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Synthesis of β-Hydroxysulfones from Sulfonyl Chlorides and Alkenes Utilizing Visible Light Photocatalytic Sequences

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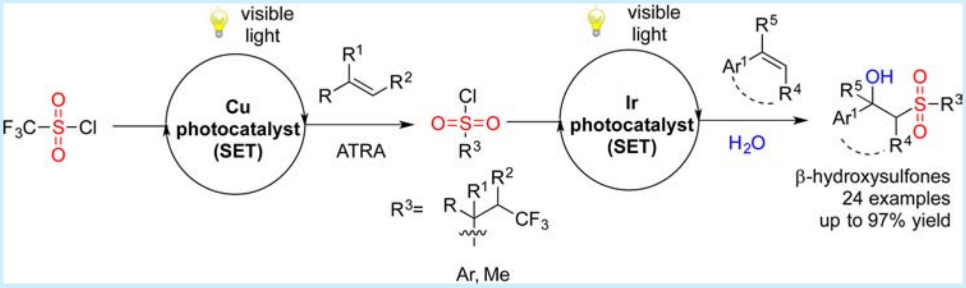
Supporting Information



ABSTRACT: The synthesis of β-hydroxysulfones from sulfonyl chlorides and styrenes in the presence of water by a visible light mediated atom transfer radical addition (ATRA)-like process utilizing *fac*[Ir(ppy)$_3$] as photoredox catalyst was developed in high yields. This process could be combined with the visible light mediated synthesis of trifluoromethylated sulfonyl chlorides via an ATRA reaction between alkenes and CF$_3$SO$_2$Cl utilizing [Cu(dap)$_2$Cl] as photoredox catalyst, demonstrating the possibility of sequential photoredox processes.

The β-hydroxysulfone is a privileged scaffold that has been utilized for several pharmaceutical drug candidates, fine chemicals, and as a precursor in the synthesis of various biologically active molecules.[1] For example, the anticancer drug bicalutamide and antifungal agents such as Sch42427 and SSY726 feature a β-hydroxysulfone moiety.[2]

In the past few years, several advancements for synthesis of β-hydroxysulfones have been reported, including the opening of epoxides with sulfinate salts,[3] chemical or bioreduction of β-ketosulfones,[4] and the addition of organometallic reagents to carbonyl compounds.[5] In particular, various approaches utilizing the addition of sulfonic acid derivatives to styrenes have been developed toward the target compounds.[6]

Given the wide availability of sulfonyl chlorides, some of them like *p*-toluenesulfonyl chloride (TsCl) being industrially produced on ton scale, this compound class appears to be attractive for the direct synthesis of β-hydroxysulfones. However, to the best of our knowledge, this has not been achieved yet by photochemical methods.[7] Recently, visible light induced photoredox catalysis has attracted great interest in organic synthesis, offering a nonpolluting, naturally abundant, endlessly clean source of energy with unique applications in synthetic chemistry.[8]

We report here the iridium-catalyzed, visible light mediated atom transfer radical addition (ATRA)-like reaction of sulfonyl chlorides and styrenes to β-hydroxysulfone, featuring mild and economic reaction conditions, high yields, and excellent regioselectivity. Moreover, since trifluoromethylated sulfonyl chlorides can be synthesized by a copper-catalyzed, visible light mediated ATRA reaction between CF$_3$SO$_2$Cl and alkenes,[9] we showcase the sequential utilization of two photoredox processes for the synthesis of the target compounds, bringing together two different photoreactions.

As a first step, we tested the feasibility of developing a photochemical ATRA-like reaction of sulfonyl chlorides to β-hydroxysulfones. Sulfinic acid salts[10] and especially sulfonyl chlorides[11] have been utilized before in photoredox processes suggesting that the generation of sulfonyl radicals by single electron transfer (SET) should be feasible.

Using α-methylstyrene **1a** and 4-nitrobenzenesulfonyl chloride **2a** as models, we tested various photoredox catalysts under visible light irradiation in aqueous solvents, aiming for the formation of hydroxysulfone **3a**. Starting with [Ru(bpy)$_3$Cl$_2$] (bpy = bipyridine; E = −0.81 V versus SCE) as catalyst under blue light irradiation ($\lambda_{\max}$ = 455 nm), we quickly realized that a combination of acetonitrile and water, ensuring both solubility of reagents and catalyst as well as having a source for introduction of the hydroxyl group, is required (Table 1, entries 1−6).

The optimal ratio of acetonitrile/water was found to be 5:1 (Table 1, entry 5) giving rise to **3a** in 90% yield. Replacing [Ru(bpy)$_3$Cl$_2$] with [Cu(dap)$_2$Cl][12] (dap =2,9-bis(*p*-anisyl)-1,10-phenanthroline; E = −1.43 V versus SCE), as an even stronger reductant in its excited state than [Ru(bpy)$_3$Cl$_2$], also gave rise to **3a**, however, in lower yields (Table 1, entry 7). Finally, *fac*[Ir(ppy)$_3$][13] (ppy = 2-phenylpyridine; E = −1.73 V versus SCE) having the strongest reducing power after

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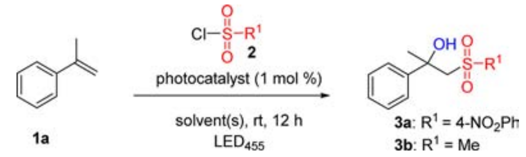
Table 1. Optimization Reactions[a]



entry	R^1 in R^1SO_2Cl	photocatalyst (1 mol %)	solvent(s)	yield (%)[b]
1	4-NO_2Ph	[Ru(bpy)$_3$Cl$_2$]	H_2O	6
2	4-NO_2Ph	[Ru(bpy)$_3$Cl$_2$]	MeCN:H_2O (1:3)	40
3	4-NO_2Ph	[Ru(bpy)$_3$Cl$_2$]	MeCN:H_2O (1:1)	51
4	4-NO_2Ph	[Ru(bpy)$_3$Cl$_2$]	MeCN:H_2O (3:1)	63
5	4-NO_2Ph	[Ru(bpy)$_3$Cl$_2$]	MeCN:H_2O (5:1)	90
6	4-NO_2Ph	[Ru(bpy)$_3$Cl$_2$]	MeCN:H_2O (7:1)	69
7	4-NO_2Ph	[Cu(dap)$_2$Cl]	MeCN:H_2O (5:1)	61
8	4-NO_2Ph	***fac*[Ir(ppy)$_3$]**	**MeCN:H_2O (5:1)**	**95**
9	4-NO_2Ph	no catalyst	MeCN:H_2O (5:1)	trace[c]
10	4-NO_2Ph	*fac*[Ir(ppy)$_3$] no light	MeCN:H_2O (5:1)	trace[c]
11[d]	Me	[Cu(dap)$_2$Cl]	MeCN:H_2O (5:1)	21
12[d]	Me	[Ru(bpy)$_3$Cl$_2$]	MeCN:H_2O (5:1)	7
13[e]	Me	***fac*[Ir(ppy)$_3$]**	MeCN:H_2O (5:1)	81

[a] Reaction conditions: **1a** (1.0 mmol), sulfonyl chloride **2** (1.5 mmol), photocatalyst (1 mol %), solvent(s) (2 mL), LED_{455}. [b] Isolated yields. [c] Detected by TLC analysis, starting materials remain unchanged. [d] 24 h irradiation time. [e] 10 h irradiation time.

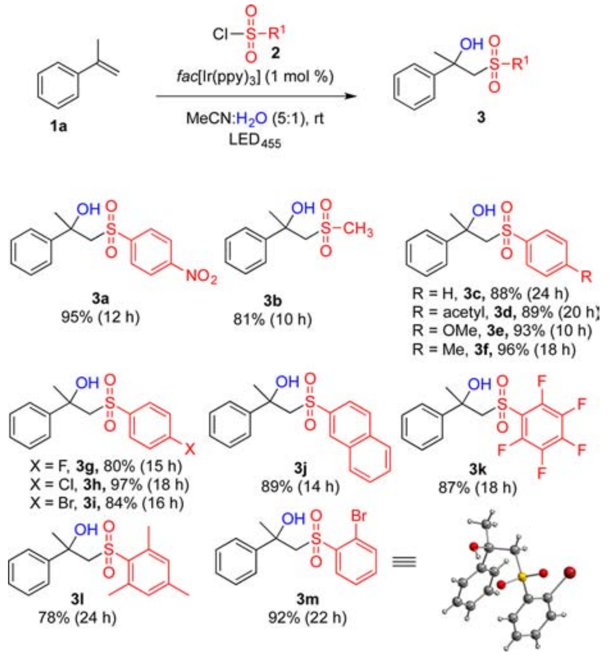
excitation of all catalysts tested allowed the isolation of **3a** in 95% yield (Table 1, entry 8). Control experiments further demonstrated that both light and a photoredox catalyst are necessary for the reaction to proceed (Table 1, entries 9 and 10).

Switching from the aromatic 4-nitrosulfonyl chloride (E = −0.44 V versus SCE) to the aliphatic mesyl chloride **2b**, having more negative reduction potential (E = −1.39 V versus SCE), only catalyst *fac*[Ir(ppy)$_3$] gave the hydroxysulfone **3b** in preparatively useful yields (Table 1, entries 11−13). Consequently, the scope and limitations for the synthesis of β-hydroxysulfones **3** were subsequently explored using the latter photocatalyst.

Various sulfonyl chlorides could be coupled with α-methylstyrene **1a** (Scheme 1), demonstrating the broad functional group tolerance for the photochemical process. A series of aryl sulfonyl chlorides bearing strong or weak electron-donating groups (−OMe, −Me) and electron-withdrawing groups (−NO_2, acetyl,−F, −Cl, −Br) afforded the desired hydroxysulfones in up to 97% yield. Notably, a nitro substituent, which is usually a limitation for photochemical[14] or radical processes,[15] was fully compatible under these conditions. Moreover, sterically demanding groups at the sulfonyl chloride such as 2-naphthyl, pentafluorophenyl, mesityl, or *o*-bromophenyl efficiently reacted with styrenes to afford the corresponding tertiary hydroxysulfones **3j−m** in 78−92% yield. Sulfonyl chlorides bearing a strong electron-deficient substituent such as trifluoromethyl are not compatible with the hydroxysulfone protocol reported here due to their fast hydrolysis under aqueous conditions. In addition to fully consistent spectroscopic data, the identity of the β-hydroxysulfones **3** was further proven by the X-ray crystal structure of *o*-bromo hydroxysulfone derivative **3m** (Scheme 1).

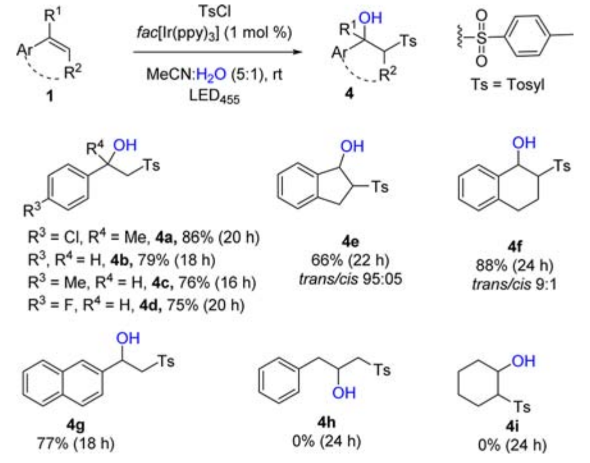
Furthermore, when tosyl chloride was used as a reaction partner (Scheme 2), a variety of styrene-type alkenes also gave the desired β-hydroxysulfones in high yields, tolerating 1,1- and

Scheme 1. Scope for Sulfonyl Chlorides[a]



[a] Reaction conditions: α-methylstyrene **1a** (1.0 mmol), sulfonyl chloride **2** (1.5 mmol), *fac*[Ir(ppy)$_3$] (1 mol %), MeCN (1.67 mL), water (0.33 mL), LED_{455} at room temperature.

Scheme 2. Scope for Alkenes[a]



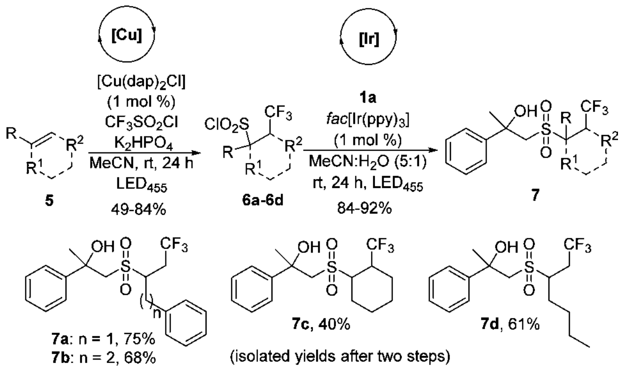
[a] Reaction conditions: alkene **1** (1.0 mmol), tosyl chloride **2f** (1.5 mmol), *fac*[Ir(ppy)$_3$] (1 mol %), MeCN (1.67 mL), distilled water (0.33 mL), LED_{455} at room temperature.

1,2-disubstitution as well as various functional groups in the aromatic moiety.

In agreement with other reported sulfonyl radical additions to alkenes,[10] the limitation of the process was found with aliphatic alkenes, which did not react at all. When *cis*-oleic acid methyl ester was employed, no isomerization of the alkene double bond was observed, indicating that the initial sulfonyl radical addition to such alkenes might already be inefficient.

However, we recently reported the [Cu(dap)$_2$Cl]-catalyzed, visible light mediated ATRA reactions[16] between alkenes and CF$_3$SO$_2$Cl ($E = -0.18$ V versus SCE) under anhydrous conditions,[17] which surprisingly led to the formation of sulfonyl chlorides,[9] in contrast to the Ru(bpy)$_3$Cl$_2$-catalyzed processes that resulted in chlorinated products.[18] Along with the process toward *β*-hydroxysulfones developed here, we explored the possibility of coupling two photocatalytic sequences together. Indeed, sulfonyl chlorides could be synthesized by the [Cu(dap)$_2$Cl]-catalyzed ATRA process followed by their *fac*[Ir(ppy)$_3$]-catalyzed addition to styrenes to yield **7a−d** (Scheme 3).

Scheme 3. Sequential Photocatalysis (Two-Flask Synthesis)[a]



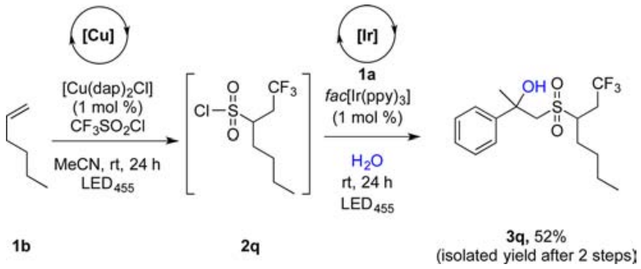
[a]Reaction conditions: (1) alkene **5** (1.0 mmol), CF$_3$SO$_2$Cl (2.0 mmol), K$_2$HPO$_4$ (2.0 mmol), [Cu(dap)$_2$Cl] (1 mol %), MeCN (2 mL), LED$_{455}$ at room temperature for 24 h; (2) *α*-methylstyrene **1a** (1.0 mmol), sulfonyl chloride **6** (1.5 mmol), *fac*[Ir(ppy)$_3$] (1 mol %), MeCN (1.67 mL), distilled water (0.33 mL), LED$_{455}$ at room temperature for 24 h.

Notably, each specific photocatalyst is required for the individual steps of the sequence: When *fac*[Ir(ppy)$_3$] is used in an attempt to synthesize the sulfonyl chlorides **6a−d**, net addition of trifluoromethyl and *chloride* instead of *sulfonyl chloride* is observed, while [Cu(dap)$_2$Cl] was not sufficient for the activation of **6a−d** to engage in the coupling with styrenes to give rise to the corresponding hydroxysulfones **7a−d** (Scheme 3).

This sequence can also be run in a single flask without the requirement of isolating the sulfonyl chlorides; for example, **7d** could be directly synthesized by first irradiating **5a** and CF$_3$SO$_2$Cl in the presence of [Cu(dap)$_2$Cl] (1 mol %) followed by the addition of water, *α*-methylstyrene (**1a**), and *fac*[Ir(ppy)$_3$] (1 mol %) (Scheme 4).

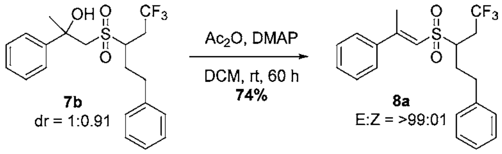
The resulting sulfones of this two-step sequence are obtained as an equimolar mixture of diastereomers, reflecting the nature of the two sequential radical addition processes. To arrive at diastereomerically pure compounds, the hydroxysulfones can be converted to vinylsulfones by a known procedure,[19] as demonstrated by the conversion of **7b** to **8a** (Scheme 5).

Scheme 4. Sequential Photocatalysis (One-Flask Synthesis)[a]



[a]Reaction conditions: 1-hexene **5a** (1.0 mmol), CF$_3$SO$_2$Cl (2.0 mmol), [Cu(dap)$_2$Cl] (1 mol %), MeCN (1.67 mL), LED$_{455}$ at room temperature for 24 h then *α*-methylstyrene **1a** (1.0 mmol, 1.0 equiv, *fac*[Ir(ppy)$_3$] (1 mol %), distilled water (0.33 mL), LED$_{455}$ at room temperature for 24 h.

Scheme 5. Synthesis of Vinyl Sulfones[a]

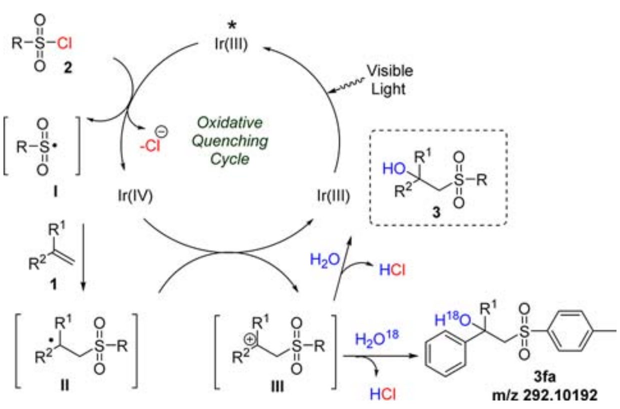


[a]Reaction conditions: **7b** (0.5 mmol), Ac$_2$O (1.0 mmol), DMAP (1.0 mmol, 2.0 equiv), DCM (7 mL), at room temperature for 60 h.

As a plausible reaction mechanism for the hydroxysulfonylation reaction, we propose the initial excitement of the Ir(III) photoredox catalyst by irradiation with blue light to generate excited *Ir(III). Single electron transfer to sulfonyl chloride **2** generates the corresponding sulfonyl radical **I** concurrent with oxidation to Ir(IV). Regioselective sulfonyl radical **I** addition to styrene **1** takes place to give the carbon-centered radical intermediate **II**, which subsequently undergoes oxidation to carbocation **III** by back-electron-transfer processes regenerating the Ir(III). The resulting carbocation **III** is trapped by water (Scheme 6). In agreement with this proposal, isotope labeling showed that the oxygen of the hydroxyl group in compound **3fa** only originated from H$_2$O^{18} (see the SI).

To summarize, we have developed a visible light mediated, iridium(III)-catalyzed ATRA-like reaction for synthesis of *β*-hydroxysulfone derivatives from readily available alkenes and sulfonyl chlorides. In combination with the visible light mediated copper(I)-catalyzed synthesis of trifluoromethyl-substituted sulfonyl chlorides, two photochemical processes

Scheme 6. Proposed Reaction Mechanism



can be connected to access the β-hydroxysulfones, demonstrating the feasibility of sequential photochemical transformations.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00734.

Experimental procedures and spectral data (PDF)
Crystallographic data for **3m** (CIF)

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Notes

The authors declare no competing financial interest.

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