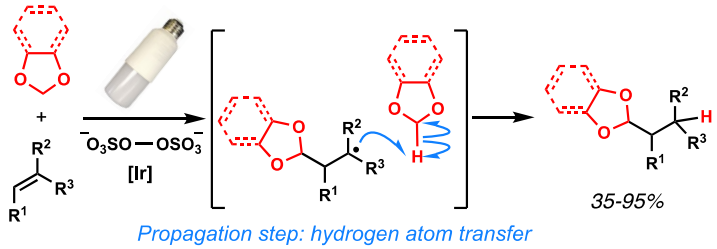
Acetal Addition to Electron-Deficient Alkenes with Hydrogen Atom Transfer as a Radical-Chain Propagation Step

Wei Chuen Chan, Jincy K. Vinod, and Kazunori Koide*

Department of Chemistry, University of Pittsburgh, 219 Parkman Avenue, Pittsburgh, Pennsylvania 15260, United States.

Supporting Information Placeholder



ABSTRACT: We describe visible-light-promoted addition of a hydrogen atom and an acetal carbon toward various electron-deficient alkenes. 1,3-Dioxolane is converted to its radical species in the presence of persulfate and an iridium catalyst upon visible light irradiation, which then reacts with electron-deficient alkenes. The reaction operates via a radical chain mechanism, a less commonly observed pathway for this class of transformation. Hydrogen atom transfer from 1,3-dioxolane to α-malonyl radicals is corroborated by experimental and DFT studies.

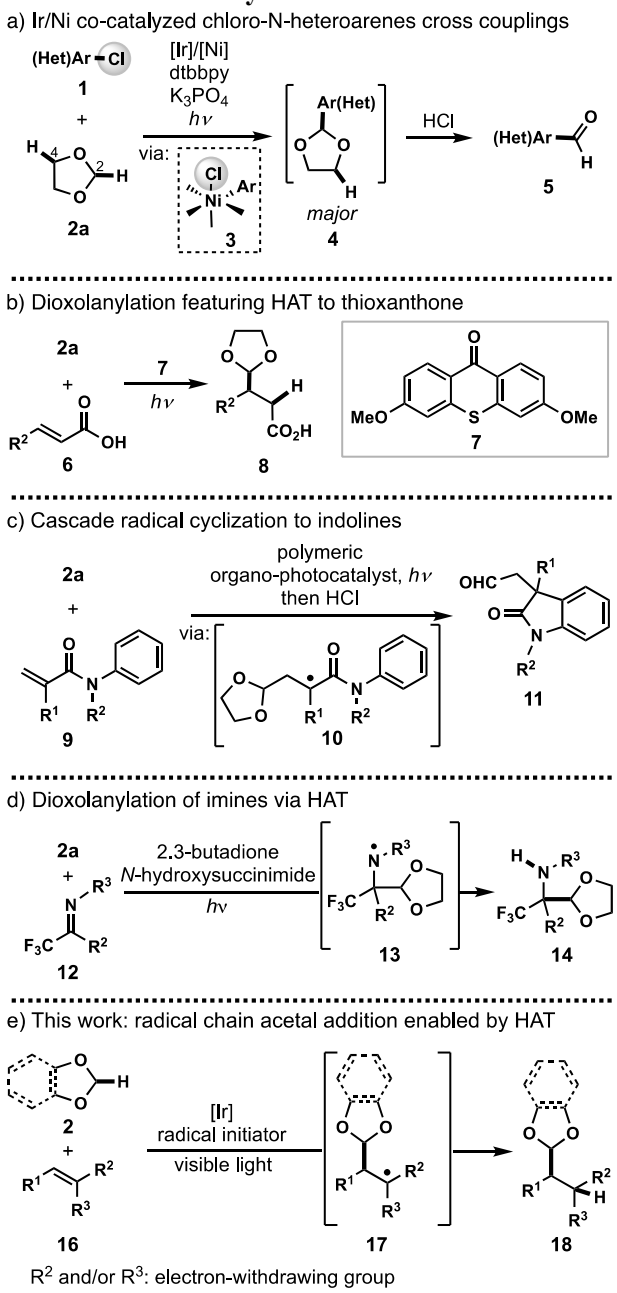
The radical hydrofunctionalization of alkenes is a useful transformation in organic synthesis.[1, 2] For example, the addition of a hydrogen and acetal carbon across a carbon-carbon double bond is an expedient route to protected complex aldehydes. 1,3-Dioxolane is a commercially available and inexpensive solvent and has recently been used as a surrogate formylating reagent. 1,3-Dioxolane has been used as a C–H donor in the formal formylation of arenes and *N*-heteroarenes.[3, 4] The successful generation and incorporation of the dioxolanyl moiety relies on a hydrogen atom transfer (HAT) from the C-2 position of 1,3-dioxolane to suitable radicals. With the advances in photochemistry,[5-7] several of these transformations can be achieved under mild conditions. For example, Doyle et al. reported the Ir/Ni co-catalyzed cross-couplings of chloro-*N*-heteroarenes and 1,3-dioxolanes to furnish dioxolane derivatives (Scheme 1a).[8, 9] They proposed HAT from 1,3-dioxolane to chlorine radicals and that requisite chlorine radicals were generate via the homolysis of ArNi(III)Cl intermediate. The dioxolane products could be deprotected to give Minisci-type products.

Besides C–H formylation of (*N*-hetero)arenes, 1,3-dioxolane also undergoes additions across carbon-carbon and carbon-nitrogen double bonds. For example, Ooi et al. disclosed the formal hydroformylation of cinnamic acids (Scheme 1b).[10] They proposed a direct HAT to the excited thioxanthone photocatalyst. Su et al. reported dioxolanylation-triggered cascade cyclizations, in which α,α-disubstituted acrylamides were employed to generate indoline products (Scheme 1c).[11] Gong and Lu reported the radical-

chain formylation of imines; HAT initially occurred via *O*-centered radical derived from *N*-hydroxysuccinimide and 2,3-butadione (Scheme 1d).[12, 13]

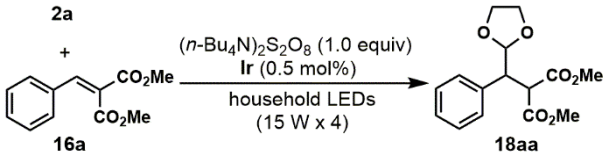
Mechanistically, a dioxolanyl moiety adds to an electrophilic acceptor. After the first radical addition step, the resulting radical may undergo single-electron transfer (SET),[14, 10, 15] trapping with a second radical acceptor,[11] or atom transfer reactions, e.g., HAT.[16, 13, 17] Amongst the three possible pathways, HAT is less commonly observed, specifically in a radical-chain mechanism.[18, 19, 12] Here, we report the visible-light-induced addition of hydrogen atom and acetal carbon to electron-deficient alkenes via a radical chain mechanism enabled by HAT as a propagating step (Scheme 1e), the transformation previously demonstrated by the Tomioka group under distinct reaction conditions.[20, 21]

Scheme 1. Dioxolanylations of alkenes or imines



We reasoned that a nucleophilic dioxolan-2-yl-radical[22] could react with electron-deficient radical acceptors. Based on literature precedents,[23, 24, 4, 9, 25] we chose the combination of soluble persulfate (n-$Bu_4N)_2S_2O_8$, Ir(III) photocatalyst, and 1,3-dioxolane to generate the desired dioxolan-2-yl radicals. Initial screenings with *trans*-chalcone as the radical acceptor gave low and irreproducible yields (Table S1, Supporting Information). We speculated that the insufficient electrophilicity of the olefins might be a reason for low yields and chose the more electrophilic olefin **16a** as the model substrate for reaction optimizations.[26] Gratifyingly, the desired product **18aa** was formed in 77–93% yields (Table 1, entries 1–5), with **Ir-1** as the optimal catalyst. Control experiments indicated that the persulfate was required (entry 6). The reaction gave **18aa** in 76% yield in the absence of the photocatalyst (entry 7), suggesting that the major pathway of the reaction might involve the homolysis of persulfate (*vide infra*). In the absence of light,[24] the starting material underwent decomposition to unidentifiable side-products (entry 8).

Table 1. Optimization of reaction conditions



entry	changes from standard conditions	yields[a]
1	*fac*-Ir(ppy)$_3$, **Ir-1**	93%
2	Ir(dFppy)3, **Ir-2**	89%
3	Ir(dtbbpy)(ppy)$_2$PF$_6$, **Ir-3**	87%
4	Ir[dF(CH$_3$)ppy]$_2$(dtbbpy)PF$_6$, **Ir-4**	85%
5	Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$, **Ir-5**	77%
6	no [O]	NR
7	no [Ir]	76%
8	no hν	dec

Scheme 2 shows the substrate scope. Arylidenemalonates with different substituents on the aryl ring were tolerated; fluoro-, chloro-, and bromo- on the *o*-, *m*-, and *p*-positions, respectively, underwent the desired reaction smoothly (**18ab** to **18ad**). Additional steric hindrance on the aryl group did not affect the reaction efficiency (**18ae**). Electron-donating substituents were also compatible (**18af** and **18ag**). Trifluoromethylthio- and trifluoromethyl substrates also reacted efficiently (**18ah** and **18ai**). *Trans*-chalcone afforded a significantly diminished yield (**18aj**). Primary and secondary alkylidenemalonates participated in the reaction successfully (**18ak** and **18al**). Sulfone **18am** was produced in 92% yield as a mixture of diastereomers.

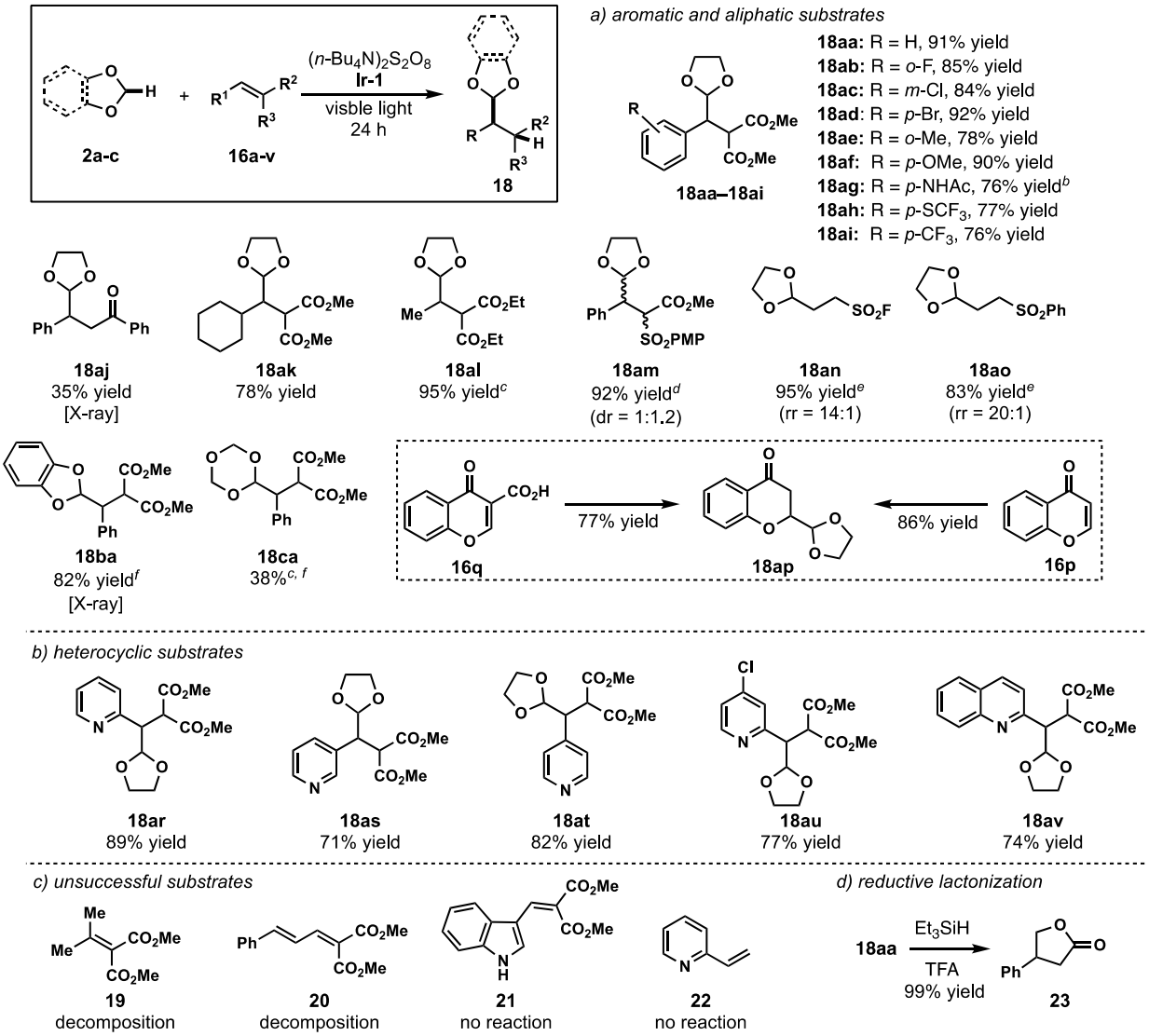
Radical acceptors containing a sulfone or sulfonyl fluoride[27, 28] were competent reactant partners (**18an** and **18ao**). Sulfonyl fluoride **18an** may be useful for SuFEx chemistry.[29, 30] Despite the potential formation of C2- and C4-regioisomers of 1,3-dioxolane,[4, 9] only **18an** and **18ao** were formed as regioisomeric mixtures. Chromones[31] were competent radical acceptors under our reaction conditions (**18ap**); carboxylic acid **16q** underwent radical addition with concomitant decarboxylation to form **18ap**.

We then tested other radical donors; enzo-1,3-dioxole[32] afforded 82% yield of **18ba**. Trioxane[25] did not afford any desired product under photolytic conditions; heating the reaction mixture to 90 ºC gave **18ca** in 38% yield.

Because previous works[4, 9] on *N*-heterocyclic substrates focused on Minisci-type reactivity, we studied for orthogonal reactivity under our reaction conditions (Scheme 2b); 2-, 3-, and 4-pyridinyl substrates reacted with no observable Minisci-type side products (**18ar** to **18at**). 4-Chloropyridinyl substrate reacted efficiently (**18au**). Quinolinyl substrate also performed well in the reaction (**18av**). A lower persulfate loading (0.50 equiv) helped to isolate several water-soluble products.

Unlike literature precedents, our reaction failed to work when one or more electron-withdrawing group was a nitrile group[26, 16] (see the SI). The sterically hindered olefin **19** (Scheme 2c) was unreactive. Dienoate **20** failed to react due to instability under our reaction conditions. The less electron-deficient indole-derived alkene **21** was not a suitable substrate (see Figure S3 for all unsuccessful substrates). Unlike literature precedents, 2-vinylpyridine **22**[16] was unreactive. Acetal **18aa** could be converted to lactone **23** with Et_3SiH and water in trifluoroacetic acid in 99% yield (Scheme 2d).

Scheme 2. Substrate Scope[a]

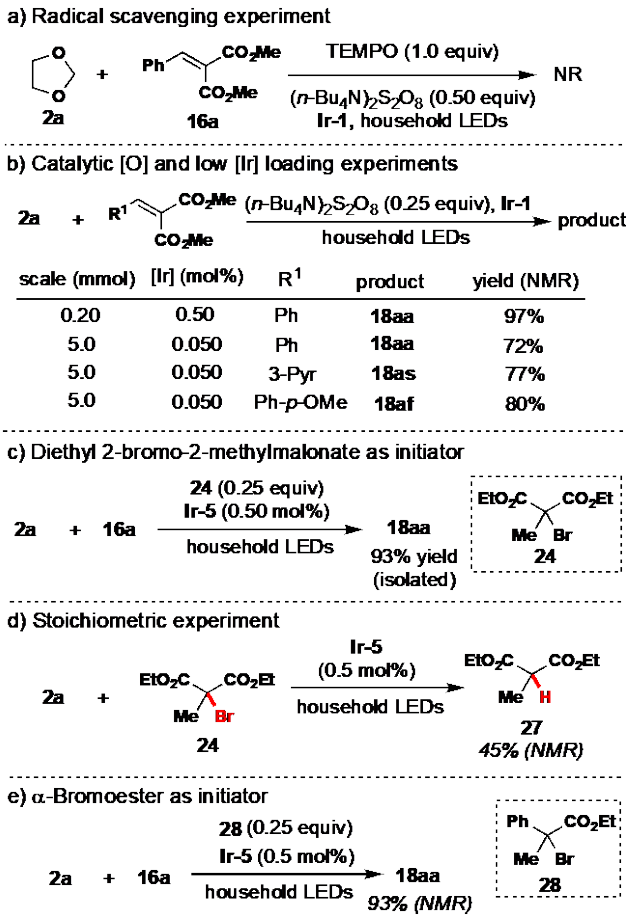


[a]General reaction conditions: alkene (1.0 equiv, 0.20 mmol), (n-$Bu_4N)_2S_2O_8$(1.0 equiv, 0.20 mmol), degassed 1,3-dioxolane (3.0 mL), fac-Ir(ppy)$_3$ (0.50 mol%), irradiated with household LEDs (15W x 4) for 24 h, external temp = 30 ºC. [b]0.50 equiv of (n-$Bu_4N)_2S_2O_8$ was used [c]0.10 mmol scale. [c]Yield was determined by ^{1}H NMR spectroscopy using mesitylene as standard. [d]dr was determined by ^{1}H NMR spectroscopy, PMP = p-methoxyphenyl. [e]Inseparable mixture of C-2/C-4, rr = regioisomeric ratio, determined by ^{1}H NMR spectroscopy. [f]Alkene (1.0 equiv, 0.20 mmol), (n-$Bu_4N)_2S_2O_8$ (1.0 equiv, 0.20 mmol), degassed MeCN (2.7 mL), *fac*-Ir(ppy)$_3$ (0.50 mol%), irradiated with household LEDs (15W x 4) for 24 h, external temp = 30 ºC.[g] (n-$Bu_4N)_2S_2O_8$(0.25 equiv, 0.05 mmol), Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6, (0.50 mol%)

Subsequently, we investigated the mechanism (Scheme 3). Addition of TEMPO resulted in no conversion, supporting the radical intermediacy (Scheme 3a). Unlike literature precedents,[4, 25] we found that 0.25 equiv of persulfate worked equally well (Scheme 3b, 97% yield). Additionally, lights-on/lights-off experiment suggested a closed catalytic cycle was not operative (Figure S2). With only 0.050 mol% of [Ir], products **18aa**, **18as**, and **18af** were produced in 72, 77, and 80% yield, respectively (Scheme 3b).

Nishibayashi's work inspired us to probe whether α-malonyl radicals undergo HAT and propagate the radical chain.[26] The combination of **Ir-5** (E_T = 61 kcal mol^{-1})[34] and bromomalonate **24**, a known source of α-malonyl radical,[33] in dioxolane reacted with **16a** to form **18aa** in 93% yield (Scheme 3c). We explored the substrate scope with this set of conditions. However, the new conditions did not yield any product with less successful and unsuccessful substrates (Scheme 2 and Figure S3), which led us to conclude that persulfate as the radical initiator works well with limited scope. With iridium catalysts, we observed a correlation with the catalyst's triplet emission energy (E_T) (see Table S2 for catalyst screening). An Ir(III) photocatalyst with a large E_T is required to promote the reaction [BDE of C(sp^3)–Br = 54–71 kcal mol^{-1}]. Bromomalonate **24** might undergo homolysis under this set of reaction conditions as an efficient radical initiator. α-Bromomalonates are known to form malonyl radicals via SET or energy transfer pathway.[35-37] In the energy transfer pathway, bromine radicals are also formed; this raised doubts about the actual radical abstracting hydrogen from 1,3-dioxolane. In this regard, we performed a stoichiometric experiment between bromomalonate **24** and 1,3-dioxolane, and malonate **27** was formed in only 45% yield (unoptimized) (Scheme 3d). This supported the possibility of direct HAT to an α-malonyl radical. Currently, the fate of 1,3-dioxolane after HAT is unclear, warranting further investigations. Nevertheless, we tentatively propose a SET mechanism of the dioxolanyl radical to the oxocarbenium ion, followed by coupling with nucleophilic species. An alternate pathway involving HAT by bromine radicals cannot be excluded at this stage (Figure S4). Encouraged by the result with bromomalonate **24**, we also tested the reaction using bromoester **28** as the initiator,[38] affording **18aa** in 93% yield (Scheme 3e).

Scheme 3. Mechanistic Studies and Scale-Up Experiments

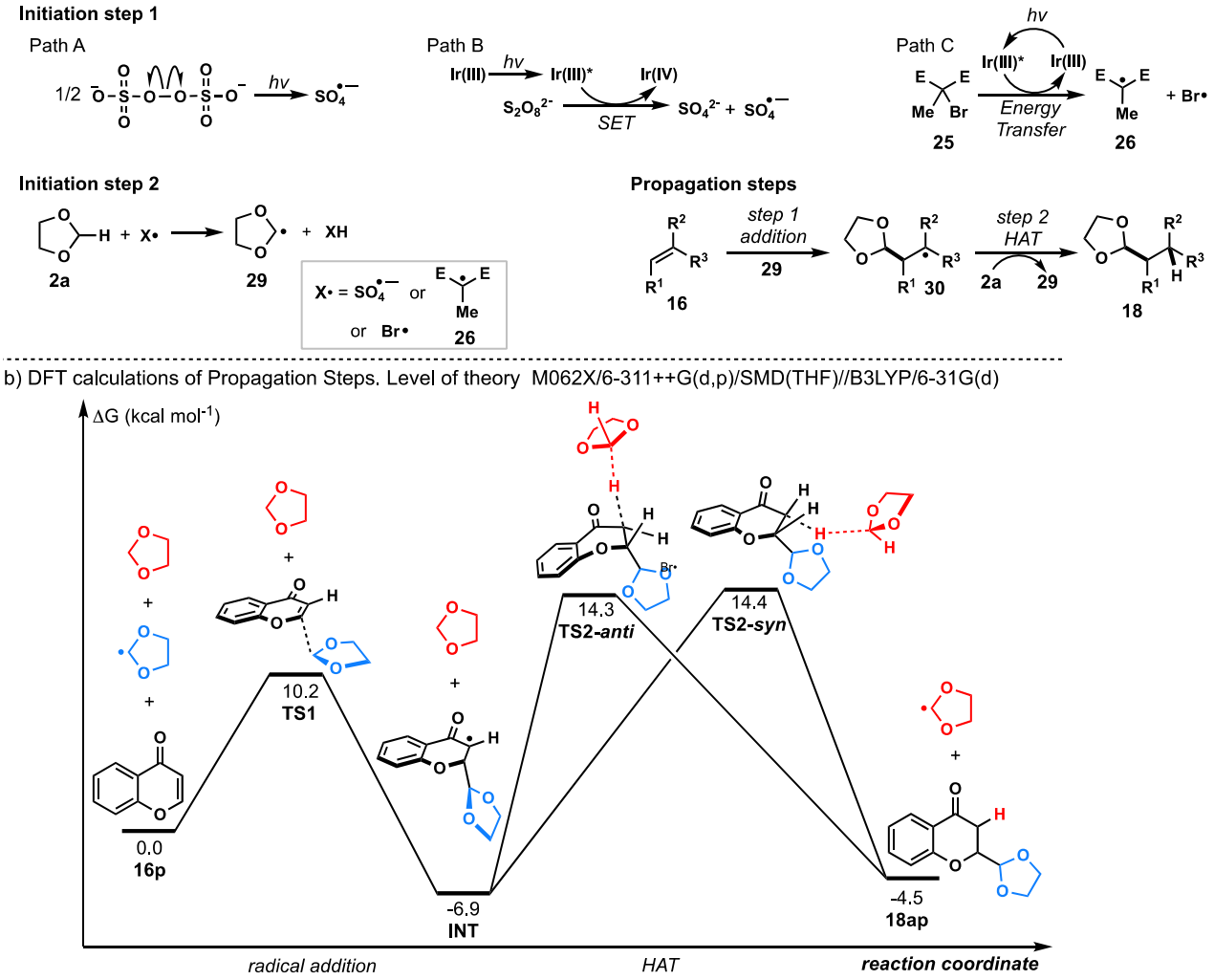


We propose a radical chain mechanism with three possible initiation pathways (Scheme 4a). When a persulfate was used, sulfate radical anions could be formed homolytically (BDE of O–O = 28.7 kcal mol^{-1}) via energy transfer (path A, major), or heterolytically via SET with Ir(III)* (path B, minor). When bromide **25** was used as initiators, it could form **26** and Br• (path C). Thereafter, radical **X•** (sulfate radical anion, α-malonyl radical **26**, or Br•) abstracts a hydrogen atom from 1,3-dioxolane. In the propagation steps, nucleophilic dioxolanyl radical **29** undergoes conjugate addition to alkene **16**. α-Malonyl radical **30** abstracts a hydrogen atom from a second molecule of 1,3-dioxolane to generate another radical **29**, propagating the radical chain.

We also studied the propagation steps of the mechanism using DFT calculations; we chose the conformationally rigid chromone **16p** as the substrate (Scheme 4b). Preliminary results obtained are in agreements with previously reported computations of related systems.[16] Our calculations show that HAT is likely the rate-determining step.[16] The reaction is overall exergonic, but the HAT step might be reversible. Intrigued by whether the energetics for chromone could be extrapolated to other electronically and sterically different substrates in Scheme 2, we computed the energetics of HAT of dioxolane by several radicals (Figure S5).

Highly electrophilic alkenes tend to react more efficiently.[39, 40] Moreover, we predict that substrates with more exergonic HAT would not necessitate large excess of C–H donors. Our hypotheses, however, still require experimental validation. Taken together, our current data not only shed light on the reactivity pattern of our substrates but may also serve as predictive tools for designing radical additions to olefins that operate by radical chain pathways.

Scheme 4. Proposed Mechanism with Diverse Initiation Pathways



In conclusion, we have found the addition of dioxolanyl group and hydrogen atom to electron-deficient alkenes via a radical chain mechanism. During our mechanistic investigations, we discovered that α-bromomalonate and α-bromoester were competent radical initiators. These results open up the possibility of several initiation pathways for our reaction.

Experimental Section

General Information and Reagents. Commercially available chemicals were purchased from Sigma-Aldrich, Alfa Aesar, Strem, ACROS or Oakwood and used without further purification, unless otherwise indicated. Glasswares were either flamed-dried immediately prior use or oven-dried (140 °C, overnight). Moisture-sensitive reactions were performed under a nitrogen atmosphere with standard Schlenk techniques unless otherwise stated. 1,3-Dioxolane was purchased from ACROS Organics and freshly degassed before each use. Acetonitrile (MeCN) and methanol (MeOH) were stored over 3Å molecular sieves. 1,4-Dioxane was purchased from Acros Organics and used as received. Solvents were degassed by sonication for 45 min or sparging with nitrogen gas for 30 min immediately before use. LEDs used are GE lighting Brightstik™ (15 W, 1600 lumen, daylight). Iridium photocatalysts were purchased from Strem or Sigma-Aldrich and stored in amber secondary containers; the catalysts were used as received. Tetrabutylammonium persulfate $(n\text{-}Bu_4N)_2S_2O_8$ was prepared using a protocol reported by Yeung et al.[25]

and stored in scintillation vial wrapped with aluminum foil at room temperature for up to two months. A sand bath with a mantle heater was used as the heat source for reactions that required heating. Solvents used for NMR spectroscopy were purchased from Cambridge Isotope Laboratories. $CDCl_3$ was stored over anhydrous K_2CO_3. All 1D and 2D NMR spectra were recorded on Bruker AVANCE III 300, 400, and 500 MHz spectrometers and calibrated using either tetramethylsilane or residual solvent peaks as internal reference. $CDCl_3$ with 1% w/w CD_3OD was used to characterize compounds with exchangeable protons. NMR yields were determined by ^1H NMR spectra of the crude reaction mixtures using mesitylene as external standard. Isolated yields refer to chromatographically purified materials, unless otherwise stated, and characterized by both NMR spectroscopy and high-resolution mass spectrometry (HRMS). The following abbreviations are used to indicate the multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; app, apparent, or combinations thereof. HRMS data were obtained on a GCT, Micromass UK Ltd and Q-Tof Ultima API, Micromass UK Ltd. X-ray data were collected on a Bruker X8 Prospector Ultra diffractometer with an ImuS Copper microfocus X-ray tube and an Apex II CCD detector. Samples were coated in FluoroLube and attached to Mitegen micromounts. Data were collected under cooled nitrogen gas at 150 K. Reactions were monitored using thin-layer chromatography (TLC) or ^1H NMR spectroscopic analysis of crude material. All reactions were monitored by TLC carried out on 0.25-mm Merck silica gel plates (60F-254) using UV light (254 nm) for visualization or *p*-anisaldehyde in EtOH, 0.2% ninhydrin in EtOH, 2.4% phosphomolybdic acid/1.4% H_3PO_4/5% H_2SO_4 in water, or alkaline $KMnO_4$ solutions as a developing agents and heat for visualization as necessary. SilicaFlash P60 (230–400 mesh) was used for flash chromatography.

General Procedure for Synthesis of Alkylidene Malonates

Aldehyde (20 mmol, 1.0 equiv) and malonate (20 mmol, 1.0 equiv) were dissolved in benzene (50 mL) in a 100 mL single neck round bottom flask. A magnetic stir bar, piperidine (2.0 mmol, 0.10 equiv), and acetic acid (4.0 mmol, 0.20 equiv) were added. Additional benzene (10 mL) was added to wash the walls of the flask. A Dean-Stark trap were attached, and additional benzene (15 mL) was added to the trap. A condenser was attached, and the mixture was stirred at reflux overnight. The solvent, piperidine, and AcOH were removed *in vacuo*. The crude material was dissolved in EtOAc (100 mL) and washed with saturated $NaHCO_3$ (20 mL × 2) and brine. The organic layer was dried over Na_2SO_4, filtered through a plug of cotton, and concentrated *in vacuo*. Crude materials were purified using flash column chromatography (SiO_2, EtOAc in hexanes) to yield the desired product. Spectroscopic data of known compounds matched those reported in the literature.[41-47]

Visible-Light Mediated Dioxolane Addition

Method A: Alkene **16** (0.20 mmol, 1.0 equiv), $(n\text{-}Bu_4N)_2S_2O_8$ (0.20 mmol, 1.0 equiv), and *fac*-$Ir(ppy)_3$ (1.0 μmol, 0.50 mol%) were mixed in a 2-dram vial. Degassed 1,3-dioxolane (3.0 mL) was added using a syringe, and the vial was flushed with argon for 1 min and sealed. The vial was stirred under household LED irradiation (15 W × 4) for 24 h. The vial was placed ca. 5 cm from each LED and ca. 15 cm from the fan. The reaction vial was shielded with an aluminum-foil wall to maximize absorption. Upon completion of reaction as indicated by TLC analysis, the solvent was removed *in vacuo*. The crude material was dissolved in EtOAc (2 mL), the resulting mixture was poured into DI water (5 mL), and the layers were partitioned. The aqueous layer was extracted with EtOAc (2 mL × 2). The combined organic layers

were filtered through a plug of Na_2SO_4 and concentrated *in vacuo*. The crude material was purified by flash column chromatography (3 mL of SiO_2).

Method B: Alkene **16** (0.20 mmol, 1.0 equiv), $(n\text{-}Bu_4N)_2S_2O_8$ (0.10 mmol, 0.50 equiv), *fac*-Ir(ppy)$_3$ (1.0 μmol, 0.50 mol%) were mixed in a 2-dram vial. Degassed 1,3-dioxolane (3.0 mL) was added using a syringe, and the vial was flushed with argon for 1 min and sealed. The vial was stirred under household LED irradiation (15W × 4) for 24 h. The vial was placed ca. 5 cm from each LED and ca. 15 cm from the fan. The reaction vial was shielded with an aluminum-foil wall to maximize absorption. Upon completion of reaction as indicated by TLC analysis, the solvent was removed *in vacuo*. The crude material was directly purified using flash column chromatography (3 mL of SiO_2).

Method C: Alkene **16** (0.20 mmol, 1.0 equiv), $(n\text{-}Bu_4N)_2S_2O_8$ (0.10 mmol, 1.0 equiv), and *fac*-Ir(ppy)$_3$ (1.0 μmol, 0.50 mol%) were mixed in a 2-dram vial. Degassed 1,3-dioxolane (3.0 mL) was added using a syringe, the vial was flushed with argon for 1 min and sealed. The vial was stirred under household LED irradiation (15W × 4) for 24 h. The vials are placed ca. 5 cm from each LED and ca. 15 cm from the fan. The reaction vial was shielded with an aluminum-foil wall to maximize absorption. Upon completion of reaction as indicated by TLC analysis, the solvent was removed *in vacuo*. Mesitylene was added as external standard (for accuracy, the mass of mesitylene was recorded instead of volume). The NMR yield was determined by comparing the peaks at δ 6.79 (aromatic C-H of mesitylene) and δ 5.14 (C2-H from dioxolanyl of product).

Method D: Alkene (0.20 mmol, 1.0 equiv), $(n\text{-}Bu_4N)_2S_2O_8$ (0.10 mmol, 1.0 equiv), *fac*-Ir(ppy)$_3$ (1.0 μmol, 0.50 mol%), and C–H donors (10 equiv) were mixed in a 2-dram vial. Degassed MeCN (2.7 mL) was added using a syringe, and the vial was flushed with argon for 1 min and sealed. The vial was stirred under household LED irradiation (15W × 4) for 24 h. The vials are placed ca. 5 cm from each LED and ca. 15 cm from the fan. The reaction vial was shielded with an aluminum-foil wall to maximize absorption. Upon completion of reaction as indicated by TLC analysis, the solvent was removed *in vacuo*. The crude material was dissolved in EtOAc (2 mL) poured into DI water (5 mL), and the layers were partitioned. The aqueous layer was extrated with EtOAc (2 mL × 2). The combined organic layers were filtered through a plug of Na_2SO_4 and concentrated *in vacuo*. The crude material was purified by flash column chromatography (3 mL of SiO_2).

Dimethyl 2-((1,3-dioxolan-2-yl)(phenyl)methyl)malonate (18aa)

Colorless oil (54 mg, 91%), synthesized using method A in the general procedure. R_f = 0.20 (20% EtOAc in hexanes); IR (neat) 2955, 2894, 1737, 1498, 1455, 1436 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.31–7.27 (m, 4H), 7.25–7.22 (m, 1H), 5.14 (d, J = 4.0 Hz, 1H), 4.08 (d, J = 11.0 Hz, 1H), 3.84–3.79 (*m*, 4H), 3.84–3.79 (*m*, 1H), 3.77 (s, 3H), 3.42 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 168.5, 167.8, 136.6, 129.2, 128.2, 127.4, 104.5, 65.1 65.0, 52.8, 52.6, 52.3, 49.0; HRMS (ESI-TOF): *m/z* for $[M+H]^+$ $C_{15}H_{19}O_6$, calcd 295.1176, found 295.1162.

Dimethyl 2-((1,3-dioxolan-2-yl)(2-fluorophenyl)methyl)malonate (18ab)

Colorless oil (53 mg, 85%), syntheszed using method A in the general procedure. R_f = 0.18 (20% EtOAc in hexanes); IR (neat) 2956, 2895, 1737, 1587, 1494, 1435 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.31 (*app* dt, J = 7.5, 1.5 Hz, 1H), 7.23 (*app* dq, J = 4.0, 2.0 Hz, 1H), 7.08 (*app* dt, J = 8.0, 1.5 Hz, 1H), 7.03 (ddd, J = 10.0, 8.0, 1.0 Hz, 1H), 5.20, (d, J = 4.0 Hz, 1H), 4.20 (d, J = 11.5, 4.5 Hz, 1H), 4.12 (*app* d, J = 11.0 Hz, 1H), 3.86 (dd, J = 6.0, 2.0 Hz, 1H), 3.85–3.81 (m, 3H), 3.78 (s, 3H), 3.47 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 168.3, 167.7, 161.0 (J_{CF} = 245 Hz), 130.0 (J_{CF} = 3.8 Hz), 129.0 (J_{CF} = 8.8 Hz), 123.9 (J_{CF}

= 13.8 Hz), 123.8 (J_{CF} = 3.8 Hz), 115.4 (J_{CF} = 22.5 Hz), 103.9, 65.10, 65.0, 52.7, 52.4, 52.2, 41.9; HRMS (ESI-TOF) *m/z* for $[M+H]^+$ $C_{15}H_{18}O_6F$, calcd 313.1082, found 313.1068.

Dimethyl 2-((3-chlorophenyl)(1,3-dioxolan-2-yl)methyl)malonate (18ac)

Pale-yellow oil (55 mg, 84%), synthesized using method A in the general procedure. R_f = 0.39 (40% EtOAc in hexanes); IR (neat) 2955, 2894, 1738, 1598, 1573, 1478, 1435 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, *J* = 1.0 Hz, 1H), 7.23–7.18 (m, 3H), 5.12 (d, *J* = 3.5 Hz, 1H), 4.05, (d, *J* = 11.5 Hz, 1H), 3.81–3.79 (m, 5H), 3.77 (s, 3H), 3.48 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 168.24, 167.7, 138.7, 134.0, 129.5, 129.4, 127.7, 127.6, 104.2, 65.24, 65.15, 52.7, 52.6, 52.5, 48.6; HRMS (ESI-TOF) *m/z* for $[M+H]^+$ $C_{15}H_{18}O_6Cl$, calcd 329.0786, found 329.0771.

Dimethyl 2-((4-bromophenyl)(1,3-dioxolan-2-yl)methyl)malonate (18ad)

Pale-yellow oil (69 mg, 92%),synthesized using method A in the general procedure. R_f = 0.13 (20% EtOAc in hexanes); IR (neat) 2959, 2892, 1748, 1492 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42 (dd, *J* = 7.0, 2.0 Hz, 2H), 7.19 (dd, *J* = 6.5, 2.0 Hz, 2H), 5.10, (d, *J* = 3.5 Hz, 1H), 4.03, (d, *J* = 11.0 Hz, 1H), 3.81–3.78 (m, 5H), 3.7 (s, 3H), 3.47 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 168.3, 167.7, 135.6, 131.3, 131.1, 121.6, 104.2, 65.22, 65.15, 52.7, 52.6, 52.5, 48.4; HRMS (ESI-TOF) *m/z* for $[M+H]^+$ $C_{15}H_{18}O_6Br$, calcd 373.02813, found 373.0266 and 376.0273.

Dimethyl 2-((1,3-dioxolan-2-yl)(o-tolyl)methyl)malonate (18ae)

Colorless oil (48 mg, 78%), synthesized using method A in the general procedure. R_f = 0.38 (30% EtOAc in hexanes); IR (neat) 2955, 2892, 1739, 1495, 1435 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.24 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.16–7.11 (m, 1H), 5.09 (d, *J* = 3.5 Hz, 1H), 4.18 (dd, *J* = 11.5, 4.0 Hz, 1H), 4.10 (d, *J* = 11.5 Hz), 3.83–3.78 (m, 4H), 3.78 (s, 3H), 3.41 (s, 3H), 2.45 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 168.71, 167.94, 137.7, 135.3, 130.3, 127.4, 127.1, 125.7, 104.8, 65.2, 65.1, 53.0, 52.7, 52.3, 43.6, 20.1; HRMS (ESI-TOF) *m/z* for $[M+H]^+$ $C_{16}H_{21}O_6$, calcd 309.1333, found 309.1318.

Dimethyl 2-((1,3-dioxolan-2-yl)(4-methoxyphenyl)methyl)malonate (18af)

Pale-yellow oil (59 mg, 90%), synthesized using method A in the general procedure. R_f = 0.30 (40% EtOAc in hexanes); IR (neat) 2955, 2896, 1738, 1613, 1515, 1435 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.8 Hz, 2H), 6.82 (d, *J* = 8.8 Hz, 2H), 5.11 (d, *J* = 3.6 Hz, 1H), 4.03 (d, *J* = 10.8 Hz, 1H), 3.83–3.76 (m, 5H), 3.77 (s, 3H), 3.76 (s, 3H), 3.45 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 168.6, 167.9, 158.8, 130.2, 128.5, 113.6, 104.7, 65.13, 65.05, 55.1, 52.9, 52.6, 52.3, 48.2; HRMS (ESI-TOF) *m/z* for $[M+H]^+$ $C_{16}H_{21}O_7$, calcd 325.1282, found 325.1267.

Dimethyl 2-((4-acetamidophenyl)(1,3-dioxolan-2-yl)methyl)malonate (18ag)

Yellow oil (53 mg, 76%), synthesized using method B in the general procedure. R_f = 0.13 (60% EtOAc in hexanes); IR (neat) 3319 (br); 3123, 2955, 2926, 2854, 1737, 1671, 1602, 1632, 1436 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.80 (br s, 1H), 7.43 (d, *J* = 8.5 Hz, 2H), 7.23 (d, *J* = 8.5 Hz, 2H), 5.10 (d, *J* = 3.5 Hz, 1H), 4.05 (d, *J* = 11.0 Hz, 1H), 3.86–3.79 (m, 5H), 3.77 (s, 3H), 3.45 (s, 3H), 2.14 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 168.5, 168.47, 168.0, 137.4, 132.1, 130.5, 129.7, 119.4, 104.5, 65.1, 65.0, 52.8, 52.6, 52.4, 48.4, 24.4; HRMS (ESI-TOF) *m/z* for $[M+H]^+$ $C_{17}H_{22}O_7N$, calcd 352.1391, found 352.1374.

Dimethyl 2-((1,3-dioxolan-2-yl)(4-((trifluoromethyl)thio)phenyl)methyl)malonate (18ah)

Pale-yellow oil (61 mg, 77%), synthesized using method A of the general procedure. R_f = 0.41(40% EtOAc in hexanes); IR (neat) 1736, 1436, 1304, 1255 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.0 Hz, 2H), 7.38 (d, *J* = 8.5 Hz, 2H), 5.14 (d, *J* = 3.5 Hz, 1H), 4.06 (d, *J* = 11.0 Hz, 1H), 3.88 (dd, *J* = 11.0, 3.5 Hz, 1H), 3.82 (dd, *J* = 1.5, 1.5 Hz, 1H), 3.81 (dd, *J* = 4.5, 3.0 Hz, 1H), 3.79 (dd, *J* = 2.0, 2.0 Hz,

1H), 3.77 (s 3H), 3.42 (s, 3H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 168.2, 167.7, 139.9, 136.0, 130.6, 104.1, 65.2, 65.1, 52.8, 52.6, 52.4, 48.7; HRMS (ESI-TOF) *m/z* for $[M+H]^+$ $C_{16}H_{16}O_6F_3S$, calcd 393.0614, found 393.0615.

Dimethyl 2-((1,3-dioxolan-2-yl)(4-(trifluoromethyl)phenyl)methyl)malonate (18ai)

Colorless oil (55 mg, 76%), synthesized using method A of the general procedure. R_f = 0.15 (20% EtOAc in hexanes); IR (neat) 2958, 2896, 1740, 1621, 1436, 1423 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.0 Hz, 2H), 7.44 (d, *J* = 8.5 Hz, 2H), 5.13 (d, *J* = 4.0 Hz, 1H), 4.10 (d, *J* = 11.0 Hz, 1H), 3.91 (dd, *J* = 11.0, 3.5 Hz, 1H), 3.82–3.79 (m, 4H), 3.78 (s, 3H), 3.46 (s, 3H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 168.1, 167.6, 140.8, 129.8, 125.1, 125.0, 104.1, 65.2, 65.1, 52.8, 52.5, 52.4, 48.7; ^{19}F NMR (471 MHz, $CDCl_3$) δ –63.6; HRMS (ESI-TOF) *m/z* for $[M+H]^+$ $C_{16}H_{17}O_6F_3$, calcd 362.0972, found 362.0931.

3-(1,3-dioxolan-2-yl)-1,3-diphenylpropan-1-one (18aj)

White solid (20 mg, 35%), synthesized using method A of the general procedure. X-ray crystals were obtained by slow evaporation in EtOAc/hexanes. R_f = 0.33 (20% EtOAc in hexanes); m.p. = 88–90 ºC; IR (thin film) 3065, 2882, 1733, 1675, 1596, 1580, 1498, 1450 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (dd, *J* = 8.1, 1.2 Hz, 2H), 7.51 (*app* dt, *J* = 8.1, 1.2 Hz, 1H), 7.43–7.41 (m, 2H), 7.38–7.35 (m, 2H), 7.32–7.28 (m, 3H), 7.26–721 (m, 1H), 5.10 (d, *J* = 3.6 Hz, 1H), 3.90–3.82 (m, 4H), 3.81–3.76 (m, 1H), 3.58 (dd, *J* = 16.8, 5.4 Hz, 1H), 3.37 (dd, *J* = 16.8, 8.1 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 198.3, 139.8, 137.2, 132.9, 128.8, 128.5, 128.3, 128.1, 126.9, 106.0, 65.2, 65.0, 44.7, 38.8, 29.7; HRMS (ESI-TOF) *m/z* for $[M+H]^+$ $C_{18}H_{19}O_3$ calcd 283.1329, found 283.1319.

Dimethyl 2-(cyclohexyl(1,3-dioxolan-2-yl)methyl)malonate (18ak)

Color oil (47 mg, 78%) using method A of the general procedure. R_f = 0.26 (20% EtOAc in hexanes); IR (neat) 2928; 2854, 1737, 1450, 1435 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.14 (d, *J* = 4.5 Hz, 1H), 3.91–3.87 (m, 2H), 3.85–3.81 (m, 2H), 2.50 (ddd, *J* = 9.0, 7.0, 4.5 Hz, 1H), 1.74–1.72 (m, 4H), 1.65–1.60 (m, 2H), 1.26–1.21 (m, 5H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 169.6, 169.5, 103.3, 64.9, 64.5, 52.3, 49.7, 47.6, 37.9, 31.6, 29.9, 26.9, 26.7, 26.4; HRMS (ESI-TOF) *m/z* for $[M+H]^+$ $C_{15}H_{25}O_6$, calcd 301.1646, found 301.1634.

Diethyl 2-(1-(1,3-dioxolan-2-yl)ethyl)malonate (18al)

Crude oil (95%, NMR), synthesized using method C from the general procedure. The crude material was not purified due to difficulties in purification using flash column chromatography.

Methyl 3-(1,3-dioxolan-2-yl)-2-((4-methoxyphenyl)sulfonyl)-3-phenylpropanoate (18am)

Pale-yelow solid, mixture of both diastereomers (75 mg, 92%, dr = 1:1.2) using method A from the general procedure. R_f = 0.30 (40% EtOAc in hexanes), 0.21 (40% EtOAc in hexanes); IR (neat) 2955, 2892, 1746, 1591, 1497, 1455 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, *J* = 9.0 Hz, 2H), 7.28 (dd, *J* = 9.0, 2.0 Hz, 2H), 7.25–7.13 (m, 9H), 7.00 (d, *J* = 9.0 Hz, 2H), 6.71 (d, *J* = 9.0 Hz, 2H), 5.73 (d, *J* = 2.5 Hz, 1H), 4.95 (d, *J* = 2.5 Hz, 1H), 4.80 (d, *J* = 10.5 Hz, 1H), 4.69 (d, *J* = 11.5 Hz, 1H), 3.90 (*app* d, *J* = 2.5 Hz, 1H), 3.88 (s, 3H), 3.85 (*app* d, *J* = 3.0 Hz, 1H), 3.82 (s, 3H), 3.81 (*app* s, 4H), 3.22–3.10 (m, 1H), 3.17 (s, 3H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 166.1, 165.4, 164.2, 163.4, 134.8, 133.8, 131.5, 130.7, 130.4, 130.1, 129.4, 127.9, 127.8, 127.7, 127.6, 114.2, 113.8, 104.6, 102.6, 72.3, 71.4, 65.4, 65.3, 65.1, 65.0, 55.7, 55.6, 52.9, 52.3, 48.6, 47.7; HRMS (ESI-TOF) *m/z* for $[M+H]^+$ $C_{20}H_{21}O_7S$, calcd 405.1003, found 405.0998.

2-(1,3-dioxolan-2-yl)ethane-1-sulfonyl fluoride (18an)

Colorless oil, as an inseparable mixture of regioisomers (70 mg, 95%, rr = 14 : 1), synthesized using method B from the general procedure. R_f = 0.35 (30% EtOAc in hexanes); IR (neat) 2959, 2897, 1738, 1404, 1365, 1256, 1198 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.06 (dd, *J* = 3.6, 3.6 Hz, 1H), 3.99 (ddd, *J*

= 11.2, 9.2, 6.4 Hz, 2H), 3.92 (ddd, *J* = 11.2, 9.2, 6.8 Hz, 2H), 3.53 (d, *J* = 8.0, 4.8 Hz, 1H), 3.51 (dd, *J* = 8.4, 4.8 Hz, 1H), 2.34 (dd, *J* = 8.0, 3.2 Hz, 1H), 2.31 (dd, *J* = 4.4, 3.2 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 100.7, 95.2, 72.6, 69.1, 65.3, 47.5, 47.3, 45.2, 45.0, 27.3; ^{19}F NMR (376 MH, $CDCl_3$) δ -151.9; HRMS (ESI-TOF) *m/z* for $[M+H]^+$ $C_5H_{10}FO_4S$ calcd 185.0284, found 185.0271.

2-(2-(phenylsulfonyl)ethyl)-1,3-dioxolane (18ao)

Pale-yellow oil, as an inseparable mixture of regioisomers (40 mg, 83%, r.r = 20 : 1), synthesized using method A from the general proceure. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (*app* d, *J* = 7.5 Hz, 2H), 7.67 (dd, *J* = 7.0, 1.0 Hz, 1H), 7.58 (m, 2H), 4.96 (*app* t, *J* = 4.0 Hz, 1H), 4.80 (s, 2H, C4-isomer), 3.91 (ddd, *J* = 11.0, 9.0, 6.5 Hz, 2H), 3.83 (ddd, *J* = 11.0, 9.0, 7.0 Hz, 2H), 3.95 (ddd, *J* = 11.0, 9.0, 6.5 Hz, 2H), 3.84 (ddd, *J* = 11.0, 9.0, 7.0 Hz, 2H), 3.23 (m, 2H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 138.9, 133.8, 133.7, 129.3, 129.2, 128.0, 127.9, 101.7, 95.0, 73.6, 69.1, 651, 52.7, 50.6, 27.0, 26.4. The NMR spectroscopic data of the major regioisomer are consistent with those reported in the literature.[48, 49]

2-(1,3-dioxolan-2-yl)chroman-4-one (18ap)

Colorless oil (38 mg, 86%), synthesized using method A of the general procedure. R_f = 0.22 (30% EtOAc in hexanes); IR (neat) 2892, 1683, 1609, 1579, 1474, 1465 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.48 (ddd, *J* = 9.0, 7.5, 1.5 Hz, 1H), 7.03 (*app* d, *J* = 8.0 Hz, 1H), 7.01 (d, *J* = 7.0 Hz), 5.20 (d, *J* = 3.5 Hz, 1H), 4.53 (*app* dt, *J* = 12.0, 4.0 Hz, 1H), 4.07–4.01 (m, 2H), 4.01–3.96 (m, 2H), 2.89 (dd, *J* = 17.0, 12.0 Hz, 1H), 2.77 (dd, *J* = 17.0, 3.5 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 191.3, 160.7, 136.0, 126.7, 121.5, 121.1, 117.9, 103.0, 65.7, 65.4, 37.1; HRMS (ESI-TOF) *m/z* for $[M+H]^+$ $C_{12}H_{13}O_4$ calcd 221.0808, found 221.0808. The spectrocopic data are consistent with those reported in the literature.[53]

Dimethyl 2-((1,3-dioxolan-2-yl)(pyridin-2-yl)methyl)malonate (18ar)

Yellow oil (53 mg, 89%), synthesized using method B of the general procedure. R_f = 0.31 (60% EtOAc in hexanes); IR (neat) 2955, 2894, 1736, 1633, 1593, 1473 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.52 (ddd, *J* = 5.0, 1.5, 1.0 Hz, 1H), 7.62 (*app* dt, *J* = 7.5, 1.5 Hz, 1H), 7.31 (*app* d, *J* = 7.5 Hz, 1H), 7.14 (ddd, *J* = 7.5, 5.0, 1.0 Hz, 1H), 5.28, (d, *J* = 5.0 Hz, 1H), 3.93, (dd, *J* = 10.5, 5.0 Hz, 1H), 3.89–3.79 (m, 4H), 3.78 (s, 3H), 3.53 (s, 3H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 169.0, 168.4, 157.3, 149.0, 136.1, 124.9, 122.0, 104.9, 65.1, 65.0, 52.6, 52.4, 51.8, 50.6; HRMS (ESI-TOF) *m/z* for $[M+H]^+$ $C_{14}H_{18}O_6N$, calcd 296.1129, found 296.1118.

Dimethyl 2-((1,3-dioxolan-2-yl)(pyridin-3-yl)methyl)malonate (18as)

Yellow oil (42 mg, 71%), synthesized using method B of the general procedure. R_f = 0.30 (100% EtOAc); IR (neat) 2956, 2895, 2362, 2341, 1735, 1700, 1653, 1577 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56 (*app* d, *J* = 2.0 Hz, 1H), 8.50 (dd, *J* = 4.5, 1.5 Hz, 1H), 7.66 (*app* dt, *J* = 8.0, 2.0 Hz, 1H), 5.14 (d, *J* = 3.0 Hz, 1H), 4.08 (d, *J* = 11.0 Hz, 1H), 3.86 (dd, *J* = 11.0, 3.5 Hz, 1H), 3.82–3.76 (m, 3H), 3.76 (s, 3H), 3.74 (dd, *J* = 3.5, 1.5 Hz, 1H), 3.46 (s, 3H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 168.1, 167.6, 150.9, 148.8, 136.9, 132.1, 123.0, 103.8, 65.3, 65.2, 52.8, 52.5, 52.4, 46.6; HRMS (ESI-TOF) *m/z* for $[M+H]^+$ $C_{14}H_{18}O_6N$, calcd 296.1129, found 296.1122.

Dimethyl 2-((1,3-dioxolan-2-yl)(pyridin-4-yl)methyl)malonate (18at)

Pale-yellow oil (48 mg, 82%), synthesized using method B of the general procedure. R_f = 0.16 (80% EtOAc in hexanes); IR (neat) 2956, 2895, 1738, 1601, 1560, 1436 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 (*app* d, *J* = 6.0 Hz, 1H), 7.24 (dd, *J* = 4.5, 1.5 Hz, 2H), 5.12 (d, *J* = 3.0 Hz, 1H), 4.09 (d, *J* = 11.0 Hz, 1H), 3.84 (*app* d, *J* = 3.5 Hz, 1H), 3.82–3.79 (m, 3H), 3.78 (s, 3H), 3.48 (s, 3H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 167.96, 167.5, 149.6, 145.7, 124.6, 103.7, 65.3, 65.2, 52.8, 52.6, 52.2, 48.3; HRMS (ESI-TOF) *m/z* for $[M+H]^+$ $C_{14}H_{18}O_6N$, calcd 296.1129, found 296.1115.

Dimethyl 2-((4-chloropyridin-2-yl)(1,3-dioxolan-2-yl)methyl)malonate (18au)

Yellow oil (51 mg, 77%), synthesized using method B of the general procedure. R_f = 0.45 (40% EtOAc in hexanes); IR (neat) 2895, 2595, 1738, 1576, 1557, 1468 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.40 (*app* d, *J* = 5.5 Hz, 1H), 7.35 (*app* d, *J* = 2.0 Hz, 1H), 7.16 (dd, *J* = 5.5, 2.0 Hz, 1H), 5.24 (d, *J* = 5.0 Hz, 1H), 3.90–3.80 (m, 5H), 3.78 (s, 3H), 3.56 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 168.8, 168.2, 159.0, 149.7, 144.1, 125.3, 122.6, 104.5, 65.2, 65.1, 52.7, 52.5, 51.7, 50.4; HRMS (ESI-TOF) *m/z* for $[M+H]^+$ $C_{14}H_{17}O_6NCl$, calcd 330.0739, found 330.0726.

Dimethyl 2-((1,3-dioxolan-2-yl)(quinolin-2-yl)methyl)malonate (18av)

Yellow oil (51 mg, 74%), synthesized using method B of the general procedure. R_f = 0.13 (30% EtOAc in hexanes); IR (neat) 2954, 2894, 1756, 1737, 1600, 1505, 1434 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.08 (*app* d, *J* = 8.5 Hz, 1H), 8.00 (*app* d, *J* = 8.5 Hz, 1H), 7.77 (*app* d, *J* = 8.0 Hz, 1H), 7.65 (*app* dt, *J* 8.5, 1.5 Hz, 1H), 7.48 (*app* dt, *J* = 8.0, 1.0 Hz, 1H), 7.44 (d, *J* = 8.5 Hz, 1H), 5.38 (d, *J* = 5.5 Hz, 1H), 4.11 (dd, *J* = 10.5, 5.5 Hz, 1H), 3.92–3.88 (m, 2H), 3.86-3.83 (m, 2H), 3.81 (app s, 4H), 3.53, (s, 3H) $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 169.2, 168.7, 157.9, 147.6, 135.9, 129.3, 129.2, 127.5, 127.2, 126.2, 122.8, 105.1, 65.1, 65.0, 52.6, 52.4, 52.1, 51.2; HRMS (ESI-TOF) *m/z* for $[M+H]^+$ $C_{18}H_{20}O_6N$ calcd 346.1285, found 346.1269.

Dimethyl 2-(benzo[d][1,3]dioxol-2-yl(phenyl)methyl)malonate (18ba)

White solid (56 mg, 82%), synthesized using method D of the general procedure. Additional note: the bulk of benzo-1,3-dioxole could be removed by drying the crude material on the high vacuum overnight prior flash column chromatography. X-ray quality crystals were obtained by slow evaporation in EtOAc/hexanes. IR (thin film) 2954, 2894, 1756, 1738, 1593, 1474, 1436 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34–7.32 (m, 2H), 7.30–7.27 (m, 2H), 7.26–7.23 (m, 2H), 6.76–6.70 (m, 3H), 6.70–6.67 (m, 1H), 4.17 (d, *J* = 10.4 Hz, 1H), 4.08 (dd, *J* = 10.4, 4.0 Hz, 1H), 3.71 (s, 3H), 3.46 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 168.2, 167.4, 147.2, 147.1, 134.7, 129.4, 128.4, 127.9, 121.6, 121.5, 110.8, 108.5, 108.4, 52.8, 52.5, 49.3; HRMS (ESI-TOF) *m/z* for $[M+H]^+$ $C_{19}H_{19}O_6$, calcd 343.1186, found 343.1159.

Dimethyl 2-(phenyl(1,3,5-trioxan-2-yl)methyl)malonate (18ca)

The crude yellow oil was obtained using method D of the general procedure. Note: because of the low yield and the scale of the reaction, we were unable to obtain accurate isolated yields for **18ca**. We have determined the yield using ^1H NMR spectroscopy. The ^1H NMR spectrum of the crude mixture is provided in the Supporting Information.

4-phenyldihydrofuran-2(3*H*)-one (23)

A solution of dimethyl 2-((1,3-dioxolan-2-yl)(phenyl)methyl)malonate **18aa** (100 mg, 0.34 mmol) in water (2.3 mL) and trifluoroacetic acid (2.3 mL) was stirred at room temperature under air atmosphere in a 25-mL, single-necked, round-bottomed flask containing a magnetic stir bar. After 2 h, Et_3SiH (540 µL, 10 equiv) was added to the stirring solution, and resulting mixture was refluxed for 5 h. On completion of the reaction as indicated by TLC analysis, the reaction flask was allowed to cool to room temperature. Then the reaction mixture was transferred to a 30-mL separatory funnel, and the organic phase was extracted with EtOAc (3 × 7 mL). Combined organic layers were washed with distilled water (2 × 10 mL) and dried by adding Na_2SO_4. After 10 min, the Na_2SO_4 was filtered out, and the resulting solution was concentrated by rotary evaporation. The crude mixture was purified by flash column chromatography (15 mL of SiO_2, 5 to 10 % EtOAc in hexanes) to obtain 4-phenyldihydrofuran-2(3*H*)-one (**23**) (74 mg, 99%) as a yellow oil. The ^1H NMR spectrum of the product was identical to that of the literature.[54]

Lights-on/Lights-off Experiment (Figure S2)

Alkene **16a** (0.30 mmol, 1.0 equiv), (n-$Bu_4N)_2S_2O_8$ (0.075 mmol, 0.25 equiv), *fac*-$Ir(ppy)_3$ (1.5 μmol, 0.50 mol%) and mesitylene (0.30 mmol, 1.0 equiv) were mixed in a Teflon-coated 2-dram vial. Degassed 1,3-dioxolane (4.5 mL) was added, and the vial was flushed with argon (1 min) and sealed. The vial was irradiated with household LEDs (15W × 4) and cooled with a fan. During the lights-off period, the vial was wrapped with aluminum foil and stirred in the dark. Aliquots (100 μL) were removed periodically (1 h, 2 h, 3 h, 5 h, 6h) using syringes, transferred to NMR tubes, diluted with $CDCl_3$ (ca. 0.6 mL) and analyzed by ^1H NMR spectroscopy.

Scale-Up experiments (Scheme 3b, 18aa, 18as, 18af)

Alkene **16a** (1.1011 g, 5.00 mmol), (n-$Bu_4N)_2S_2O_8$ (0.8463 g, 1.25 mmol, 0.25 equiv), and *fac*-$Ir(ppy)_3$ (1.6 mg, 0.0025 mmol, 0.050 mol%) were mixed in a 150-mL pressure tube. Degassed 1,3-dioxolane (68 mL) was added using a syringe, and the pressure tube was flushed with argon for 1 min and sealed. The reaction mixture was stirred under household LED irradiation (15W × 4) for 24 h and was placed ca. 5 cm from each LED and ca. 15 cm from the fan. The reaction vessel was shielded with an aluminum-foil wall to maximize absorption. Upon completion of reaction as indicated by TLC analysis, the solvent was removed *in vacuo*. Mesitylene (600 mg) was added as an external standard. The yield was determined by NMR spectroscopic analysis; specifically, the peaks at δ 6.79 (aromatic C-H of mesitylene) and δ 5.14 (C2-H from dioxolanyl of product) were compared to calculate the yield.

Screening of [Ir] for α-Bromomalonate Radical Initiator (Table S2)

Alkene **16a** (0.20 mmol, 1.0 equiv), bromomalonate (0.050 mmol, 0.25 equiv), and *fac*-$Ir(ppy)_3$ (0.0010 mmol, 0.50 mol%) were mixed in a 2-dram vial. Degassed 1,3-dioxolane (3.0 mL) was added using a syringe, the vial was flushed with argon for 1 min and sealed. The vial was stirred under household LED irradiation (15W × 4) for 24 h. The solvent was removed *in vacuo*. The vials are placed ca. 5 cm from each LED and ca. 15 cm from the fan. The reaction vial was shielded with an aluminum-foil wall to maximize absorption. Mesitylene was added as external standard (for accuracy, the mass of mesitylene was recorded instead of volume). The NMR yield was determined by comparing the peaks at δ 6.79 (aromatic C-H of mesitylene) and δ 5.14 (C2-H from dioxolanyl of product). Although **Ir-4** (entry 4) afforded partial conversion, only the reaction with **Ir-5** (entry 5) that had full conversion was worked up and analyzed.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. CCDC 2027551 (**18aj**) and 2027552 (**18ba**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

Experimental procedures, computational details and characterization data for new compounds (PDF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: koide@pitt.edu.

ORCID

Wei Chuen Chan: 0000-0003-0199-8960
Jincy K. Vinod: 0000-0003-4269-2159

Kazunori Koide: 0000-0001-8894-8485

Author Contributions

All authors contributed to writing the manuscript and have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

This research was supported in part by the University of Pittsburgh Center for Research Computing through the resources provided and the US National Science Foundation (CHE-1955758). Professor. Eugene Wagner (University of Pittsburgh) is acknowledged for his assistance with LED light wavelength measurement.

REFERENCES

(1) Yi, H.; Zhang, G.; Wang, H.; Huang, Z.; Wang, J.; Singh, A. K.; Lei, A., Recent advances in radical C–H activation/radical cross-coupling. *Chem. Rev.* **2017,** *117*, 9016–9085.

(2) Crossley, S. W. M.; Obradors, C.; Martinez, R. M.; Shenvi, R. A., Mn-, Fe-, and Co-catalyzed radical hydrofunctionalizations of olefins. *Chem. Rev.* **2016,** *116*, 8912–9000.

(3) Liu, D.; Liu, C.; Li, H.; Lei, A. W., Direct functionalization of tetrahydrofuran and 1,4-dioxane: Nickel-catalyzed oxidative C(sp^3)-H arylation. *Angew. Chem., Int. Ed.* **2013,** *52*, 4453–4456.

(4) Jin, J.; MacMillan, D. W. C., Direct α-arylation of ethers through the combination of photoredox-mediated C-H functionalization and the minisci reaction. *Angew. Chem., Int. Ed.* **2015,** *54*, 1565–1569.

(5) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C., Visible light photoredox catalysis with transition metal complexes: Applications in organic synthesis. *Chem. Rev.* **2013,** *113*, 5322–5363.

(6) Skubi, K. L.; Blum, T. R.; Yoon, T. P., Dual catalysis strategies in photochemical synthesis. *Chem. Rev.* **2016,** *116*, 10035–10074.

(7) Ravelli, D.; Protti, S.; Fagnoni, M., Carbon-carbon bond forming reactions via photogenerated intermediates. *Chem. Rev.* **2016,** *116*, 9850–9913.

(8) Shields, B. J.; Doyle, A. G., Direct C(sp^3)-H cross coupling enabled by catalytic generation of chlorine radicals. *J. Am. Chem. Soc.* **2016,** *138*, 12719–12722.

(9) Nielsen, M. K.; Shields, B. J.; Liu, J.; Williams, M. J.; Zacuto, M. J.; Doyle, A. G., Mild, redox-neutral formylation of aryl chlorides through the photocatalytic generation of chlorine radicals. *Angew. Chem., Int. Ed.* **2017,** *56*, 7191–7194.

(10) Zhu, K. L.; Ohtani, T.; Tripathi, C. B.; Uraguchi, D.; Ooi, T., Formal hydroformylation of α,β-unsaturated carboxylic acids under photoexcited ketone catalysis. *Chem. Lett.* **2019,** *48*, 715–717.

(11) Ou, W.; Zhang, G.; Wu, J.; Su, C., Photocatalytic cascade radical cyclization approach to bioactive indoline-alkaloids over donor–acceptor type conjugated microporous polymer. *ACS Catal.* **2019,** *9*, 5178–5183.

(12) Zeng, H.; Yang, S.; Li, H.; Lu, D.; Gong, Y.; Zhu, J.-T., Site-specific functionalization of 1,3-dioxolane with imines: A radical chain approach to masked α-amino aldehydes. *J. Org. Chem.* **2018,** *83*, 5256–5266.

(13) Yang, S.; Zhu, S.; Lu, D.; Gong, Y., Formylation of fluoroalkyl imines through visible-light-enabled H-atom transfer catalysis: Access to fluorinated α-amino aldehydes. *Org. Lett.* **2019,** *21*, 2019–2024.

(14) Huang, H.; Yu, C.; Zhang, Y.; Zhang, Y.; Mariano, P. S.; Wang, W., Chemo- and regioselective organo-photoredox catalyzed hydroformylation of styrenes via a radical pathway. *J. Am. Chem. Soc.* **2017,** *139*, 9799–9802.

(15) Capaldo, L.; Merli, D.; Fagnoni, M.; Ravelli, D., Visible light uranyl photocatalysis: Direct C-H to C-C bond conversion. *ACS Catal.* **2019,** *9*, 3054–3058.

(16) Fan, X.-Z.; Rong, J.-W.; Wu, H.-L.; Zhou, Q.; Deng, H.-P.; Tan, J. D.; Xue, C.-W.; Wu, L.-Z.; Tao, H.-R.; Wu, J., Eosin Y as a direct hydrogen-atom transfer photocatalyst for the functionalization of C−H bonds. *Angew. Chem., Int. Ed.* **2018,** *57*, 8514–8518.

(17) Capaldo, L.; Ertl, M.; Fagnoni, M.; Knör, G.; Ravelli, D., Antimony–oxo porphyrins as photocatalysts for redox-neutral C–H to C–C bond conversion. *ACS Catal.* **2020,** *10*, 9057–9064.

(18) Manfrotto, C.; Mella, M.; Freccero, M.; Fagnoni, M.; Albini, A., Photochemical synthesis of 4-oxobutanal acetals and of 2-hydroxycyclobutanone ketals. *J. Org. Chem.* **1999,** *64*, 5024–5028.

(19) Mosca, R.; Fagnoni, M.; Mella, M.; Albini, A., Synthesis of monoprotected 1,4-diketones by photoinduced alkylation of enones with 2-substituted-1,3-dioxolanes. *Tetrahedron* **2001,** *57*, 10319–10328.

(20) Yamada, K.; Maekawa, M.; Akindele, T.; Nakano, M.; Yamamoto, Y.; Tomioka, K., Chemoselective conjugate addition of dimethylzinc-mediated ether and acetal radicals to alkylidenemalonates and asymmetric reactions. *J. Org. Chem.* **2008,** *73*, 9535–9538.

(21) Yamada, K.; Maekawa, M.; Yamamoto, Y.; Nakano, M.; Akindele, T.; Tomioka, K., Iron chloride enhancement of dimethylzinc-mediated radical conjugate addition of ethers and an amine to alkylidenemalonates. *Tetrahedron Lett.* **2009,** *50*, 6040–6043.

(22) De Vleeschouwer, F.; Van Speybroeck, V.; Waroquier, M.; Geerlings, P.; De Proft, F., Electrophilicity and nucleophilicity index for radicals. *Org. Lett.* **2007,** *9*, 2721–2724.

(23) Jung, J. C.; Choi, H. C.; Kim, Y. H., Direct facile tetrahydrofuranylation of alcohols through radical coupling with $(bu_4n)_2S_2O_8$. *Tetrahedron Lett.* **1993,** *34*, 3581–3584.

(24) Jung, J. C.; Kim, Y. H.; Lee, K., Practical β-masked formylation and acetylation of electron-deficient olefins utilizing tetra(*n*-butyl)ammonium peroxydisulfate. *Tetrahedron Lett.* **2011,** *52*, 4662–4664.

(25) Ganley, J. M.; Christensen, M.; Lam, Y.-h.; Peng, Z.; Angeles, A. R.; Yeung, C. S., Metal- and acid-free C-H formylation of nitrogen heterocycles: Using trioxane as an aldehyde equivalent enabled by an organic-soluble oxidant. *Org. Lett.* **2018,** *20*, 5752–5756.

(26) Miyake, Y.; Nakajima, K.; Nishibayashi, Y., Visible-light-mediated utilization of α-aminoalkyl radicals: Addition to electron-deficient alkenes using photoredox catalysts. *J. Am. Chem. Soc.* **2012,** *134*, 3338–3341.

(27) Chen, Q.; Mayer, P.; Mayr, H., Ethenesulfonyl fluoride: The most perfect michael acceptor ever found? *Angew. Chem., Int. Ed.* **2016,** *55*, 12664–12667.

(28) Xu, R.; Xu, T.; Yang, M.; Cao, T.; Liao, S., A rapid access to aliphatic sulfonyl fluorides. *Nat. Commun.* **2019,** *10*, 3752.

(29) Dong, J. J.; Krasnova, L.; Finn, M. G.; Sharpless, K. B., Sulfur(VI) fluoride exchange (SuFEx): Another good reaction for click chemistry. *Angew. Chem., Int. Ed.* **2014,** *53*, 9430–9448.

(30) Barrow, A. S.; Smedley, C. J.; Zheng, Q.; Li, S.; Dong, J.; Moses, J. E., The growing applications of SuFEx click chemistry. *Chem. Soc. Rev.* **2019,** *48*, 4731–4758.

(31) Liu, J.; Yu, D.; Yang, Y.; You, H.; Sun, M.; Wang, Y.; Shen, X.; Liu, Z.-Q., Free-radical-promoted dehydrogenative coupling of polyfluorinated alcohol with quinone, chromone, and coumarin. *Org. Lett.* **2020,** *22*, 4844–4847.

(32) Ravelli, D.; Albini, A.; Fagnoni, M., Smooth photocatalytic preparation of 2-substituted 1,3-benzodioxoles. *Chem.-Eur. J.* **2011,** *17*, 572–579.

(33) Teegardin, K.; Day, J. I.; Chan, J.; Weaver, J., Advances in photocatalysis: A microreview of visible light mediated ruthenium and iridium catalyzed organic transformations. *Org. Process Res. Dev.* **2016,** *20*, 1156–1163.

(34) Curran, D. P.; Bosch, E.; Kaplan, J.; Newcomb, M., Rate constants for halogen atom transfer from representative α-halocarbonyl compounds to primary alkyl radicals. *J. Org. Chem.* **1989,** *54*, 1826–1831.

(35) Staveness, D.; Bosque, I.; Stephenson, C. R. J., Free radical chemistry enabled by visible light-induced electron transfer. *Acc. Chem. Res.* **2016,** *49*, 2295–2306.

(36) Alpers, D.; Brasholz, M.; Rehbein, J., Photoredox-induced radical 6-*exo-trig* cyclizations onto the indole nucleus: Aromative versus dearomative pathways. *Eur. J. Org. Chem.* **2017**, 2186–2193.

(37) Li, Q.; Yin, Y.; Li, Y.; Zhang, J.; Huang, M.; Kim, J. K.; Wu, Y., A simple approach to indeno-coumarins *via* visible-light-induced cyclization of aryl alkynoates with diethyl bromomalonate. *Org. Chem. Front.* **2019,** *6*, 3238–3243.

(38) Fors, B. P.; Hawker, C. J., Control of a living radical polymerization of methacrylates by light. *Angew. Chem., Int. Ed.* **2012,** *51*, 8850–8853.

(39) Walling, C., *Free radicals in solution*. John Wiley & Sons, Inc.: New York, 1957.

(40) Roberts, B. P., Polarity-reversal catalysis of hydrogen-atom abstraction reactions: Concepts and applications in organic chemistry. *Chem. Soc. Rev.* **1999,** *28*, 25–35.

(41) Cardillo, G.; Fabbroni, S.; Gentilucci, L.; Gianotti, M.; Tolomelli, A., A straightforward method for the synthesis of alkylidene and arylidene malonates through proline-catalyzed Knoevenagel condensation. *Synth. Commun.* **2003,** *33*, 1587–1594.

(42) Dias, D. A.; Kerr, M. A., Domino synthesis of bridged bicyclic tetrahydro-1,2-oxazines: Access to stereodefined 4-aminocyclohexanois. *Org. Lett.* **2009,** *11*, 3694–3697.

(43) Novikov, R. A.; Timofeev, V. P.; Tomilov, Y. V., Stereoselective double Lewis acid/organo-catalyzed dimerization of donor–acceptor cyclopropanes into substituted 2-oxabicyclo[3.3.0]octanes. *J. Org. Chem.* **2012,** *77*, 5993–6006.

(44) Rogness, D. C.; Markina, N. A.; Waldo, J. P.; Larock, R. C., Synthesis of pyrido[1,2-*a*]indole malonates and amines through aryne annulation. *J. Org. Chem.* **2012,** *77*, 2743–2755.

(45) Gu, X.; Georg, G. I., Lithium perchlorate-, acetic anhydride-, and triphenylphosphine-assisted multicomponent syntheses of 4-unsubstituted 2,5-dioxooctahydroquinoline-3-carboxylates and 3-carbonitriles. *Tetrahedron* **2013,** *69*, 9406–9416.

(46) Ogiwara, Y.; Takahashi, K.; Kitazawa, T.; Sakai, N., Indium(III)-catalyzed Knoevenagel condensation of aldehydes and activated methylenes using acetic anhydride as a promoter. *J. Org. Chem.* **2015,** *80*, 3101–3110.

(47) Chen, H.; Wedi, P.; Meyer, T.; Tavakoli, G.; van Gemmeren, M., Dual ligand-enabled nondirected C-H olefination of arenes. *Angew. Chem., Int. Ed.* **2018,** *57*, 2497–2501.

(48) Gaoni, Y.; Tomažič, A.; Potgieter, E., Stereochemistry of addition of organocopper reagents and of the hydride ion to 1-(arylsulfonyl)bicyclo[1.1.0]butanes. *J. Org. Chem.* **1985,** *50*, 2943–2947.

(49) Holmbo, S. D.; Pronin, S. V., A concise approach to anthraquinone-xanthone heterodimers. *J. Am. Chem. Soc.* **2018,** *140*, 5065–5068.

(50) Chen, R.; Yu, J.-T.; Cheng, J., Site-specific hydroxyalkylation of chromones via alcohol mediated minisci-type radical conjugate addition. *Org. Biomol. Chem.* **2018,** *16*, 1823–1827.

(51) González-Martínez, D.; Rodríguez-Mata, M.; Méndez-Sánchez, D.; Gotor, V.; Gotor-Fernández, V., Lactonization reactions through hydrolase-catalyzed peracid formation. Use of lipases for chemoenzymatic Baeyer–Villiger oxidations of cyclobutanones. *J. Mol. Catal. B: Enzym.* **2015,** *114*, 31–36.