Moreover, these highly conductive COFs can also find applications as electrode materials in Li-ion batteries[10] and in organic photovoltaics, organic electronics, and photocatalysis.

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Decarboxylative C(sp^3)–S Coupling via Cu–Photoredox Catalysis

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In this issue of *Chem*, Liu, Li, and co-workers report the synergistic use of copper and photoredox catalysis to reveal a general platform to form C(sp^3)–S bonds via redox-active esters of abundantly available aliphatic carboxylic acids with organosulfinates under mild conditions.

Within the field of organic chemistry, the efficient construction of C(sp^3)–S bonds is vital because of the prevalence of sulfur-containing motifs in a wide array of natural products, pharmaceuticals, and functional materials. Among the top 100 small-molecule drugs, by sales in 2018, 21 drugs have at least one C(sp^3)–S bond, corresponding to approximately $37.4 billion per year.[1] In particular, organosulfones are of great importance not only because of their occurrence in pharmaceuticals but also because of their versatility as synthetic intermediates in organic synthesis.[2] Sulfone-containing compounds have long been recognized as one of the most privileged structural manifolds in pharmaceutical chemistry because of widespread presence in approved pharmaceuticals and pre-clinical chemical entities such as antibiotics or nervous system drugs (Figure 1A).[3]

Recent synthetic efforts have mainly focused on C(sp^2)–$S_{sulfonyl}$ bond formation.[2] For example, the Cu-catalyzed, aerobic decarboxylative sulfonylation of alkenyl carboxylic acids with sodium sulfonates $NaSO_2R$ provides vinyl–$S_{sulfonyl}$ bonds[4] whereas Pd-catalyzed sulfonylation of aryl halides Ar-X with sulfonates $LiSO_2Ar'$ (prepared from Li-Ar' and the SO_2 surrogate DABSO [1,4–diazabicyclo[2.2.2]octane bis(sulfur dioxide) adduct]) leads to diaryl sulfones Ar-SO_2Ar'.[5] On the other hand, C(sp^3) sulfonylation methods heavily rely on the classical nucleophilic sulfonylation of electrophiles or electrophilic sulfonylation with organometallic reagents.[2] Other methods include Reed's chlorosulfonylation of alkanes[6] and radical decarboxylative sulfonylation of Barton's esters by using liquid SO_2, both under UV irradiation (Figure 1B).[7]

The recent progress in sulfonyl radical addition to unsaturated bonds serves as stepping stone for C(sp^3)–$S_{sulfonyl}$ bond formation.[2] A wide range of aryl diazonium salts, aryl halides, or diaryldiazonium salts have been used to generate aryl radicals Ar•, which might undergo reaction with SO_2 to form the corresponding arylsulfonyl radicals $ArSO_2$•. The latter can be intercepted by olefins and alkynes to form a sulfonated product. Likewise, recent development of dual photoredox-transition metal catalysis (metallaphotocatalysis) has enabled major breakthroughs in the development of

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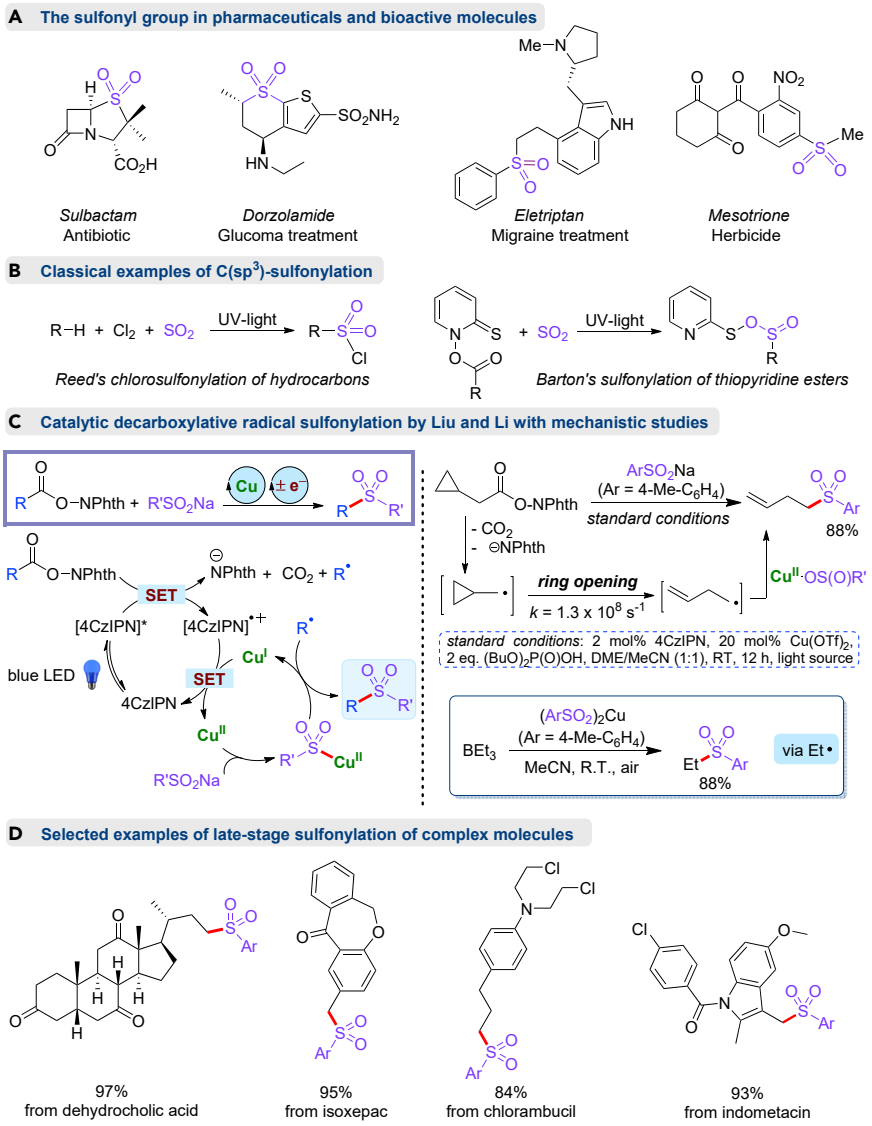

Figure 1. The Prevalence of Sulfones and Their Synthetic Pathways

(A) The sulfonyl group is prevalent in FDA-approved therapeutics and other bioactive molecules.

(B) Representative examples of C(sp^3) sulfonylation via radicals by Reed and Barton.

(C) Novel method for radical sulfonylation of redox-active esters under Cu catalysis with supporting mechanistic studies.

(D) Late-stage sulfonylation of complex substrates.

a wide range of previously inaccessible redox-neutral transformations that would be energetically unfeasible under non-irradiative conditions such as decarboxylative radical cross couplings for C–X (X = C, N, O, P, and S) bond-forming reactions.[8]

To overcome the challenge of sulfonylation at C(sp^3) centers, Liu, Li and co-workers implemented decarboxylative radical sulfonylation employing redox-active esters derived from alkyl carboxylic acids RCOOH with readily available sodium sulfinates $NaSO_2R'$.[9] Sulfonylated products $R–SO_2R'$ result from an operationally simple protocol involving discrete photo- and Cu-catalyzed cycles (Figure 1C). This method benefits from the use of widely available carboxylic acids that might be easily converted to their corresponding redox-active *N*-hydroxyphthalimide esters RC(O)O–NPhth (NPhth = phthalimido) upon condensation with *N*-hydroxyphthalimide. Utilizing a visible-light-induced energy-transfer strategy, the authors effectively activate alkyl *N*-hydroxyphthalimide esters RC(O)O–NPhth via a single-electron transfer (SET) process with the organic photocatalyst 1,2,3,5-tetrakis(carbazol–9–yl)–4,6–dicyanobenzene (4CzIPN) to generate alkyl radicals R• with concomitant extrusion of CO_2. At the same time, salt metathesis between $NaSO_2R'$ and $Cu(OTf)_2$ generates the cupric sulfinate $Cu(SO_2R')_2$ capable of alkyl radical R• capture to afford the sulfonylated product $R–SO_2R'$.

This protocol operates at room temperature under redox-neutral conditions without any external reducing or oxidizing agents. Careful reaction optimization demonstrated that $(BuO)_2P(O)OH$ or CF_3COOH must be used as an additive to obtain high yields, perhaps by buffering the reaction. Additionally, the dibutyl phosphite additive inhibits the generation of an alkene byproduct resulting from β-H atom abstraction of the R• radical observed with some secondary carboxylates.

This method offers both broad substrate scope and functional group compatibility. A wide range of primary and secondary alkyl carboxylates as their redox-active derivatives RC(O)O–NPhth function in this protocol, allowing the incorporation of alkenes, alkynes, aldehyde, ketones, esters, and amides via the R• radical generated via decarboxylation. Moreover, diverse (hetero)aryl and alkyl organosulfinates $M–SO_2R'$ might be used, including those relevant to medicinal chemistry, such as pyridyl or cyclopropyl sulfinates.

The direct, late-stage functionalization of natural product derivatives and pharmaceuticals holds great promise for the development of new libraries for drug screening. Accordingly, the new

methodology by Liu and Li allows for the late-stage modification of steroids such as dehydrocholic acid and chenodeoxycholic acid to furnish the corresponding sulfones in excellent yields. Other bioactive carboxylic acids such as isoxepac (non-steroidal anti-inflammatory), chlorambucil (chemotherapy), mycophenolic acid (antibiotic), gibberellic acid (plant hormone), or indomethacin (non-steroidal anti-inflammatory) could also be efficiently converted to the corresponding sulfones (Figure 1D).

Careful mechanistic studies unambiguously show the intermediacy of alkyl radicals R• generated from RC(O)O-NPhth via photoredox catalysis of 4CzIPN. For instance, the NHPI ester of cyclopropylacetic acid provides the ring-opened sulfonylation product in 88% yield, consistent with the generation of the cycloproylmethyl radical that rapidly opens to the allylmethyl radical. In a similar manner, the authors demonstrate that the ethyl radical Et• (generated from exposure of BEt_3 to air) might be captured by $Cu(OS(O)(p\text{-tolyl}))_2$ to form the corresponding Et–SO_2(*p*-tolyl) product in 81% yield.

The key C(sp^3)–$S_{sulfonyl}$ bond-forming step takes advantage of Jay Kochi's groundbreaking work on C(sp^3) radical capture by simple cupric salts CuX_2. For instance, generation of Bu• radicals in the presence of CuX_2 (X = O_2CR, Cl, Br, I, SCN, N_3, and CN) results in the formation of functionalized products Bu–X.[10] This key observation is central to many new families of C(sp^3)–H functionalization reactions that broadly enable the conversion of R-H substrates to functionalized products R-FG via alkyl radical R• capture by [Cu^{II}]–FG (functional group) intermediates.[11]

The new method by Liu and Li[9] offers a versatile method to convert easily accessible alkyl carboxylic acids RC(O)OH to the corresponding sulfones R–SO_2R′ via redox-active esters RC(O)O–NPhth under light and Cu catalysis. This methodology is amenable to a variety of alkyl radicals R• generated via photocatalyzed decarboxylation from redox-active esters RC(O)O–NPhth to provide broad families of alkyl sulfones R-SO_2R′. As mechanistic studies demonstrate that the C(sp^3)–$S_{sulfone}$ bond forms by R• capture by cupric sulfinates $Cu(SO_2R')_2$, this approach might enable new C(sp^3)–H sulfonylation protocols by formation of alkyl radicals R• via H-atom abstraction reactions of substrates R-H. Such a complementary C(sp^3)–sulfonylation approach could further extend the reach of the present methodology to potentially allow single-step access to a diverse array of organosulfones that serve important roles in synthetic chemistry, pharmaceuticals, agrochemicals, and material science.

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