Carbon-Selective Difluoromethylation of Soft Carbon Nucleophiles with Difluoromethylated Sulfonium Ylide

Jiansheng Zhu,[a] Hanliang Zheng,[b] Xiao-Song Xue,*[,b] Yisa Xiao,[a] Yafei Liu[a] and Qilong Shen*[,a]

ABSTRACT A highly carbon-selective difluoromethylation of soft carbon nucleophiles including β-ketoesters, malonates, oxindoles, benzofuranones and ketene silyl acetals with a difluoromethylated sulfonium ylide under mild conditions was described. Mechanistic studies suggest that these difluoromethylating reactions proceed via a difluorocarbene pathway.

KEYWORDS fluorine, electrophilic substitution, ylides, regioselectivity

Introduction

Difluoromethyl group (-CF_2H), an analog of well-recognized trifluoromethyl group (-CF_3), has attracted considerable recent attention from both academia and the pharmaceutical industry.[1] The difluoromethyl group has well-known common beneficial properties of the fluoroalkyl moiety such as high lipophilicity that may improve the molecule's cell membrane permeability, and strong electron-withdrawing ability that may increase the drug's metabolic stability.[2] In addition, because the C-H bond in the difluoromethyl groups is slightly acidic, the difluoromethyl group is generally considered as a surrogate of a hydroxyl or a thiol group,[3] that may improve the drug molecule's enzyme binging selectivity. Thus, incorporation of the difluoromethyl group into leading drug candidates has become an indispensable strategy for new drug discovery. Consequently, over the past decade, significant progress has been achieved in the development of efficient method for the introduction of the difluoromethyl group into small molecules.[4]

One straightforward and attractive route for the preparation of difluoromethylated compounds is the direct nucleophilic attack of a nucleophile with an *in situ* generated difluorocarbene species under mild conditions.[5] In this respect, a variety of different difluorocarbene precursors[6] have been invented and their reactions with different nucleophiles have been extensively studied. For example, reaction of difluorocarbene with a heteroatom-centered nucleophile such as phenol,[7] alcohol,[8] thiol[6d,7i-j,8b,9] or amine[10] occurred quite efficiently to afford the corresponding difluoromethyl ether, thioether or amine in good yields. Alternatively, difluorocarbene may react with an alkene or alkyne to give *gem*- difluorocyclopropane or *gem*-difluorocyclopropene.[6e-f,8b,11] Furthermore, hard carbon nucleophiles such as alkyl zinc reagents also reacted efficiently with difluorocarbene, as reported by Dilman and coworkers.[12] In these reactions, the *in situ* generated difluorocarbene reacted with nucleophile to form an alkyl-substituted difluoromethyl anion, which was then trapped by different electrophiles to give difluoromethylene compounds in high yields.

Despite of the tremendous success in the reactions of difluorocarbene with different nucleophiles, the reactions of difluorocarbene with soft carbon nucleophiles such as β-ketoesters were problematic. For example, Shibata and coworkers reported that reactions of several β-ketoesters with *S*-(bromodifluoromethyl)diarylsulfonium salts **1** in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave a mixture of C- and O-difluoromethylated products with a ratio of 2.3:1-7.3:1 in moderate yields. In addition, a carbon brominated side product which was difficult to separate was also generated.[13] Likewise, when *N*,*N*-dimethyl-*S*-difluoromethyl-*S*-phenylsulfonximinium tetrafluoroborate **2** was used under the similar conditions, the C- and O-difluoromethylated products were formed with a ratio of <2:1.[14] Magnier and coworkers also reported that β-ketoester derivated from indanone reacted with *N*-tosyl-*S*-difluoro-methyl-*S*-phenylsulfoximine **3** or *N*-triflyl-*S*-difluoro-methyl-*S*-phenylsulfoximine **4** using DBU as a base to give, again, a mixture of C- and O-difluoromethylated products with a ratio of 1.3:1 in moderate yields (Figure 1).[15] In these reactions, a mechanism involved a nucleophilic attack of the enolate on the *in situ* formed difluorocarene was proposed. Nevertheless, the low regioselectivity of the reactions makes them less applicable. Thus, clearly, development of an efficient method for the highly carbon-selective difluoromethylation of soft carbon nucleophiles such as β-ketoesters is highly desirable.

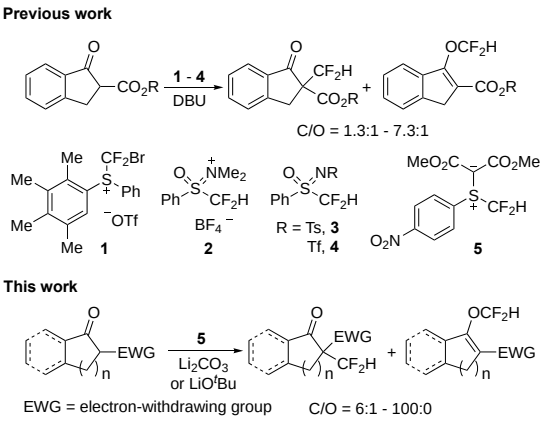

Figure 1 Reactions of β-ketoesters with different difluorocarbene reagents.

Herein, we reported that when Li_2CO_3 or LiO^tBu was used as a base, reactions of a variety of soft carbon nucleophiles including β-ketoesters, malonates, oxindoles, benzofuranones, and ketene silyl acetals with a difluoromethylated sulfonium ylide **5**, which was developed previously in our group as an electrophilic difluoromethylating reagent that can react with alcohols in the presence of a Lewis acid or BrØnsted acid,[16] occurred to give the difluoromethylated products with excellent C/O regioselectivity in high yields (Figure 1). Mechanistic studies suggest that these difluoromethylating reactions proceed via a difluorocarbene pathway.

Results and Discussion

Initially, we chose the reaction of β-ketoester methyl

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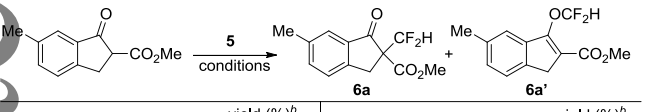
6-methul-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate with reagent **5** as a model reaction to optimize the reaction conditions. To our surprise, when an organic base such as DBU, Et_3N or 4-dimethylaminopyridine (DMAP) was used as the base,[17] the formation of the difluoromethylated compounds were observed in less than 10% yields (Table 1, entries 1-3). Instead, the *N*-difluoromethylated side product of the base was generated in high yields. In contrast, when an inorganic base such as Na_2CO_3, K_2CO_3, Cs_2CO_3, KOAc, NaOAc, $NaHCO_3$, K_3PO_4, NaOH, the reactions occurred smoothly to give the C-difluoromethylated product **6a** in moderate 20-44% yields (Table 1, entries 4-11). To our delight, the yield of **6a** was improved significantly to 76% when Li_2CO_3 was use as the base (Table 1, entry 12). Interestingly, in these cases, the O-difluoromethylated product **6a'** was generated in less than 2%, as determined by ^{19}F NMR spectroscopy of the reaction mixture. Next, we studied the effect of the solvents on the yields and the regioselectivity of the reaction. It was found that the polarity of the solvent plays a decisive role for the high yielding formation of compound **6**. Reactions using Li_2CO_3 as the base in less polar solvents such as toluene, CH_2Cl_2 did not take place at all and the same reaction in THF or CH_3CN occurred in less than 10% yields, while reactions in polar aprotic solvents such as dimethylacetamide (DMAc) or *N*-methyl-2-pyrrolidone (NMP) occurred in high yields (Table 1, entries 13-18). We then further investigated the effect of other lithium bases. As shown in entries 19-22, the yields were slightly lower when LiOH•H_2O, LiOH, LiOAc or LiOMe was used as the base than that using Li_2CO_3 as the base. Finally, the amount of reagent **5** could be further decrease to 1.3 equivalents without erosion of the yield (Table 1, entries 23-24). Again, the formation of the O-difluoromethylated side product **6a'** in these cases was less than 2%.

Table 1 Optimization of the conditions for the reaction of β-ketoester with reagent **5** in the presence of different bases.[a]

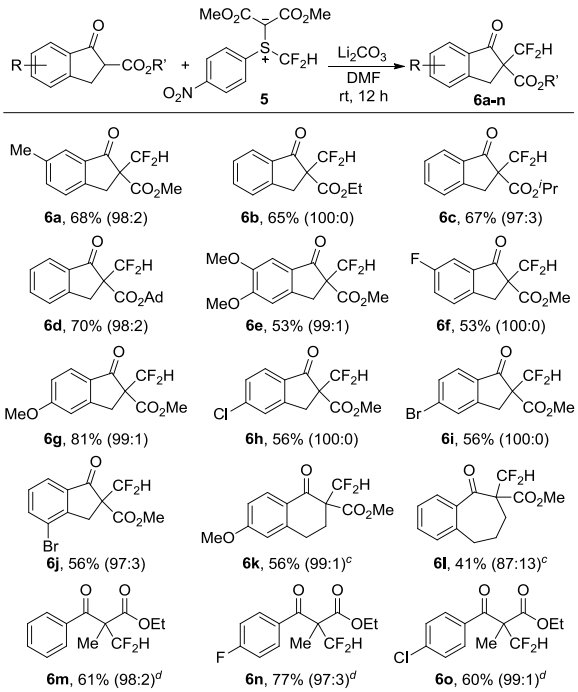


entry	base	solvent	yield (%)[b] 6a	6a'	entry	base	solvent	yield (%)[b] 6a	6a'
1	DBU	DMF	8	<2	13	Li_2CO_3	toluene	-	<2
2	Et_3N	DMF	-	<2	14	Li_2CO_3	CH_2Cl_2	-	<2
3	DMAP	DMF	-	<2	15	Li_2CO_3	THF	8	<2
4	Na_2CO_3	DMF	44	<2	16	Li_2CO_3	MeCN	10	<2
5	K_2CO_3	DMF	34	<2	17	Li_2CO_3	DMAc	78	<2
6	Cs_2CO_3	DMF	33	<2	18	Li_2CO_3	NMP	68	<2
7	KOAc	DMF	17	<2	19	LiOH•H_2O	DMF	58	<2
8	NaOAc	DMF	20	<2	20	LiOH	DMF	67	<2
9	$NaHCO_3$	DMF	23	<2	21	LiOAc	DMF	51	<2
10	K_3PO_4	DMF	28	<2	22	LiOMe	DMF	68	<2
11	NaOH	DMF	20	<2	23	Li_2CO_3	DMF	74[c]	<2
12	Li_2CO_3	DMF	76	<2	**24**	**Li_2CO_3**	**DMF**	**76[d]**	**<2**

[a] Reaction conditions: β-ketoester (0.1 mmol), reagent **5** (0.15 mmol), base (0.2 mmol) in solvent (0.5 mL) at room temperature for 12 h; [b] Yields were determined by ^{19}F NMR spectroscopy with 1-fluoronaphthalene as the internal standard; [c] 0.1 mmol of reagent **5** was used; [d] 0.13 mmol of reagent **5** was used.

Having the suitable conditions for the highly carbon-selective difluoromethylation of β-ketoesters identified, we next explored the generality of the difluoromethylation protocol. As summarized in Scheme 1, a variety of β-ketoesters were difluoromethylated in moderate to high yields with high C/O regioselectivity. In general, the substituents on the ester group have negligible effect on the yields and the C/O selectivity of the reactions. For example, reaction of ethyl, isopropyl or adamantyl ester of β-ketoester derived from indanone with reagent **5** occurred to full conversion to give **6b-d** in 65%, 67% and 70%, respectively, with excellent C/O selectivity (Scheme 1, **6b**-**d**). Likewise, β-ketoesters with both electron-donating or electron-withdrawing substituted groups on the arene moiety did not affect the yields or the selectivtivity of the reactions (Scheme 1, **6e**-**j**). Reaction of β-ketoesters derived from tetralone was also found to be good substrate for difluoromethylation and furnished the product **6k** in 56% yields and excellent C/O regioselectivity, while the regioselectivity (87:13) was decreased for the reaction of β-ketoester derived from 1-benzosuberone with reagent **5** under the standard conditions (Scheme 1, **6k**-**l**). Interestingly, linear β-ketoesters also reacted with reagent **5** to give the corresponding difluoromethylated products **6m**-**o** in high yields with high C/O regioselectivities (Scheme 1, **6m**-**o**).

Scheme 1 Scope for the reactions of reagent 5 with β-ketoesters.[a,b]

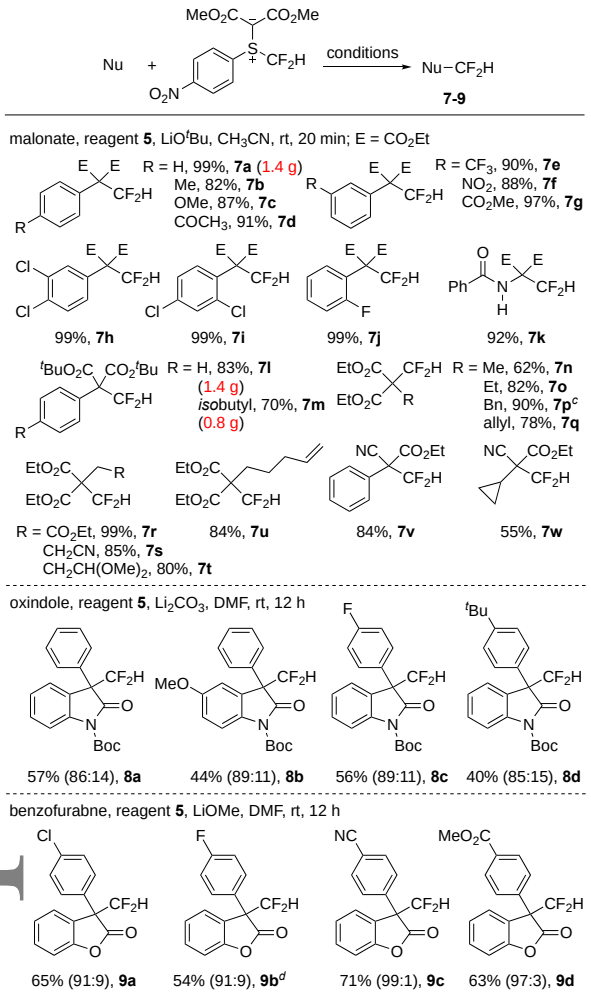


[a] Reaction conditions: β-ketoester (0.5 mmol), reagent **5** (0.65 mmol), Li_2CO_3 (1.0 mmol) in DMF (2.5 mL) at room temperature for 12 h; [b] Isolated yields. The C/O ratio was shown in parenthesis as determined by ^{19}F NMR spectroscopy of the reaction crude with 1-fluoronaphthalene as the internal standard; [c] LiOH was used instead of Li_2CO_3; [d] LiO^tBu was used as the base at -40 °C for 1.0 h.

Encouraged by excellent C/O difluoromethylation selectivity for the reactions of β-ketoesters with reagent **5**, we next tried to extend this difluoromethylation protocol to other soft carbon nucleophiles such as malonates, oxindoles and benzofuranones. As summaried in Scheme 2, a variety of malonate derivatives were difluoromethylated in moderate to high yields when LiO^tBu was used as the base. In general, only the C-difluoromethylated products were observed, while the O-difluoromethylated products were not detected by ^{19}F NMR spectroscopy of the reaction mixture. Both 2-aryl or 2-alkyl-substituted malonates reacted with reagent **5** to generate the corresponding difluoromethylated malonates in high yields. For example, reactions of diethyl 2-(3,4-dichlorophenyl)malonate and triethyl ethane-1,1,2-tricarboxylate with reagent **5** occurred to full conversion to give compounds **7i** and **7r** in quantitative yield, respectively (Scheme 2, **7i** and **7r**). In addition, electron-donating or electron withdrawing substituted groups on the arene moiety of diethyl 2-arylmalonates did not affect the yields of the reactions (Scheme 2, **7a**-**j**). Likewise, the substituted group of the ester moiety of the malonate did not affect the yields of the reaction as well. For example, di-*tert*-butyl-2-phenylmalonate reacted with regent **5** to give the corresponding product **7l** in 83% yields. Furthermore, ethyl cyanozcylate also reacted efficiently (Scheme 2, **7v**-**w**). Besides, reactions of oxindoles and

benzofuranones with reagent **5** occurred in good yields with good to excellent C/O regioselectivities (85:15-99:1) (Scheme 2, **8a**-**d**, **9a**-**d**). Because of the mild conditions, common functional groups such as chloride (**7h**-**i**, **9a**), fluoride (**7j**, **8c**, **9b**), nitro (**7f**), cyano (**7s**, **9c**), enolizable ketone (**7d**), protected aldehyde (**7t**), and amide (**7k**) were compatible. Importantly, the reaction conducted at gram-scale worked equally well (Scheme 2, **7a** and **7l**-**m**).

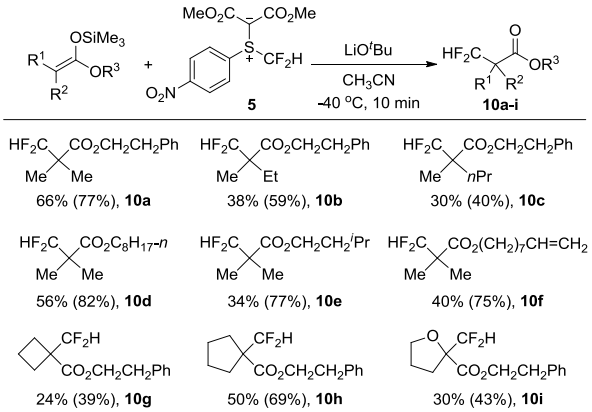
Scheme 2 Scope for the reactions of reagent 5 with malonates, oxindoles and benzofuranones.[a,b]



[a] Reaction conditions as indicated in the table; [b] Isolated yields. The C/O ratio was shown in parenthesis as determined by ^{19}F NMR spectroscopy of the reaction crude with 1-fluoronaphthalene as the internal standard; [c] DMF was used as the solvent; [d] LiO^{t}Bu was used as the base.

Finally, it was found that ketene silyl acetals reacted efficiently with reagent **5** to give the C-difluoromethylated products in good yields when the reactions were coducted in MeCN at -40 ^{o}C for 10 min using LiO^{t}Bu as the base (see Supporting Information for details).[18-20] The formation of the O-difluoromethylated products were not detected. As shown in Scheme 3, reactions of ketene silyl acetals bearing C-C double bond, four and five-membered rings with reagent **5** occurred smoothly gave the corresponding difluoromethylated products in moderate yields.

Scheme 3 Scope for the reactions of reagent **5** with ketene silyl acetals.[a,b]



[a] Reaction conditions: ketene silyl acetal (1.0 mmol), reagent **5** (1.5 mmol), LiO^{t}Bu (2.0 mmol) in CH_3CN (5.0 mL) at -40 ^{o}C for 10 min; [b] Isolated yields. The yields determined by ^{19}F NMR spectroscopy of the reaction mixture with 1-fluoronaphthalene as the internal standard were shown in the parenthesis.

Mechanistically, the carbon-selective α-difluoromethylation of β-ketoester might proceed via three different pathways, as shown in Figure 2. 1) A single-electron transfer (SET) process may take place between the enolate and reagent **5**, followed by the cleavage of S-CF_2H bond to generate a difluoromethyl radical, which may add to the enolate radical cation to give the product (Pathway I). 2) The enolate may directly nucleophilic attack of the difluoromethyl group of reagent **5** (Pathway II). 3) In the presence of a base, reagent **5** may undergo deprotonation to generate difluorocarbene, which is then attacked by the enolate of β-ketoester (Pathway III).

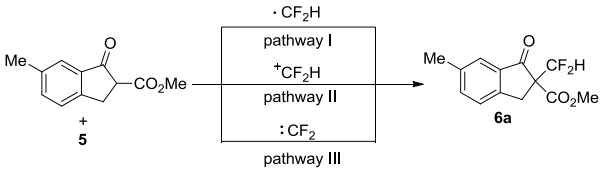
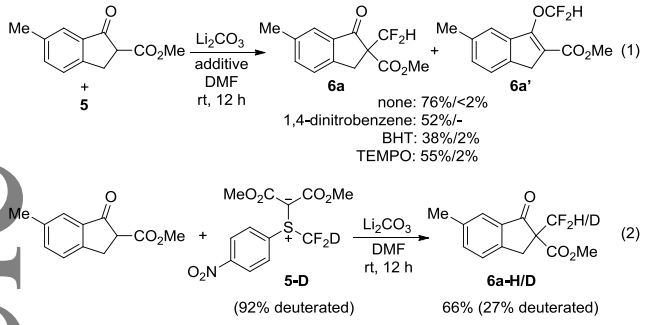


Figure 2 Reactions of β-ketoesters with different difluorocarbene reagents.

To probe whether the reaction proceeds via a SET process, we studied the reaction in the presence of 1.0 equivalent of SET inhibitor 1,4-dinitrobenzene or 2,6-di-tert-butyl-4-methylphenol (BHT) and a free radical trap (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO). It was found that the yields in the presence of these reagents were slightly lower. Likewise, the yields of the C-difluoromethylated products for reactions of other nucleophile with reagent **5** in the presence of these SET inhibitors decreased slightly. Yet, the reactions were not completely inhibited (Eq. 1). These results clearly exclude the SET pathway I.

To distinguish pathways II and III, we synthesized a deuterated difluoromethyl-substituted sulfonium ylide **5**-**D** and subjected it to the difluoromethylating reactions. Theoretically, if the reaction proceeds via a difluorocarbene pathway, the product derived from significant H/D exchange would be expected. Otherwise, low H/D exchange would be observed for the direct nucleophilic substitution pathway. Experimentally, reactions of β-ketoester with reagent **5**-**D** generated compound **6a-H/D** in 66% yield with 27% deuteration (Eq. 2). Since both reagent **5**-**D** and the difluomethylated product did not undergo H/D exchange under the reaction conditions, these observations are inconsistent with a direct nucleophile subsitition pathway. Likewise, reactions of other nucleophiles such as malonates, oxindoles and benzofuranones with reagent **5**-**D** generated the corresponding products with deuterated-scrambling (see SI for details). These

results clearly support that the carbon-selective difluoromethylating reaction proceeds highly likely via a difluorocarbene pathway.



To gain more support for the difluorocarbene pathway, we studied the reaction of β-ketoester with reagent **5** by DFT calculation.[21] As shown in Figure 3, these studies showed that the formation of difluorocarbene by treatment of reagent **5** with Li_2CO_3 is an exothermic process (ΔG = -1.3 kcal/mol) with a barrier of 15.6 kcal/mol. In addition, the relative free energy of the transition structure **TS-C-1** for the nucleophilic attack of the carbon is energetically lower by 1.6 kcal/mol than that of the transition structure **TS-O-1** for the nucleophilic attack of the oxygen (Fig. 4), which corresponds to a ratio of C/O-difluoromethylated product of 94:6 in favor of the C-difluoromethylated product. These results are consistent with the C/O regioselectivity observed experimentally. Furthermore, these studies also showed that the barrier (15.6 kcal/mol) for the formation of difluorocarbene is much higher than that of nucleophilic attack of enolate to difluorocarbene (5.7 kcal/mol), which suggests that the rate limiting step of the reaction is the formation of difluorocarbene. Experimentally, it was found that the percentage of deuteration of reagent **5** increased during the reaction. As shown in Eq. 3, reaction of β-ketoester with 1.3 equivalents of 43% deuterated reagent **5** under standard conditions occurred to full conversion to give the desired product in 56% yield with 8% deuteration, while the percentage of deuteration of the remaining reagent **5** increased to 60%. These results indicate a significant kinetic isotope effect for the difluoromethylation of β-ketoester with reagent **5**, which is consistent with the theoretical studies that the formation of difluorocarbene is the rate limiting step.

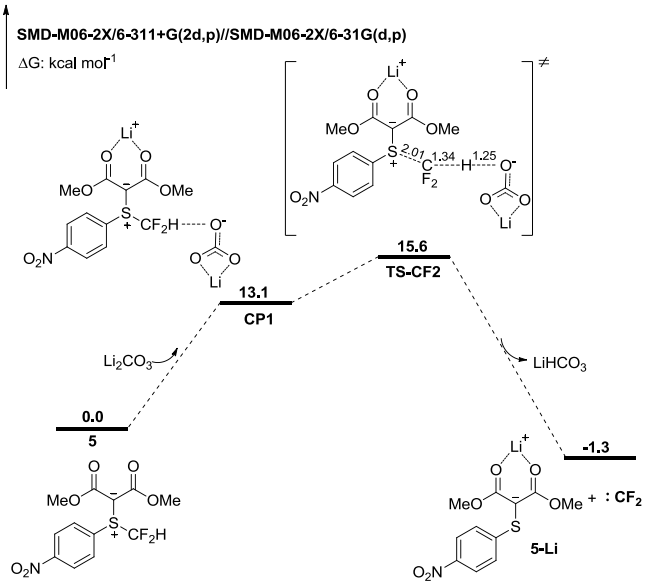


Figure 3 Energy profile (ΔG in kcal/mol) computed at the MD-M06-2X/6-311+G(2d, p)//SMD-M06-2X/6-31G(d, p) level of theory for difluorocarbene formation from reagent **5**.

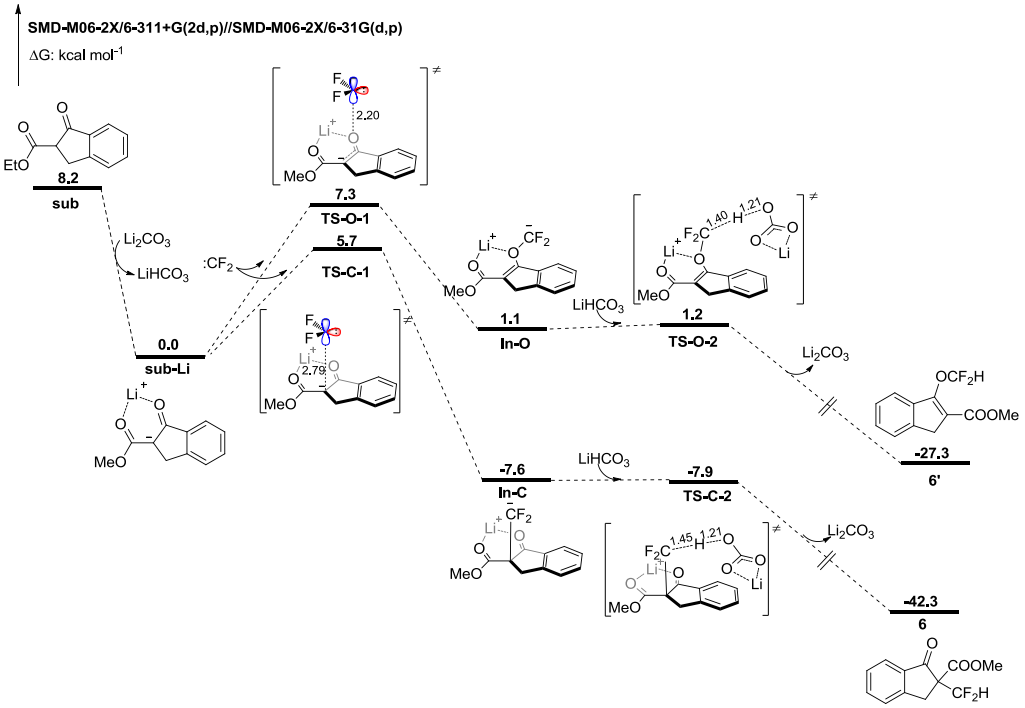
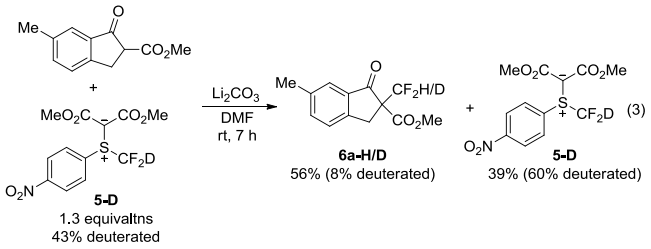


Figure 4 Energy profile (ΔG in kcal/mol) computed at the SMD-M06-2X/6-311+G(2d, p)//SMD-M06-2X/6-31G(d, p) level of theory for the formation of C- and O- difluoromethylated products proceeding via difluorocarbene mechanism.



Finally, as an example of the applicability of the current difluoromethylation protocol, we tried to synthesize the difluoromethylated analog Ibuprofen, an anti-inflammatory and analgesic drug. As shown in Figure 5, treatment of compound **7m**, which was obtained in gram scale from the reaction of di-*tert*-butyl 2-(4-*iso*butylphenyl)malonate with reagent **5**, with CF_3COOH in CH_2Cl_2 at room temperature for 3.0 h to give the corresponding acid. Without further purification, the acid underwent decarboxylation after 12 h in acetone at room temperature to give compound **11** in 76% yield. To the best of our knowledge, it represents the first efficient method for the preparation of difluoromethylated analog of ibuprofen.

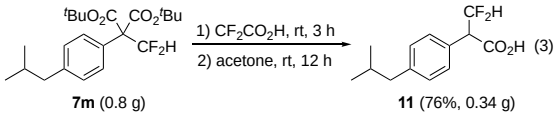


Figure 5 Synthesis of the analog of Ibuprofen.

Conclusions

In conclusion, we have developed a new protocol for carbon-selective difluoromethylation of soft carbonyl compounds including β-ketoesters, malonates, oxindoles, benzofuranones and ketene silyl acetals under mild conditions. For most of the substrates, excellent C/O regioselectivities were achieved. Mechanistic studies suggest that these difluoromethylating reactions proceed via a difluorocarbene pathway. In addition, the method can be applied in the preparation of the difluoromethylated analog of Ibuprofen. Development of the asymmetric difluoromethylation of these soft carbon nucleophiles is undergoing currently in our laboratory.

Experimental

General information.

All solvents were purified by standard method. ^{1}H NMR spectra were recorded on a 500 MHz, 400 MHz or 300 MHz spectrometer. ^{19}F NMR spectra were recorded on a 376 MHz or 282 MHz spectrometer. ^{13}C NMR spectra were recorded on a 125 or 100 MHz spectrometer. ^{1}H NMR and ^{13}C NMR chemical shifts were determined relative to internal standard TMS at δ 0.0 and ^{19}F NMR chemical shifts were determined relative to $CFCl_3$ as inter standard. Chemical shifts (δ) are reported in ppm, and coupling constants (*J*) are in Hertz (Hz). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Flash column chromatograph was carried out using 300-400 mesh silica gel at medium pressure.

General Procedure for Difluoromethylation of β-Ketoester

β-ketoester (0.50 mmol), Li_2CO_3 (74 mg, 1.0 mmol), and reagent **5** (218 mg, 0.65 mmol) were placed into an oven-dried Schlenk tube that was equipped with a stirring bar. The tube was quickly sealed with a rubber stopper and 2.5 mL of freshly distilled DMF was added. The reaction mixture was stirred at room temperature for 12 h. Then 20 mL of distilled water and 20 mL of Et_2O was added and the organic phase was separated. The aqueous phase was extracted with Et_2O (2 x 20 mL) and the combined organic layer was washed with brine (2 x 20 mL). The separated organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The product was purified by flash chromatography on silica gel.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2018xxxxx.

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Entry for the Table of Contents

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Carbon-Selective Difluoromethylation of Soft Carbon Nucleophiles with Difluoromethylated Sulfonium Ylide

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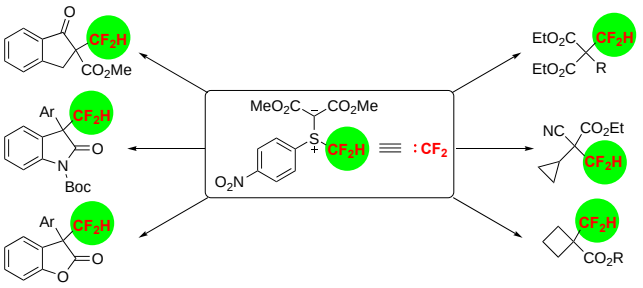

A highly carbon-selective difluoromethylation of soft carbon nucleophiles including β-ketoesters, malonates, oxindoles, benzofuranones and ketene silyl acetals with a difluoromethylated sulfonium ylide under mild conditions was described. Mechanistic studies suggest that these difluoromethylating reactions proceed via a difluorocarbene pathway.