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Photochemical carbosulfonylative cross-coupling of alkenes

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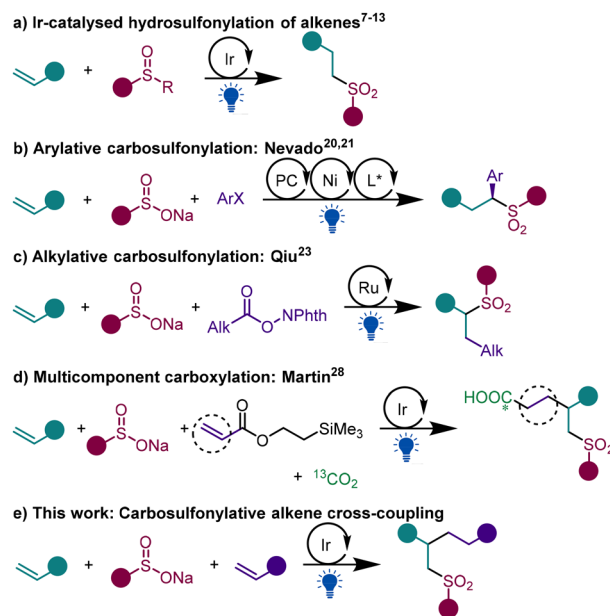
A photochemical carbosulfonylative protocol for the formation of C–S and C–C bonds between sulfinate salts and alkenes is reported. This approach couples two alkene molecules to give access to highly functionalized sp³ sulfone products. Homo-coupled and polarity mismatched cross-coupled products were obtained. The utility of the methodology is highlighted by further transformations of the novel sulfone products.

Introduction

Organosulfones are an important class of sulfur compound. In particular alkyl sulfones have found numerous applications as targets as agrochemicals, materials and pharmaceuticals.^{1–3} Often called “chemical chameleons” sulfones are also highly versatile intermediates in organic chemistry.^{4,5} Sulfinate salts have emerged as valuable starting materials for the synthesis of organosulfones.⁶ More recently sulfinate salts have been used in photochemical hydrosulfonylation reactions by Yu and Duan (Scheme 1a).^{7,8} Hydrosulfonylations of alkenes using iridium photocatalysis have also been reported by Ley, Gouverneur, Willis, Yan, Gao and Su using different sulfonyl radical precursors.^{9–13} Other than Ir-catalysis alone, the sulfonylation of alkenes using sulfonyl imines has been reported under Ir/Cu dual photocatalysis and using Cu as a sole photocatalyst with sulfonyl chlorides.^{14–17} Dual Ir/Ni photocatalysis has been used for the multifunctionalisation of butadiene *via* carbosulfonylation.¹⁸ Finally, a novel organic photocatalyst has been developed by Deagostino and co-workers allowing for the hydrosulfonylation of alkenes.¹⁹

The difunctionalization of alkenes *via* radical carbosulfonylation reactions enables highly complex molecules to be constructed in a single step. Dual photoredox and Ni catalysis has been employed by Nevado to develop a number of protocols for the carbofunctionalization of alkenes (Scheme 1b).^{20,21} Non-conjugated dienes have also been used in the metallaphotoredox carbosulfonylation protocol reported by Rueping.²² Recently, Qiu reported an alkylative carbosulfonylation of alkenes and alkynes that proceeds with Markovnikov selectivity (Scheme 1c).²³

Cross-coupling of alkene molecules is of high synthetic significance as it enables the construction of more highly functionalized compounds from readily available feedstock chemicals. Radical alkene cross-coupling has been reported by Baran *via* a metal-hydride hydrogen atom transfer (MHAT) route.^{24–26} Melchiorre has detailed the reductive cross-coupling of alkenes under photochemical conditions.²⁷ These routes provide access to functionalized sp³-rich molecules. While this project was underway, Martin reported a multicomponent carboxylation reaction of alkenes and sulfinate salts (Scheme 1d).²⁸ This multi-component methodology focused on the synthesis of ¹³C-labelled carboxylic acids. To the best of



Scheme 1 Hydro- and carbosulfonylation of alkenes; multicomponent carbosulfonylation with alkene coupling.

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our knowledge, there are no other reports on the cross-coupling of alkenes that allow for the concurrent incorporation of a sulfone group. As part of our research on photochemical reactions involving sulfonates,^{29–31} we report here the development of a carbosulfonylative cross-coupling protocol for the synthesis of alkyl sulfones from readily available sulfinate salts and alkenes (Scheme 1e). A variety of functional groups can be incorporated making it complementary to the method of Martin where 2-(trimethylsilyl)ethyl acrylate was used as an ethylene surrogate.

Results and discussion

Our work began with developing a photochemical carbosulfonylation procedure using sodium 4-toluenesulfinate **1a** and methyl acrylate **2a** as our model substrates. After screening (Table 1) we found that the desired sulfone product **3a** could be isolated in 55% yield (entry 1) upon irradiation with blue LEDs with an iridium photocatalyst and both AcOH and K₂HPO₄·3H₂O. We observed decreased yields of the desired product upon changing to more oxidizing iridium photocatalyst (Ir[dF(CF₃)ppy]₂(dtbpy))PF₆ (entry 2) and the metal-free photocatalyst 4CzIPN (entry 3). Similarly, reducing the equivalents of alkene and increasing reaction concentration negatively impacted the yield of sulfone **3a** (entries 4 and 5). A solvent screen confirmed DMF to be the best solvent for the reaction (entries 6–8). In terms of control experiments, light, photocatalyst and acid were found to be essential for reactivity (entries 9–11). The reaction proceeds in the absence of base,

however reduced yields of desired product **3a** were obtained (entry 12). To confirm that K₂HPO₄·3H₂O acts as a buffer, we carried out the reaction using the organic buffer HEPES (entry 13). The desired product **3a** was formed in a 25% yield. The major competing pathways are hydrosulfonylation and polymerization (see SI for additional optimisation data).

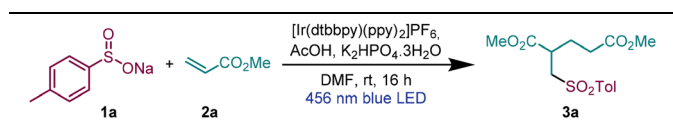
Following these optimization studies, we then set about exploring the scope of this method, first by investigating the two-component variant of this reaction (Scheme 2). Moving to benzyl acrylate gave the desired product **3b** in a 58% yield. We found that other alkenes with electron-withdrawing groups such as acrylonitrile and *N*-phenylacrylamide were successful, giving **3c** and **3d** in yields of 48% and 55%, respectively. Moving to vinyl acetate as the starting material gave a yield of just 8% for sulfone **3e**. The use of *gem*-substituted methyl methacrylate gave desired product **3f** in 44% yield. Styryl derivatives can be employed in the method with varying success. Unsubstituted styrene gave **3g** in a 27% yield, while the use of 4-CF₃-substituted styrene afforded product **3h** in a 38% yield. Moving to the electron-rich 6-MeO-substituted naphthalene **3i** gave a low yield of just 11%. Diethyl diallylmalonate was investigated as an example of a diene substrate. This gave rise to the 5-*exo-trig* product **3j**, albeit in a low yield of 14%. Details of unsuccessful alkenes (*e.g.*, tri-substituted) are given in the SI.

We then set about screening the sulfonates that could be used in this reaction. We found that both aryl sulfonates bearing unsubstituted phenyl or naphthyl rings and 4- and 3-halogen substituents (**3k–n**) were suitable reaction partners for this carbosulfonylative alkene coupling protocol. Of note is entry **3m**, as when a 4-Cl substituent was present, purification of the final compound was significantly simpler. Unfortunately, alkyl sulfonates appear to be incompatible with our methodology as in the case of **3o**, where the desired product could not be isolated.

We then turned our attention to developing a three-component version of this reaction, in which two different alkenes could be used to give access to more diversely functionalized sulfone products, using 4-chlorobenzenesulfinate **1c** as our model substrate (Scheme 3). We first investigated the reaction using the electronically different alkenes, ethyl vinyl ether and acrylonitrile. We found product **4a** was formed in a 30% yield. We then investigated using methyl acrylate as a substrate, as it was one of the best performing alkenes in the two-component reaction. We first tested methyl acrylate with a 4-CF₃-substituted styrene. Surprisingly, this yielded the polarity mismatched product **4b** in a 45% yield.

Intrigued by the formation of the unexpected polarity mismatched product we carried out an optimisation study on this reaction, focusing on the stoichiometry of alkenes and overall reaction concentration (Table 2). In the three-component reaction, the use of two different alkenes can generate up to six possible products (C–H) in addition to oligomer/polymerization products. It was found that the standard conditions using 1.1 equivalents of each alkene and a concentration of 0.05 M gave the highest ratio of this unusual polarity mis-

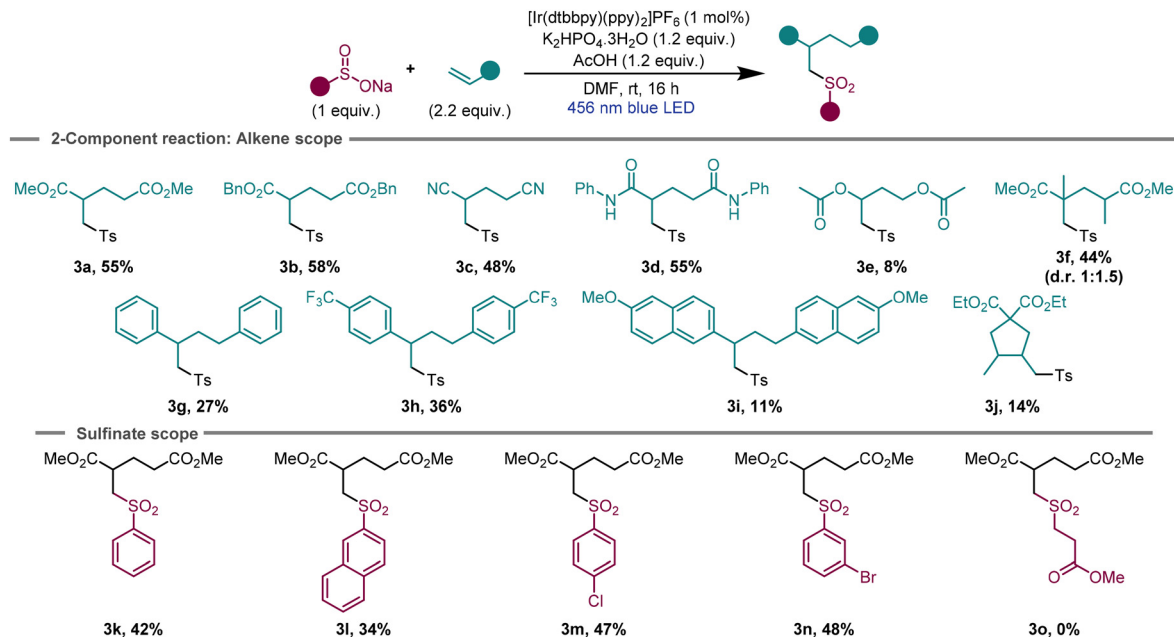
Table 1 Optimization of reaction conditions^a



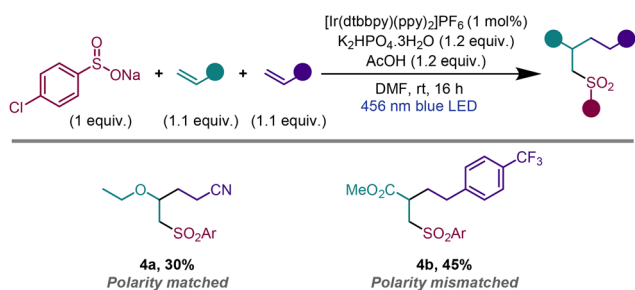
Entry	Deviation from standard conditions	Yield ^{b,c} (%)
1	None	63 ^b (55 ^c)
2	(Ir[dF(CF ₃)ppy] ₂ (dtbpy))PF ₆ not [Ir(dtbbpy)(ppy) ₂]PF ₆	20 ^b
3	4CzIPN not [Ir(dtbbpy)(ppy) ₂]PF ₆	46 ^b (39 ^c)
4	4 equiv. 2a	26 ^b
5	Concentration 0.1 M w.r.t. 1a	55 ^b (51 ^c)
6	DMSO instead of DMF	37 ^b
7	DCE instead of DMF	21 ^b
8	MeCN instead of DMF	20 ^b
9	No light	0 ^b
10	No photocatalyst	0 ^b
11	No acid	0 ^b
12	No base	34 ^b
13	HEPES ^d instead of K ₂ HPO ₄ ·3H ₂ O	25 ^b

^a Standard reaction conditions: sulfinate **1a** (0.1 mmol, 0.05 M), alkene **2a** (0.22 mmol), AcOH (0.12 mmol), K₂HPO₄·3H₂O (0.12 mmol) and catalyst (1 mol%) in DMF (2 mL) were irradiated with blue LEDs (456 nm, 40 W) in an N₂ atmosphere. ^b Yields determined by ¹H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. ^c Isolated yields. ^d HEPES = 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid.





Scheme 2 Scope of the two-component carbosulfonylative alkene coupling reaction.



Scheme 3 Observation of polarity mismatch product in the three-component reaction.

match product **C**. It was noted that under these conditions none of the corresponding polarity matched product **H** was observed.

Following on from this we then tested methyl acrylate with other alkenes with aryl rings (Scheme 4). We found that 6-OMe vinylnaphthalene and 2-vinylpyridine gave the corresponding sulfones **4c** and **4d** both in a 37% yield. Vinyltrimethylsilane afforded **4e** in a 19% yield. We then tested methyl acrylate with other electron-deficient alkenes such as acrylonitrile, which gave product **4f** in a 45% yield. When 4-chlorobenzenesulfinate and methyl acrylate were reacted with *N*-phenylacrylamide, the product **4g** with the vinyl amide bonded to sulfinate was obtained in a 22% yield. Similarly, when *N*-phenylacrylamide was used with 4- CF_3 styrene, **4h** was isolated in a 46% yield. The 4- CF_3 -substituted styrene was further investigated as a substrate with the *gem*-substituted methyl methacrylate, giving

Table 2 Optimisation of reaction conditions for the three-component reaction^a

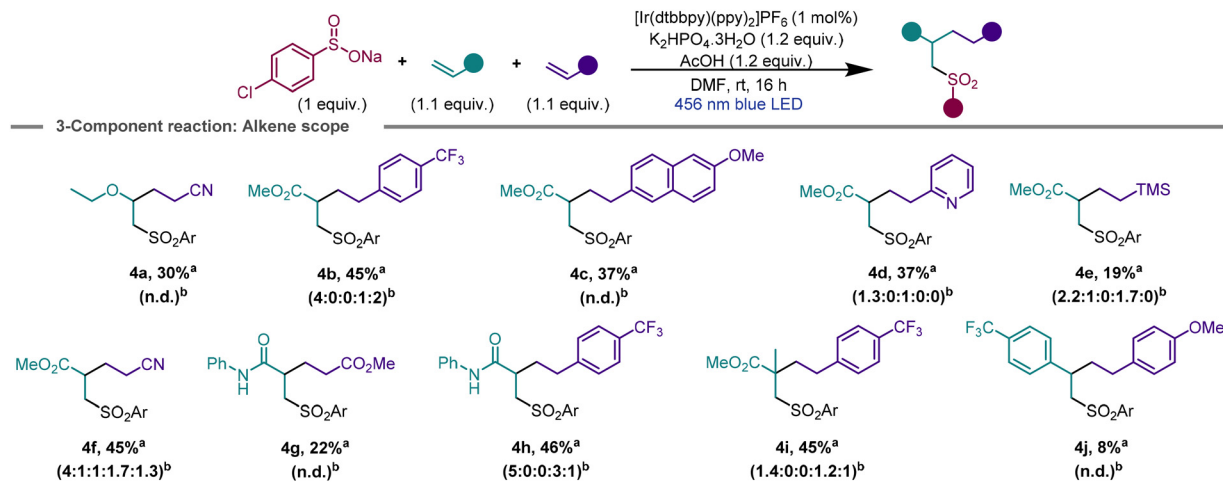
Possible products:

0% in all cases

Entry	Deviation from standard conditions	Ratio C : D : E : F : G ^b	Yield of C ^{c,d} (%)
1	None	4 : 0 : 0 : 1 : 2	52 ^c (45 ^d)
2	1 equiv. of each alkene	1.5 : 1 : 0 : 1.7 : 1.2	17 ^c
3	2 equiv. of each alkene	2.1 : 1.5 : 0 : 0 : 2.8	16 ^c
4	2 equiv. methyl acrylate, 1 equiv. styrene	2 : 1 : 0 : 2.8 : 0	23 ^c
5	1 equiv. methyl acrylate, 2 equiv. styrene	1 : 0 : 0 : 0 : 1	25 ^c
6	0.1 M reaction concentration	3 : 0 : 0 : 2 : 1.4	32 ^c
7	0.025 M reaction concentration	4 : 1 : 0 : 1 : 2.6	34 ^c

^a Standard reaction conditions: sulfinate **1c** (0.1 mmol, 0.05 M), alkene **2a** (0.11 mmol), alkene **2h** (0.11 mmol), AcOH (0.12 mmol), $\text{K}_2\text{HPO}_4 \cdot 3\text{H}_2\text{O}$ (0.12 mmol) and $[\text{Ir}(\text{dtbbpy})(\text{ppy})_2]\text{PF}_6$ (1 mol%) in DMF (2 mL) were irradiated with blue LEDs (456 nm, 40 W) in an N_2 atmosphere. ^b Ratio determined by ^1H NMR spectroscopy. ^c Yields determined by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. ^d Isolated yield.

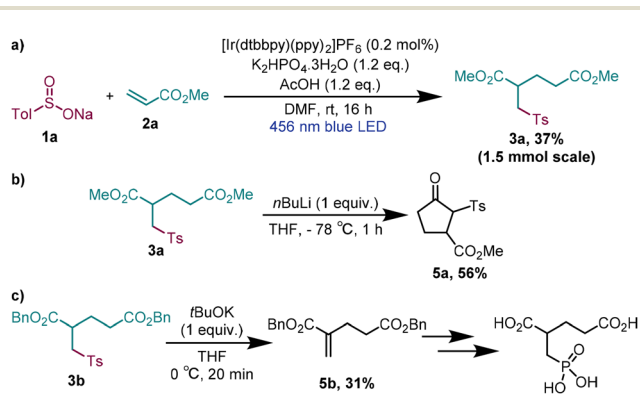




Scheme 4 Scope of the three-component cross-coupling reaction. ^a Isolated yield. ^b Ratio of possible products C : D : E : F : G determined by ¹H NMR spectroscopy where possible.

sulfone **4i** in a 45% yield. As a final test of the methodology the 4-CF₃ styrene was reacted with a 4-OMe-substituted styrene, giving product **4j** in a low yield of 8%. Details of unsuccessful alkenes (*e.g.*, tri-substituted) are given in the SI. The isolation of the desired product from complex mixtures was challenging in some cases, and this contributed to decreased isolated yields. For cases **4b–4j** when the polarity mismatched product was formed as the major product of the reaction, none of the corresponding polarity matched product was observed.

To demonstrate the utility of our methodology we set about performing a scale-up reaction. Our standard reaction was successfully scaled up to a 1.5 mmol scale, with a reduction in catalyst loading, giving the corresponding product **3a** in a 37% yield (Scheme 5a). Next, we turned our attention to the applications of our novel products and found that upon treatment of **3a** with *n*BuLi, a novel 2,3-substituted cyclopentanone **5a** could be synthesised in a 56% yield (Scheme 5b). In contrast, we found that upon treatment with *t*BuOK the sulfone group in **3b** could be removed to give alkene **5b** in a 31% yield

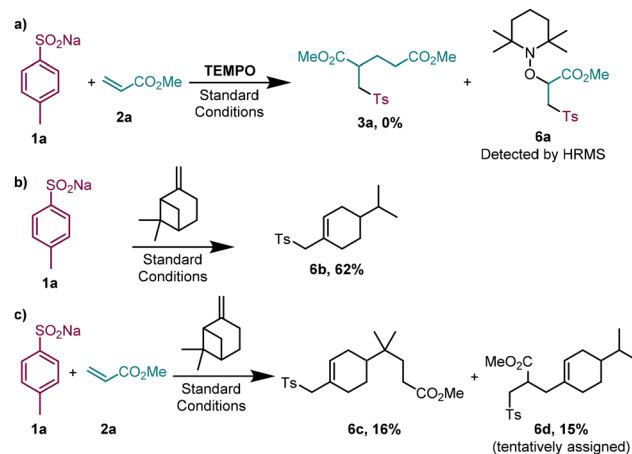


Scheme 5 Scale up reaction and applications of novel sulfone **3a** and **3b**.³²

(Scheme 5c). Alkene **5b** is a precursor to 2-(phosphonomethyl)-pentandioic acid (2-PMPA) a potent glutamate carboxypeptidase II inhibitor.³²

To gain an insight into the reaction mechanism we first set about performing a quenching experiment with the radical scavenger TEMPO (Scheme 6a). Addition of TEMPO to the standard reaction conditions stopped the formation of product **3a**, and instead the TEMPO adduct **6a** was detected by HRMS. We also performed a radical clock experiment using β -pinene, as radical addition is known to open the cyclobutyl ring.³³ The reaction of β -pinene and sulfinate **1a** under standard conditions afforded the corresponding ring-opened product **6b** in a 62% yield (Scheme 6b). β -Pinene was also used as a radical clock in a reaction with sulfinate **1a** and methyl acrylate **2a**. This gave adduct **6c** in a 16% yield and what is tentatively assigned as impure adduct **6d** which co-eluted with other species in a ~15% yield (Scheme 6c).

One of the side products of our protocol is compound **7a**, which can be formed *via* a radical or polar pathway. This,



Scheme 6 Radical quenching and radical clock experiments.



along with the detection of adducts **6a** and **6d**, caused us to consider the possibility that **7a** could be an intermediate structure that reacts under our standard conditions to give desired product **3a**. To investigate this, we carried out a control experiment in which **7a** was resubjected to standard reaction conditions (Scheme 7). The desired product was not formed in this case and we recovered **7a** in an 84% recovery.

Based on these experiments and previous literature,^{7,8,22} we propose the pathway in Scheme 8. Excitation of the photocatalyst to generate PC* occurs on the absorption of blue light. PC* then oxidizes sulfinate **1a** to form sulfonyl radical **I** ($E_{1/2}(\text{PhO}_2\text{S}^{\bullet}/\text{PhSO}_2\text{Na}) = -0.37$ vs. SCE)³⁴ along with PC^{•-} ($E_{1/2}(\text{PC}^*/\text{PC}^{\bullet-}) = 0.66$ vs. SCE).³⁵ Sulfonyl radical **I** then reacts with the first alkene to generate alkyl radical **J**. Radical **J** then reacts in a similar manner with the next alkene to generate radical **K**. Radical **K** then undergoes SET with PC^{•-} to generate anion **L**. Anion **L** is then protonated in solution to give the desired product. We propose that the use of both AcOH and K₂HPO₄·3H₂O in equimolar amounts acts as a buffer system to prevent premature quenching (leading to hydrosulfonylation) and allows radical **J** to add to the second alkene. In a similar manner, the catalyst and reagents are essential to enable conversion of **K** to product before polymerization can occur. This raises the possibility that such mechanisms could be used to tune polymerization reactions, where turning on a light could enable temporal control over a process.

Regarding the order of addition observed in the three-component reaction, one would anticipate that addition of the electrophilic sulfonyl radical **I** to the more electron-rich alkene would occur preferentially.³⁶ However, the major products we

obtain results from a polarity mismatch addition pathway. We note that sulfonyl radicals have previously been shown to undergo addition to electron-deficient alkenes in hydrosulfonylation reactions^{9,10} and do so in our 2-component protocol. We propose, based on existing literature,^{28,37} that the reaction outcome observed is not determined by the reaction of **I** with alkene. If the addition of sulfonyl radical **I** to more electron-rich alkenes is reversible, then the reaction of radical **J** with alkene can be the selectivity-determining step. When radical **J** has been generated from the reaction of methyl acrylate with sulfonyl radical **I**, both substituents tend to make the radical electrophilic and thus work in concert to make radical **J** more electrophilic than sulfonyl radical **I**. Thus, its reaction with electron-rich styryl radicals is faster. This leads to the major product observed. In contrast, reaction of styrenes with sulfonyl radical **I** generates a benzylic radical that has a lower nucleophilic nature due to the presence of the electron-withdrawing sulfonyl substituent. We speculate that this can explain the apparent polarity mismatched outcome.

Conclusions

In conclusion, we have demonstrated a new protocol for carbonylative cross-coupling of alkenes using readily available aryl sulfinate salts and alkenes.³⁸ We have proposed a rationale for the generation of polarity mismatched cross-coupled products. This method allows for the formal coupling of two alkene molecules to give access to highly functionalized sulfones bearing an sp³-rich backbone. We have highlighted the utility of this chemistry through investigating further transformations of the novel products formed.

Author contributions

V. E. B. conceptualization, investigation, methodology, writing. M. B. R. conceptualization. E. M. M. conceptualization, supervision, writing. All authors have approved the final version of this manuscript.

Conflicts of interest

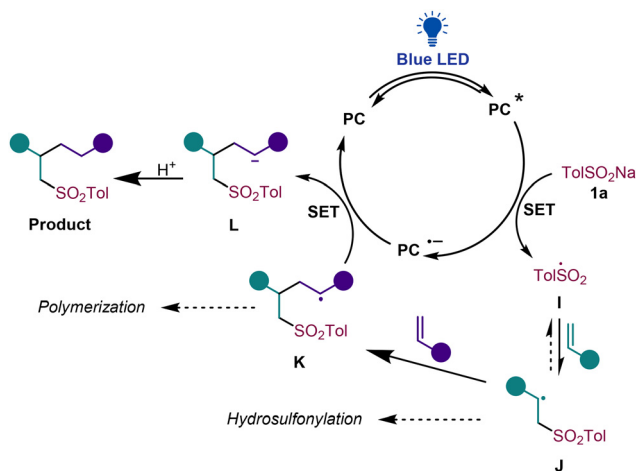
There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the SI: these comprise experimental procedures, ¹H and ¹³C NMR spectra for all new compounds, and fid files. See DOI: <https://doi.org/10.1039/d5ob01229e>.



Scheme 7 Control experiment.



Scheme 8 Proposed reaction pathway.



Acknowledgements

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