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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.

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 sp^3 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 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 method[55] 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 alkyl–arylations of simple olefins[48–55] (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 1,1-disubstituted simple alkenes with alkylmetal reagents,[55] as well as an Fe-catalyzed protocol that can employ mono- and 1,2-disubstituted 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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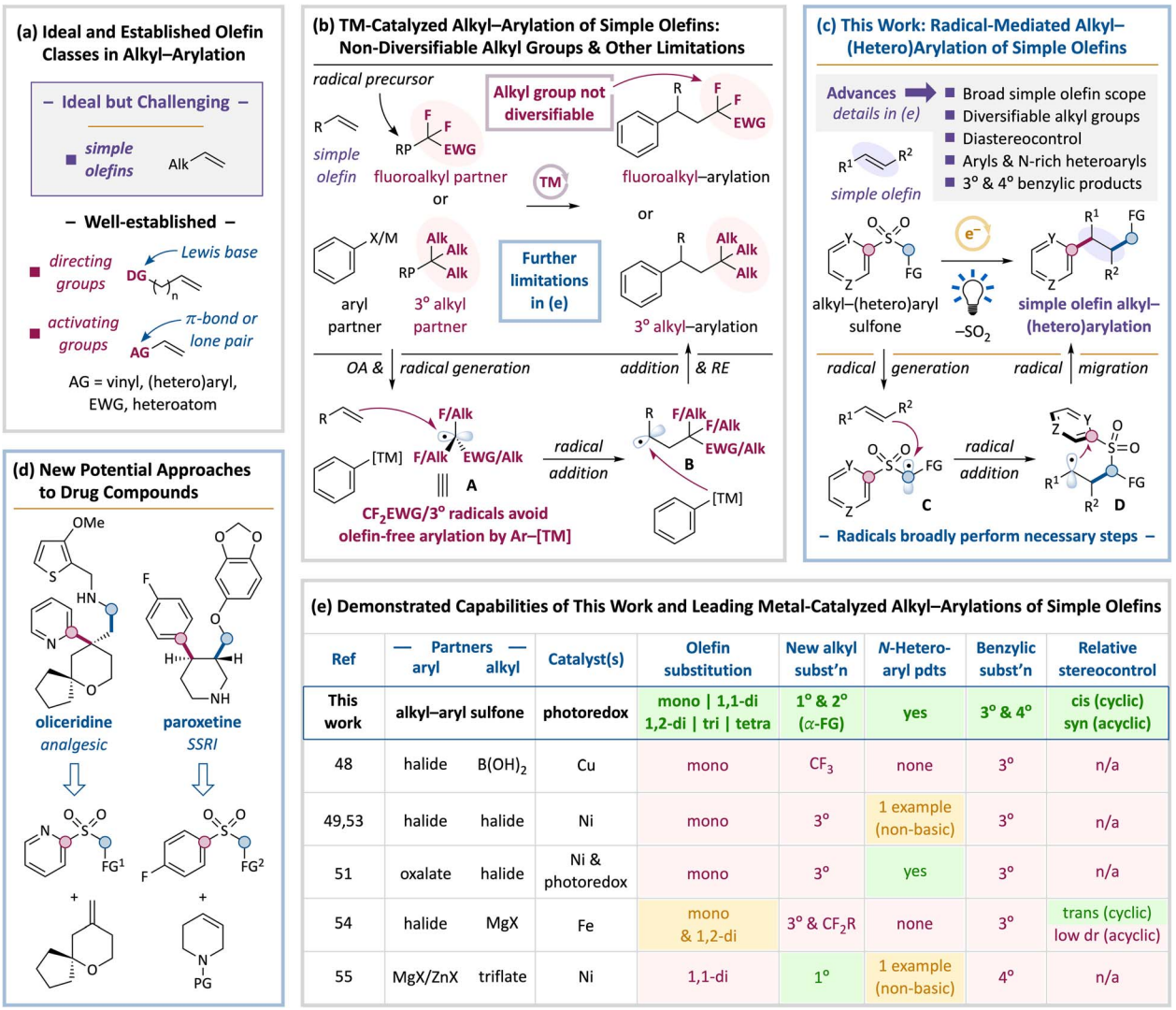


(e) Demonstrated Capabilities of This Work and Leading Metal-Catalyzed Alkyl–Arylations of Simple Olefins

Ref	Partners aryl	Partners 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_2R	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 products[55] (with this exception generating only quaternary products).

Design plan

We thus hypothesized that a completely free-radical approach[60,61] 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 steps[64,65] from alkyl halides and (hetero)aryl sulfinates or thiols, could add their alkyl and (hetero)aryl groups across an olefin under photoredox activation[66–68] and extrude SO_2. Mechanistically, electrophilic sulfone-derived alkyl radical **C** would add to the olefin, generating the desired C(sp^3)–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(sp^3)–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 privileged[92] N-rich heteroaryl groups that often inhibit transition-metal catalysts. Finally, (5) elongated open-shell transition

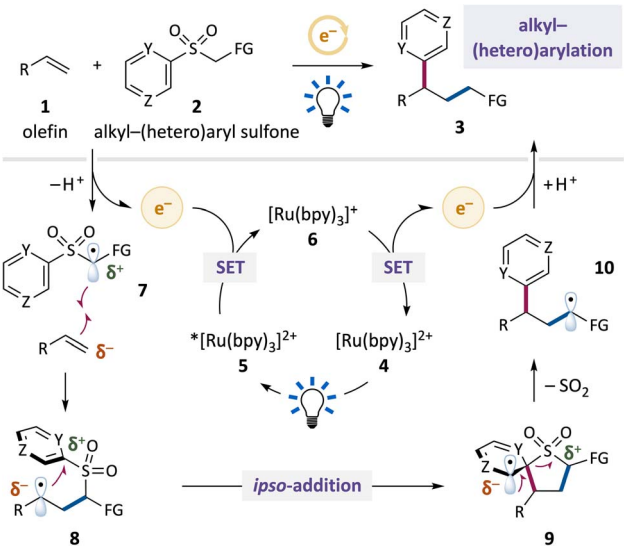


Fig. 2 Mechanistic design of radical-mediated olefin alkyl–(hetero)arylation. See text for details.

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

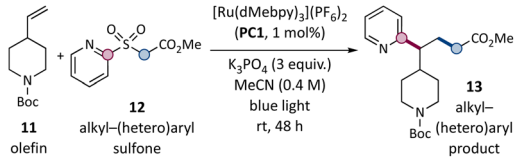
New synthetic approaches to bioactive molecules potentially empowered by this approach are illustrated in Fig. 1d. The colored, bold bonds would be forged by the proposed alkyl–(hetero)arylation, and standard functional-group manipulations would complete the peripheries.

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 ($E^{red}_{1/2}$ [$PhSO_2(COPh)CH^{\bullet}$/$PhSO_2(COPh)CH^{-}$] = +0.78 V *vs.* SCE in DMSO)[94] by an excited-state photoredox catalyst (**4**, $E^{red}_{1/2}$[*Ru(bpy)$_3^{2+}$ (**5**)/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 radical[89] 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 SO_2. Resulting electron-poor alkyl radical **10** ($E^{red}_{1/2}$ [(EtCO)(Me)CH$^{\bullet}$/(EtCO)(Me)CH^{-}] = −0.55 V *vs.* SCE in DMSO)[97] would react with reduced, ground-state photoredox catalyst (**6**, $E^{red}_{1/2}$[Ru(bpy)$_3^{2+}$ (**4**)/Ru(bpy)$_3^{+}$ (**6**)] = −1.33 V *vs.* 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 K_3PO_4 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]



Entry	Derivation from standard conditions	Yield (%)
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	*fac*-[Ir(ppy)]$_3$ photocatalyst	23
7	4CzIPN photocatalyst	73
8	K_2CO_3 base	0
9	K_2HPO_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

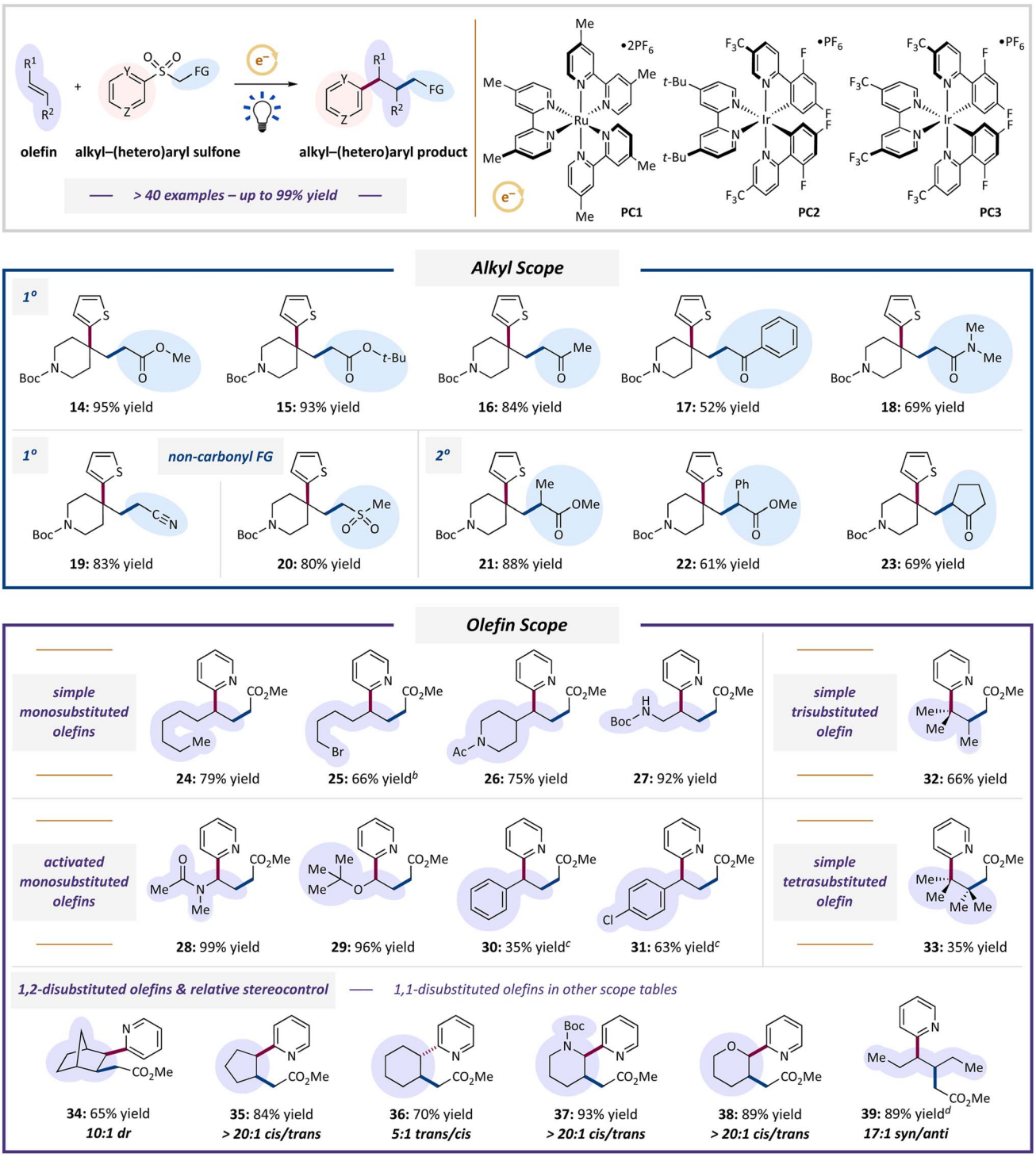
[a] Olefin **11** (3 equiv.), sulfone **12** (0.4 mmol, 1 equiv.), K_3PO_4 (3 equiv.), and [Ru(dMebpy)$_3$](PF$_6$)$_2$ (**PC1**, 1 mol%) were irradiated with blue light (440 nm) in MeCN (0.4 M in **12**) at rt for 48 h with variations as noted. NMR yields. See ESI for detailed procedures.

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.

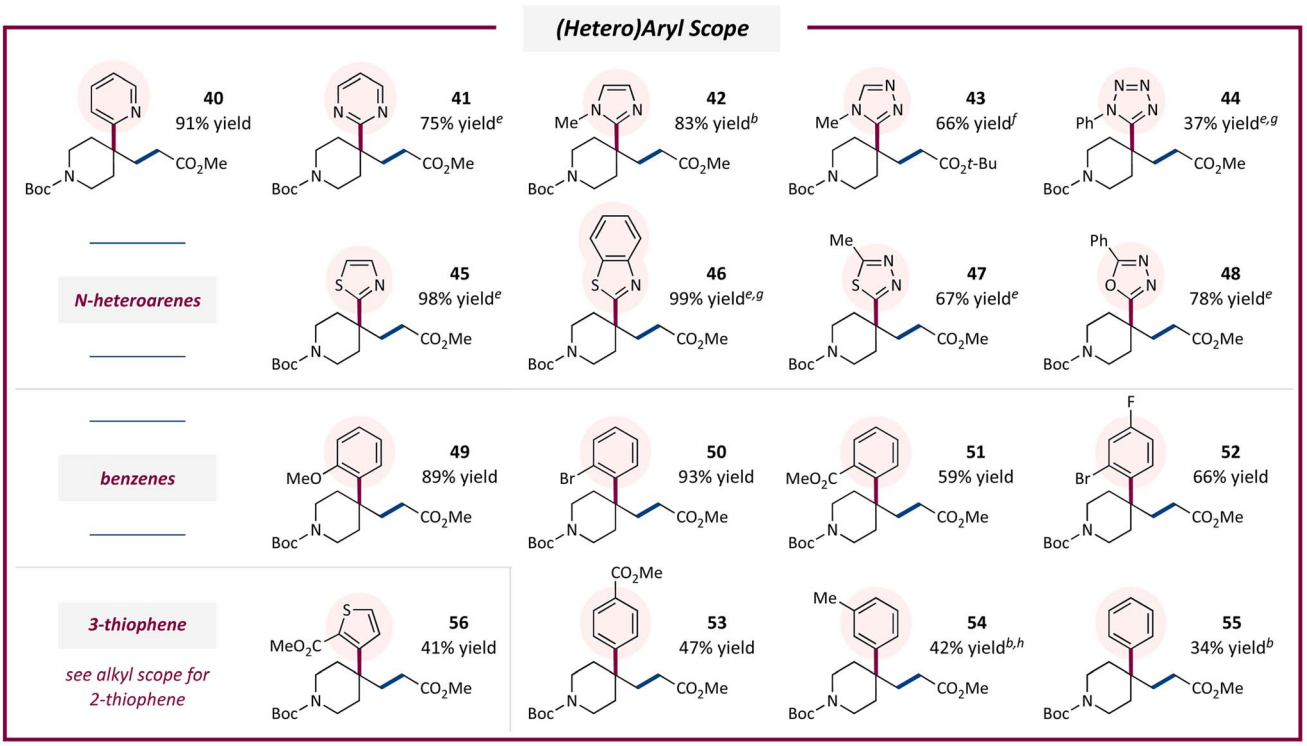
Addressing challenge (1), a range of primary alkyl groups featuring carbonyls (esters, ketones, and an amide), nitrile, or

Table 2 Scope of free-radical alkyl–(hetero)arylation of olefins[a]



[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, **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.)



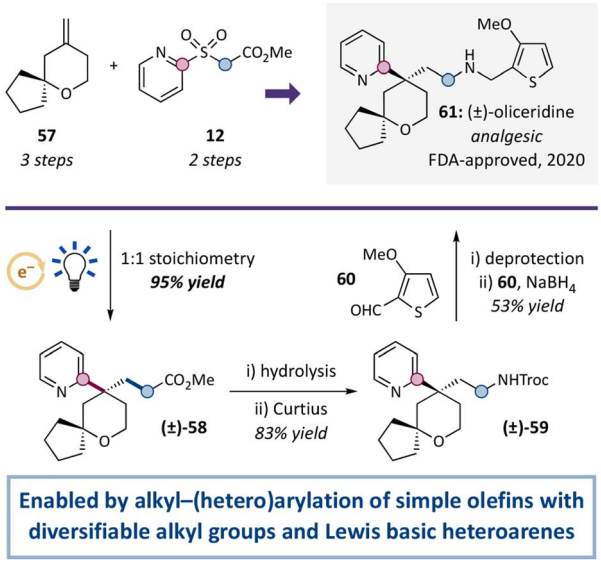
sulfonyl functionalities were added to a simple olefin, accompanied by a 2-thienyl unit (**14–20**, 52–95% yields). Secondary alkyl groups were also added without complication, affording tertiary alkyl products **21–23** in 61–88% yields.

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. Electron-deficient 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*-CO_2Me, **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.

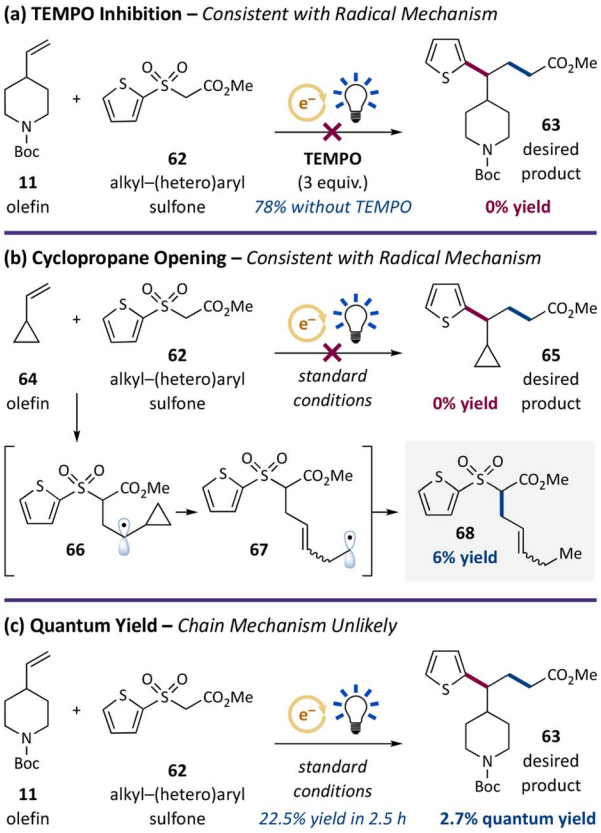
Throughout these scope studies that afforded 42 products, 14 tertiary benzylic products and 28 quaternary products were obtained, successfully addressing challenge (5).



Scheme 1 Concise synthesis of (±)-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 (±)-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 pain-killer 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



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 radical-mediated 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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Notes and references

1 *Comprehensive Organic Synthesis*, ed. P. Knochel, Elsevier, Amsterdam, 2nd edn, 2014.
2 J. Zhu, Q. Wang and M. Wang, *Multicomponent Reactions in Organic Synthesis*, Wiley-VCH, 2014.
3 M. J. C. M. Hulce, Tandem Vicinal Difunctionalization: β-Addition to α,β-Unsaturated Carbonyl Substrates Followed by α-Functionalization, *Org. React.*, 1990, **38**, 225–653.
4 R. I. McDonald, G. Liu and S. S. Stahl, Palladium(II)-catalyzed alkene functionalization via nucleopalladation: stereochemical pathways and enantioselective catalytic applications, *Chem. Rev.*, 2011, **111**, 2981–3019.
5 H. Egami and M. Sodeoka, Trifluoromethylation of alkenes with concomitant introduction of additional functional groups, *Angew. Chem., Int. Ed.*, 2014, **53**, 8294–8308.
6 G. Yin, X. Mu and G. Liu, Palladium(II)-Catalyzed Oxidative Difunctionalization of Alkenes: Bond Forming at a High-Valent Palladium Center, *Acc. Chem. Res.*, 2016, **49**, 2413–2423.
7 X.-W. Lan, N.-X. Wang and Y. Xing, Recent Advances in Radical Difunctionalization of Simple Alkenes, *Eur. J. Org Chem.*, 2017, **2017**, 5821–5851.
8 R. K. Dhungana, S. Kc, P. Basnet and R. Giri, Transition Metal-Catalyzed Dicarbofunctionalization of Unactivated Olefins, *Chem. Rec.*, 2018, **18**, 1314–1340.
9 J. Derosa, V. T. Tran, V. A. van der Puyl and K. M. Engle, Carbon–Carbon π Bonds as Conjunctive Reagents in Cross-Coupling, *Aldrichimica Acta*, 2018, **51**, 21–32.
10 R. Giri and S. Kc, Strategies toward Dicarbofunctionalization of Unactivated Olefins by Combined Heck Carbometalation and Cross-Coupling, *J. Org. Chem.*, 2018, **83**, 3013–3022.
11 J. S. Zhang, L. Liu, T. Chen and L. B. Han, Transition-Metal-Catalyzed Three-Component Difunctionalizations of Alkenes, *Chem.–Asian J.*, 2018, **13**, 2277–2291.
12 J. Derosa, O. Apolinar, T. Kang, V. T. Tran and K. M. Engle, Recent developments in nickel-catalyzed intermolecular dicarbofunctionalization of alkenes, *Chem. Sci.*, 2020, **11**, 4287–4296.
13 X. Qi and T. Diao, Nickel-Catalyzed Dicarbofunctionalization of Alkenes, *ACS Catal.*, 2020, **10**, 8542–8556.
14 H. Yao, W. Hu and W. Zhang, Difunctionalization of Alkenes and Alkynes via Intermolecular Radical and Nucleophilic Additions, *Molecules*, 2020, **26**, 105.
15 L. M. Wickham and R. Giri, Transition Metal (Ni, Cu, Pd)-Catalyzed Alkene Dicarbofunctionalization Reactions, *Acc. Chem. Res.*, 2021, **54**, 3415–3437.
16 S. Zhu, X. Zhao, H. Li and L. Chu, Catalytic three-component dicarbofunctionalization reactions involving radical capture by nickel, *Chem. Soc. Rev.*, 2021, **50**, 10836–10856.
17 P. Gao, Y. J. Niu, F. Yang, L. N. Guo and X. H. Duan, Three-component 1,2-dicarbofunctionalization of alkenes involving alkyl radicals, *Chem. Commun.*, 2022, **58**, 730–746.
18 M. Beller, J. Seayad, A. Tillack and H. Jiao, Catalytic Markovnikov and anti-Markovnikov functionalization of alkenes and alkynes: recent developments and trends, *Angew. Chem., Int. Ed.*, 2004, **43**, 3368–3398.
19 L. Liao, R. Jana, K. B. Urkalan and M. S. Sigman, A palladium-catalyzed three-component cross-coupling of conjugated dienes or terminal alkenes with vinyl triflates and boronic acids, *J. Am. Chem. Soc.*, 2011, **133**, 5784–5787.
20 B. J. Stokes, L. Liao, A. M. de Andrade, Q. Wang and M. S. Sigman, A palladium-catalyzed three-component-coupling strategy for the differential vicinal diarylation of terminal 1,3-dienes, *Org. Lett.*, 2014, **16**, 4666–4669.
21 X. Wu, H. C. Lin, M. L. Li, L. L. Li, Z. Y. Han and L. Z. Gong, Enantioselective 1,2-Difunctionalization of Dienes Enabled by Chiral Palladium Complex-Catalyzed Cascade Arylation/Allylic Alkylation Reaction, *J. Am. Chem. Soc.*, 2015, **137**, 13476–13479.
22 Z. Liu, T. Zeng, K. S. Yang and K. M. Engle, beta,gamma-Vicinal Dicarbofunctionalization of Alkenyl Carbonyl Compounds via Directed Nucleopalladation, *J. Am. Chem. Soc.*, 2016, **138**, 15122–15125.
23 B. Shrestha, P. Basnet, R. K. Dhungana, S. Kc, S. Thapa, J. M. Sears and R. Giri, Ni-Catalyzed Regioselective 1,2-Dicarbofunctionalization of Olefins by Intercepting Heck

Intermediates as Imine-Stabilized Transient Metallacycles, *J. Am. Chem. Soc.*, 2017, **139**, 10653–10656.

24 P. Basnet, S. Kc, R. K. Dhungana, B. Shrestha, T. J. Boyle and R. Giri, Synergistic Bimetallic Ni/Ag and Ni/Cu Catalysis for Regioselective gamma,delta-Diarylation of Alkenyl Ketimines: Addressing beta-H Elimination by In situ Generation of Cationic Ni(II) Catalysts, *J. Am. Chem. Soc.*, 2018, **140**, 15586–15590.

25 J. Derosa, R. Kleinmans, V. T. Tran, M. K. Karunananda, S. R. Wisniewski, M. D. Eastgate and K. M. Engle, Nickel-Catalyzed 1,2-Diarylation of Simple Alkenyl Amides, *J. Am. Chem. Soc.*, 2018, **140**, 17878–17883.

26 P. Gao, L. A. Chen and M. K. Brown, Nickel-Catalyzed Stereoselective Diarylation of Alkenylarenes, *J. Am. Chem. Soc.*, 2018, **140**, 10653–10657.

27 S. Thapa, R. K. Dhungana, R. T. Magar, B. Shrestha, S. Kc and R. Giri, Ni-catalysed regioselective 1,2-diarylation of unactivated olefins by stabilizing Heck intermediates as pyridylsilyl-coordinated transient metallacycles, *Chem. Sci.*, 2018, **9**, 904–909.

28 D. Anthony, Q. Lin, J. Baudet and T. Diao, Nickel-Catalyzed Asymmetric Reductive Diarylation of Vinylarenes, *Angew. Chem., Int. Ed.*, 2019, **58**, 3198–3202.

29 J. Derosa, T. Kang, V. T. Tran, S. R. Wisniewski, M. K. Karunananda, T. C. Jankins, K. L. Xu and K. M. Engle, Nickel-Catalyzed 1,2-Diarylation of Alkenyl Carboxylates: A Gateway to 1,2,3-Trifunctionalized Building Blocks, *Angew. Chem., Int. Ed.*, 2020, **59**, 1201–1205.

30 R. K. Dhungana, R. R. Sapkota, L. M. Wickham, D. Niroula and R. Giri, Ni-Catalyzed Regioselective 1,2-Dialkylation of Alkenes Enabled by the Formation of Two C(sp(3))-C(sp(3)) Bonds, *J. Am. Chem. Soc.*, 2020, **142**, 20930–20936.

31 T. Yang, Y. Jiang, Y. Luo, J. J. H. Lim, Y. Lan and M. J. Koh, Chemoselective Union of Olefins, Organohalides, and Redox-Active Esters Enables Regioselective Alkene Dialkylation, *J. Am. Chem. Soc.*, 2020, **142**, 21410–21419.

32 V. Aryal, L. J. Chesley, D. Niroula, R. R. Sapkota, R. K. Dhungana and R. Giri, Ni-Catalyzed Regio- and Stereoselective Alkylarylation of Unactivated Alkenes in γ,δ-Alkenylketimines, *ACS Catal.*, 2022, **12**, 7262–7268.

33 F. Lovering, J. Bikker and C. Humblet, Escape from flatland: increasing saturation as an approach to improving clinical success, *J. Med. Chem.*, 2009, **52**, 6752–6756.

34 E. Geist, A. Kirschning and T. Schmidt, sp3-sp3 Coupling reactions in the synthesis of natural products and biologically active molecules, *Nat. Prod. Rep.*, 2014, **31**, 441–448.

35 T. Qin, J. Cornella, C. Li, L. R. Malins, J. T. Edwards, S. Kawamura, B. D. Maxwell, M. D. Eastgate and P. S. Baran, A general alkyl-alkyl cross-coupling enabled by redox-active esters and alkylzinc reagents, *Science*, 2016, **352**, 801–805.

36 L. Zhang, G. J. Lovinger, E. K. Edelstein, A. A. Szymaniak, M. P. Chierchia and J. P. Morken, Catalytic conjunctive cross-coupling enabled by metal-induced metallate rearrangement, *Science*, 2016, **351**, 70–74.

37 J. Derosa, V. T. Tran, M. N. Boulous, J. S. Chen and K. M. Engle, Nickel-Catalyzed beta,gamma-Dicarbofunctionalization of Alkenyl Carbonyl Compounds via Conjunctive Cross-Coupling, *J. Am. Chem. Soc.*, 2017, **139**, 10657–10660.

38 M. Kischkewitz, K. Okamoto, C. Muck-Lichtenfeld and A. Studer, Radical-polar crossover reactions of vinylboron ate complexes, *Science*, 2017, **355**, 936–938.

39 S. Kc, R. K. Dhungana, B. Shrestha, S. Thapa, N. Khanal, P. Basnet, R. W. Lebrun and R. Giri, Ni-Catalyzed Regioselective Alkylarylation of Vinylarenes via C(sp(3))-C(sp(3))/C(sp(3))-C(sp(2)) Bond Formation and Mechanistic Studies, *J. Am. Chem. Soc.*, 2018, **140**, 9801–9805.

40 M. W. Campbell, J. S. Compton, C. B. Kelly and G. A. Molander, Three-Component Olefin Dicarbofunctionalization Enabled by Nickel/Photoredox Dual Catalysis, *J. Am. Chem. Soc.*, 2019, **141**, 20069–20078.

41 M. Chierchia, P. Xu, G. J. Lovinger and J. P. Morken, Enantioselective Radical Addition/Cross-Coupling of Organozinc Reagents, Alkyl Iodides, and Alkenyl Boron Reagents, *Angew. Chem., Int. Ed.*, 2019, **58**, 14245–14249.

42 S. Kc, R. K. Dhungana, N. Khanal and R. Giri, Nickel-Catalyzed alpha-Carbonylalkylarylation of Vinylarenes: Expedient Access to gamma,gamma-Diarylcarbonyl and Aryltetralone Derivatives, *Angew. Chem., Int. Ed.*, 2020, **59**, 8047–8051.

43 R. S. Mega, V. K. Duong, A. Noble and V. K. Aggarwal, Decarboxylative Conjunctive Cross-coupling of Vinyl Boronic Esters using Metallaphotoredox Catalysis, *Angew. Chem., Int. Ed.*, 2020, **59**, 4375–4379.

44 X. Wei, W. Shu, A. Garcia-Dominguez, E. Merino and C. Nevado, Asymmetric Ni-Catalyzed Radical Relayed Reductive Coupling, *J. Am. Chem. Soc.*, 2020, **142**, 13515–13522.

45 R. K. Dhungana, R. R. Sapkota, L. M. Wickham, D. Niroula, B. Shrestha and R. Giri, Ni-Catalyzed Arylbenzylation of Alkenylarenes: Kinetic Studies Reveal Autocatalysis by ZnX(2), *Angew. Chem., Int. Ed.*, 2021, **60**, 22977–22982.

46 M. J. Cabrera-Afonso, A. Sookezian, S. O. Badir, M. El Khatib and G. A. Molander, Photoinduced 1,2-dicarbofunctionalization of alkenes with organotrifluoroborate nucleophiles via radical/polar crossover, *Chem. Sci.*, 2021, **12**, 9189–9195.

47 P. Dey, S. K. Jana, P. Rai and B. Maji, Dicarbofunctionalizations of an Unactivated Alkene via Photoredox/Nickel Dual Catalysis, *Org. Lett.*, 2022, **24**, 6261–6265.

48 F. Wang, D. Wang, X. Mu, P. Chen and G. Liu, Copper-catalyzed intermolecular trifluoromethylarylation of alkenes: mutual activation of arylboronic acid and CF3+ reagent, *J. Am. Chem. Soc.*, 2014, **136**, 10202–10205.

49 A. Garcia-Dominguez, Z. Li and C. Nevado, Nickel-Catalyzed Reductive Dicarbofunctionalization of Alkenes, *J. Am. Chem. Soc.*, 2017, **139**, 6835–6838.

50 A. Garcia-Dominguez, R. Mondal and C. Nevado, Dual Photoredox/Nickel-Catalyzed Three-Component

Carbofunctionalization of Alkenes, *Angew. Chem., Int. Ed.*, 2019, **58**, 12286–12290.

51 L. Guo, H. Y. Tu, S. Zhu and L. Chu, Selective, Intermolecular Alkylarylation of Alkenes via Photoredox/Nickel Dual Catalysis, *Org. Lett.*, 2019, **21**, 4771–4776.

52 X. L. Lv, C. Wang, Q. L. Wang and W. Shu, Rapid Synthesis of gamma-Arylated Carbonyls Enabled by the Merge of Copper- and Photocatalytic Radical Relay Alkylarylation of Alkenes, *Org. Lett.*, 2019, **21**, 56–59.

53 W. Shu, A. Garcia-Dominguez, M. T. Quiros, R. Mondal, D. J. Cardenas and C. Nevado, Ni-Catalyzed Reductive Dicarbofunctionalization of Nonactivated Alkenes: Scope and Mechanistic Insights, *J. Am. Chem. Soc.*, 2019, **141**, 13812–13821.

54 L. Liu, W. Lee, C. R. Youshaw, M. Yuan, M. B. Geherty, P. Y. Zavalij and O. Gutierrez, Fe-catalyzed three-component dicarbofunctionalization of unactivated alkenes with alkyl halides and Grignard reagents, *Chem. Sci.*, 2020, **11**, 8301–8305.

55 H. Wang, C. F. Liu, R. T. Martin, O. Gutierrez and M. J. Koh, Directing-group-free catalytic dicarbofunctionalization of unactivated alkenes, *Nat. Chem.*, 2022, **14**, 188–195.

56 J. R. Bour, N. M. Camasso and M. S. Sanford, Oxidation of Ni(II) to Ni(IV) with Aryl Electrophiles Enables Ni-Mediated Aryl-CF3 Coupling, *J. Am. Chem. Soc.*, 2015, **137**, 8034–8037.

57 M. Yuan, Z. Song, S. O. Badir, G. A. Molander and O. Gutierrez, On the Nature of C(sp(3))-C(sp(2)) Bond Formation in Nickel-Catalyzed Tertiary Radical Cross-Couplings: A Case Study of Ni/Photoredox Catalytic Cross-Coupling of Alkyl Radicals and Aryl Halides, *J. Am. Chem. Soc.*, 2020, **142**, 7225–7234.

58 W. Xue, X. Jia, X. Wang, X. Tao, Z. Yin and H. Gong, Nickel-catalyzed formation of quaternary carbon centers using tertiary alkyl electrophiles, *Chem. Soc. Rev.*, 2021, **50**, 4162–4184.

59 Two further protocols (**7f**, **h**) feature single examples of 3-pyridyl products. These reactions may be special cases of *N*-heteroarenes, however, because (a) these isomers avoid catalyst deactivation by chelation that is often a problem for 2-azaheteroarenes, and (b) both examples feature an electronegative substituent on that lowers the basicity of the nitrogen atom that can be essential for biological activity and a problem for transition-metal catalysts.

60 Open-shell approaches have also been developed featuring alkyl-radical addition to an alkene followed by Minisci addition of the resulting olefin-derived alkyl radical to a heteroarene, but these protocols are inherently restricted to electrophilic *N*-heteroaromatic substrates and products. For a leading example, see the reference immediately below.

61 T. McCallum and L. Barriault, Direct alkylation of heteroarenes with unactivated bromoalkanes using photoredox gold catalysis, *Chem. Sci.*, 2016, **7**, 4754–4758.

62 While we were completing this work, the report in the reference immediately below described nine examples of simple olefin alkyl–arylation with analogous sulfone reagents. The key synthetic challenges that plague transition-metal-catalyzed systems and that we sought to solve remained mostly unaddressed, however, as only monosubstituted alkenes were competent substrates (meaning that quaternary benzylic products and diastereocontrol were also absent), and only one example of any heteroaryl group (2-benzothiazole) appeared in the scope.

63 S. Hong, M. Kim, K. Lee and S. Kim, Photoinduced Carboarylation of Alkenes by Using Bifunctional Reagents, *Synlett*, 2023, **34**, 1437–1441.

64 Bromoalkyl–aryl sulfones have been employed to a similar end via C–Br reduction using a stroichiometric thiol that is not commercially available. These sulfones also require 3–4 steps to access (4 steps whenever primary alkyl groups are added to the olefin), and no functional handles beyond halogens were tolerated near the reactive alkyl carbon, although they do permit the incorporation of alkyl groups devoid of functionality.

65 J. Liu, S. Wu, J. Yu, C. Lu, Z. Wu, X. Wu, X. S. Xue and C. Zhu, Polarity Umpolung Strategy for the Radical Alkylation of Alkenes, *Angew. Chem., Int. Ed.*, 2020, **59**, 8195–8202.

66 M. H. Shaw, J. Twilton and D. W. MacMillan, Photoredox Catalysis in Organic Chemistry, *J. Org. Chem.*, 2016, **81**, 6898–6926.

67 C. S. Wang, P. H. Dixneuf and J. F. Soule, Photoredox Catalysis for Building C-C Bonds from C(sp(2))-H Bonds, *Chem. Rev.*, 2018, **118**, 7532–7585.

68 J. D. Bell and J. A. Murphy, Recent advances in visible light-activated radical coupling reactions triggered by (i) ruthenium, (ii) iridium and (iii) organic photoredox agents, *Chem. Soc. Rev.*, 2021, **50**, 9540–9685.

69 A. Studer and M. Bossart, Radical aryl migration reactions, *Tetrahedron*, 2001, **57**, 9649–9667.

70 Z. M. Chen, X. M. Zhang and Y. Q. Tu, Radical aryl migration reactions and synthetic applications, *Chem. Soc. Rev.*, 2015, **44**, 5220–5245.

71 X. Wu and C. Zhu, Radical-Mediated Remote Functional Group Migration, *Acc. Chem. Res.*, 2020, **53**, 1620–1636.

72 X. Q. Chu, D. Ge, Y. Y. Cui, Z. L. Shen and C. J. Li, Desulfonylation via Radical Process: Recent Developments in Organic Synthesis, *Chem. Rev.*, 2021, **121**, 12548–12680.

73 X. Wu, Z. Ma, T. Feng and C. Zhu, Radical-mediated rearrangements: past, present, and future, *Chem. Soc. Rev.*, 2021, **50**, 11577–11613.

74 A. R. Allen, E. A. Noten and C. R. J. Stephenson, Aryl Transfer Strategies Mediated by Photoinduced Electron Transfer, *Chem. Rev.*, 2022, **122**, 2695–2751.

75 R. Loven and W. N. Speckamp, A novel 1,4 arylradical rearrangement, *Tetrahedron Lett.*, 1972, **13**, 1567–1570.

76 W. Kong, M. Casimiro, E. Merino and C. Nevado, Copper-catalyzed one-pot trifluoromethylation/aryl migration/desulfonylation and C(sp2)-N bond formation of conjugated tosyl amides, *J. Am. Chem. Soc.*, 2013, **135**, 14480–14483.

77 T. M. Monos, R. C. McAtee and C. R. J. Stephenson, Arylsulfonylacetamides as bifunctional reagents for alkene aminoarylation, *Science*, 2018, **361**, 1369–1373.
78 J. Yu, Z. Wu and C. Zhu, Efficient Docking-Migration Strategy for Selective Radical Difluoromethylation of Alkenes, *Angew. Chem., Int. Ed.*, 2018, **57**, 17156–17160.
79 D. M. Whalley, H. A. Duong and M. F. Greaney, Alkene Carboarylation through Catalyst-Free, Visible Light-Mediated Smiles Rearrangement, *Chemistry*, 2019, **25**, 1927–1930.
80 M. Wang, H. Zhang, J. Liu, X. Wu and C. Zhu, Radical Monofluoroalkylative Alkynylation of Olefins by a Docking-Migration Strategy, *Angew. Chem., Int. Ed.*, 2019, **58**, 17646–17650.
81 C. Hervieu, M. S. Kirillova, T. Suarez, M. Muller, E. Merino and C. Nevado, Asymmetric, visible light-mediated radical sulfinyl-Smiles rearrangement to access all-carbon quaternary stereocentres, *Nat. Chem.*, 2021, **13**, 327–334.
82 Y. Wei, H. Zhang, X. Wu and C. Zhu, Alkene Difunctionalization Triggered by a Stabilized Allenyl Radical: Concomitant Installation of Two Unsaturated C-C Bonds, *Angew. Chem., Int. Ed.*, 2021, **60**, 20215–20219.
83 A. R. Allen, J. F. Poon, R. C. McAtee, N. B. Watson, D. A. Pratt and C. R. J. Stephenson, Mechanism of Visible Light-Mediated Alkene Aminoarylation with Arylsulfonylacetamides, *ACS Catal.*, 2022, **12**, 8511–8526.
84 D. Wang, C. Muck-Lichtenfeld, C. G. Daniliuc and A. Studer, Radical Aryl Migration from Boron to Carbon, *J. Am. Chem. Soc.*, 2021, **143**, 9320–9326.
85 E. A. Noten, R. C. McAtee and C. R. J. Stephenson, Catalytic intramolecular aminoarylation of unactivated alkenes with aryl sulfonamides, *Chem. Sci.*, 2022, **13**, 6942–6949.
86 N. Radhoff and A. Studer, 1,4-Aryl migration in ketene-derived enolates by a polar-radical-crossover cascade, *Nat. Commun.*, 2022, **13**, 3083.
87 C. He, K. Zhang, D. N. Wang, M. Wang, Y. Niu, X. H. Duan and L. Liu, Visible-Light-Induced Alkylarylation of Unactivated Alkenes via Radical Addition/Truce-Smiles Rearrangement Cascade, *Org. Lett.*, 2022, **24**, 2767–2771.
88 J. Yu, X. Zhang, X. Wu, T. Liu, Z.-Q. Zhang, J. Wu and C. Zhu, Metal-free radical difunctionalization of ethylene, *Chem*, 2023, **9**, 472–482.
89 F. Parsaee, M. C. Senarathna, P. B. Kannangara, S. N. Alexander, P. D. E. Arche and E. R. Welin, Radical philicity and its role in selective organic transformations, *Nat. Rev. Chem*, 2021, **5**, 486–499.
90 A. Studer and M. Bossart, Stereoselective radical aryl migrations from sulfur to carbon, *Chem. Commun.*, 1998, **1998**, 2127–2128.
91 S. Amrein, M. Bossart, T. Vasella and A. Studer, Stereoselective radical aryl migration from silicon to carbon, *J. Org. Chem.*, 2000, **65**, 4281–4288.
92 E. Vitaku, D. T. Smith and J. T. Njardarson, Analysis of the structural diversity, substitution patterns, and frequency of nitrogen heterocycles among U.S. FDA approved pharmaceuticals, *J. Med. Chem.*, 2014, **57**, 10257–10274.
93 M. W. Wong, A. Pross and L. Radom, Addition of tert-Butyl Radical to Substituted Alkenes: A Theoretical Study of the Reaction Mechanism, *J. Am. Chem. Soc.*, 2002, **116**, 11938–11943.
94 F. G. Bordwell, J. A. Harrelson and X. Zhang, Homolytic bond dissociation energies of acidic carbon-hydrogen bonds activated by one or two electron acceptors, *J. Org. Chem.*, 1991, **56**, 4448–4450.
95 T. S. Teets, Y. Wu and D. Kim, Photophysical Properties and Redox Potentials of Photosensitizers for Organic Photoredox Transformations, *Synlett*, 2021, **33**, 1154–1179.
96 We also measured the oxidation potentials of some of the conjugate bases of the sulfones used in this study. These values ranged from +0.67 V to +0.91 V *vs.* SCE in MeCN (see ESI†).
97 M. S. Alnajjar, X. M. Zhang, G. J. Gleicher, S. V. Truksa and J. A. Franz, Equilibrium acidities and homolytic bond dissociation energies of acidic C-H bonds in alpha-arylacetophenones and related compounds, *J. Org. Chem.*, 2002, **67**, 9016–9022.
98 S.-J. Chang, D. McNally, S. Shary-Tehrany, H. S. M. James and R. H. Boyd, Heats of combustion and strain energies of bicyclo[n.m.O]alkanes, *J. Am. Chem. Soc.*, 1970, **92**, 3109–3118.
99 N. L. Allinger, M. T. Tribble, M. A. Miller and D. H. Wertz, Conformational analysis. LXIX. Improved force field for the calculation of the structures and energies of hydrocarbons, *J. Am. Chem. Soc.*, 1971, **93**, 1637–1648.
100 X. T. Chen, P. Pitis, G. Liu, C. Yuan, D. Gotchev, C. L. Cowan, D. H. Rominger, M. Koblish, S. M. Dewire, A. L. Crombie, J. D. Violin and D. S. Yamashita, Structure-activity relationships and discovery of a G protein biased mu opioid receptor ligand, [(3-methoxythiophen-2-yl) methyl](2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro-[4.5]decan-9-yl] ethyl)amine (TRV130), for the treatment of acute severe pain, *J. Med. Chem.*, 2013, **56**, 8019–8031.
101 A. Markham, Oliceridine: First Approval, *Drugs*, 2020, **80**, 1739–1744.
102 H. S. Tan and A. S. Habib, Oliceridine: A Novel Drug for the Management of Moderate to Severe Acute Pain - A Review of Current Evidence, *J. Pain Res.*, 2021, **14**, 969–979.
103 A. A. H. Azzam and D. G. Lambert, Preclinical discovery and development of oliceridine (Olinvyk(R)) for the treatment of post-operative pain, *Expert Opin. Drug Discovery*, 2022, **17**, 215–223.