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Air- and Light-Stable *S*-(Difluoromethyl)sulfonium Salts: *C*-Selective Electrophilic Difluoromethylation of *β*-Ketoesters and Malonates

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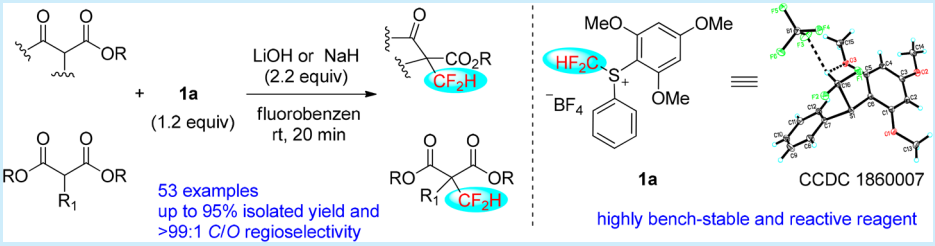
Supporting Information



ABSTRACT: Air- and light-stable electrophilic difluoromethylating reagents, *S*-(difluoromethyl)-*S*-phenyl-*S*-(2,4,6-trialkoxyphenyl) sulfonium salts were successfully developed, and the introduction of intramolecular hydrogen bonds plays a crucial role for the stabilities and reactivities of these reagents. *C*-selective difluoromethylation of a broad range of *β*-ketoesters and malonates proceeded smoothly under mild reaction conditions to give good to excellent yields with excellent C/O regioselectivities.

The difluoromethyl group (CF_2H) is a key structural motif in pharmaceuticals, agrochemicals, and materials.[1] Therefore, the introduction of a CF_2H group into common organic molecules represents a significant synthetic goal. Among all existing strategies for the synthesis of difluoromethylated compounds, the electrophilic approach is one of the most powerful tools for incorporation of the CF_2H unit into the electron-rich sites of organic molecules. In past decades, many difluorocarbene precursors have been developed.[2,3c,5b,c] However, few direct electrophilic difluoromethylating reagents were recorded (see Figure 1),[3] although several functionalized

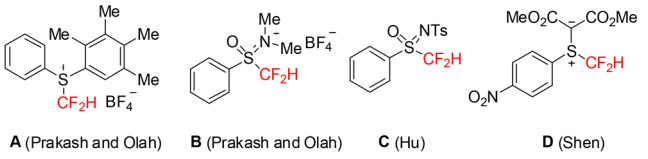


Figure 1. Electrophilic difluoromethylating reagents.

electrohilic difluoromethylating reagents were reported.[4−8] Prakash and co-workers first disclosed that an *S*-difluoromethyl-*S*-phenyl-*S*-(2,3,4,5-tetramethylphenyl) sulfonium reagent (see **A** in Figure 1) is effective for transferring a CF_2H group into various *N*-, *S*-, and *P*-nucleophiles.[3a] However, **A** is a very unstable semisolid and is not suitable for the difluoromethylation of carbon nucleophiles and phenols. Later on, the same group published difluoromethylation of *N*-, *S*-, and *P*-nucleophiles with the Johnson-type difluoromethylating reagent (**B** in Figure 1),[3b] which was formed in situ, because of its rapid decomposition. Xiao et al. reported a modified *S*-(difluoromethyl)diarylsulfonium salt for *O*-difluoromethylation of 1,3-diketones.[9] Recently, Akita has also demonstrated another modified *S*-(difluoromethyl)-diarylsulfonium salt for the amino-difluoromethylation of aromatic alkenes in moderate yields via a radical pathway by using visible-light photoredox catalysis.[10] Hu and co-workers synthesized the *α*-difluoromethyl sulfoximine (**C** in Figure 1) as a difluorocarbene precursor for difluoromethylation of *S*- and *N*-nucleophiles,[3c] along with limited scope of *Csp*-centered nucleophiles. In 2016, the Shen group reported a difluoromethyl-(4-nitrophenyl)-bis(carbomethoxy) methylide sulfonium ylide (**D** in Figure 1) as a direct electrophilic difluoromethylating reagent for the difluoromethylation of alcohols,[3d] whereas 2.0 equiv of alcohols was required.

In sharp contrast to the extensively investigated electrophilic trifluoromethylation reactions, the electrophilic difluoromethylation is still quite underdeveloped, possibly because of the lack of suitable electrophilic difluoromethylating reagents for transferring a CF_2H group to a wide variety of nucleophiles, particularly *C*-nucleophiles. For example, compared to the

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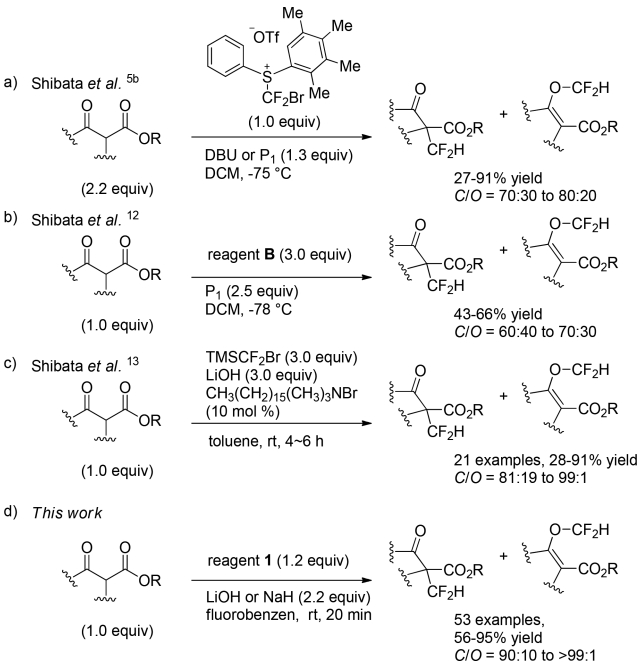
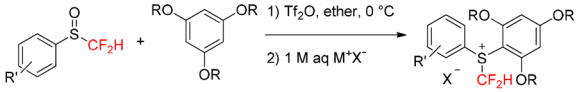
exclusively *C*-regioselective trifluoromethylation of *β*-ketoesters,[11] difluoromethylation of *β*-ketoesters normally gave poor to moderate *C*/*O* regioselectivities, as reported by the Shibata group (see Schemes 1a and 1b).[5b,12] During preparation of this manuscript, the same group described another protocol affording an enhanced *C*/*O* regioselectivity (see Scheme 1c).[13] Therefore, the development of more-stable, more-reactive, and more-versatile electrophilic difluoromethylating reagents is still highly in demand. Herein, we disclose new difluoromethylating reagents, namely *S*-difluoromethyl-*S*-phenyl-*S*-(2,4,6-trialkoxyphenyl) sulfonium salts **1**. They have proven to be very stable and are capable of transferring a CF_2H group into the tertiary carbon center of *β*-ketoesters and malonates in good to excellent yields with excellent *C*/*O* regioselectivities (see Scheme 1d).

Scheme 1. Regioselective Electrophilic Difluoromethylation of *β*-Ketoesters

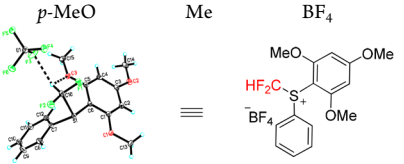


The investigation commenced with the design and synthesis of new electrophilic difluoromethylating reagents. At present, the existing electrophilic difluoromethylating reagents have many drawbacks, such as instability, unsatisfactory reactivity, and relatively hard-acid character, leading to limited substrate scope. The principal task is to solve the stability problem of the reagents, which probably results from the acidity and high electrophilicity of the $^+CF_2H$ moiety. Apart from introducing electron-donating groups, we thought that we could modulate its acidity and electropositivity via an intramolecular hydrogen bond at the $^+CF_2H$ unit. With this in mind, reagents **1** containing a 2,4,6-trialkoxyphenyl group were designed, and readily synthesized from difluoromethylsulfoxides and 1,3,5-trialkoxybenzenes in good yields (66%−86%) as a white crystalline powder in up to 20-g scale (see Table 1). The nonclassical intramolecular hydrogen bond between the H atom in the CF_2H unit and the O atom in the *ortho*-methoxy substituent of the aryl moiety were confirmed by a single-crystal X-ray crystallographic analysis. Compound **1a** was found to be very stable, and no decomposition was observed even after keeping it on the bench for six months at ambient temperature.

Table 1. Design and Synthesis of Bench-Stable Electrophilic Difluoromethylating Reagents (1)[a]



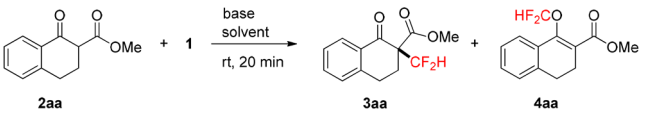
1	R	R′	X	yield (%)
1a	H	Me	BF_4	86
1b	H	Et	BF_4	66
1c	H	Me	PF_6	82
1d[b]	*p*-Br	Me	BF_4	55
1e	*p*-MeO	Me	BF_4	82



[a]For details, see the Supporting Information. [b]Proceeded at −20 °C.

With these bench-stable reagents in hand, their reactivities were initially evaluated by difluoromethylation of *β*-ketoesters (see Table 2), and methyl tetralone carboxylate **2aa** was employed as a model substrate. The reaction proceeded smoothly at room temperature in THF by using NaH as a base. Interestingly, the *C*−CF_2H product **3aa** was predominantly

Table 2. Survey of Reaction Conditions[a]



entry	1	base (equiv)	solvent	yield (%)	3aa/4aa ratio
1	**1a**	NaH (1.2)	THF	56	95:5
2	**1a**	Et_3N (1.2)	THF	NR	
3	**1a**	DBU (1.2)	THF	NR	
4	**1a**	Cs_2CO_3 (1.2)	THF	28	88:12
5	**1a**	KOH (1.2)	THF	26	80:20
6	**1a**	LiOH (1.2)	THF	54	95:5
7	**1b**	NaH (1.2)	THF	40	85:15
8	**1c**	NaH (1.2)	THF	45	90:10
9	**1d**	NaH (1.2)	THF	43	86:14
10	**1e**	NaH (1.2)	THF	46	87:13
11	**1a**	NaH (1.5)	THF	59	95:5
12	**1a**	NaH (2.2)	THF	67	94:6
13[b]	**1a**	NaH (2.2)	THF	68	94:6
14	**1a**	NaH (2.2)	CH_3CN	72	94:6
15	**1a**	NaH (2.2)	toluene	88	94:6
16	**1a**	NaH (2.2)	*p*-xylene	74	95:5
17	**1a**	NaH (2.2)	chlorobenzene	83	97:3
18	**1a**	NaH (2.2)	fluorobenzene	93(86)[c]	97:3
19	**1a**	LiOH (2.2)	fluorobenzene	94(87)[c]	97:3

[a]Reaction conditions (unless otherwise specified): **2aa** (0.1 mmol), base, **1a** (1.2 mmol, 1.2 equiv), fluorobenzene (1.0 mL), rt, 20 min. Yields and the ratio of **3aa**/**4aa** were determined by ^{19}F NMR spectroscopy with *p*-chlorofluorobenzene as an internal standard. [b]The reaction was allowed to proceed at 0 °C. [c]Yields of isolated products are given in parentheses.

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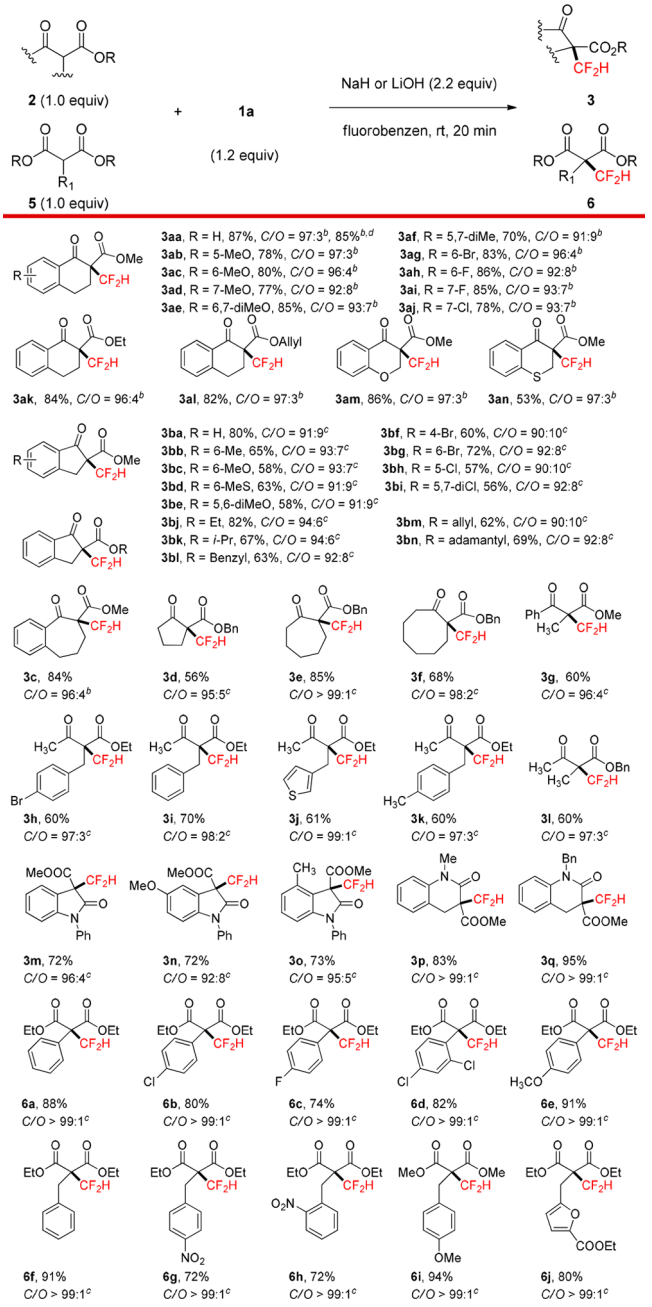
obtained in 56% yield with only a trace of *O*-CF_2H product **4aa**, as can be substantiated by ^{19}F NMR spectral analysis (entry 1 in Table 2). Encouraged by this result, we further examined a variety of common bases, including Et_3N, DBU, Cs_2CO_3, and KOH. The organic bases were ineffective for this reaction (entries 2 and 3 in Table 2), while KOH and Cs_2CO_3 gave lower yields and poor *C*/*O* regioselectivities (entries 4 and 5 in Table 2). LiOH was also identified as a potentially appropriate base (entry 6 in Table 2). The screening of reagents **1b**−**1e** did not give better results (entries 7−10 in Table 2). The yields were slightly improved to 59% and 67% with a similar level of *C*/*O* regioselectivity when 1.5 and 2.2 equiv of NaH were used, respectively (see entries 11 and 12 in Table 2). Decreasing the reaction temperature to 0 °C did not obviously improve the yield and *C*/*O* regioselectivity (see entry 13 in Table 2). The yield was dramatically increased to 88% without any loss of *C*/*O* regioselectivity, using toluene as a solvent (entry 15 in Table 2). Screening of other arene solvents indicated that fluorobenzene was the best choice, affording 93% yield with a *C*/*O* ratio of 97:3 (entry 18 in Table 2). The use of LiOH instead of NaH gave a similar result (94%, 97:3 *C*/*O* regioselectivity) (see entry 19 in Table 2).

Under the optimized reaction conditions (entries 18 and 19 in Table 2), the scope of *β*-ketoesters **2** (Scheme 2) was explored. A broad range of tetralone and indanone carboxylates were smoothly transferred into the corresponding *C*-selective CF_2H products **3aa**−**3an**, **3ba**−**3bn** containing a quaternary carbon center in good to excellent yields (up to 87%). Notably, this reaction was not sensitive to the electronic nature and position of the substituents on the phenyl ring of the methyl carboxylates (**3aa**−**3aj**, **3ba**−**3bi**). Moreover, a wide variety of alkyl indanone and tetralone carboxylates also readily underwent a reaction to furnish **3bj**−**3bn** and **3ak** and **3al** in high yields (up to 84%) with high *C*/*O* regioselectivies (up to 97:3). The heterocycloketoesters **2am** and **2an** were also compatible, providing **3am** and **3an** in 86% and 53% yields, respectively, with a *C*/*O* regioselectivity of 97:3. *β*-Ketoesters containing cycloheptanone and cyclooctanone moieties proved to be suitable in this reaction, offering **3c**, **3e**, and **3f** in 84%, 85%, and 68% yields, respectively, with high *C*/*O* regioselectivities (up to >99:1). Benzyl 2-oxocyclopentanecarboxylate **2d** was also converted to **3d** in 56% yield with a *C*/*O* regioselectivity of 95:5. Remarkably, the usually less-reactive acyclic *β*-ketoesters **2g**−**2l** were also tolerated, producing *C*-CF_2H products **3g**−**3l** in good yields (60%−70%) without any influence on the *C*/*O*-regioselectivities. The current process was readily scalable, as demonstrated by the gram-scale synthesis of **3aa** (85% yield) under the standard reaction conditions.

In order to highlight the synthetic utility of this process, some pharmaceutically important heterocyclic compounds **3p** and **3q** were delivered in 83% and 95% yields, respectively, with distinguished *C*/*O* regioselectivities (>99:1), and **3m**, **3n** and **3o** were obtained in yields of 72%, 72%, and 73%, respectively, with high *C*/*O* regioselectivities (up to 96:4). Further applications of **1a** in a direct *C*-difluoromethylation for malonates were also evaluated under the standard conditions. A variety of monoaryl and arylalkyl-substituted malonates **5a**−**5j** were successfully transferred to the corresponding *C*-CF_2H products **6a**−**6j** bearing a quaternary carbon center in high to excellent yields (72%−94%). Notably, malonates exhibited much more predominant *C*/*O* regioselectivities than *β*-ketoesters, and all selected cases showed *C*/*O* regioselectivities of >99:1.

Scheme 2. Electrophilic *C*-Selective Difluoromethylation of *β*-Ketoesters and Malonates[a]



[a]Reaction conditions (unless otherwise specified): 2 or 5 (0.2 mmol, 1.0 equiv), base (2.2 mmol, 2.2 equiv), 1a (1.2 mmol, 1.2 equiv), fluorobenzene (2.0 mL), rt, 20 min. Yields are for the isolated *C*-selective products 3 or 6, and *C*/*O*-regioisomeric ratio was determined by ^{19}F NMR spectroscopy. [b]LiOH was used as a base. [c]NaH was used as a base. [d]Gram-scale synthesis of **3aa**. Me = methyl, Et = ethyl, *i*-Pr = *i*-propyl, Bn = benzyl, Ph = phenyl.

Although the reason for such excellent *C*/*O* regioselectivity is still unclear in the difluoromethyaltion of *β*-ketoesters and malonates, the intramolecular hydrogen bond and electron-donating effect of the 2,4,6-trialkoxyphenyl group in reagents **1** should play a key role in decreasing the electrophilicity of the sulfonium salts, which may render reagent **1** to become a soft

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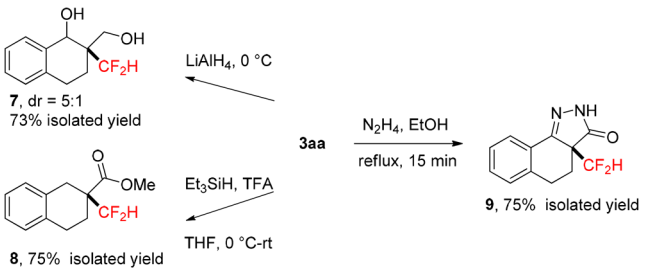
electrophilic difluoromethylating reagent, therefore orientating its reactivity toward *C*-nucleophiles to achieve a high *C*/*O* regioselectivity. Moreover, the substituents in the aryl sulfoxide can also adjust the reactivity of the final reagents.

In addition, the asymmetric difluoromethylation of *β*-ketoesters was also surveyed. No enantioselectivity and low yields were obtained under the same and modified conditions as that of asymmetric trifluoromethylation by Gade et al. (with Cu ^{II}/ligands; for details, see Table S2 in the Supporting Information (SI)). Furthermore, cinchona alkaloids were employed for this asymmetric transformation. After exhaustive optimization, no satisfactory enantiomeric excess (ee) was achieved (up to 26% ee; for details, see Table S3 in the SI). Therefore, the asymmetric difluoromethylation of *β*-ketoesters remains challenging, and further investigation is required.

The synthetic application of the C-CF_2H product **3aa** was further demonstrated (see Scheme 3). Thus, compounds **7** and

Scheme 3. Synthetic Utilization of 3aa

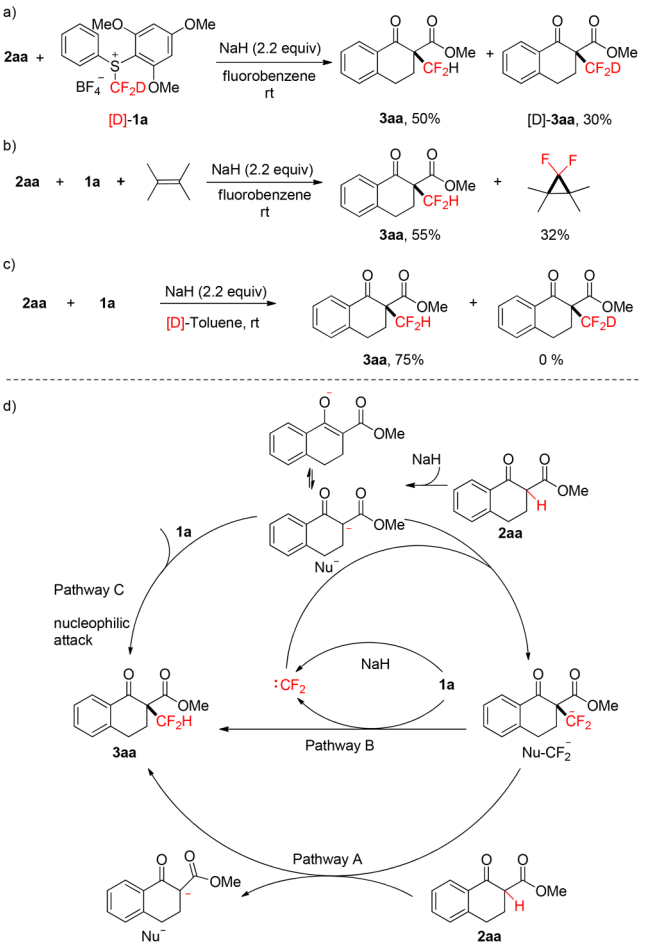


8 were obtained via $LiAlH_4$ and Et_3SiH/TFA reduction in 73% and 75% yields, respectively. Most importantly, the highly efficient cyclization of **3aa** and hydrazine offered fused-heterocyclic molecule **9** in 75% yield, which is of potential pharmaceutical interest.[14]

Mechanistically, both direct nucleophilic substitution and difluorocarbene pathways are possible during the difluoromethylation of **2** with **1**. To gain insight into the reaction mechanism, some control experiments were performed (see Scheme 4). The use of a deuterium-labeled reagent [D]-**1a** gave a higher yield of nondeuterated product **3aa** than deuterated product [D]-**3aa** (Scheme 4a). In addition, when tetramethylethylene was injected into the reaction system of **2aa** and **1a** (see Scheme 4b), difluorocarbene intermediate was trapped to form 3,3-difluoro-1,1,2,2,-tetramethylcyclopropane in 30% yield. Furthermore, no deuterated product was detected when deuterated toluene was used as solvent (see Scheme 4c). These results clearly suggest that the difluorocarbene pathway of the capturing proton from substrate **2** to produce nondeuterated product is predominant (see Pathway A in Scheme 4d). The proposed mechanism starts with the deprotonation of **2** by a base to generate a nucleophile (Nu^-), which combines with CF_2 to afford an anion ($Nu\text{-}CF_2^-$). A difluorocarbene intermediate can be formed in situ from **1** and a base, or $Nu\text{-}CF_2^-$ (see pathway B in Scheme 4d). Finally, the anion $Nu\text{-}CF_2^-$ abstracts a proton from substrate **2**, along with the production of a new Nu^- (see pathway A in Scheme 4d), or captures a proton from reagent **1** (see pathway B in Scheme 4d) to give the target compound. However, the direct nucleophilic attack pathway could not be completely ruled out (see pathway C in Scheme 4d).

In conclusion, we have successfully obtained bench-stable and easy-to-handle electrophilic difluoromethylating reagents

Scheme 4. Control Experiments and Plausible Reaction Mechanism for the Difluoromethylation of *β*-Ketoesters by 1a



1. An intramolecular hydrogen bond interaction and electronic effect are both essential in the design of **1**. When **1** were allowed to react with a wide variety of *β*-ketoesters and malonates, C-CF_2H products bearing quaternary carbon centers were predominantly accessed in good to excellent yields (up to 95%, and a *C*/*O* ratio of >99:1) under mild reaction conditions. Control experiments revealed that this difluoromethylation reaction mainly involves a difluorocarbene intermediate. Further investigations of reagents **1** toward other types of nucleophiles are underway in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03067.

Detailed experimental procedures, characterization data, ^1H, ^{13}C, ^{19}F NMR spectra, and HRMS (PDF)

Accession Codes

CCDC 1860007 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.

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