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Catalytic AgF-Initiated Intramolecular 1,3-Sulfonyl Migration of *gem*-Difluorovinyl Sulfonates to α,α-Difluoro-β-ketosulfones

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Cite This: https://dx.doi.org/10.1021/acs.orglett.0c03492 Read Online

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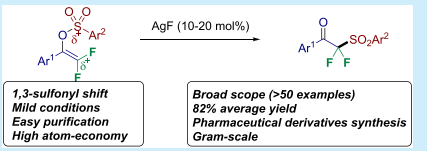
ABSTRACT: A 1,3-sulfonyl migration of difluorovinyl sulfonates initiated by a catalytic amount of silver fluoride is presented. α,α-Difluoro-β-ketosulfones were successfully prepared in excellent yields. This method features high chemoselectivity, good functional group tolerance, high atom economy, and mild, environmentally benign reaction conditions. Furthermore, mechanistic experiments indicate that this migration proceeds in an intermolecular pathway and the corresponding sulfinates are possible intermediates.



Organic sulfones have been widely used as protecting groups or activating groups in organic synthesis, offering substantial synthetic versatility,[1] and thus play an important role in synthetic chemistry. In particular, β-ketosulfone derivatives have drawn considerable interest owing to the presence of this moiety in broad biologically active compounds or functional materials.[2] Substantial efforts have been made on the development for the synthesis of β-ketosulfone compounds, such as acylation of alkyl sulfones,[3] oxidation of β-ketosulfides/β-hydroxysulfones,[4] and alkylation of metallic aryl sulfinates.[5] However, these approaches require strong bases or harsh reaction conditions along with poor functional group tolerance. In recent years, radical sulfonylation has also been developed as a useful approach to β-ketosulfone derivatives, involving the addition of sulfonyl radicals to alkenes/alkynes,[6] while external oxidants and a large excess amount of sulfonylation reagents are generally required in these reports.

Recently, sulfonyl migrations have garnered significant attention due to their potential applications in highly functionalized heterocycles.[7] Compared with the representative protocols described above, the synthesis of β-ketosulfone derivatives via sulfonyl migrations is extremely rare: (1) In 2017, Li's group reported a photoinduced rearrangement of vinyl sulfonates to β-ketosulfones;[8] (2) Feng et al. reported an iridium-catalyzed visible-light-promoted sulfonyl migrations for the construction of α-sulfonylated amides[9] (Figure 1a).

On the other hand, the difluoromethyl moiety acting as an exceptional structure in pharmaceuticals[10] has received increasing attention due to its unique physicochemical properties.[11] α-Functionalized fluorinated sulfones proved to be of important value in organic synthesis[12] and could be the subject of a series of transformations.[13] Therefore, developing an efficient and practical protocol for the synthesis of ketosulfone derivatives containing a difluoromethyl moiety is of great significance. However, so far, there are few reports for the preparation of these derivatives. The substitution of β-ketosulfones with electrophilic fluorination reagents under basic conditions provides a direct pathway to synthesize α,α-

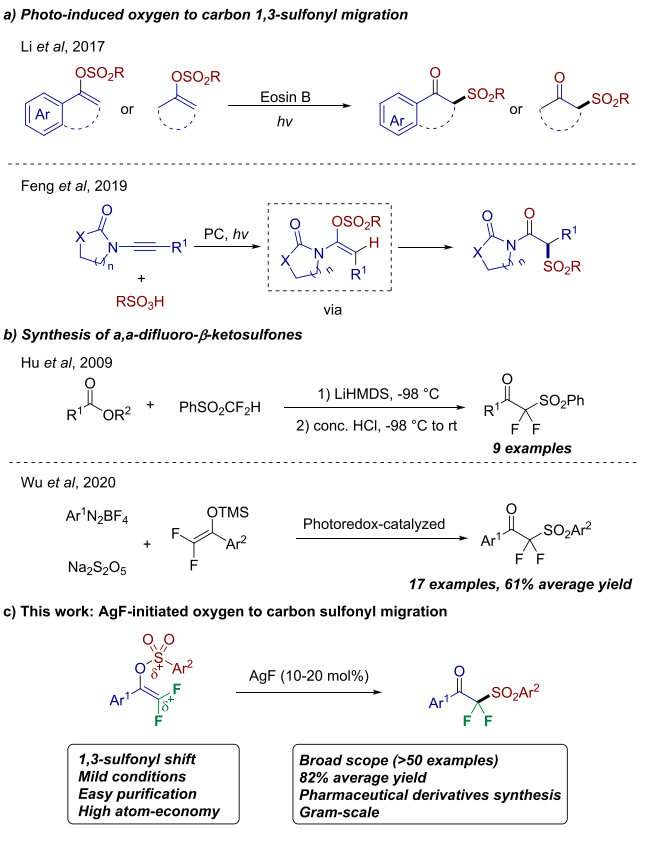


Figure 1. Oxygen to carbon 1,3-sulfonyl migration and synthesis of α, α-difluoro-β-ketosulfones.

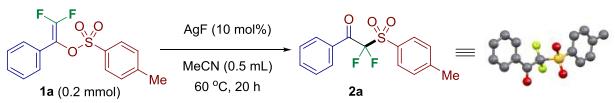
Received: October 20, 2020

difluoro-β-ketosulfones, but this method generally suffers from the monofluorinated products along with low yields of difluorinated products and limited substrate scope.[14] In 2009, Hu et al. reported nucleophilic fluoroalkylation of esters to synthesize fluorinated β-ketosulfones.[15] In 2020, Wu et al. reported a photocatalyzed three-component sulfonylation of aryldiazonium tetrafluoroborates with sodium metabisulfite and 2,2-difluoro enol silyl ethers.[16] Owing to the harsh conditions and the poor accessibility of starting materials, these approaches are confronted with limited functional group tolerance (Figure 1b).

Based on a serendipitous discovery, we found a 1,3-sulfonyl migration (from oxygen to carbon) of difluorovinyl sulfonates to α,α-difluoro-β-ketosulfones initiated by a catalytic amount of AgF (Figure 1c). Advantages of this method include high atom-economy, broad substrate scope, excellent yields, and mild reaction conditions. Notably, this method can be applied to the facile preparation of derivatives of natural products and bioactive compounds, which are challenging for the reported methods.[14−16]

Our study began by evaluating the intramolecular migration of **1a**. As for the synthesis of the starting material **1a**, there are two reported methods to achieve it. One way is initiated from commercially available benzaldehyde, treated with the trifluoromethylation of aldehyde, sulfonylation of benzyl alcohol and HF elimination under basic conditions to generate **1a**.[17] The alternative pathway to form **1a** is the palladium-catalyzed cross-coupling reaction between iodobenzene and 2,2-difluoro-1-(tributylstannyl)vinyl 4-methylbenzenesulfonate.[18] After screening with different fluoride sources, we found that the corresponding product α,α-difluoro-β-ketosulfone (**2a**) could be isolated in an excellent yield (93% yield) under the condition using AgF (10 mol %) as a reaction promotor, MeCN as solvent at 60 °C (Table 1, entry 1). The structure of **2a** was confirmed by X-ray crystallography. Using other fluoride sources such as CsF and KF resulted in lower yields, and after 20 h part of the starting material (**1a**) was recovered (entries 2 and 3). In addition, the use of LiF and CuF_2 afforded none of the desired product (entries 4 and 5). Different solvents were tested, and we found that acetone, DMF, and DMA led to slightly decreased yields (entries 7−9). Replacing MeCN with DMSO led to a significantly decreased yield of **2a** (entry 10). The reaction carried out in DCE or H_2O did not work, and the starting material (**1a**) was recovered (entries 11 and 12). Further investigation of the reaction temperature indicated that half of **1a** remained unreacted after 20 h when decreasing the temperature to 40 °C (entry 13), while increasing the temperature to 80 °C caused a slight decrease in the yield (entry 14). Control experiments indicated AgF is essential for this transformation (entry 15).

Table 1. Optimization of the Reaction Conditions[a]



entry	deviation from the standard conditions	yield of **2a**[b] (%)	recovery for **1a**[b] (%)
1	none	96 (93)[c]	nd
2	CsF instead of AgF	42	46
3	KF instead of AgF	65	29
4	LiF instead of AgF	0	94
5	CuF_2 instead of AgF	0	95
6	NMP instead of MeCN	93	nd
7	acetone instead of MeCN	94	nd
8	DMF instead of MeCN	89	nd
9	DMA instead of MeCN	90	nd
10	DMSO instead of MeCN	73	11
11	DCE instead of MeCN	0	99
12	H_2O instead of MeCN	0	97
13	40 °C instead of 60 °C	43	50
14	80 °C instead of 60 °C	91	nd
15	no AgF	0	98

[a]Reaction conditions: **1a** (62.0 mg, 0.2 mmol), AgF (2.5 mg, 10 mol %), MeCN (0.5 mL), 60 °C, 20 h. [b]Yields were determined by ^{19}F NMR analysis using benzotrifluoride as the internal standard. [c]Isolated yield in the parentheses.

After establishing the optimized reaction conditions, we turned to evaluate the substrate scope of this transformation. Various substituted sulfonyl (Ar^1 group) difluorostyrenes were transformed smoothly. As shown in Scheme 1, the difluorovinyl sulfones bearing a phenyl or an alkylbenzene group afforded the sulfonyl migration products in excellent yields (**2b−2e**). However, a lower yield was obtained for **2f** with a methyl group at the *ortho* position, which might be caused by the hindrance effect. Naphthalene and biphenyl derivatives delivered the desired products (**2g−2i**) in 80−96% yields. Notably, the halide (fluoride, chloride, bromide, and iodide) substituted substrates all led to clean formation of the corresponding products in high yields (**2j−2n**, 73−98%). Examination of electron-deficient substrates revealed that ketone and ester moieties could be tolerated (**2o−2p**). In addition, MeO- and Me_2N-substituted difluorovinyl sulfones (**2q−2s**) were obtained in 52−91% yields under the standard conditions, and the substrate utilizing dihydrobenzofuran as a substituent produced **2t** in 90% yield.

Next, we studied the influence of the substitution of Ar^2 group. Excellent yields were obtained when substrates contained alkyl groups (**2u−2w**) as well as naphthalene and biphenyl derivatives (**2x−2y**). Electron-rich substrates such as difluorovinyl sulfones bearing a MeO, EtO, PhO, or morpholine group were found to be highly effective in this protocol (**2z−2ac**). In addition, substrates (**1ad−1ae**) with an OTs or OCF_3 group were also well-tolerated. We then tested the compatibility with unprotected phenol groups and obtained **2af** in 77% yield. Interestingly, the ability to tolerate a diverse set of aryl halides (**2ag−2aj**) left enough room for subsequent manipulation. The presence of electron-poor groups also appeared to be suitable substrate in this reaction (**2ak−2ao**), although the CN group seemed less effective (**2am**). Furthermore, we turned our attention to investigate the scope of substrates with a range of heterocycles, and high yields were obtained for the derivatives containing indole, quinoline, and thiophene moieties (**2ap−2at**).

Encouraged by these results, we intended to extend this approach to small complex molecules containing natural products or druglike scaffolds. L-(−)-Menthol derivative worked efficiently, giving **2au** in 80% yield. Substrates derived from amino acids such as L-phenylalanine and D-proline could be transformed with high efficiency in this protocol (**2av−2ax**). The utility of the method was also demonstrated by a late-stage functionalization of tocopherol, fructose, and pregnenolone derivatives (**2ay−2aaa**) in good yields. These

https://dx.doi.org/10.1021/acs.orglett.0c03492
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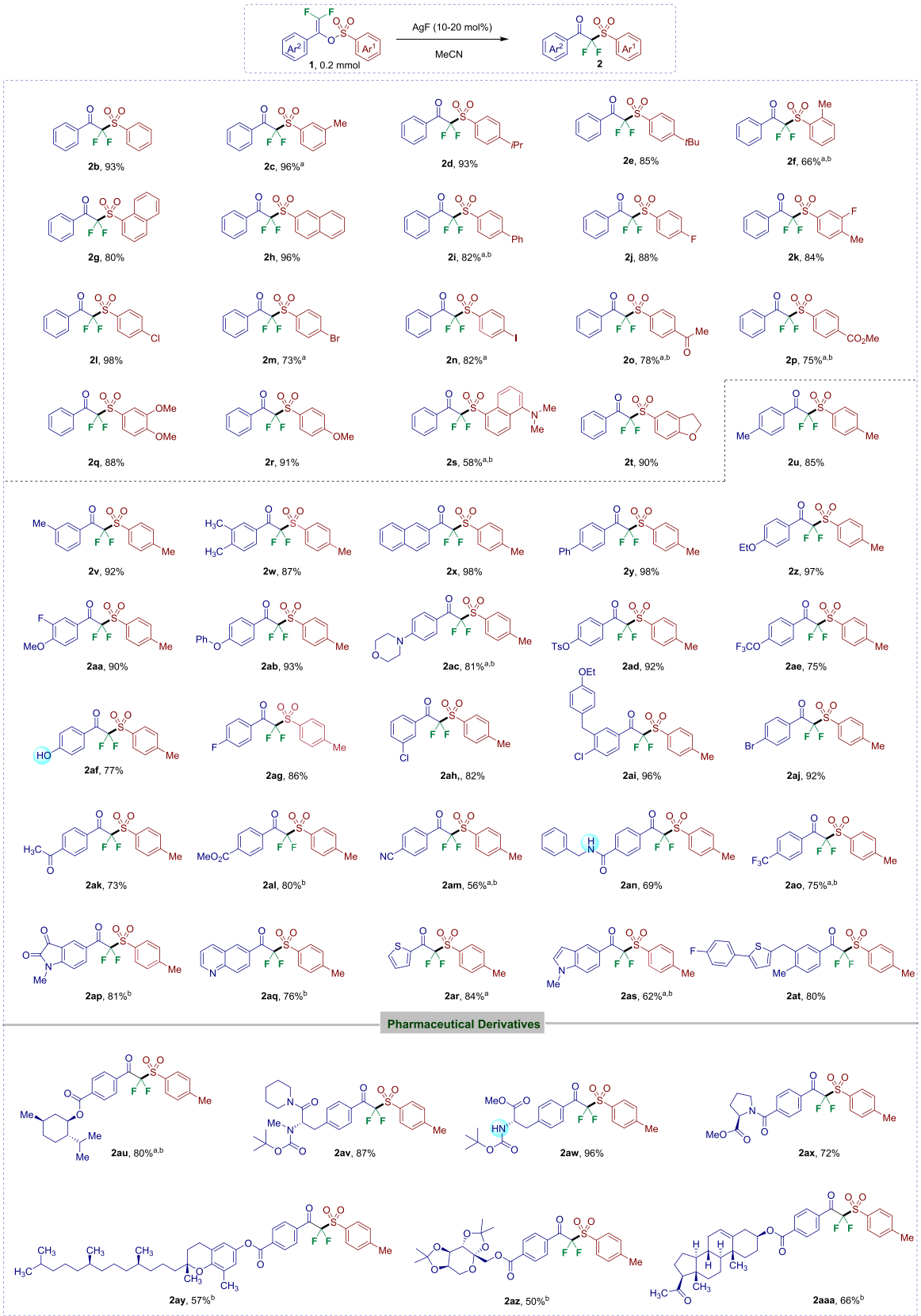
Scheme 1. Substrate Scope of α,α-Difluoro-β-ketosulfones*



*Standard conditions: difluorovinyl tosylates (0.2 mmol), AgF (2.5 mg, 10 mol %), MeCN (0.5 mL), 60 °C, 20 h. [a]80 °C instead of 60 °C. [b]AgF (20 mol %) was used.

https://dx.doi.org/10.1021/acs.orglett.0c03492
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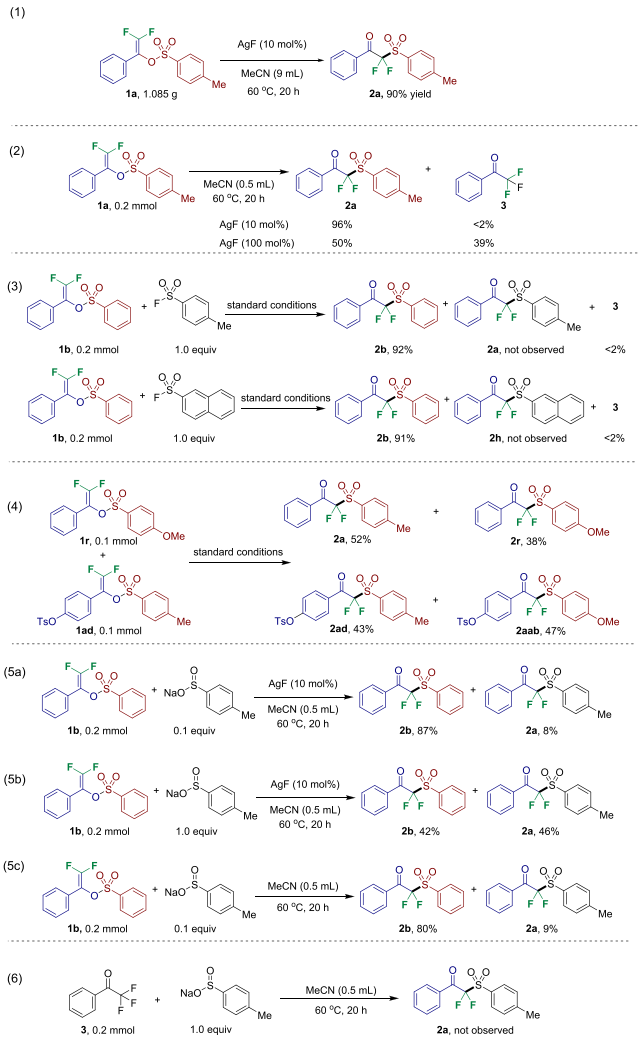
results highlight that this protocol is potential for the late-stage modification of complex molecules and provide an approach to access valuable molecules in pharmaceutical chemistry. Furthermore, the practicability of this method has also been demonstrated in a gram-scale reaction, and α,α-difluoro-β-ketosulfone (**2a**) could be obtained in 90% yield (Scheme 2-1).

Scheme 2. Gram-Scale Reaction and Preliminary Mechanistic Studies



To gain more insight about this transformation, we carried out several control experiments. First, adding a stoichiometric amount of AgF led to the yield of **2a** being reduced to 50%, and the side product trifluoro-1-phenylethanone (**3**) was isolated in 39% yield (Scheme 2-2). Second, the stoichiometric reactions with *p*-toluenesulfonyl fluoride or naphthalene-2-sulfonyl fluoride under the standard conditions only afforded trace amounts of **3** and **2b** in similar yields, while the crossover products (**2a** and **2h**) were not observed (Scheme 2-3). These results firmly rule out the transformation proceeding via the difluoroalkyl anion attacking sulfonyl group pathway.[19] Next, a crossover experiment was performed in order to confirm whether this reaction proceeded in an intermolecular or intramolecular fashion (Scheme 2-4). The experiment was conducted by applying an equivalent amount of **1r** and **1ad** to the standard conditions. It was found that four crossover products (**2a**, **2r**, **2ad**, and **2aab**) were formed in similar yields (52%, 38%, 43%, and 47%). This result provided the evidence for the migration of sulfonyl group via an intermolecular process.

Accordingly, aryl sulfinate may be produced during the reaction. Controlled experiments of **1b** with a catalytic amount of sodium *p*-toluenesulfinate under the standard conditions yielded the crossover products **2a** and **2b** in 8% and 87% yield, respectively, which strongly indicated aryl sulfinate was involved in this transformation (Scheme 2-5a). This assumption was further enhanced by the fact that **1b** could react with 1.0 equiv of sodium *p*-toluenesulfinate to produce **2a** and **2b** in 46% and 42% yields, respectively (Scheme 2-5b). Furthermore, we found that a similar result could be achieved when using a catalytic amount of sodium *p*-toluenesulfinate in the absence of AgF, indicating AgF only played a role in producing the corresponding *p*-toluenesulfinate (Scheme 2-5c). Finally, we found that the side product **3** did not react with sodium *p*-toluenesulfinate to afford the desired compound **2a** (Scheme 2-6).

On the basis of the controlled experiments above, a plausible mechanism is presented for this 1,3-sulfonyl migration. First, silver fluoride reacts with difluorovinyl sulfonates (A) to produce the side product (trifluoromethyl)acetophenone (B) and the corresponding aryl sulfinate (C).[20] Subsequently, nucleophilic attack of the formed intermediate C occurs on the highly electron-deficient carbon of *gem*-difluorostyrenes to form the desired product α,α-difluoro-β-ketosulfones (D). Meanwhile, the formed aryl sulfinate takes part in the next cycle (Figure 2).

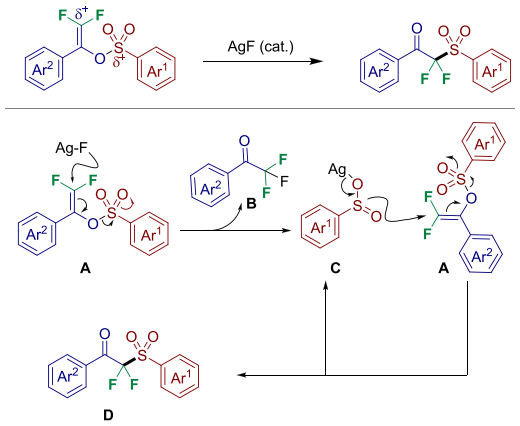


Figure 2. Proposed mechanism of the transformation.

In summary, we have discovered a 1,3-sulfonyl migration of difluorovinyl sulfonates to α,α-difluoro-β-ketosulfones initiated by catalytic amount of silver fluoride. This method features very broad functional group tolerance, high atom economy, and mild, environmentally benign reaction conditions. A series of α,α-difluoro-β-ketosulfones could be produced in excellent yields. Finally, mechanistic investigations indicated that this intramolecular migration proceeded in an intermolecular manner and the corresponding sulfinates are possible intermediates.

https://dx.doi.org/10.1021/acs.orglett.0c03492
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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03492.

Experimental procedures along with characterization data and copies of ^{1}H, ^{13}C and ^{19}F NMR spectra (PDF)

Accession Codes

CCDC 2022858 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work is supported by the National Natural Science Foundation (21901168), "1000-Youth Talents Plan", and Sichuan University.

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(20) The reaction was quenched by adding concd HCl, and the corresponding sulfinic acid was detected by LC−MS. For the experimental details, see the Supporting Information.

https://dx.doi.org/10.1021/acs.orglett.0c03492
Org. Lett. XXXX, XXX, XXX−XXX