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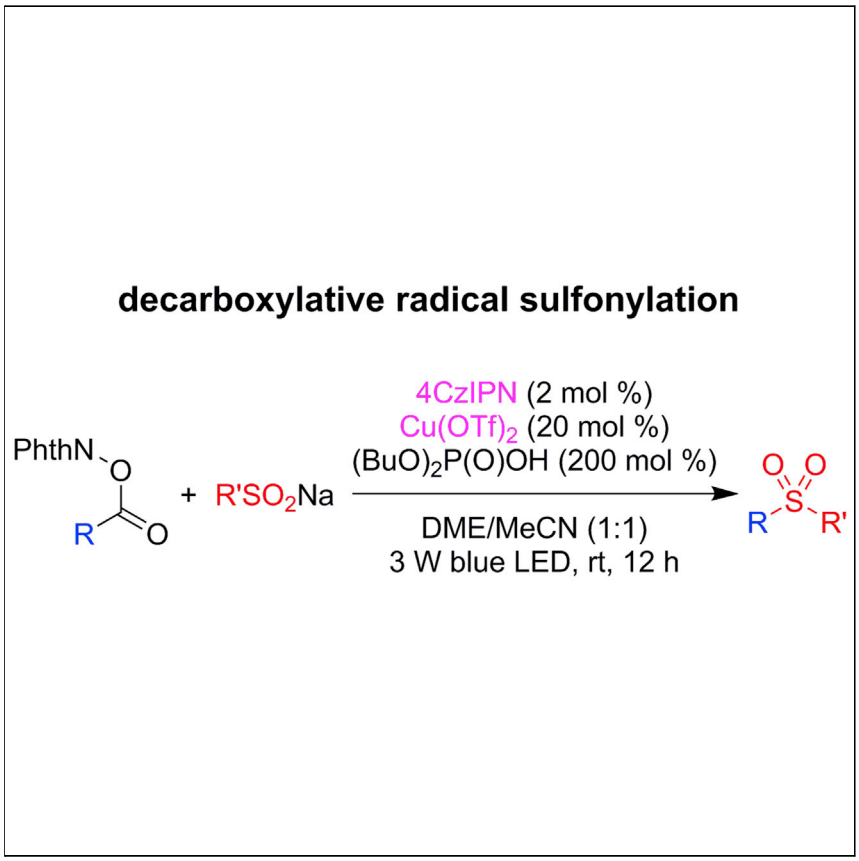
Catalytic Decarboxylative Radical Sulfonylation



Sulfones are not only important structural motifs in pharmaceuticals and agrochemicals but also versatile intermediates in organic synthesis. However, C(sp^3)-sulfonyl bond formations remain underdeveloped. In this issue of Chem, Li and co-workers demonstrate that the merger of photo-organocatalysis and copper-catalysis enables the decarboxylative radical sulfonylation with organosulfinates at room temperature under redox-neutral conditions. The method leads to the improved synthesis of anti-prostate cancer drug bicalutamide and should find more important applications in drug discovery.

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HIGHLIGHTS

Decarboxylative sulfonylation enabled by copper catalysis and photoredox catalysis

Broad substrate scope and wide functional group compatibility

Improved synthesis of anti-prostate cancer drug bicalutamide

He et al., Chem 6, 1–11
May 14, 2020
https://doi.org/10.1016/j.chempr.2020.02.003

Please cite this article in press as: He et al., Catalytic Decarboxylative Radical Sulfonylation, Chem (2020), https://doi.org/10.1016/j.chempr.2020.02.003

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Catalytic Decarboxylative Radical Sulfonylation

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SUMMARY

Sulfones are key structural motifs in pharmaceuticals and agrochemicals, and their synthesis is of paramount importance in organic chemistry. While nucleophilic and electrophilic C(sp^3)-sulfonylation are well documented, radical C(sp^3)-sulfonylation remains elusive. Herein, we report the decarboxylative radical sulfonylation with sulfinates. With the merger of 4CzIPN (1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene) and $Cu(OTf)_2$ as catalysts, the visible-light-induced reaction of redox-active esters of aliphatic carboxylic acids with organosulfinates at room temperature provides the corresponding decarboxylative sulfonylation products in satisfactory yields. This redox-neutral protocol exhibits broad substrate scope and wide functional group compatibility, enabling the late-stage modification of complex natural products and bioactive pharmaceuticals. The synthetic utility of the method is further demonstrated by the improved synthesis of anti-prostate cancer drug bicalutamide. A mechanism involving sulfonyl group transfer from Cu(II)–SO_2R to alkyl radicals is proposed.

INTRODUCTION

Sulfones are ubiquitous in nature. They possess a wide variety of biological activities and thus serve as important structural motifs in pharmaceuticals and agrochemicals. For example, bicalutamide (CASODEX, AstraZeneca's blockbuster drug) is an orally active, nonsteroidal anti-androgen for the treatment of prostate cancer (Figure 1).[1,2] Certinib (Zykadia, Novartis) is a new drug approved by FDA (U.S. Food and Drug Administration) in 2014 to treat anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer.[3] Another example is oral drug apremilast (Otezla, Celgene), the only phosphodiesterase 4 (PDE4) inhibitor approved by FDA to treat active psoriatic arthritis and plaque psoriasis with an annual sales of over 1.2 billion US dollars.[4] In the meantime, sulfones are also versatile synthetic intermediates in organic chemistry. They serve as the key building blocks or reagents in many chemical transformations such as Julia–Lythgoe olefination[5–7] and fluoroalkylation.[8] As a consequence, the synthesis of sulfones has received a considerable attention and significant progress has been achieved in recent years.[9–13] However, recent advances focus mainly on C(sp^2)-sulfonyl bond formations such as aromatic or vinylic sulfonylation, whereas C(sp^3)-sulfonyl bond formations remain underdeveloped. Conventional C(sp^3)-sulfonylation methods include (1) nucleophilic sulfonylation of electrophiles such as alkyl halides, epoxides, or Michael acceptors with organosulfinates or thiosulfonates under basic conditions[14] (Scheme 1A) and (2) electrophilic sulfonylation of sulfonic acid derivatives such as sulfonate esters or sulfonyl chlorides with organometallic reagents (Scheme 1B). However, the former suffers from the competing O-alkylation (to give sulfinate esters), while the latter often leads to the corresponding sulfoxides.[9] The recently developed sulfonyl radical addition to unsaturated bonds such as alkenes provides a powerful means for C(sp^3)-sulfonyl bond formations (Scheme 1C). This method

The Bigger Picture

Sulfones are not only important structural motifs in pharmaceuticals and agrochemicals but also versatile synthetic intermediates in organic chemistry. Despite the significant progress in the synthesis of sulfones in recent years, C(sp^3)-sulfonyl bond formations remain underdeveloped. In particular, there have been no reports to date of general methods for the sulfonylation of alkyl radicals. In this article, we introduce the copper-catalyzed cross coupling of sulfinates with alkyl radicals generated via photoredox-catalyzed decarboxylation of redox-active esters derived from aliphatic carboxylic acids. This unprecedented protocol exhibits broad substrate scope and wide functional group compatibility, allowing the late-stage sulfonylation of complex molecules. The synthetic utility of the method is further demonstrated by the improved synthesis of anti-prostate cancer drug bicalutamide.

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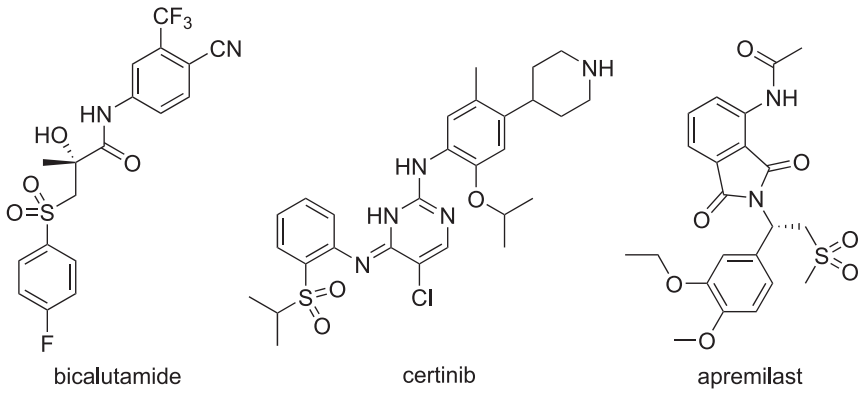

Figure 1. Structures of Representative Sulfone-Based Drugs Bicalutamide, Certinib, and Apremilast

can be extended to three-component condensation involving the fixation of SO_2.[12,13] Nevertheless, the strategy is mainly limited to arenesulfonyl radicals (or aryl radicals plus SO_2), while examples[14–17] of alkyl radical addition to SO_2 (e.g., Reed reaction[17]) are rare due to the fast desulfonylation of alkanesulfonyl radicals. In fact, there have been no reports to date of general methods for the sulfonylation of alkyl radicals. Given that alkyl radicals are common intermediates easily generated from various types of organic compounds, it is certainly highly desirable to develop efficient and general methods for the sulfonylation of alkyl radicals (Scheme 1D). In particular, the decarboxylative sulfonylation of aliphatic carboxylic acids should be an important transformation useful in organic synthesis. To meet the challenge, we propose the concept of "RSO_2-group-transfer from Cu(II)–SO_2R to alkyl radicals," in accordance with our previous ideas of Cu(II)-assisted CF_3-group-transfer[18–20] or F-atom-transfer.[21] Specifically, we target the copper-catalyzed cross coupling of sulfinates with alkyl radicals generated via photoredox-catalyzed[22–27] decarboxylation of redox-active esters[28–33] derived from aliphatic carboxylic acids.[34–43]

RESULTS AND DISCUSSION

Carboxylic acids and sulfinates[44] are both attractive raw materials for chemical synthesis due to their ready availability, high stability, and low cost. Decarboxylative cross coupling of aliphatic carboxylic acids with sulfinates should therefore be an ideal method for sulfone synthesis. Given that sulfinates are much easier to be oxidized than the corresponding carboxylic acids, direct oxidative decarboxylative coupling is not feasible. Reductive decarboxylation of redox-active esters of carboxylic acids might provide the solution.

We then commenced our investigations with the redox-active ester of 4-phenylbutanoic acid (**1a**) and sodium 4-methylbenzenesulfinate (**2a**) as the model substrates. The redox-active ester was easily prepared by condensation of 4-phenylbutanoic acid with *N*-hydroxyphthalimide (NHPI). After extensive screening of reaction conditions (see Table S1 for details), we were pleased to find that, with 2 mol % 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4CzIPN)[45,46] and 20 mol % $Cu(OTf)_2$ as catalysts and 2 equiv of dibutyl hydrogen phosphate as the additive, the visible-light-induced reaction of ester **1a** and sulfinate **2a** at room temperature (RT) for 12 h afforded the desired sulfone **3a** in 95% yield (Table 1, entry 1). When the reaction was performed in the absence of $(BuO)_2P(O)OH$, the yield dropped to 65% (Table 1, entry 2). Switching the additive to trifluoroacetic acid also led to a high

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https://doi.org/10.1016/j.chempr.2020.02.003

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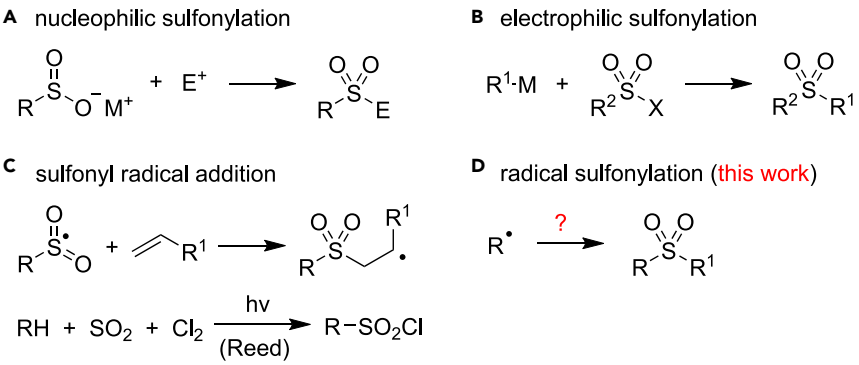

Scheme 1. C(sp^3)-Sulfonylation

product yield (Table 1, entry 3), while weak acids such as acetic acid showed no improvement (Table 1, entry 4). Interestingly, the addition of 2,2′-bipyridine (20 mol %) significantly inhibited the reaction (Table 1, entry 5). Control experiments revealed that photocatalyst 4CzIPN, copper catalyst, and visible light were all essential for the transformation (Table 1, entries 6–8). In addition, the redox-active ester could be prepared *in situ* without purification, providing the sulfonylation product in 85% yield (Table 1, entry 9). It is worth mentioning that the use of free 4-methylbenzenesulfinic acid in place of sodium 4-methylbenzenesulfinate resulted in a very low (7%) yield of **3a**. However, the combination of 4-methylbenzenesulfinic acid with a weak base such as $NaHCO_3$ or CF_3CO_2Na increased the product yield to 51% and 89%, respectively (see Table S2). These experiments suggest that $(BuO)_2P(O)OH$ or trifluoroacetic acid might serve as a buffer to adjust the pH value of reaction solution. The use of $(BuO)_2P(O)OH$ or trifluoroacetic acid as the additive proved to be even more critical in the decarboxylative sulfonylation of secondary alkyl acids, resulting in a sharp increase in product yield by inhibiting the generation of the alkene byproduct (see Table S2). While the detailed mechanism remains unclear for the remarkable acid effect, it might be possible that the presence of an acid decreases the basicity of sulfinate and thus retards α-deprotonation of alkyl radicals (to give alkene radical anions and hence alkenes after electron transfer). Note that the CH groups adjacent to a carbon radical center are quite acidic as pointed out by Studer and co-workers.[47,48]

With the optimized conditions in hand, we examined the scope of the method. As shown in Scheme 2, various NHPI esters derived from primary and secondary alkyl acids underwent smooth decarboxylative sulfonylation with sulfinate **2a** to provide the corresponding sulfones **3a–3v** in good to excellent yields. The presence of a wide range of functional groups was tolerated by the process. For example, terminal alkenes, alkynes, alkyl or aryl bromides, aldehydes, ketones, esters, amides, sunfonamides, ethers, and unprotected indoles all proved to be compatible with the reaction. Protected α-amino acids were also suitable substrates, as evidenced by the synthesis of sulfone **3m**. The reaction could be operated in gram scale without the loss of efficiency. The method was also applicable to NHPI esters derived from tertiary alkyl acids, albeit in a lower efficiency (e.g., **3w**) presumably because of steric hindrance.

The protocol has also shown a broad scope in terms of organosulfinates, as demonstrated in Scheme 3. A number of arenesulfinates with either electron-withdrawing or electron-donating substituents on the aromatic ring all underwent sulfonylation reactions furnishing the corresponding sulfones **4a–4d** in satisfactory yields. Moreover, the protocol was also applicable to alkanesulfinates. Primary, secondary, and tertiary

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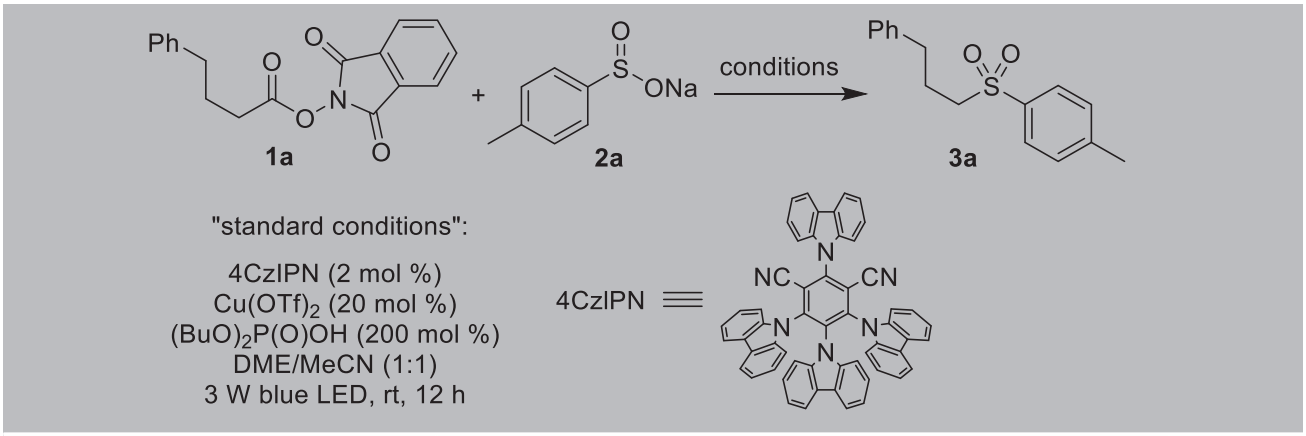
Table 1. Optimization of Conditions



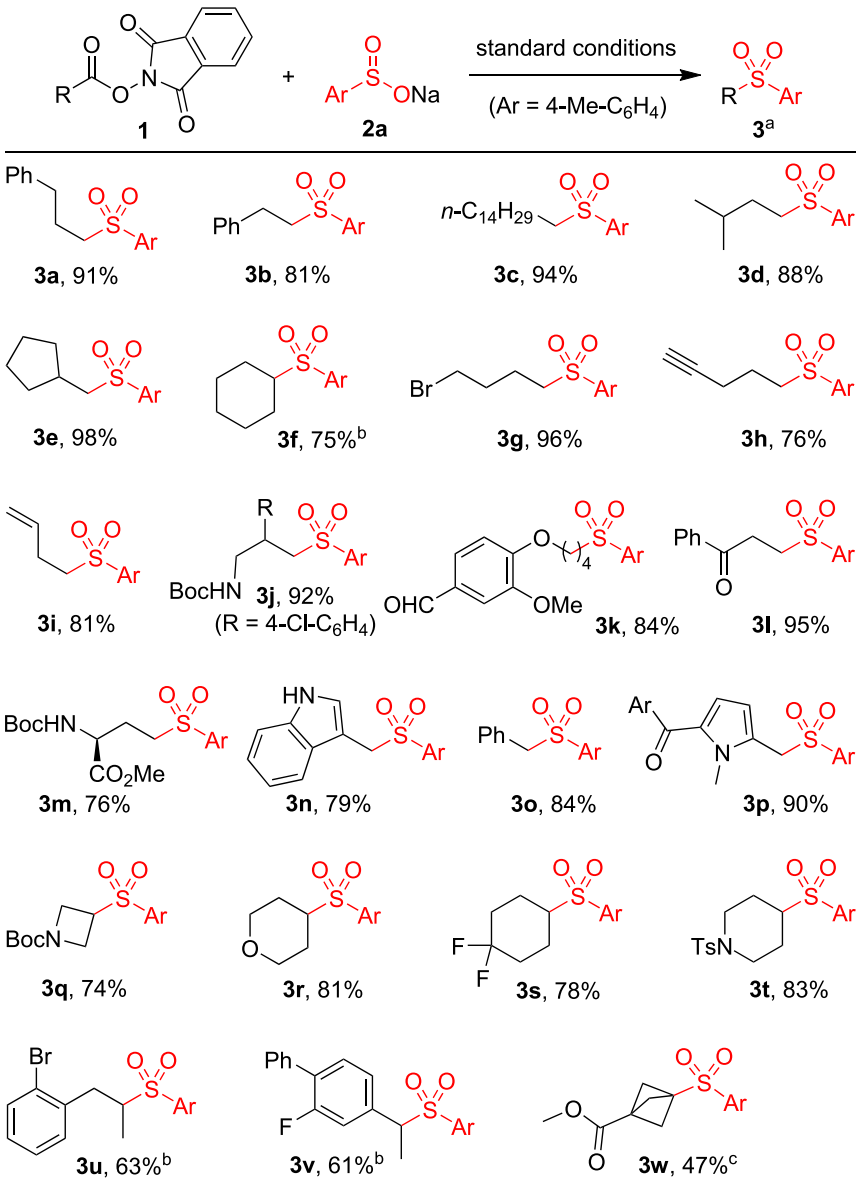
Entry[a]	Variation from the "Standard Conditions"	Yield (%)[b]
1	none	95 (92)
2	without $(BuO)_2P(O)OH$	65
3	CF_3CO_2H in place of $(BuO)_2P(O)OH$	93 (91)
4	CH_3CO_2H in place of $(BuO)_2P(O)OH$	51
5	with 2,2′-bipyridine (20 mol %)	0
6	without blue LED	0
7	without 4CzIPN	0
8	without $Cu(OTf)_2$	0
9	*In situ* generation of **1a**	85

[a]0.20 mmol scale, 2 equiv of **2a** was used.
[b]^{1}H NMR yield based on **1a** with dibromomethane as the internal standard, isolated yield in parentheses.

alkanesulfinates were all suitable partners in the cross coupling, as exemplified by the efficient synthesis of sulfones **4e–4k**. An excellent chemoselectivity was observed in the reaction of 1-allylcyclopropanesulfinate furnishing sulfones **4j** and **4k** in which the allyl group remained intact. Nevertheless, the sulfonylation with pyridine-3-sulfinate afforded sulfone **4l** in a low yield due to the competing Minisci alkylation, and no desired product could be observed in the sulfonylation with trifluoromethanesulfinate. The results also indicated that sulfonyl radicals were unlikely to be involved in the reaction given the fast desulfonylation of alkanesulfonyl radicals.

The above results clearly demonstrate the broad substrate scope and wide functional group compatibility of the method. In addition, the reactions were run at room temperature under redox-neutral conditions free from external reducing or oxidizing agents. These characteristics enabled the late-stage modification of complex natural products or drug molecules (Scheme 4). For example, steroids such as dehydrocholic acid or chenodeoxycholic acid were readily converted to the corresponding sulfones **5a** or **5b** in high to excellent yield. Drug molecules such as isoxepac, chlorambucil, mycophenolic acid, gibberellic acid, or indometacin were all transformed into the corresponding sulfones highly efficiently. The protocol was also applicable to carbohydrate-containing acids, as evidenced by the synthesis of **5f** in 91% yield.

To further demonstrate the synthetic utility of the sulfonylation method, we chose the anti-prostate cancer drug bicalutamide as the target molecule. Bicalutamide and its analogs were achieved by multi-step synthesis starting from the commercially



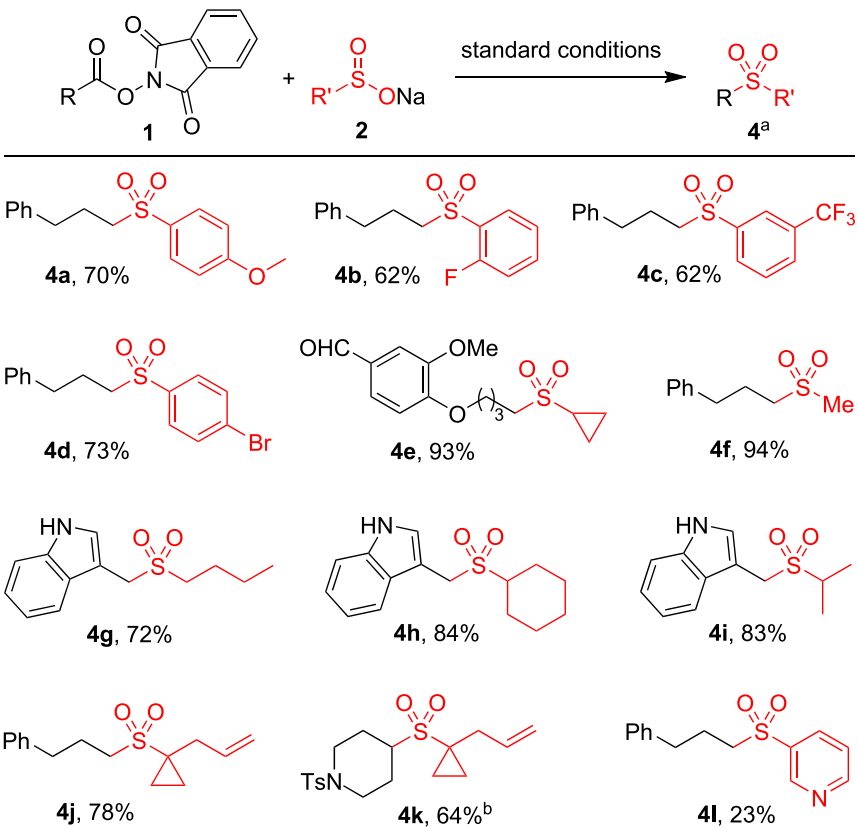
Scheme 2. Variation of NHPI Esters

[a]Conditions: **1** (0.20 mmol), **2** (0.40 mmol), $(BuO)_2P(O)OH$ (0.40 mmol), $Cu(OTf)_2$ (0.04 mmol), 4CzIPN (0.004 mmol), DME (1.0 mL), MeCN (1.0 mL), 3 W blue LED, RT, 12 h. Isolated yield based on **1**.

[b]5 equiv of $(BuO)_2P(O)OH$ were used.

[c]2 equiv of CF_3CO_2H were used.

available and inexpensive (*S*)-malic acid (**6**). However, three steps were required for the installation of the sulfonyl group in bicalutamide consisting of (1) Barton decarboxylative bromination of acid **7** with $CBrCl_3$, (2) nucleophilic substitution of the resulting bromide with 4-fluorobenzenethiol, and (3) subsequent oxidation with mCPBA (*meta*-chloroperoxybenzoic acid). With the newly developed decarboxylative sulfonylation method, the three steps could be shortened into one (Scheme 5). Specifically, the condensation of acid **7** with NHPI and DIC (diisopropylcarbodiimide) produced the corresponding NHPI ester, which, without purification, was subjected to the treatment with *p*-fluorobenzenesulfinate under the optimized

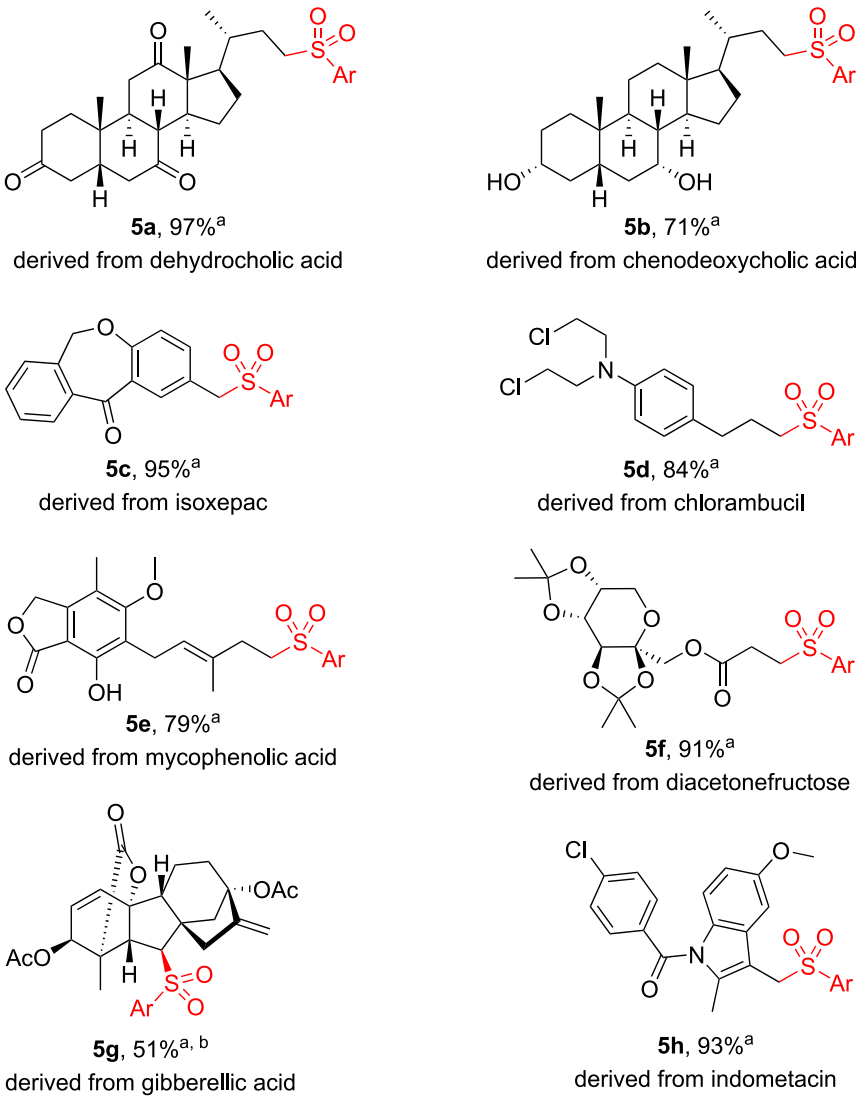


Scheme 3. Variation of Sulfinates

[a,b] See Scheme 2.

conditions to provide sulfone **8** in 60% yield. The following hydrolysis of **8** with KOH in aqueous methanol at room temperature afforded cleanly compound **9**, which, without purification, was subjected to the condensation with 4-cyano-3-trifluoromethylaniline according to the literature procedure,[49] furnishing (*R*)-bicalutamide in 91% yield based on **8**. The new synthetic route offers a more concise and efficient entry to bicalutamide and avoids the use of toxic $CBrCl_3$, odorous *p*-fluorobenzenethiol, and dangerous mCPBA.

To gain further insight into the sulfonylation, mechanistic studies were carried out (Scheme 6). The reaction of the NHPI ester derived from cyclopropylacetic acid (**10**) under the optimized conditions produced exclusively the ring-opening sulfonylation product **3i** in 88% yield. When the NHPI ester of hept-6-enoic acid (**11**) was subjected to the treatment with sulfinate **2a** under the optimized conditions, the cyclized product **3e** was obtained in 50% yield along with the uncyclized product **12** isolated in 25% yield. These radical clock experiments unambiguously demonstrated the intermediacy of alkyl radicals. Additionally, radical trapping experiment with 1,1-diphenylethylene also suggested the involvement of alkyl radicals rather than sulfonyl radicals (see Scheme S1). Furthermore, copper(II) *p*-toluenesulfinate prepared from $Cu(OH)_2$ and sodium *p*-toluenesulfinate was treated with an equimolar amount of triethylborane (as the ethyl radical precursor) in acetonitrile at room temperature under aerobic conditions, and ethylsulfone **13** was achieved in 81% yield. This experiment provided a solid evidence for the proposed mechanism of Cu(II)-assisted RSO_2 group transfer. Finally, fluorescence quenching experiments of 4CzIPN with **1a**, $Cu(OTf)_2$, or 4-methylbenzenesulfinic acid



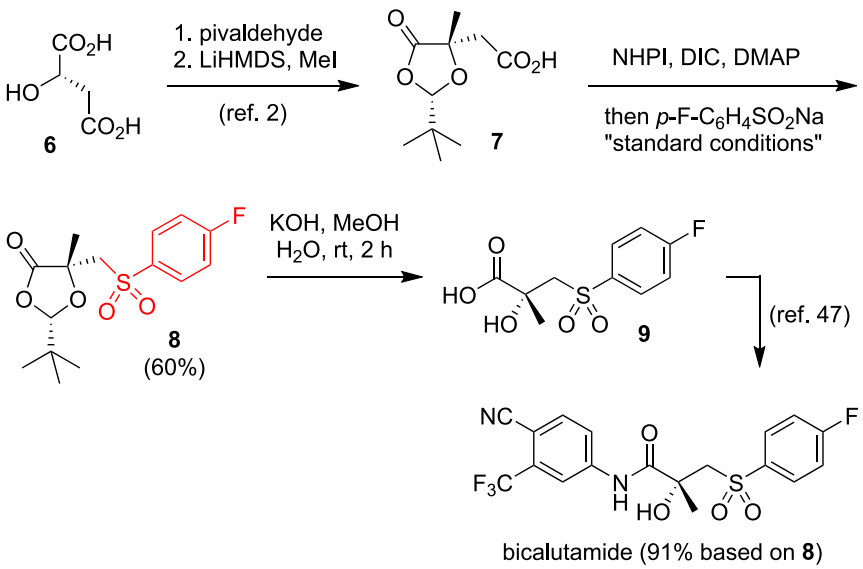
Scheme 4. Late-Stage Sulfonylation of Complex Molecules

[a,b] See Scheme 2.

indicated the feasibility of electron transfer between 4CzIPN and redox-active esters (see Figure S1).

On the basis of the above results, a plausible mechanism is proposed as depicted in Figure 2. Excitation of photocatalyst 4CzIPN generates the long-lived triplet-excited-state [4CzIPN]* that undergoes single electron transfer with a NHPI ester to give the 4CzIPN radical cation and the NHPI ester radical anion. The N–O bond cleavage takes place for the NHPI ester radical anion to produce a carboxyl radical, which upon extrusion of CO_2 generates the corresponding alkyl radical. In the meantime, transmetalation of sulfinate anion forms the Cu(II)–SO_2R intermediate. The alkyl radical is then intercepted by Cu(II)–SO_2R to provide the sulfone product and Cu(I). Finally, Cu(I) is oxidized by 4CzIPN radical cation, leading to the regeneration of both Cu(II) and 4CzIPN catalysts.

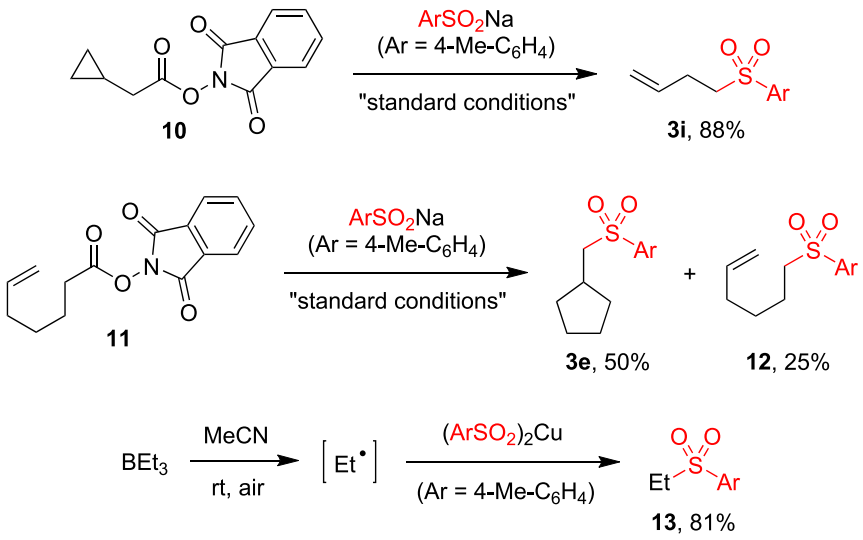
The interception of alkyl radicals by Cu(II)–SO_2R may proceed either via direct RSO_2 group transfer or via the formation of R–Cu(III)–SO_2R complex followed by reductive



Scheme 5. Application in the Synthesis of Bicalutamide

elimination. Given that uncomplexed copper(II) sulfinate is a mild oxidant rather than a reducing agent and the presence of 2,2′-bipyridine inhibits the sulfonylation, the direct RSO_2 group transfer seems more likely the case. More mechanistic studies are certainly required to provide a detailed understanding on the mechanism.

The ratio of cyclized product **3e** versus uncyclized product **12** was 2:1 in the radical clock experiment shown in Scheme 6. The rate constant for the cyclization of hex-5-en-1-yl radical at 20°C is known to be approximately $2.3 \times 10^5\ s^{-1}$, as determined by Ingold and co-workers.[50] By assuming that the active intermediate species responsible for sulfonylation is of the same concentration as the catalyst $Cu(OTf)_2$ (0.02 M) and remains constant throughout the reaction, the rate constant for the toluenesulfonyl group transfer from Cu(II)–SO_2Tol to a primary alkyl radical can



Scheme 6. Mechanistic Experiments

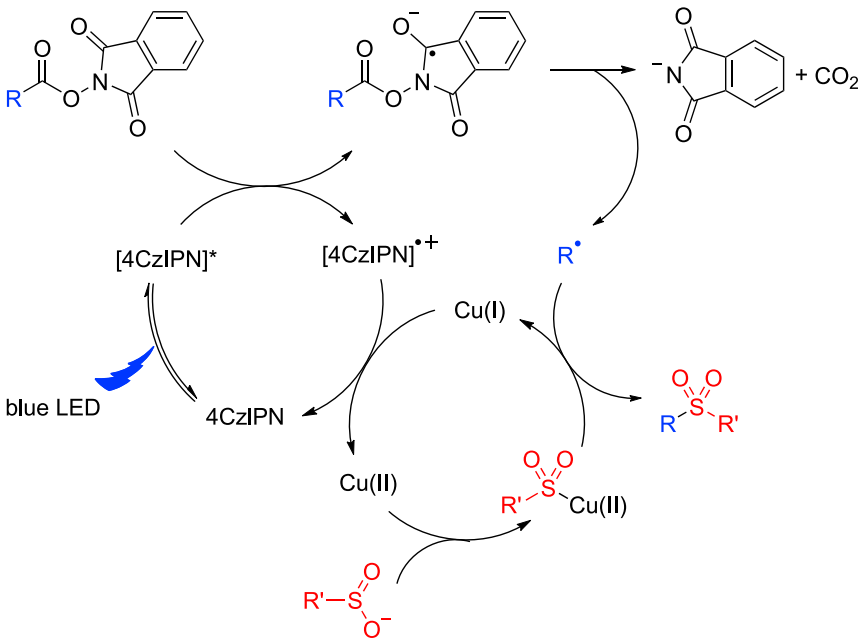


Figure 2. Proposed Mechanism of Decarboxylative Sulfonylation

then be calculated to be around $2.3 \times 10^7\ M^{-1}s^{-1}$, which is much larger than the rate constant for primary alkyl radical addition to an unactivated monosubstituted alkene ($10^3 \sim 10^4\ M^{-1}s^{-1}$)[51] or to benzene ($3.8 \times 10^2\ M^{-1}s^{-1}$).[52] This well explains the remarkable chemoselectivity in the reaction of 1-allylcyclopropanesulfinate (to give **4j** and **4k**). Furthermore, it may also account for the low efficiency in the reaction of pyridine-3-sulfinate (to give **4l**), given that rate constants for radical addition to protonated 4-cyanopyridine (Minisci alkylation) range from $8.9 \times 10^5\ M^{-1}s^{-1}$ for *n*-butyl radical to $6.3 \times 10^7\ M^{-1}s^{-1}$ for *t*-butyl radical.[52] Thus, the rate constant for RSO_2 group transfer determined above offers a quantitative view on the reaction mechanism and sets the stage for the rational design of new synthetic methodology based on radical sulfonylation.

Conclusions

In conclusion, the merger of photo-organocatalysis and copper catalysis enables the successful development of a practical protocol for the sulfonylation of alkyl radicals generated from aliphatic carboxylic acids. As the procedure is operationally simple, catalytic in copper, broad in scope, free from external reducing or oxidizing agents, tolerant of sensitive functional groups, and utilizes cheap and stable sulfinates, the method should find widespread applications in sulfone synthesis. It is also conceivable that more new methods of radical sulfonylation will be developed given that alkyl radicals can be generated by many other ways (such as hydrogen atom abstraction, olefin radical addition, etc.). Furthermore, the proposed mechanism of Cu(II)-assisted RSO_2 group transfer should stimulate further research toward the cross coupling of alkyl radicals with nucleophiles other than sulfinates. The research in this direction is currently underway in our laboratory.

SUPPLEMENTAL INFORMATION

Supplemental Information can be found online at https://doi.org/10.1016/j.chempr.2020.02.003.

ACKNOWLEDGMENTS

This project was supported by the National Natural Science Foundation of China (grants 21421002, 21532008, 21602239, and 21871285), the Strategic Priority Research Program of the Chinese Academy of Sciences (grant XDB20020000), the Shanghai Scientific and Technological Innovation Project (18JC1410600), the Natural Science Foundation of the Jiangsu Higher Education Institutions of China (grant 18KJA350001), and the Priority Academic Program Development of the Jiangsu Higher Education Institutes (PAPD).

AUTHOR CONTRIBUTIONS

J.H., F.L., and C.L. initiated the project. J.-R.C., W.-J.X., F.L., and C.L. conceived and designed the experiments. J.H., G.C., and B.Z. conducted the experiments and analyzed the data. C.L. wrote the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

Received: October 29, 2019
Revised: December 28, 2019
Accepted: February 7, 2020
Published: March 5, 2020

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