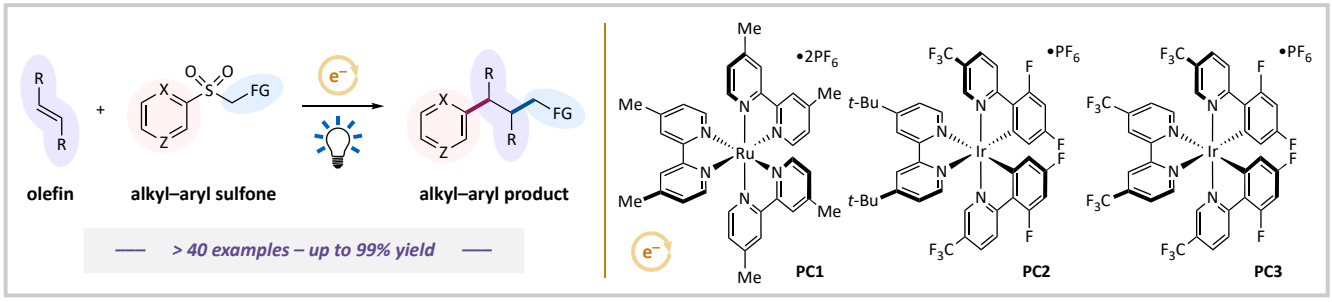


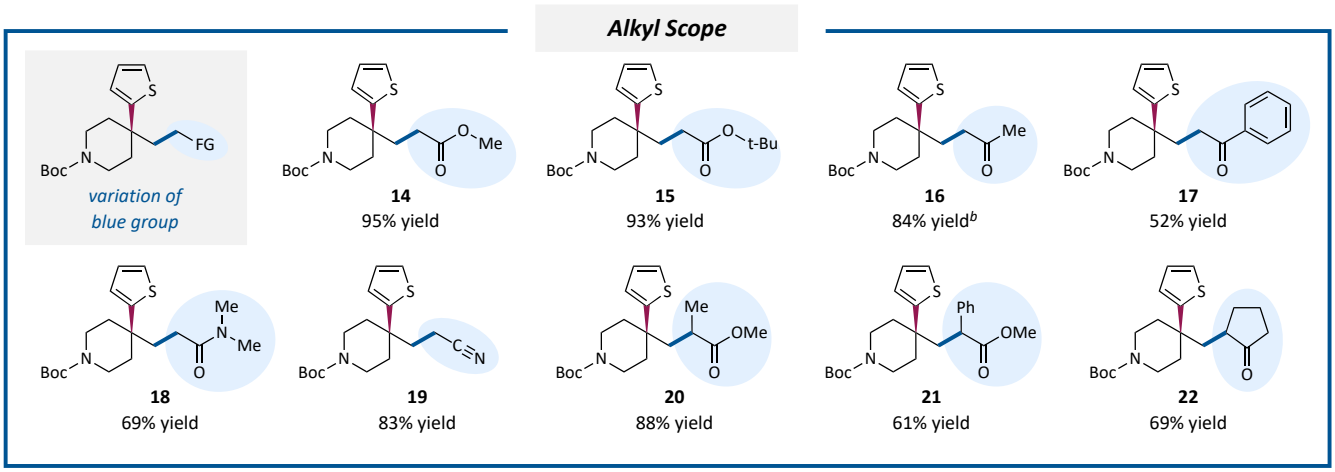
entry	deviation from standard conditions	yield (%)
1	none	81
2	$[Ru(bpy)_3](PF_6)_2$ (**4**) photocatalyst	71
3	$[Ir(dFCF_3ppy)_2(dtbbpy)]PF_6$ photocatalyst	73
4	$[Ir(dFCF_3ppy)_2(dCF_3bpy)]PF_6$ photocatalyst	7
5	$[Ir(ppy)_2(dtbbpy)]PF_6$ photocatalyst	74
6	*fac*-$[Ir(ppy)]_3$ photocatalyst	23
7	K_2CO_3 base	0
8	K_2HPO_4 base	0
9	DBU base	8
10	2 equiv olefin	74
11	1 equiv olefin	51
12	no degassing	78
13	open to air	79
14	no photocatalyst	0
15	no light	0
16	no base	0

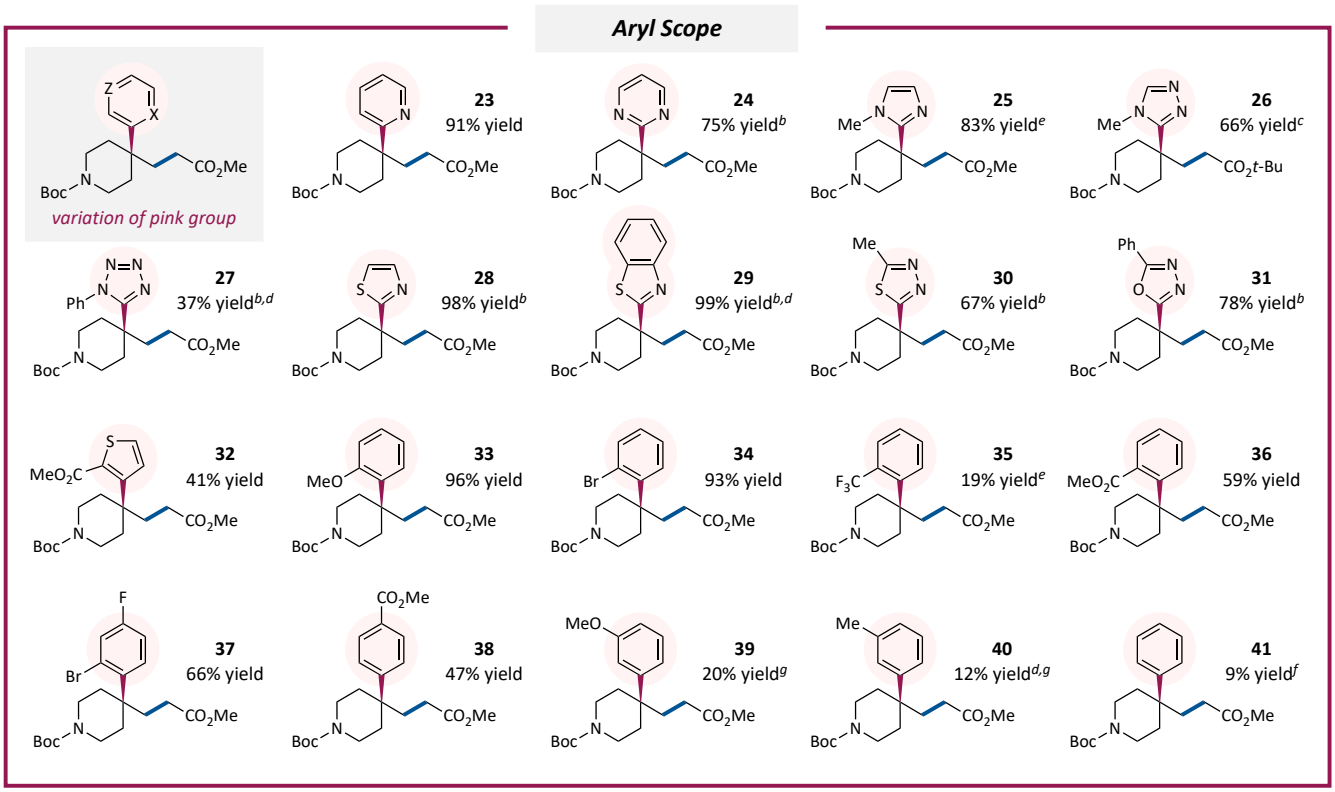
[a] Olefin **11** (3 equiv.), sulfone **12** (0.4 mmol), K_3PO_4 (3 equiv.), and $[Ru(dMebpy)_3](PF_6)_2$ (**PC1**, 1 mol%) were irradiated with blue light in MeCN (0.4 M in **12**) at rt for 48 h, with variations as noted. NMR yields. See SI for experimental procedures.

concentration of the limiting alkyl–aryl sulfone substrate (0.4 M) and a modest excess of the olefin (3 equiv.), the desired product was obtained in 81% yield after 48 h at ambient temperature (entry 1). $[Ru(bpy)_3](PF_6)_2$ gave a slightly lower yield (entry 2, 71% yield), which we attribute to Minisci-type additions of alkyl radicals to the unsubstituted bipyridyl ligands. Common Ir-based photoredox catalysts (up to 74% yield, entries 3–6) were also competent, as long as they were not highly oxidizing (7% yield, entry 4) or reducing (23% yield, entry 6).

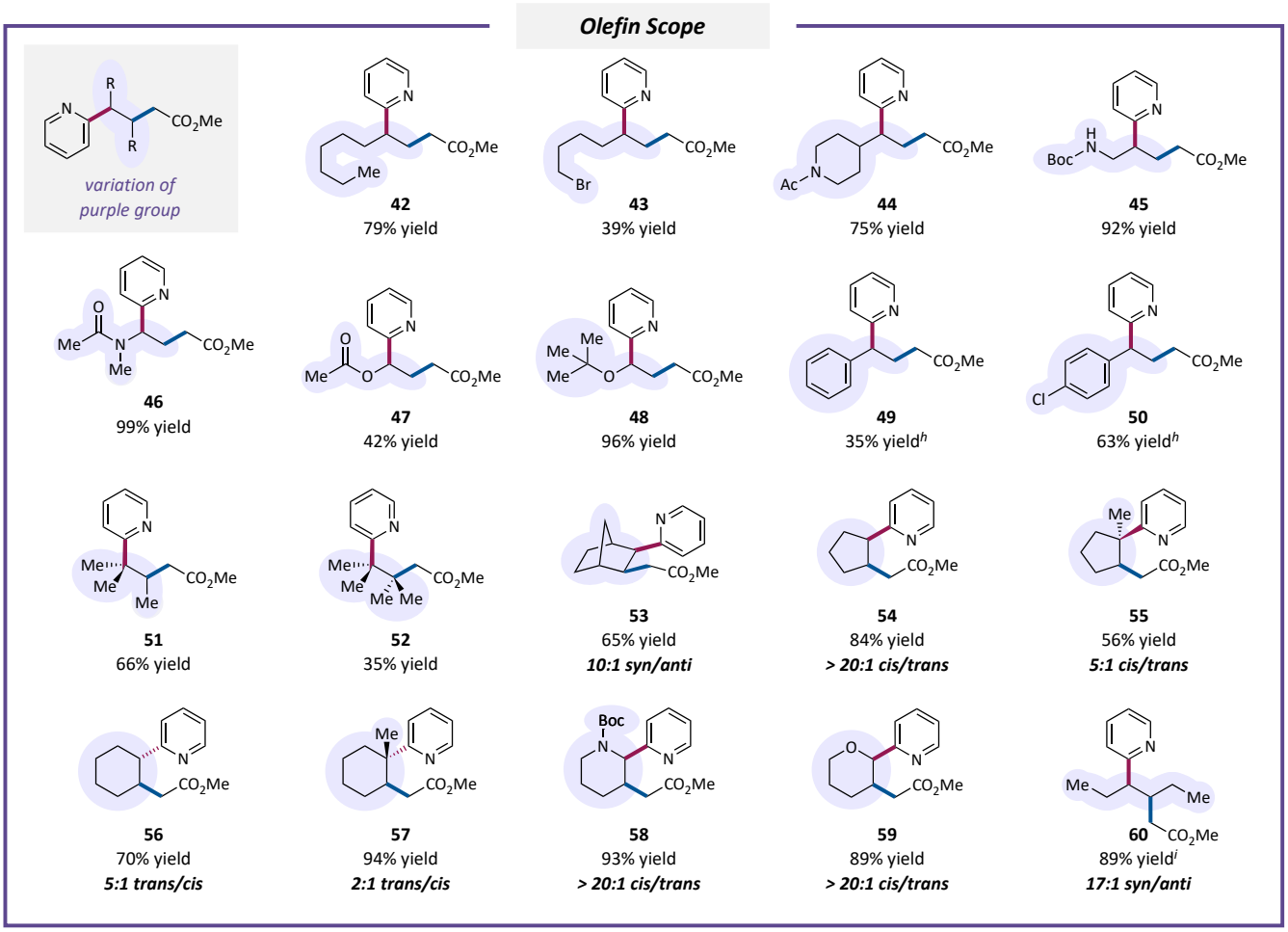
Table 2. Scope of Free-Radical Alkyl–Arylation of Olefins.[a]







(Table 2 Continued)



[a] Standard conditions follow Table 1, entry 1. Yields of isolated products. All chiral products are racemic. See SI for experimental procedures. [b] Catalyst **PC2** (1 mol%). [c] Catalyst **PC3** (1 mol%). [d] DMSO as solvent or cosolvent. [e] NMR yield. [f] LC yield. [g] Mixture of regioisomers, see SI. [h] Green LED lamp. [i] Results with *trans*-3-hexene. With *cis*-3-hexene, **60** was obtained in 88% yield and 15:1 *syn*/*anti*.

A selection of common inorganic or organic bases other than K_3PO_4 were unsuccessful (entries 7–9, 0–8% yields). Only a minimal decrease in efficiency occurred when a smaller excess of olefin was used (entry 10, 2 equiv., 74% yield), whereas 51% yield was obtained at equimolar stoichiometry (entry 11). More-substituted olefins, however, reacted efficiently in 1:1 stoichiometries (95% yield, see Scheme 1). Yields were unaffected when the mixture was not degassed or when the reaction was performed open to air (entries 12–13, 79–80% yields). The photoredox catalyst, light, and base were all essential for obtaining the desired product (entries 14–16, 0% yield).

The scope of the free-radical olefin alkyl–arylation is detailed in Table 2. The alkyl group featured a selection of resonance-withdrawing functionalities adjacent to the reactive alkyl site in the sulfone, including esters, ketones, amides, and nitriles (**14**–**19**, 52–95% yields). The electron-withdrawing group may assist in many elementary steps (see Figure 2 and discussion), but we hypothesize that it is mainly required to facilitate the single-electron reduction of the final open-shell intermediate (**10**, Figure 2). Additional substitution on the alkyl group was well-tolerated, with methyl, phenyl, and cyclic, branched products obtained in 61–88% yields (**20**–**22**). All alkyl groups added regioselectively to the olefin, forming the more-stable radical following the first radical-addition step in the proposed mechanism (**8**, Figure 2).

A range of useful aryl groups, which are added to the olefin by radical migration, were tolerated. Heteroaromatic motifs with different ring sizes and multiple Lewis basic nitrogen atoms reacted well. Specifically, products with pyridine, pyrimidine, imidazole, triazole, tetrazole, thiazole, benzothiazole, thiadiazole, oxadiazole, and thiophene rings added to the olefin were obtained in modest-to-excellent efficiencies (**23**–**32**, 37–99% yields). Benzene derivatives could also be introduced. *ortho*-Substituted phenyl groups performed best, followed by *para*-, and then *meta*-substituted congeners. *ortho*-Methoxy, bromo, CF_3, and CO_2Me substituents, as well the disubstituted *o*-bromo-*p*-fluoro pattern on the migrating phenyl ring gave products **33**–**37** in 19–96% yields (all above 50% yield except for CF_3 product **35**). An electron-withdrawing *para*-CO_2Me substituent was also tolerated (**38**, 43% yield). Finally, *meta*- and unsubstituted phenyl substrates afforded products **39**–**41** in low yields (9–20%), with **39** and **40** isolated as mixtures of *ortho*- and *para*-products (see SI). In contrast to many transition-metal-catalyzed cross-coupling manifolds,[10] arylated

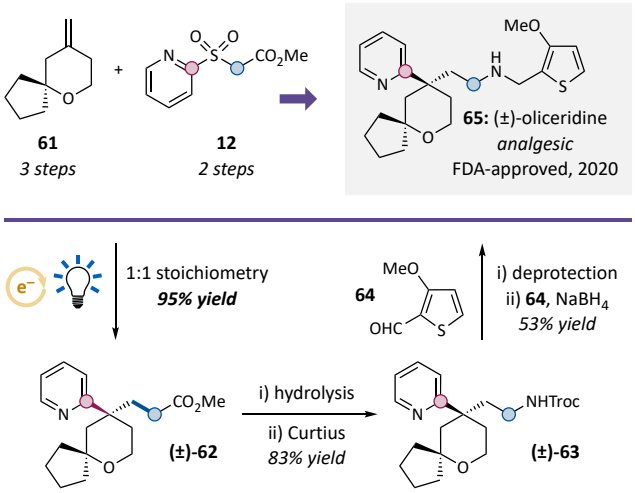
quaternary centers were generated without complication throughout this study. In some cases, especially those involving electron-poor aryl groups in the sulfone, more-oxidizing Ir-based photoredox catalysts **PC2** or **PC3** provided superior yields (see SI).

A structurally diverse range of olefins also successfully underwent the alkyl–arylation, further demonstrating the synthetic potential of this free-radical approach. Monosubstituted olefins reacted well, including 1-octene, examples bearing a distal alkyl bromide or amide, and a Boc-protected allylic amine (**42**–**45**, 39–92% yields). Electron-rich olefins including an enamide, an enol ester, and an enol ether also reacted efficiently (**46**–**48**, 42–99% yields). Styrene (**49**, 35% yield) and *p*-chlorostyrene (**50**, 63% yield) were viable olefin partners. Notably, even products derived from tri- and even tetrasubstituted olefins were cleanly isolated (**51**, 66% yield and **52**, 35% yield, respectively). Electron-poor olefins such as acrylates were unproductive. Lastly, we generated vicinal stereoarrays by employing 1,2-disubstituted or trisubstituted olefins. *syn*-Products were obtained in good yields and stereoselectivities when starting from rigid norbornene (**53**, 65% yield, 10:1 dr) and five-membered cyclopentene (**54**, 84% yield, >20:1 *cis*/*trans*), presumably because the putative *cis*-fused intermediates in these systems are much more stable than their *trans*-fused counterparts.[25] Product **55** bearing a quaternary benzylic center, derived from 1-methylcyclopentene, was generated in lower dr (56% yield, 5:1 *cis*/*trans*). Six-membered products derived from cyclohexenes and heterocyclic analogs efficiently provided cyclohexane, pipreridine, and tetrahydropyran products **56**–**59** (70–93% yields). Interestingly, the 6-membered heterocyclic alkenes underwent *syn*-alkyl–arylation in high distereoselectivity (>20:1 *cis*/*trans* for **58** and **59**), whereas *trans*-selectivity was observed for cyclohexane product **56** (5:1 *trans*/*cis*, see SI for a detailed discussion). Analogously to the five-membered products, cyclohexane **57**, derived from 1-methylcyclohexene and featuring a new quaternary center, gave lower dr (2:1 *trans*/*cis*). Lastly, internal, acyclic *trans*-3-hexene afforded **60** in 89% yield and good 17:1 *syn*-selectivity. The isomeric starting material, *cis*-3-hexene, delivered same product was obtained in similar efficiency and *syn*-selectivity (88% yield, 15:1 *syn*/*anti*). We postulate that this stereochemical convergence arises from rotameric equilibration between alkyl-radical intermediates arising from addition of the olefin to the initial, electrophilic alkyl radical, but before radical migration (e.g., **8** in Figure 2), which is unaffected by the geometry of the olefin substrate (see SI).[17c,f]

Finally, we sought to demonstrate the utility of this alkyl–arylation in a new synthesis of oliceridine, a novel painkiller approved by the FDA in 2020 (Scheme 1).[26] To this end, olefin **61** (3 steps from 3-buten-1-ol and cyclopentanone) underwent alkyl–arylation with sulfone **12** (2 steps from 2-mercaptopyridine and methyl bromoacetate) using 1:1 stoichiometry, forming alkyl–arylation product **62**in 95% yield. The methyl ester was first converted to protected amine **63** by hydrolysis and a modified Curtius rearrangment (83% yield over 2 steps), and oliceridine was ultimately obtained by Troc deprotection and reductive amination with thienyl aldehyde **64** (53% yield from **63** over 2 steps; 44% from **62** over 4 steps).

In conclusion, a free-radical cascade approach was leveraged to develop a synthetically versatile alkyl–arylation of olefins. Owing to its free-radical mechanistic elements, this transformation engages an excellent range of olefins, from mono- to tetrasubstituted, without requiring directing or electronically activating groups. Key synthetic outcomes resulting from the intramolecular nature of the aryl migration, such as the facile generation of quaternary centers and the introduction of heteroaryl groups with Lewis basic nitrogen atoms, further complement transition-metal-catalyzed alkyl–arylation. Finally, this method can generate vicinal stereoarrays, often exhibiting good diastereoselectivity. We are confident that new cascades featuring intramolecular radical migration will ultimately empower a further suite of complexity-generating transformations.

Scheme 1. Concise Synthesis of (±)-oliceridine Featuring a Key Olefin Alkyl–Arylation.[a]



[a] Alkyl–arylation of olefin **61** (1 equiv.) with alkyl–aryl sulfone **12** (1 equiv.) served as a key step in a new synthesis of (±)-oliceridine (**65**). See SI for detailed procedures.

Acknowledgments

The authors are grateful for financial support from the Pennsylvania State University Eberly College of Science (ECoS). S.M.S. was supported by a National Science Foundation REU program (CHE-250927), and A.S. thanks ECoS an Erickson Discovery Grant. David Iwig and the Booker group (Penn State University) are thanked extensively for obtaining HRMS data. Christy George (Penn State University) provided support in the acquisition of NMR data.

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