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Introduction

Transformations that form multiple C–C bonds can significantly expedite the synthesis of valuable organic compounds such as medicines, agrochemicals, materials, fragrances, and food products.¹⁻¹⁷ Olefins are attractive substrates since they are ubiquitous in both chemical feedstocks and complex natural products, they can be installed in a variety of settings,¹⁸ and they are inherently well-suited to vicinal difunctionalization by spanning adjacent carbons. Intermolecular difunctionalizations forming two C–C bonds have thus received significant interest over the past 10–15 years.^{3–17,19–32}

Given the importance of aromatic moieties in bioactive compounds and the continued underrepresentation of sp³ content in pharmaceuticals,^{33,34} alkyl–arylations of olefins are critical tools in the synthetic arsenal. Transition-metal-catalyzed conjunctive couplings between an olefin, an aromatic partner, and an aliphatic partner have received the most attention to this end.^{35–47} Productive olefins, however, have overwhelmingly required either an activating group (conjugated π -bond or heteroatom) or a Lewis basic directing group (Fig. 1a, bottom) to promote olefin–catalyst binding, which restricts the alkenes that can be valorized and the products that can be

A free-radical design featuring an intramolecular migration for a synthetically versatile alkyl–(hetero) arylation of simple olefins†

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A free-radical approach has enabled the development of a synthetically versatile alkyl–(hetero)arylation of olefins. Alkyl and (hetero)aryl groups were added concurrently to a full suite of mono- to tetrasubstituted simple alkenes (*i.e.*, without requiring directing or electronically activating groups) for the first time. Key advances also included the introduction of synthetically diversifiable alkyl groups featuring different degrees of substitution, good diastereocontrol in both cyclic and acyclic settings, the addition of biologically valuable heteroarenes featuring Lewis basic nitrogen atoms as well as simple benzenes, and the generation of either tertiary or quaternary benzylic centers. The synthetic potential of this transformation was demonstrated by leveraging it as the key step in a concise synthesis of oliceridine, a new painkiller that received FDA approval in 2020.

obtained. To unlock the full potential of alkyl-arylations, they must equally engage simple olefins (Fig. 1a, top).

Some metal-catalyzed alkyl-arylations of simple alkenes have thus been developed.48-55 With one exception,55 they all engage the alkyl partner as an alkyl radical (A, Fig. 1b), leveraging the better propensity of these radicals than of transition metals to add to simple alkenes. This step generates a new alkyl radical (B) that binds to the metal catalyst, forming the desired product after reductive elimination. To avoid the counterproductive olefin-free arylation of the alkyl partner, however, these strategies have only succeeded with tertiary or fluoroalkyl groups that are themselves reluctant to undergo metal-mediated arylation.56-58 These fully substituted alkyl groups are synthetically non-diversifiable, which limits the versatility of these alkyl-arylations (the non-radical method⁵⁵ adds primary alkyl groups, but only restricted 1,1-disubstituted simple alkenes were productive, and its use of alkylmetal reagents compromises its functional-group tolerance).

Further key synthetic challenges have pervaded these alkylarylations of simple olefins⁴⁸⁻⁵⁵ (Fig. 1e). Beyond (1) the addition of non-diversifiable tertiary or fluoroalkyl groups that features only a single exception,⁵⁵ (2) these systems are mostly restricted to monosubstituted simple alkenes. The only two exceptions are the aforementioned alkyl-arylation that only engages 1,1disubstituted simple alkenes with alkylmetal reagents,⁵⁵ as well as an Fe-catalyzed protocol that can employ mono- and 1,2disubstituted congeners and that relies on aryl Grignard reagents.⁵⁴ Moreover, only single, disparate reports describe (3) stereocontrol (affording *trans*-alkyl-aryl products for cyclic olefin substrates and proving unselective with an acyclic congener),⁵⁴ (4) the introduction of biologically valuable *N*-



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Diversifiable alkyl groups

Aryls & N-rich heteroaryls

3° & 4° benzylic products

simple olefin alkyl-

(hetero)arylation

radical migration

Diastereocontrol

-SO₂

radica

addition

FG

С







	Ref	— Partr aryl	ners — alkyl	Catalyst(s)	Olefin substitution	New alkyl subst'n	N-Hetero- aryl pdts	Benzylic subst'n	Relative stereocontrol
	This work	alkyl–aryl	sulfone	photoredox	mono 1,1-di 1,2-di tri tetra	1° & 2° (α-FG)	yes	3° & 4°	cis (cyclic) syn (acyclic)
:	48	halide	B(OH) ₂	Cu	mono	CF ₃	none	3°	n/a
	49,53	halide	halide	Ni	mono	3°	1 example (non-basic)	3°	n/a
	51	oxalate	halide	Ni & photoredox	mono	3°	yes	3°	n/a
	54	halide	MgX	Fe	mono & 1,2-di	3° & CF ₂ R	none	3°	trans (cyclic) low dr (acyclic)
	55	MgX/ZnX	triflate	Ni	1,1-di	1°	1 example (non-basic)	4°	n/a

Fig. 1 Comparison of leading transition-metal (TM)-catalyzed olefin alkyl-arylations to this work. (a) Simple olefins are ideal for alkyl-arylation but have proven challenging to engage. Most productive olefins feature directing or activating groups. (b) TM-catalyzed alkyl-arylations of simple olefins activate the alkyl partner as a radical and employ non-diversifiable tertiary or fluoroalkyl groups to avoid metal-mediated coupling of this radical to the aryl partner. (c) This work employs alkyl-aryl sulfones under free-radical conditions to deliver alkyl and aryl groups to olefins, which affords several synthetic advances. (d) Representative synthetic approaches to bioactive targets enabled by this work. (e) Comparison of key synthetic capabilities of this work to TM-catalyzed alkyl-arylations of simple olefins.

heteroarenes,^{51,59} and (5) the generation of quaternary benzylic products⁵⁵ (with this exception generating only quaternary products).

Design plan

We thus hypothesized that a completely free-radical approach60,61 could underpin a more versatile platform. As shown in Fig. 1c, we envisioned that simple alkyl-(hetero)aryl sulfones,62,63 straightforwardly prepared in 1-2 steps64,65 from alkyl halides and (hetero)aryl sulfinates or thiols, could add their alkyl and (hetero)aryl groups across an olefin under photoredox activation⁶⁶⁻⁶⁸ and extrude SO₂. Mechanistically, electrophilic sulfone-derived alkyl radical C would add to the olefin, generating the desired C(sp³)-alkyl bond and new alkyl radical

D. The latter intermediate would be well-poised for a radical migration (radical Smiles-Truce rearrangement) and desulfonylation to forge the C(sp³)-aryl bond.⁶⁹⁻⁸⁸ This design should enable several advances. (1) Desulfonylation from the alkyl fragment and the use of a second, simple functional group at this position should enable the introduction of synthetically diversifiable alkyl groups with multiple substitution patterns. (2) A wide scope of simple olefins should add to electrophilic radical C.89 (3) The cyclic intermediates generated by the intramolecular radical-mediated migration should provide opportunities to confer stereocontrol.^{77,90,91} (4) In addition to simple benzenes, the metal-free migratory $C(sp^3)$ -(hetero)aryl bond-forming step should also accommodate biologically privileged⁹² N-rich heteroaryl groups that often inhibit transitionmetal catalysts. Finally, (5) elongated open-shell transition



Fig. 2 Mechanistic design of radical-mediated olefin alkyl-(hetero) arylation. See text for details

states should facilitate the generation of either tertiary or quaternary benzylic centers,93 which is also challenging for transition metals.

New synthetic approaches to bioactive molecules potentially empowered by this approach are illustrated in Fig. 1d. The colored, bold bonds would be forged by the proposed alkyl-(hetero)arylation, and standard functional-group manipulations would complete the peripheries.

The detailed mechanistic design for the alkyl-(hetero)arylation of olefins (1) with alkyl-(hetero)aryl sulfones (2) to afford products 3 is illustrated in Fig. 2. Deprotonation of 2 (pK_a]- $PhSO_2(COPh)CH_2$ = 11.4 in DMSO)⁹⁴ and single-electron oxidation of the resulting anion $(E_{1/2}^{\text{red}} [PhSO_2(COPh)CH'/$ $PhSO_2(COPh)CH^{-} = +0.78 V \nu s. SCE in DMSO)^{94}$ by an excitedstate photoredox catalyst (4, $E_{1/2}^{\text{red}}[\text{*Ru(bpy)}_3^{2+} (5)/\text{Ru(bpy)}_3^+ (6)]$ = +0.77 V vs. SCE in MeCN)^{95,96} would generate alkyl radical 7. Addition of simple olefin 1 to this electrophilic radical⁸⁹ would form the first C-C bond and new alkyl radical 8. The latter intermediate would be well-poised for a [1,4]-(hetero)aryl migration, forging the second desired C-C bond via intermediate 9 and extruding SO2. Resulting electron-poor alkyl radical **10** $(E_{1/2}^{\text{red}} [(EtCO)(Me)CH'/(EtCO)(Me)CH^{-}] = -0.55 \text{ V} \text{ vs. SCE in}$ DMSO)97 would react with reduced, ground-state photoredox catalyst (6, $E_{1/2}^{\text{red}}[\text{Ru}(\text{bpy})_3^{2+}(4)/\text{Ru}(\text{bpy})_3^{+}(6)] = -1.33 \text{ V} \nu s.$ SCE in DMSO)⁹⁵ to generate an anion such as an enolate $(pK_a](-$ EtCO)(Me)CH] = 27.1 in DMSO),⁹⁷ protonation of which would afford the desired alkyl-(hetero)aryl product.

Results

Model studies between simple olefin 11 and alkyl-(hetero)aryl sulfone 12 to afford 13 identified optimal conditions employing commercially available $[Ru(dMebpy)_3](PF_6)_2$ (PC1) as the photocatalyst and K₃PO₄ as the base in MeCN (Table 1). Using a modest excess of the olefin (3 equiv.), the desired product was

Table 1 Control experiments for alkyl–(hetero)arylation of olefins^a



1

1	None	81	
2	$[Ru(bpy)_3](PF_6)_2$ (4) photocatalyst	71	
3	[Ir(dFCF ₃ ppy) ₂ (dtbbpy)]PF ₆ photocatalyst	73	
4	[Ir(dFCF ₃ ppy) ₂ (dCF ₃ bpy)]PF ₆ photocatalyst	7	
5	[Ir(ppy) ₂ (dtbbpy)]PF ₆ photocatalyst	74	
6	<i>fac</i> -[Ir(ppy)] ₃ photocatalyst	23	
7	4CzIPN photocatalyst	73	
8	K ₂ CO ₃ base	0	
9	K ₂ HPO ₄ base	0	
10	DBU base	8	
11	2 equiv. olefin	74	
12	1 equiv. olefin	51	
13	No degassing	78	
14	Open to air	79	
15	No photocatalyst	0	
16	No light	0	
17	No base	0	

^a Olefin 11 (3 equiv.), sulfone 12 (0.4 mmol, 1 equiv.), K₃PO₄ (3 equiv.), and [Ru(dMebpy)₃](PF₆)₂ (PC1, 1 mol%) were irradiated with blue light (440 nm) in MeCN (0.4 M in 12) at rt for 48 h with variations as noted. NMR yields. See ESI for detailed procedures.

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). 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). 4CzIPN could also be used in this role (entry 7, 73% yield), enabling a fully transition-metal-free protocol. A selection of alternate inorganic or organic bases were unsuccessful (entries 8-10, 0-8% yields). A minimal decrease in efficiency occurred when using a smaller excess of olefin (entry 11, 2 equiv., 74% yield), and 51% yield was obtained at equimolar stoichiometry (entry 12). Other olefins, however, reacted efficiently in 1:1 stoichiometries (see synthesis of oliceridine below). Yields were unaffected when the mixture was not degassed or when the reaction was performed open to air (entries 13-14, 79-80%) yields). The photoredox catalyst, light, and base were all essential (entries 15-17, 0% yield).

The scope of this transformation is detailed in Table 2. We sought to demonstrate clearly that this system could simultaneously address all the above-mentioned challenges: (1) using diversifiable and differently substituted alkyl groups, (2) engaging simple alkenes with any degree of substitution, (3) affording diastereocontrol, (4) adding benzenes and N-heteroarenes, and (5) generating tertiary and quaternary benzylic centers.

Addressing challenge (1), a range of primary alkyl groups featuring carbonyls (esters, ketones, and an amide), nitrile, or

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^{*a*} Standard conditions follow Table 1, entry 1. Yields of isolated products. See ESI for experimental procedures. ^{*b*} NMR yield. ^{*c*} Olefin (1 equiv.) and green light (510–575 nm). ^{*d*} Using *trans*-3-hexene. With *cis*-3-hexene, **39** was obtained in 88% yield and 15:1 *syn/anti*. ^{*e*} Catalyst **PC2** (1 mol%). ^{*f*} Catalyst **PC3** (1 mol%). ^{*g*} DMSO as solvent or cosolvent. ^{*h*} Mixture of regioisomers, see ESI.

Table 2 (contd.)



sulfonyl functionalities were added to a simple olefin, accompanied by a 2-thienyl unit (**14–20**, 52–95% yields). Secondary alkyl groups were also added without complication, affording tertiary alkyl products **21–23** in 61–88% yields.

Addressing challenge (2), a full suite of olefin substitution patterns was tolerated. Monosubstituted olefins reacted well, including 1-octene, examples bearing an alkyl bromide or amide, and a Boc-protected allylic amine (24–27, 66–92% yields). Electron-rich olefins including an enamide and an enol ether reacted very efficiently, affording products 28–29 in 96– 99% yields. Styrene (product 30, 35% yield) and *p*-chlorostyrene (product 31, 63% yield) were also viable alkenes. Notably, products 32 and 33 represented the first successful alkyl–arylations of simple tri- and tetrasubstituted olefins. Electrondeficient olefins such as acrylates were unproductive.

Next, 1,2-disubstituted alkenes underwent alkyl–(hetero) arylation diastereoselectively, addressing challenge (3). Products were obtained in good yields and *syn*-selectivities using rigid norbornene (**34**, 65% yield, 10:1 dr) and five-membered cyclopentene (**35**, 84% yield, >20:1 *cis/trans*), presumably because the putative *cis*-fused intermediates in these systems are the most-stable diastereomers.^{98,99} Six-membered cyclohexane, piperidine, and tetrahydropyran products **36–38** were also formed efficiently (70–93% yields). Interestingly, 6-membered heterocyclic alkenes underwent *syn*-alkyl–arylation in high distereoselectivity (>20:1 *cis/trans* for **37** and **38**), whereas *trans*-selectivity was observed when using cyclohexene (**36**, 5:1 *trans/cis*). Lastly, internal, acyclic *trans*-3-hexene

afforded **39** in 89% yield and 17:1 *syn*-selectivity (*cis*-3-hexene gave a nearly identical outcome: 88% yield, 15:1 *syn/anti*), representing the first stereoselective alkyl–arylation of a simple acyclic olefin. The stereochemical convergence observed for **39** likely arises from equilibration between alkyl-radical rotamers generated by addition of the olefin to the initial, electrophilic alkyl radical, but before (hetero)aryl migration (*e.g.*, **8** in Fig. 2). This equilibrium is unaffected by the geometry of the olefin substrate.⁷⁷ A preliminary explanation of all these stereochemical outcomes is included in the ESI.[†]

Addressing challenge (4), a range of useful (hetero)aryl groups was competent in this transformation. *N*-Heteroaromatic motifs with different ring sizes and even multiple Lewis basic nitrogen atoms reacted well, affording products with pyridine, pyrimidine, imidazole, triazole, tetrazole, thiazole, benzothiazole, thiadiazole, and oxadiazole groups (40–48, 37–99% yields, only 44 was below 66% yield). Benzene derivatives were also reliably obtained. *Ortho*-methoxy, bromo, and carbomethoxy substituents, as well the disubstituted *o*-bromo-*p*-fluoro pattern on the new phenyl ring gave products 49–52 in 59–96% yields. Substituents were also tolerated at the *para*- (*p*-CO₂Me, 53, 47% yield) and *meta*- (*m*-Me, 54, 42% yield) positions. Unsubstituted phenyl product 55 (34% yield) and 3-thienyl product 56 (41% yield) were also generated in modest efficiencies.

Throughout these scope studies that afforded 42 products, 14 tertiary benzylic products and 28 quaternary products were obtained, successfully addressing challenge (5).



Scheme 1 Concise synthesis of (\pm) -oliceridine featuring a key olefin alkyl–(hetero)arylation. Reaction of olefin 57 (1 equiv.) with alkyl–aryl sulfone 12 (1 equiv.) served as a key step in a new synthesis of (\pm) -oliceridine (61). See ESI† for detailed procedures.

We then sought to demonstrate the utility of this alkyl-(hetero)arylation in a new synthesis of oliceridine, a novel painkiller approved by the FDA in 2020 (Scheme 1).¹⁰⁰⁻¹⁰³ To this end, olefin 57 (prepared in 3 steps from 3-buten-1-ol and cyclopentanone) underwent alkyl-(hetero)arylation with sulfone 12 (prepared in 2 steps from 2-mercaptopyridine and methyl bromoacetate). Using ideal 1:1 stoichiometry, alkyl-arylation product 58 was isolated in 95% yield. The methyl ester was then converted to protected amine 59 by hydrolysis and a modified Curtius rearrangement (83% yield over 2 steps), and oliceridine (61) was ultimately obtained by amine deprotection and reductive amination with aldehyde 60 (53% yield from 59; 44% yield from 58). Critically, the alkyl-(hetero)arylation of simple olefin 57 concurrently added a primary, synthetically diversifiable alkyl group and a Lewis basic 2-pyridyl group. Achieving either of these synthetic outcomes on their own has proven challenging in alkyl-arylations of simple olefins, and no previously reported systems have achieved them together.

Since we proposed that many of this method's synthetic advantages result from its free-radical mechanism, we performed preliminary experiments to assess whether open-shell intermediates are indeed generated in this system. First, the formation of representative product **63** was completely shut down when a radical inhibitor (TEMPO, 3 equiv.) was added to the reaction (compared to 78% yield without TEMPO, Scheme 2a). Second, when vinylcyclopropane (**64**) was used as the olefin, none of desired product **65** was obtained. Instead, byproduct **68** was formed, which could arise from ring-opening of radical intermediate **66** (Scheme 2b). Only minimal consumption of the reactants occurred in this case, possibly because the formation of **68** from ring-opened radical **67** may not efficiently close the photoredox catalytic cycle, thereby deactivating the catalyst. Together, these outcomes are best (a) TEMPO Inhibition - Consistent with Radical Mechanism



(b) Cyclopropane Opening – Consistent with Radical Mechanism





Scheme 2 Preliminary mechanistic experiments were consistent with the proposed radical mechanism (Fig. 2). (a) Addition of a persistent radical TEMPO completely inhibited the reaction. (b) Using vinylcyclopropane (64) as the olefin afforded only ring-opened byproduct 68 and none of desired product 65. (c) A low quantum yield (2.7%) was measured, which disfavors a chain mechanism. See ESI† for detailed procedures.

explained if the alkyl-(hetero)arylation proceeded through a radical manifold. Lastly, we measured the quantum efficiency throughout the formation of product **63** (Scheme 2c). The relatively low value (2.7% quantum yield) suggests that a radical-chain mechanism is unlikely.

Finally, fluorescence-quenching experiments confirmed that the excited-state photocatalyst activated the conjugate base of the sulfone as proposed in Fig. 2 (see ESI[†]).

Conclusions

A free-radical approach was leveraged to develop a synthetically versatile alkyl–(hetero)arylation of olefins. This transformation engaged a complete range of simple olefins, from mono- to tetrasubstituted. Further key outcomes included the use of synthetically diversifiable alkyl groups with different degrees of substitution, good stereocontrol in cyclic and acyclic systems, the introduction of heteroaryl groups with Lewis basic nitrogen atoms in addition to simple benzenes, and the efficient formation of either tertiary or quaternary benzylic centers. We are confident that a further suite of synthetically empowering transformations will be enabled by strategies featuring radicalmediated migrations.

Data availability

The data supporting this article have been uploaded as part of the ESI.†

Author contributions

D. J. B., A. J. W., J. L. B., S. M. S., and A. S. performed experiments. All authors analyzed data. D. J. B. and E. D. N. designed experiments. E. D. N. conceived of the project.

Conflicts of interest

There are no conflicts to declare.

Note added after first publication

This article replaces the version published on 2nd February 2024 which contained errors in Fig. 1a and 2. The RSC apologises for any confusion.

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