

# Visible Light-Induced Sulfonylation/Arylation of Styrenes in a Double Radical Three-Component Photoredox Reaction

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**Abstract:** Simultaneous sulfonylation/arylation of styrene derivatives is achieved in a photoredox-catalyzed three-component reaction using visible light. A broad variety of difunctionalized products is accessible in mostly excellent yields and high diastereoselectivity. The developed reaction is scalable and suitable for the modification of styrene-functionalized biomolecules. Mechanistic investigations suggest the transformation to be operating through a designed sequence of radical formation and radical combination.

Multicomponent reactions (MCRs) are one-pot transformations of at least three substrates furnishing a product which ideally contains all atoms of the starting materials.<sup>[1]</sup> As several bonds are formed in a single operation, MCRs grant fast and easy access to products of elaborate molecular complexity.<sup>[2]</sup> They have thus become a key tool in drug discovery,<sup>[3]</sup> natural product synthesis,<sup>[4]</sup> heterocyclic chemistry,<sup>[5]</sup> and bioconjugation.<sup>[6]</sup> Advantages of MCRs over traditional stepwise synthesis include a lower step count, the reduction of resource usage and chemical waste. Thus, MCRs are often particularly efficient and eco-friendly.<sup>[1, 7]</sup>

The same goals have contributed to the recent resurgence of photoredox catalysis.<sup>[8]</sup> A photoexcited catalyst may be converted back to its electronic ground state via two consecutive single-electron transfer (SET) events.<sup>[8a]</sup> Substrates and intermediates can participate in both SETs, allowing for net-redox neutral transformations to be performed in a one-pot fashion.<sup>[8a]</sup> Considering the advantageous features of MCRs and photoredox catalysis, merging both concepts is particularly attractive.<sup>[9]</sup> Among all photocatalyzed MCRs, the difunctionalization of alkenes (especially styrenes), plays a dominant role.<sup>[9a, 10]</sup> Such transformations are commonly initiated by the oxidative or reductive formation of radicals (scheme 1). Radical addition to the styrene's double bond produces an intermediate benzylic radical which is either further oxidized to the corresponding cation (typical)<sup>[9a, 10]</sup> or reduced to the carbanion (rarely reported)<sup>[11]</sup>. These species are subsequently trapped by a nucleophile<sup>[12]</sup> or

an electrophile<sup>[11]</sup> in a sequence to be classified as radical-polar crossover (scheme 1a).<sup>[9a]</sup>

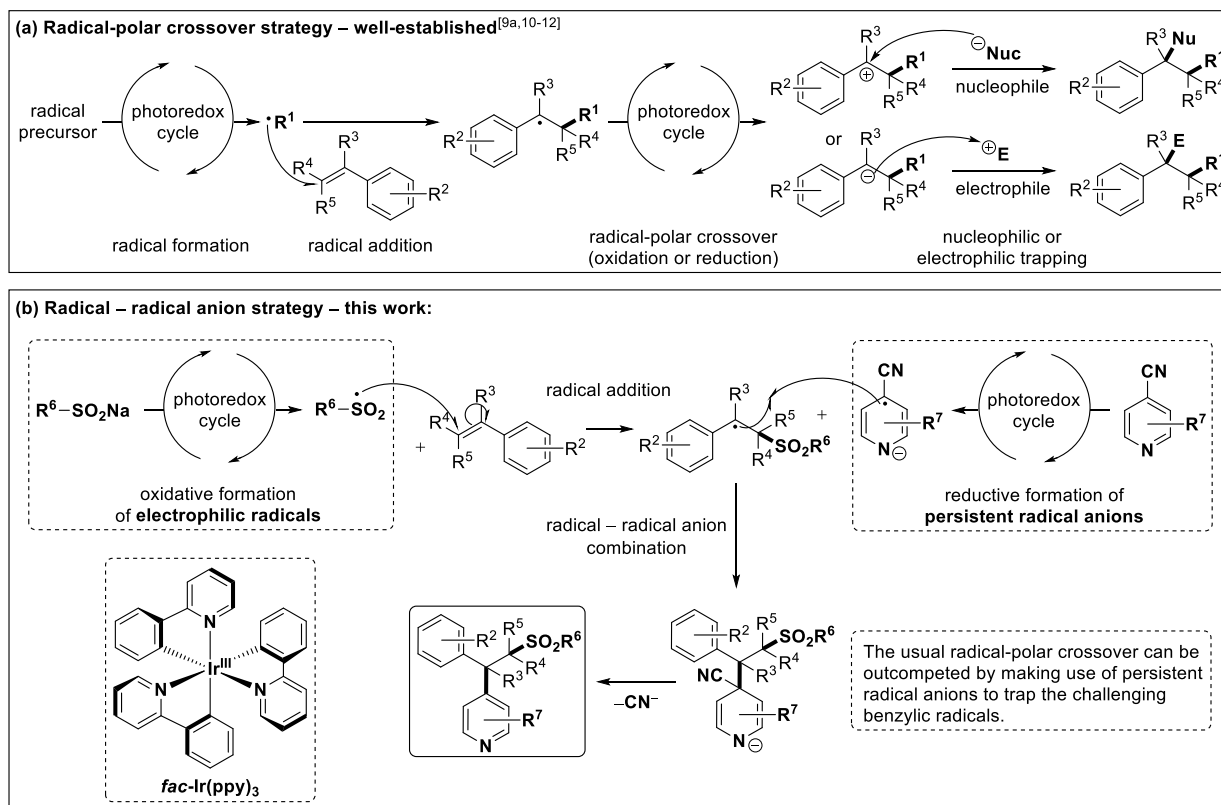
The intermediate benzylic radical can however also be trapped by a second radical species.<sup>[9a]</sup> Such double radical approaches are highly desirable as they expand the limited scope of classical radical-polar crossover difunctionalizations due to the exergonic terminal bond formation and the compatibility with numerous functional groups. To the best of our knowledge, this has only been reported for potent H-atom donors<sup>[13]</sup> or O<sub>2</sub><sup>[14]</sup> as radical traps. Despite the undisputed synthetic value of these transformations, the molecular complexity to be achieved is limited and atom-economy is reduced in the case of hydroalkylations. Radical trapping competes with oxidation or reduction (see scheme 1a) of the intermediate radical adduct, with di- and polymerization, rendering the choice of a suitable radical coupling partner highly challenging.<sup>[9a, 14b]</sup>

Concerning the efficient trapping of benzylic radicals in a radical combination process, our lab<sup>[15]</sup> and others<sup>[16]</sup> have shown that persistent radical anions of heteroaromatic nitriles such as 4-cyanopyridine (4-CP) are suitable reaction partners. On this basis, the three-component reaction (3-CR) highlighted in scheme 1b was envisioned. Oxidation of a sulfinate ion affords an electrophilic sulfonyl radical which adds to the styrene under formation of a benzylic radical.<sup>[17]</sup> At the same time, reduction of 4-CP affords a persistent radical anion which does not homodimerize due to electrostatic repulsion and instead selectively traps the benzylic radical (cf. the persistent radical effect).<sup>[15c, 18]</sup> Product formation is completed by the elimination of cyanide.<sup>[19]</sup> All SET steps are part of a photoredox catalytic cycle using visible light as the sole energy source. Very recently, the group of Chu independently reported a comparable transformation exploiting a similar strategy using trifluoromethyl radicals derived from the Togni II-reagent in the presence of 1.5 equivalents of Hantzsch ester as a photoreductant.<sup>[20]</sup> Due to the net-redox neutral nature of the sulfonylation/arylation presented here, stoichiometric reagents that do not become part of the products can be avoided. The presented light-induced 3-CR is operationally simple, highly atom-economic and grants rapid access to products of appreciable molecular complexity. We assume that the presented approach may represent a general approach for styrene difunctionalization. The usual radical-polar crossover step is outcompeted by making use of persistent radical anions to trap the challenging benzylic radicals. This might significantly expand the synthetic horizon of such transformations. First, the difunctionalization of styrene (2.0 equiv.) using *p*-ToISO<sub>2</sub>Na (2.0 equiv.) and 4-CP (1.0 equiv.) in aqueous MeCN with some common photoredox catalysts was investigated (supporting information, table S1).

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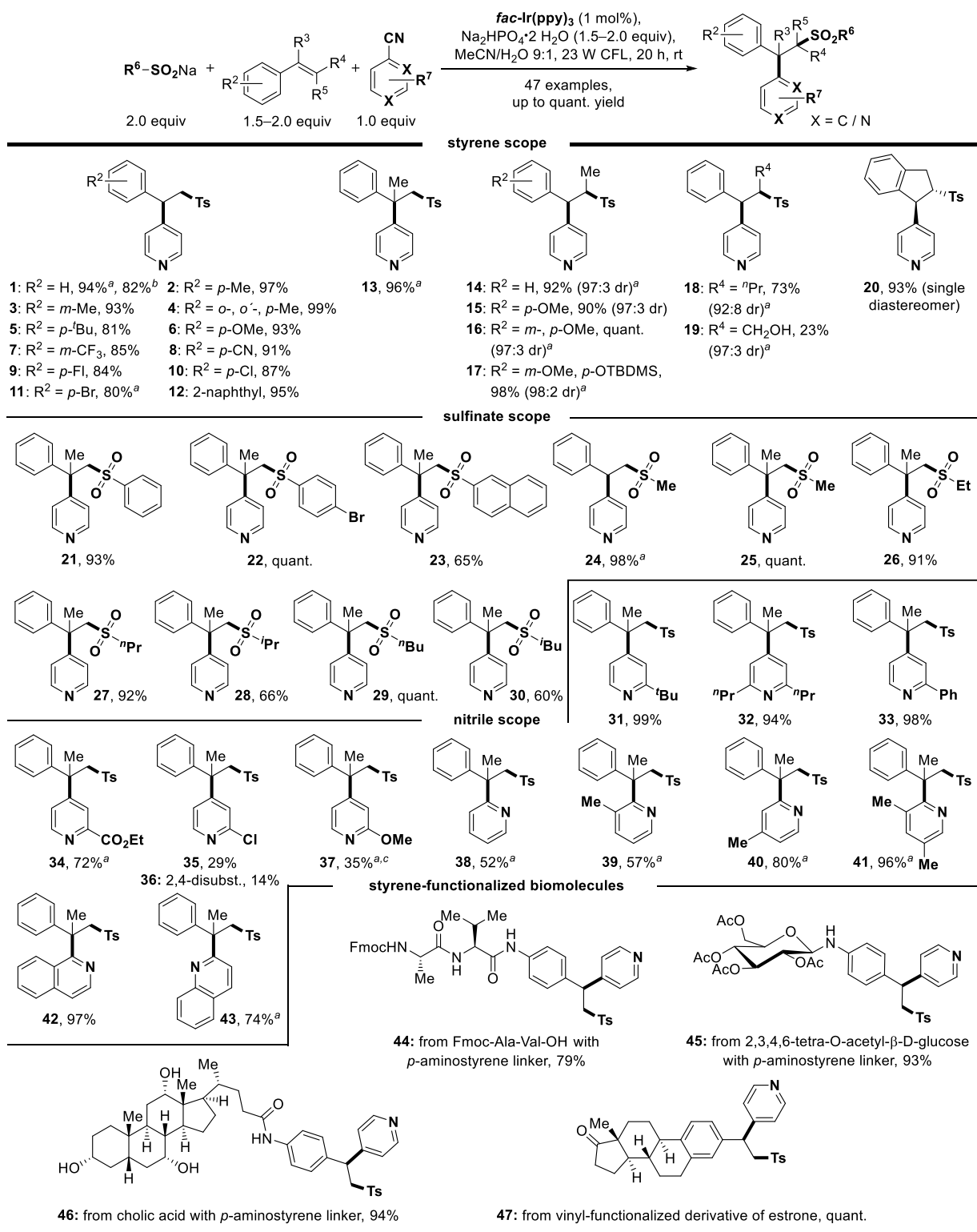


**Scheme 1.** Strategies for the photoredox-catalyzed difunctionalization of styrene derivatives

The desired product **1** was obtained in appreciable yields (61% and 63%) when employing either phenanthrene (Phen, 50 mol%) or *fac*-Ir(ppy)<sub>3</sub> (2 mol%) as strongly reducing photoredox catalysts ( $E_{1/2}([\text{Ir}^{\text{IV}}(\text{ppy})_3]^+ / [\text{Ir}^{\text{III}}(\text{ppy})_3]^*) = -1.73 \text{ V}$ ,<sup>[8a]</sup>  $E_{1/2}(\text{Phen}^{+}/[\text{Phen}]^*) = -2.07 \text{ V}$ ,<sup>[21]</sup>  $E_{1/2}(4\text{-CP}/4\text{-CP}^-) = -1.66 \text{ V}$ ,<sup>[22]</sup> all values in MeCN vs. SCE). In further optimization studies (supporting information, tables S2 and S3), the yield of **1** could be increased to 94% with concomitant reduction of the catalyst loading to 1 mol%. The best results were obtained using 4-CP as limiting reagent, 1.5–2.0 equiv of styrene, 2.0 equiv of *p*-TolSO<sub>2</sub>Na, *fac*-Ir(ppy)<sub>3</sub> (1 mol%) as the catalyst and Na<sub>2</sub>HPO<sub>4</sub> (2.0 equiv) as an additive in 9:1-MeCN/H<sub>2</sub>O (0.02 M in 4-CP).

Under these optimized conditions, the scope of the developed styrene difunctionalization was investigated (scheme 2). A large variety of substituents at the styrene's aromatic core is tolerated, including electron donating (compounds **2–6**) and electron withdrawing groups (compounds **7–11**). The products were obtained in 80–99% yield and the reaction could be scaled up (1.5 g of 4-CP afforded 4.8 g of sulfone **1** in a single run, 82%). The use of Cl- and Br-substituted styrenes allows for the further modification of the products **10** and **11** by means of classical Pd-catalyzed cross-couplings. The reaction proceeded equally well with 2-vinylnaphthalene (product **12**, 95%) and with  $\alpha$ -methylstyrene (product **13**, 96%). From  $\beta$ -substituted styrenes, products **14–18** were obtained in good to excellent yields (73%–quant.). The presence of an unprotected hydroxymethyl group in  $\beta$ -position led to a moderate result (compound **19**, 23%).

Remarkably, all tested reactions displayed excellent diastereoselectivity ( $dr \geq 92:8$ ) and in the case of indene (compound **20**, 93%), only a single product diastereomer was identified, the relative configuration of which was elucidated based on X-ray crystallography (see the supporting information, figure S11). The relative configuration of all major diastereomers of compounds **14–16**, and **18–20** was determined by comparison of calculated and experimental NMR data (DP4+-probability).<sup>[23]</sup> All results are compiled in the supporting information (chapter V), alongside with a possible explanation of the observed relative configuration. The reaction allowed for variation within the sulfinate's aromatic core without significant impact on the excellent yield (compounds **21** and **22**, 93% and quant. yield). Again, a Br- substituent was well tolerated offering the possibility of further derivatization. Alkyl sulfonates are also amenable to the MCR (compounds **24–30**). As before, steric hindrance seems to have a major influence on the reaction outcome with linear alkyl sulfonates giving higher yields than their branched counterparts. Next, the scope of cyanopyridines was investigated. Alkyl substituents and a phenyl-moiety were well tolerated (products **31–33**, 94–99%) and so was a carboxyethyl-group (compound **34**, 72% yield). As expected, cyanopyridines bearing strongly electron-donating substituents afford only moderate yields (compound **37**, 35%). This is likely attributed to a lower stability of the corresponding radical anion or to a less favorable kinetics of the SET step leading to its formation. The designed 3-CR should be expected to overcome regioselectivity issues observed in



**Scheme 2.** Scope of the developed photoredox-catalyzed sulfonylation and arylation of styrene derivatives. All yields are those of isolated products. 1.5 equiv of styrene were used unless stated otherwise. <sup>a</sup>2.0 equiv of styrene. <sup>b</sup>From 1.5 g of 4-CP. <sup>c</sup>Purification by preparative HPLC

traditional Minisci-type reactions by simply installing the cyanide leaving group in pyridine's 2-position.<sup>[24]</sup> Indeed, 2-CP afforded the desired product **38** in 52% yield, an appreciable figure considering the difficulties associated with such a transformation.<sup>[25]</sup> To gain deeper insight into this *ipso*-substitution, the spin density distribution for the radical anions of 2-, and 4-CP

as well as for their protonated forms was calculated (supporting information, figure S7). Protonation might occur since the reaction is carried out in an aqueous solvent. For the radical anion of 4-CP and its protonated form, the largest spin density is located at the nitrile-substituted carbon explaining the excellent yields obtained with such nitriles. In contrast, the radical anions of 2-CP and its protonated form display multiple sites of

large spin density including the 5-position within the radical anion and the 4-position within its protonated counterpart. As expected, the designed 3-CR afforded excellent yields, when blocking these positions with methyl groups (compounds **39–41**, 57%–quant.). 2-Cyanoisoquinoline and 2-cyanoquinoline furnished products **42** and **43** in yields of 97% and 74%, respectively. Thus, papaverine-like structures containing a sulfone moiety are accessible. The developed MCR was applied to styrene-functionalized biomolecules (scheme 2). Peptide-, carbohydrate- and cholic acid-derived products **44–47** were obtained in excellent yields (79%–quant.).

A plausible mechanism for the developed 3-CR is indicated in scheme 1b and provided in more detail in the supporting information (scheme S1). Upon excitation by visible light, *fac*-Ir(ppy)<sub>3</sub> is converted to a long-lived (1.9 μs emission lifetime in degassed MeCN at 25 °C)<sup>[26]</sup> <sup>3</sup>MLCT-state being a strong reductant ( $E_{1/2}([\text{Ir}^{\text{IV}}(\text{ppy})_3]^+ / [\text{Ir}^{\text{III}}(\text{ppy})_3]^*) = -1.73 \text{ V vs. SCE}$ ).<sup>[8a]</sup> Oxidative quenching by a heteroaromatic nitrile such as 4-CP ( $E_{1/2}(4\text{-CP}/4\text{-CP}^-) = -1.66 \text{ V}$ )<sup>[22]</sup> should be thermodynamically feasible. Indeed, the luminescence of the excited catalyst is quenched efficiently by this nitrile but not by  $\text{ToISO}_2\text{Na}$  (supporting information, figure S5). The resulting Ir<sup>IV</sup>-species ( $E_{1/2}([\text{Ir}^{\text{IV}}(\text{ppy})_3]^+ / [\text{Ir}^{\text{III}}(\text{ppy})_3]) = +0.77 \text{ V vs SCE}$ )<sup>[8a]</sup> is sufficiently oxidizing to abstract an electron from sodium sulfonates, the oxidation potentials of which range from approximately +0.3 V to +0.7 V vs SCE, thereby closing the catalytic cycle.<sup>[17b]</sup> The sulfonyl radical adds to the double bond of a styrene to produce an intermediate benzylic radical,<sup>[17]</sup> which could be trapped with TEMPO (supporting information, scheme S3). The persistent radical anions do not dimerize but selectively combine with benzylic radicals, followed by the elimination of cyanide.<sup>[15, 16b]</sup> An extensive mechanistic investigation including control experiments, calculated Gibbs free energies for all plausible SET steps, spectroscopic data, and calculated spin density distributions as well as NBO charges for the radical anions and their protonated forms is provided in the supporting information (chapter IV).

In conclusion, a photoredox-catalyzed net-redox neutral tandem sulfonylation/arylation of styrene derivatives driven by visible light was developed. It allows for significant variation within each of the three components and displays high diastereoselectivity. The reaction proved to be scalable and suitable for the late-stage functionalization of complex molecules of biological importance. Mechanistic investigations suggest a sequence of radical formation and radical combination to be operative. The reaction reported herein is based on a radical – radical anion coupling strategy for the difunctionalization of styrene derivatives, which has been developed independently by the group of Chu and ourselves.<sup>[20]</sup>

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