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Regioselective Sulfonylvinylation of the Unactivated C(sp^3)−H Bond via a C-Centered Radical-Mediated Hydrogen Atom Transfer (HAT) Process

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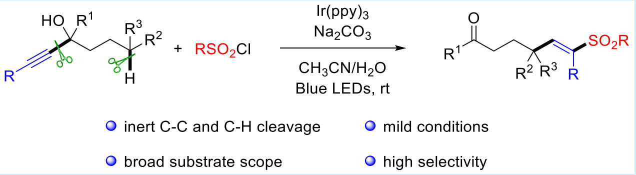
Supporting Information



ABSTRACT: Given the similarity of multiple sp^3 C−H bonds in electronic properties and bond dissociation energy (BDE), regioselective sp^3 C−H bond functionalization remains a paramount challenge. Here, we report a C-centered radical-mediated approach for site-specific sulfonylvinylation of the C(sp^3)−H bond via the hydrogen atom transfer (HAT) process. The reaction features mild conditions, broad substrate scope, and high regioselectivity and stereoselectivity, manifesting the nontrivial synthetic potential.

In the perspective of atom economy and step economy, the direct transformation of ubiquitous C(sp^3)−H bonds into other valuable chemical bonds largely enhances the synthetic efficiency.[1] Because of the identical bond strength and electronic property of multiple C(sp^3)−H bonds, regioselective functionalization of C(sp^3)−H bonds still remains challenging, which has prompted numerous organic chemists to devote attention to C(sp^3)−H activation over the past few decades. Among these efforts, transition-metal-mediated C(sp^3)−H activation has been extensively studied, in which the regiocontrol is generally achieved by harnessing the strategically placed directing groups.[2] Recently, the renaissance of radical-mediated regioselective C(sp^3)−H bond functionalization has attracted broad interest,[3] complementary to the transition-metal catalysis. Hydrogen atom transfer (HAT) mediated by N- or O-centered radicals has proven to be among the ingenious tactics used to address the regioselectivity issue for C(sp^3)−H activation.[4] In contrast, functionalization of remote C(sp^3)−H bonds mediated by C-centered radicals has been scarcely reported.[5]

Given the unique chemical and biological activities, e.g., Michael acceptor, 2π partner in cycloaddition, and inhibitor of cysteine protease, α,β-unsaturated sulfones are regarded as important intermediates in synthetic chemistry.[6] The conventional synthetic methods mainly focus on the alkyl sulfones-involved Knoevenagel reaction, the oxidation of sulfides or sulfoxides, and acetylenic sulfone mediated addition or reduction.[7] However, they sometimes suffer from the limited substrate scope and tedious synthetic approach for starting materials. Thus, seeking a new efficient strategy to prepare α,β-unsaturated sulfones bearing a diversity of skeletons is still in demand.

Inspired by our recent findings in the radical olefination of remote C(sp^3)−H bonds,[5b] it is assumed that the similar strategy might be suitable for the preparation of structurally complex α,β-unsaturated sulfones that are otherwise difficult to make. Mechanistically, addition of the sulfonyl radical, which is obtained from sulfonyl chloride, to the readily available propargyl alcohol generates a vinyl radical that triggers the subsequent HAT process and functional group migration (FGM),[8] leading to α,β-unsaturated sulfones (Scheme 1, top). Herein, we provide the concrete support for the hypothesis. The site-specific sulfonylvinylation of C(sp^3)−H bonds is enabled by the vinyl-radical-mediated 1,5-HAT process.[9] Notably, consecutive scission of an inert C−C and C−H bond readily proceeds in the reaction. A variety of sulfone-substituted *E*-olefins are furnished in good yields, which could be further converted to valuable di/tetrahydropyrans (Scheme 1, bottom). The reaction features mild conditions, broad substrate scope, and high regioselectivity and stereoselectivity.

The initial investigation of reaction conditions was performed with propargyl alcohol **1a** and tosyl chloride in the presence of photocatalyst and visible-light irradiation (Table 1). Base was added to remove byproduct HCl that suppressed the reaction outcome. Among the screened organic solvents, acetonitrile afforded the desired product **2a** in a higher yield (Table 1, entries 1−5).The reaction proceeded efficiently in biphasic solution, in which H$_2$O helped dissolve inorganic bases, whereas, in a solely organic solvent, the reaction yield was sharply decreased (Table 1, entry 6). The alkene in **2a** was formed with exclusive *E*-configuration. A

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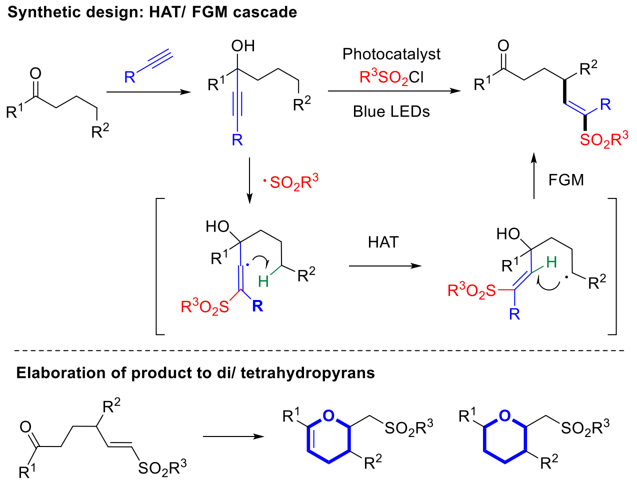
Scheme 1. C-Centered Radical-Mediated $C(sp^3)-H$ Sulfonylvinylation

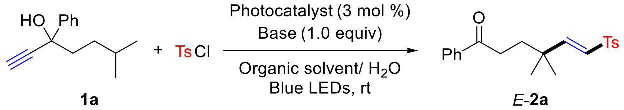


variety of bases were then examined (Table 1, entries 7−10), showing that the use of 1.0 equiv of Na_2CO_3 gave rise to 90% yield (Table 1, entry 9). Compared to other photosensitizers, *fac*-Ir(ppy)$_3$ offered the best catalytic efficiency under blue LEDs irradiation (Table 1, entries 11−14). Control experiments revealed that the reaction gave lower yield in the absence of base (Table 1, entry 15), and no reaction occurred without photocatalyst or in darkness (Table 1, entries 16 and 17).

With the optimized reaction conditions in hand, the generality of the protocol, as well as the scope of propargyl alcohols, were evaluated (see Scheme 2). Electronic effects did not have much impact on the reaction outcome, as propargyl alcohols bearing either electron-donating or electron-withdrawing substituents were smoothly converted to the desired products in excellent yields (**2a**−**2q**). The bromide residue in product **2n** is synthetically useful, which offered a platform for further modification by cross-coupling reactions. The reaction solely occurred at a terminal alkyne rather than an internal alkyne, indicating a great chemoselectivity (**2r**). Cyclic $C(sp^3)-H$ bond was also reactive, affording the vinylated product in good yields (**2s**). In addition to the tertiary $C(sp^3)-H$ bonds, the secondary ones, including benzylic and aliphatic $C(sp^3)-H$ bonds, were also readily functionalized (**2t**−**2w**). Remarkably, only the vinylation of δ-$C(sp^3)-H$ bonds via 1,5-HAT was allowed (**2w**), manifesting an exclusive regioselectivity. The $C(sp^3)-H$ bond adjacent to heteroatoms such as oxygen was also apt for the remote vinylation (**2x**). The supreme chemoselectivity of this protocol was further demonstrated in the reaction with the heteroaryl-substituted substrates. Although we have previously disclosed the migratory aptitude of heteroaryls,[8f] herein, the migration of the vinyl occurred in preference to the heteroaryls, leading the unique vinyl-migrated products (**2y**−**2ac**). The method was also suitable for the synthesis of trisubstituted alkenes by using the less-reactive internal propargyl alcohols (**2ad**−**2ae**). The configuration of **2ad** and **2ae** was ambiguously assigned by NOE analysis.

The scope of sulfonyl chlorides were next defined (see Scheme 3). Both aryl and alkyl sulfonyl chlorides were compatible with the mild conditions. It seemed that electronic and steric effects did not influence the transformation. While a series of aryl sulfonyl chlorides bearing either electron-donating (**2ag**−**2ah**) or electron-withdrawing (**2ai**−**2ak**) substituents led to the corresponding products in high yields, alkyl sulfonyl chlorides delivered lower yields (**2al**−**2am**). Intriguingly, naturally occurring camphor skeleton could be

Table 1. Survey of Reaction Parameters[a]



entry	photocatalyst	base (equiv)	solvent	yield[b] (%)
1	*fac*-Ir(ppy)$_3$	K_2HPO_4 (1.5)	DMSO	trace
2	*fac*-Ir(ppy)$_3$	K_2HPO_4 (1.5)	acetone	85
3	*fac*-Ir(ppy)$_3$	K_2HPO_4 (1.5)	CH_3CN	87
4	*fac*-Ir(ppy)$_3$	K_2HPO_4 (1.5)	DCM	84
5	*fac*-Ir(ppy)$_3$	K_2HPO_4 (1.5)	CH_3OH	trace
6[c]	*fac*-Ir(ppy)$_3$	K_2HPO_4 (1.5)	CH_3CN	56
7	*fac*-Ir(ppy)$_3$	Na_2HPO_4 (1.5)	CH_3CN	86
8	*fac*-Ir(ppy)$_3$	K_2CO_3 (1.5)	CH_3CN	87
9	*fac*-Ir(ppy)$_3$	Na_2CO_3 (1.5)	CH_3CN	88
10	*fac*-Ir(ppy)$_3$	Na_2CO_3 (1.0)	CH_3CN	90
11	Ir(ppy)$_2$(dtbbpy)(PF$_6$)	Na_2CO_3 (1.5)	CH_3CN	83
12	Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)(PF$_6$)	Na_2CO_3 (1.5)	CH_3CN	80
13	Ru(bpy)$_3$Cl$_2$	Na_2CO_3 (1.5)	CH_3CN	42
14	Eosin Y	Na_2CO_3 (1.5)	CH_3CN	37
15	*fac*-Ir(ppy)$_3$	–	CH_3CN	50
16	–	Na_2CO_3 (1.0)	CH_3CN	0
17[d]	*fac*-Ir(ppy)$_3$	Na_2CO_3 (1.0)	CH_3CN	0

[a] Reaction conditions: propargyl alcohol **1a** (0.2 mmol), TsCl (1.5 equiv), base (as shown), and photocatalyst (3 mol %) in organic solvent/H_2O (2.0 mL/0.2 mL), irradiated with 30 W blue LEDs at room temperature (rt). [b] Yields of isolated products. [c] In dry CH_3CN, without H_2O. [d] In darkness.

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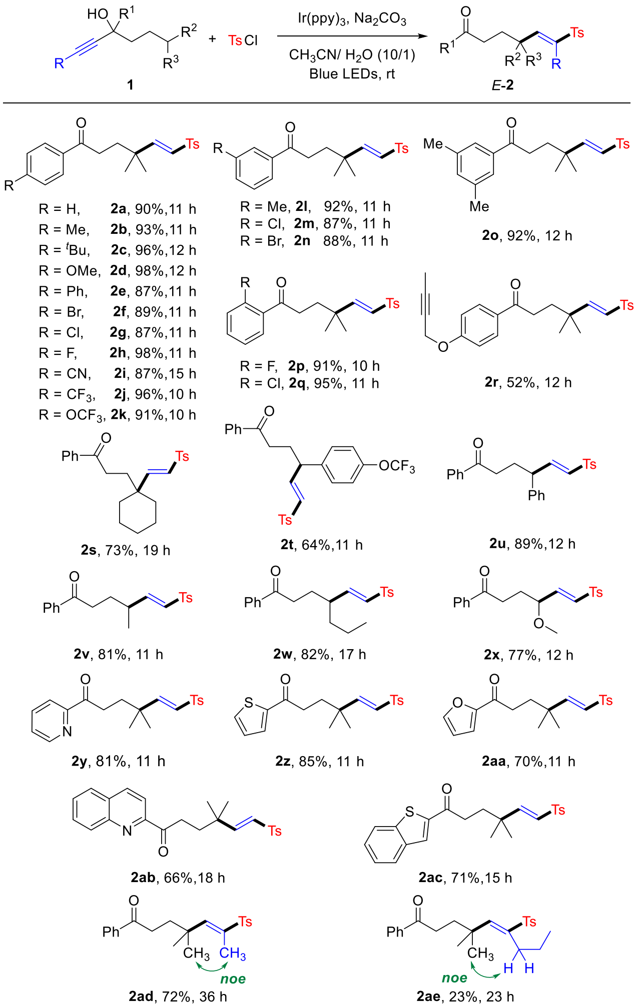
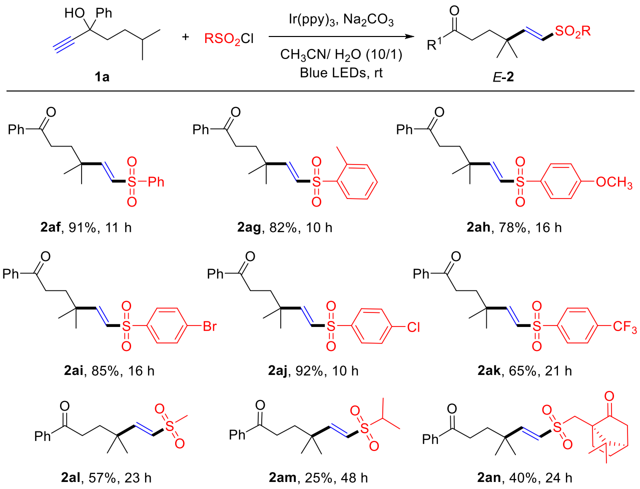
Scheme 2. Scope of Propargyl Alcohols[a]



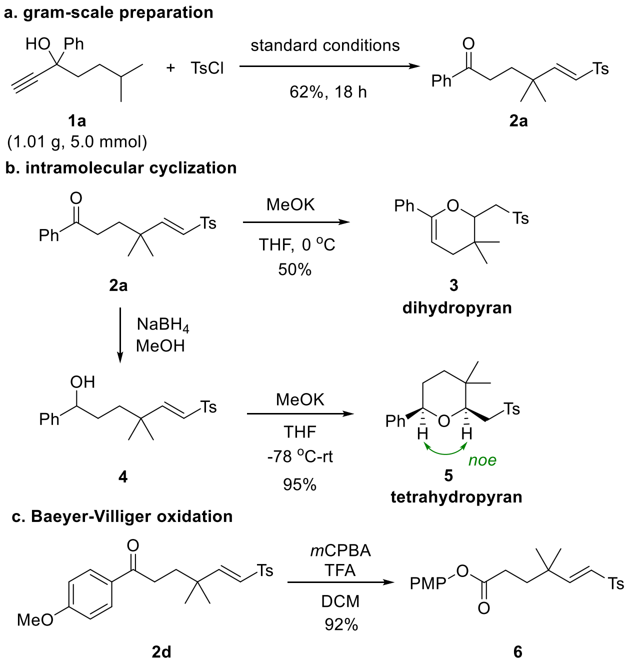
[a]Reaction conditions: propargyl alcohol **1** (0.2 mmol), TsCl (1.5 equiv), Na_2CO_3 (1.0 equiv), and *fac*-Ir$(ppy)_3$ (3 mol %) in CH_3CN/H_2O (2.0 mL/0.2 mL), irradiated with 30 W blue LEDs at rt. Yields of isolated products are given.

Scheme 3. Scope of Sulfonyl Chlorides[a]



[a]Reaction conditions: propargyl alcohol **1a** (0.2 mmol), TsCl (1.5 equiv), Na_2CO_3 (1.0 equiv), and *fac*-Ir$(ppy)_3$ (3 mol %) in CH_3CN/H2O (2.0 mL/0.2 mL), irradiated with 30 W blue LEDs at rt. Yields of isolated products are given.

Scheme 4. Synthetic Applications



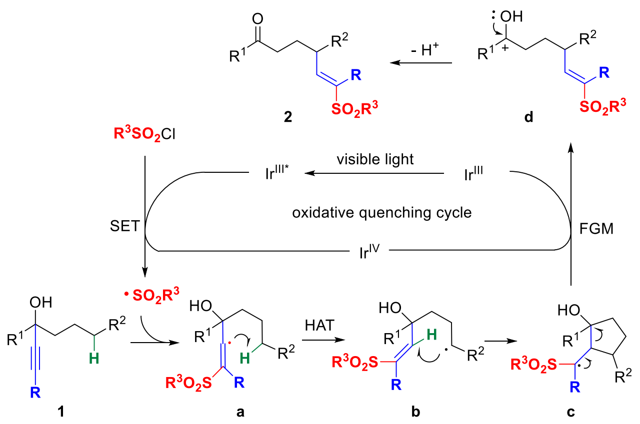
easily incorporated into alkenes by using (+)-10-camphorsulfonyl chloride (**2an**).

The reaction could be performed at gram-scale, affording product **2a** in synthetically useful yield (Scheme 4a). Treating **2a** with potassium methoxide at 0 °C furnished the dihydropyran derivative **3**; reduction of **2a** to alcohol **4**, followed by the treatment of potassium methoxide, gave the sole *cis*-diastereomer, tetrahydropyran derivative **5**, in almost quantitative yield through the intramolecular Michael addition (Scheme 4b). Moreover, the ketone in product **2d** could be transformed to the corresponding ester **6** in 92% yield by the Baeyer−Villiger oxidation (Scheme 4c).

The proposed mechanism is depicted in Scheme 5. Initially, a sulfonyl radical generated from the single-electron reduction of sulfonyl chloride by excited photocatalyst Ir^{III}* complex adds to propargyl alcohol **1**, leading to the reactive vinyl radical species **a**. Because of the high bond dissociation energy (BDE) of the alkenyl C(sp^2)−H bond (∼110 kcal/mol),[10] the vinyl radical-mediated 1,5-HAT readily proceeds to generate the alkyl radical intermediate **b**. The addition of **b** to alkene triggers the intramolecular vinyl migration via the five-membered cyclic transition state.[11] The subsequent oxidation by Ir^{IV} complex provides the cation **d** and perpetuates the photocatalytic cycle.[12] The deprotonation of **d** gave the final product **2**.

In summary, we have disclosed a novel site-selective sulfonylvinylation of unactivated C(sp^3)−H bonds via the vinyl radical-mediated HAT and intramolecular FGM process. The inert C−H and C−C bonds are readily cleaved in sequence under the photocatalytic conditions. A vast array of the sulfone-substituted *E*-olefins are obtained in good yields. The reaction features mild conditions, broad functional group tolerance, and unique regioselectivity/stereoselectivity, thus rendering a practical strategy for remote C(sp^3)−H vinylation and the synthesis of valuable α,β-unsaturated sulfones.

Scheme 5. Proposed Mechanism



ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01734.

Experimental details, compound characterization data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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