ARTICLE

Generation of Free and Metal Difluorocarbenes and Introduction of Fluorinated One Carbon Units into Carbonyl and Related Compounds

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Difluorocarbene is a simple and versatile one-carbon unit for synthesizing acyclic and cyclic organofluorine compounds. However, the use of difluorocarbene in organic synthesis has been relatively limited because of the harsh conditions required for its generation, the toxicity of the precursors, and undesired dimerization. This account describes (i) the generation of free and metal difluorocarbenes from trimethylsilyl 2,2-difluoro-2-(fluorosulfonyl)acetate (TFDA) or $BrCF_2CO_2Li/Na$ and (ii) their application to the facile synthesis of valuable organofluorine compounds. The difluorocarbenes thus generated react with (thio)carbonyl compounds and silyl dienol ethers to provide a wide variety of products such as (a) difluoromethyl (thio)ethers, (b) fluorinated thiophenes, (c) fluorinated thia/oxazoles, (d) fluorinated cyclopentanones and (e) difluoroalkenes.

1. Introduction

Organofluorine compounds have long been used in life sciences such as medicinal and agricultural chemistry because the fluorine substituent increases the lipophilicity of the original molecule and enhances the efficiency of drug absorption and transport in vivo.[1] In addition, owing to its small steric demand, the fluorine atom acts as a mimic of the hydrogen atom, which allows fluorine-containing drug molecules to approach the active sites of enzymes, resulting in enhanced biological activities and altered activity spectra. Currently, the utility of fluorine is rapidly expanding to materials science applications such as organic electronics, leading to the development of new functional materials.[2]

Among the fluorinated compounds, *O*- and *S*-difluoromethylated compounds (Fig. 1a) and ring-fluorinated compounds (Fig. 1b) often possess potent bioactivities. For example, difluoromethyl ethers such as pantoprazole,[3]

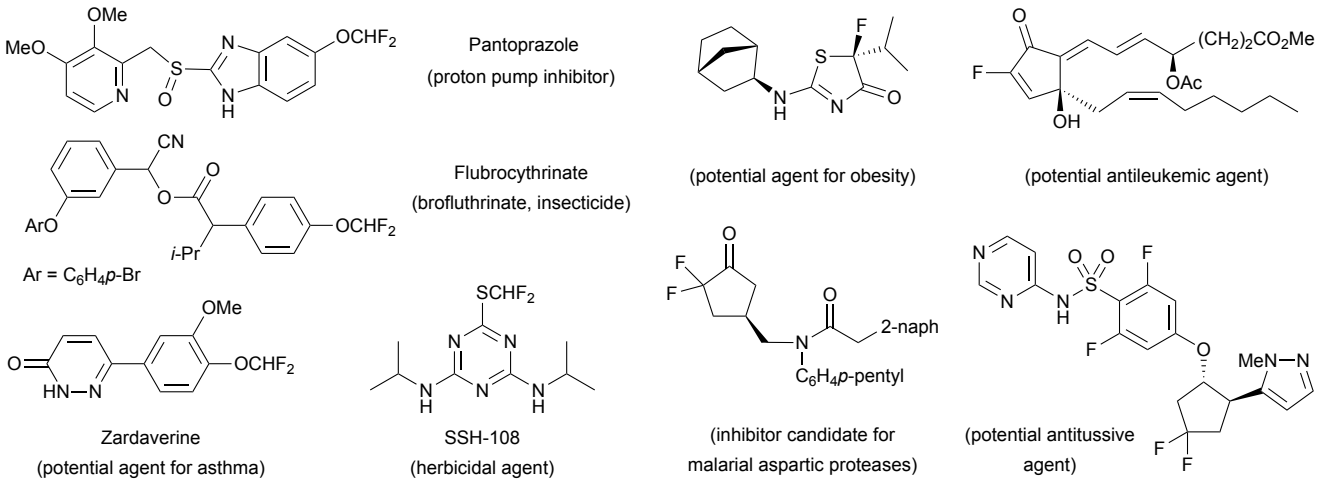

Fig. 1 Biologically active *O*-/*S*-difluoromethylated compounds and ring-fluorinated compounds.

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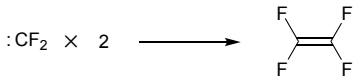
flubrocythrinate (brofluthrinate)[4] and zardaverine[5] function as a proton pump inhibitor, an insecticide and a potential antiasthma agent, respectively. The difluoromethyl thioether SSH-108 exhibits herbicidal activity.[6] Moreover, ring-fluorinated heterocyclic and carbocyclic compounds such as fluorothiazolines and difluorocyclopentanones have pharmacological activities, including antiobesity,[7] antimalarial,[8] antileukemic[9] and antitussive properties.[10]

Difluorocarbene ($:CF_2$), one of the smallest fluorine-containing carbon units, allows introducing difluoromethyl (CHF_2–), difluoromethylene (–CF_2–), fluoromethyne (–CF=), and difluoromethylidene (CF_2=) moieties into substrates.[11] However, the use of difluorocarbene in organic synthesis has been relatively limited because of a series of issues related to its generation, such as the harsh conditions required and toxicity of the precursors. For example, the pyrolysis of $ClCF_2CO_2Na$ and hexafluoropropylene oxide requires high temperatures (>120 °C[12] and >150 °C,[13] respectively). Meanwhile, reactions that proceed at lower temperatures, such as the dehydrochlorination of chlorodifluoromethane, have emerged as alternatives to pyrolysis. Generally, α-eliminations require strongly basic conditions,[14] whereas those triggered by nucleophilic substitutions on carbonyl[15] and sulfonyl groups[16] have been recently reported to proceed under milder conditions.[17] The decomposition of trifluoromethyl metal reagents provides another route to difluorocarbene. Thus, phenyl(trifluoromethyl)mercury[18] and trimethyl(trifluoromethyl)stannane[19] release difluorocarbene when combined with sodium iodide. However, the use of a stoichiometric amount of toxic metal reagents should be avoided, particularly in large-scale preparations.

In addition to the problems associated with the harsh conditions and toxicity in the generation of difluorocarbene, its generation rate must be controlled. Because of its low reactivity and harsh generation conditions, the reactions of difluorocarbene with substrates require vigorous conditions, which result in undesired overreactions and selectivity loss. Furthermore, difluorocarbene undergoes dimerization to form tetrafluoroethylene (Scheme 1),[20] leading to the requirement to use an excess amount of the precursors. Thus, to promote difluorocarbene-based synthesis, particularly of complex molecules, control of difluorocarbene generation is critical.



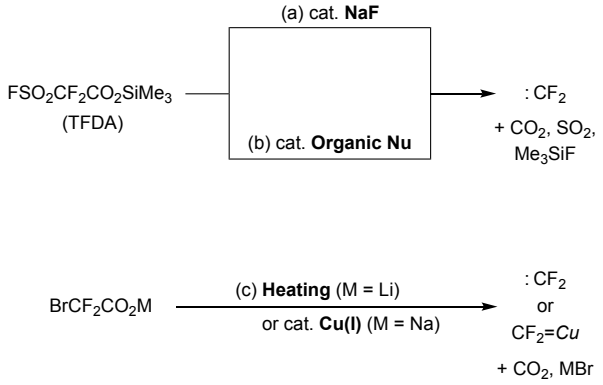
Scheme 1 Dimerization of difluorocarbene.

To overcome these difficulties, a remarkable development in this area has been achieved in the past two decades. A variety of difluorocarbene precursors, such as CF_3SiMe_3 (Ruppert–Prakash reagent),[21] $BrCF_2SiMe_3$,[22] $BrCF_2PO(OEt)_2$,[23] HCF_2OTf[24] and $Ph_3P^+CF_2CO_2^-$ (PDFA),[25] have been developed to generate free difluorocarbene under milder conditions. Excellent reviews regarding difluorocarbene precursors and their application in synthesis are available,[11] while this account discusses our advances in difluorocarbene chemistry.[26]

2. Results and Discussion

2.1 Strategy

To address the controlled generation of difluorocarbene, selection of an appropriate precursor is essential. Trimethylsilyl 2,2-difluoro-2-(fluorosulfonyl)acetate ($FSO_2CF_2CO_2SiMe_3$, TFDA), which was developed by Dolbier,[27] was previously treated with a sodium fluoride catalyst to generate difluorocarbene, with the concomitant formation of fluoro(trimethyl)silane, carbon dioxide and sulfur dioxide (Scheme 2a, inorganic catalyst). We envisioned that sodium fluoride could be replaced with *organic nucleophiles* including *organic fluorides (salts with organic cations)*, whose modification would allow controlling the generation rate of difluorocarbene under milder conditions (Scheme 2b, organocatalysts).[28] In addition, we adopted readily available $BrCF_2CO_2Li/Na$ as an improved reagent of the less reactive $ClCF_2CO_2Na$ (Scheme 2c).[12f] Bromodifluoroacetate salts are easy to handle and ready to undergo metal exchange followed by decarboxylation, which would facilitate metal carbene formation.



Scheme 2 (a) NaF-catalyzed, (b) organocatalyzed and (c) heat-promoted (M = Li) / copper(I)-catalyzed (M = Na) generation of free and metal difluorocarbenes.

Herein we describe the synthesis of *O*-/*S*-difluoromethylated, ring-fluorinated and difluoromethylenated compounds by introduction of CHF_2–, –CF_2–, –CF= and CF_2= groups using TFDA or $BrCF_2CO_2Li/Na$, which can generate free or metal difluorocarbenes with adjusted generation rates and reactivities depending on the carbene acceptors. The reactions of the difluorocarbenes with carbonyl and related compounds afforded a broad diversity of products, which are summarized in Fig. 2.

2.2 Reactions with ketones, amides and thioamides: Introduction of CHF_2– group

The difluoromethyl (CHF_2) group attracts considerable interest[29] in the synthesis of pharmaceuticals and agrochemicals not only as a nonnucleophilic proton donor for hydrogen bonding[30] but also as a substituent to improve the lipophilicity of the original molecules.[31] In this study, ketones, secondary amides and secondary thioamides were found to react with difluorocarbene to afford *O*- and *S*-difluoromethylated compounds.

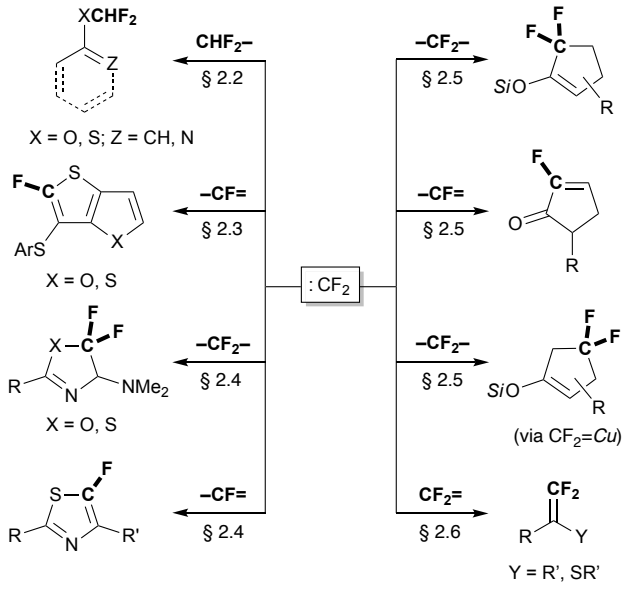
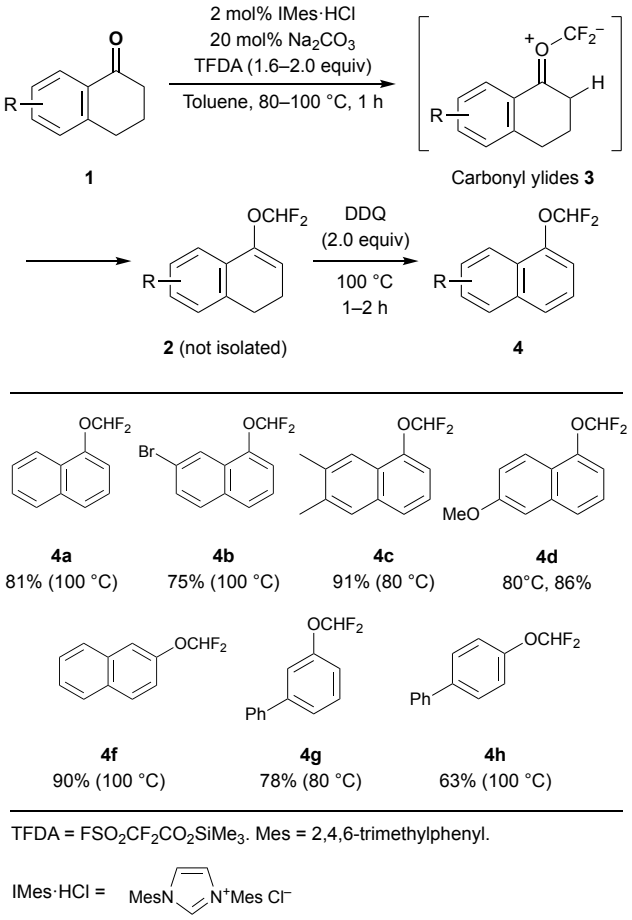


Fig. 2 Introduction of CHF_2–, $–CF_2–$, –CF= and CF_2= groups with free and metal difluorocarbenes leading to *O*-/*S*-difluoromethylated, ring-fluorinated and difluoromethylenated compounds.

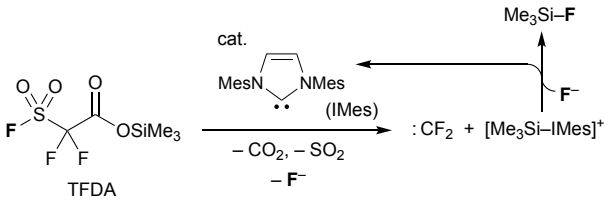
Six-membered ketones **1** such as cyclohexanones and tetralones were treated with TFDA in the presence of a catalytic amount of 1,3-dimesitylimidazol-2-ylidene (IMes), which was generated in situ in toluene (Scheme 3).[32] Difluorocarbene was generated as expected (Scheme 4) to provide difluoromethyl vinyl ethers **2** via carbonyl ylide intermediates **3** at 80 °C–100 °C. The obtained ethers **2** were then subjected to aromatization with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone in a one-pot operation to afford (difluoromethoxy)arenes **4**. Notably, the IMes catalyst is essential for this reaction: when the reaction was performed with the original NaF catalyst at 115 °C–140 °C, difluorocyclopropanation of the produced difluoromethyl vinyl ethers **2** proceeded as an overreaction (not shown).[33]

When the above *O*-difluoromethylation was applied to cyclic secondary amides **5** and **6**, the corresponding (difluoromethoxy)pyridine **7** and quinoline **8** were, respectively, obtained (Scheme 5).[34] Meanwhile, acyclic secondary amides **9** produced the corresponding difluoromethyl imidates **10** (Scheme 6). These reactions were completely *O*-selective, and no *N*-difluoromethylated amides were observed in the reaction mixture. Notably, 1,2,4-triazol-3-ylidene, which is less nucleophilic than IMes, was the catalyst of choice for the reaction with amides.

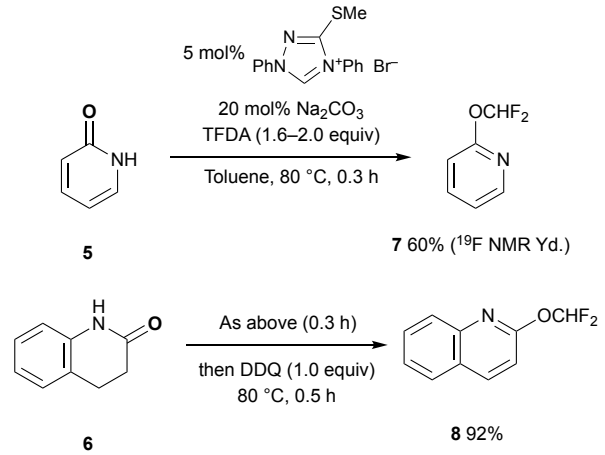
Chupp[35] and Jónczyk[36] previously reported the difluoromethylation of secondary amides with difluorocarbene under basic conditions. However, anionic amidate ions generated in situ were sufficiently reactive to cause nonselective *O*- and *N*-difluoromethylation. By contrast, the selective synthesis of *O*-difluoromethyl imidates was achieved by our method of generating difluorocarbene from TFDA under nearly neutral conditions.



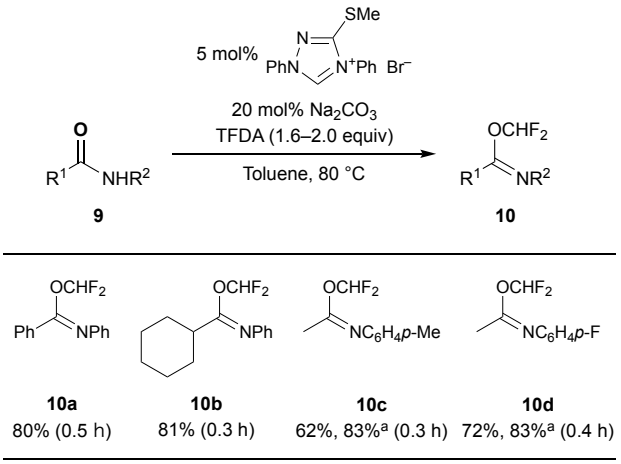
Scheme 3 Synthesis of (difluoromethoxy)arenes via *O*-difluoromethylation.



Scheme 4 Difluorocarbene generation from TFDA by an IMes catalyst.



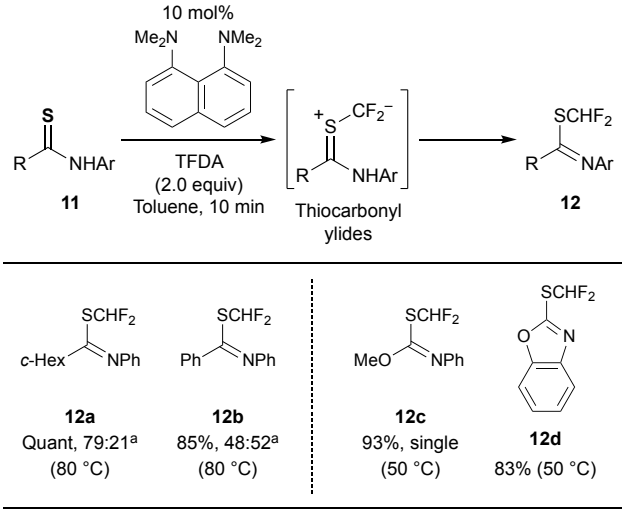
Scheme 5 Synthesis of (difluoromethoxy)pyridines via *O*-difluoromethylation.



Products were obtained as a single *E* / *Z* isomer (not determined).
[a] ^{19}F NMR yield.

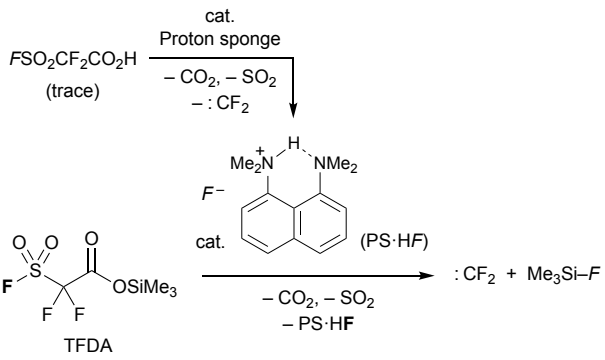
Scheme 6 Synthesis of difluoromethyl imidates via *O*-difluoromethylation.

In our study, *S*-difluoromethylation was also accomplished by adopting a similar system.[37] 1,8-Bis(dimethylamino)naphthalene (proton sponge) proved to be an effective catalyst for the difluoromethylation of thioamides **11a,b** (Scheme 7). The desired difluoromethylated products, i.e., *S*-difluoromethyl thioimidates **12a,b**, were obtained selectively at 80 °C via thiocarbonyl ylide intermediates. Thiocarboxamic esters **11c,d**, which are more electron-rich and reactive, underwent *S*-difluoromethylation at temperatures as low as 50 °C, yielding the corresponding products **12c,d**. A mechanistic investigation suggested that the residual acid ($FSO_2CF_2CO_2H$, <2 mol% according to a ^{19}F NMR analysis) reacts with the proton sponge to form proton sponge–HF salt (PS·HF) as the actual catalyst (Scheme 8).[38]



[a] *E* / *Z* ratio (the imine geometry was not determined).

Scheme 7 Synthesis of difluoromethyl thioimidates via *S*-difluoromethylation.



Scheme 8 Generation of difluorocarbene by a proton sponge catalyst.

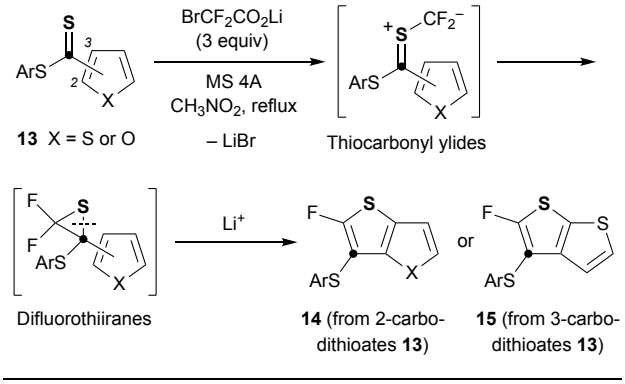
When generated at high temperatures, difluorocarbene was reported to react with secondary thioamides to form *N*-difluoromethylated products (not shown), which are more stable than the corresponding *S*-difluoromethylated products by ca. 10 kcal/mol. In our study, the proton sponge-catalyzed generation of difluorocarbene from TFDA, which proceeds at lower temperatures, enabled the synthesis of *S*-difluoromethylated products for the first time.

2.3 Reactions with dithioesters: Introduction of –CF= group

Dithioesters are useful difluorocarbene acceptors. The generated difluorothiiranes bearing thienyl and furyl groups underwent facile ring expansion to afford ring-fluorinated thienothiophenes and thienofurans, respectively.[39] In this case, difluorocarbene generation from $BrCF_2CO_2Li$ was suitably accelerated using molecular sieves 4A. Although Amii reported the use of $BrCF_2CO_2Na$ as a difluorocarbene source,[12f] difluorocarbene generation from lithium salt is critical to favor the ring expansion over desulfurization (vide infra, §2.6).

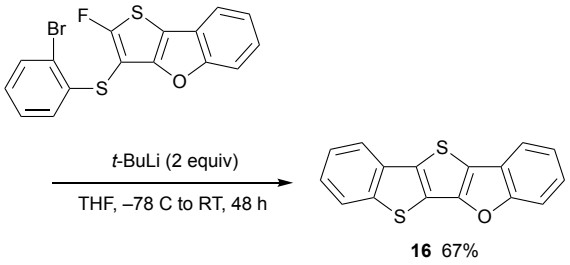
Thiophene- and furancarbodithioates **13** reacted with $BrCF_2CO_2Li$ in the presence of molecular sieves 4A (Scheme 9). [2 + 1] Cycloaddition occurred via thiocarbonyl ylide intermediates to form the corresponding difluorothiiranes bearing a thiophene or furan ring. The presence of the lithium ion promoted regioselective ring expansion (vide infra,§2.5) in spite of dearomatization, leading to abnormal [4 + 1] cycloaddition. Subsequent dehydrofluorination proceeded readily because of rearomatization to afford sulfanylated fluorothienothiophenes **14** (X = S), **15** or fluorothienofurans **14** (X = O) depending on the substrate (–CF= introduction).

Intramolecular fluorine substitution (S_NAr) in a brominated fluorothienofuran enabled further thiophene ring construction, providing dibenzothienothienofuran **16**, which is promising as an organic semiconducting material (Scheme 10).[39]



[a] Microwave, 140 °C (sealed).

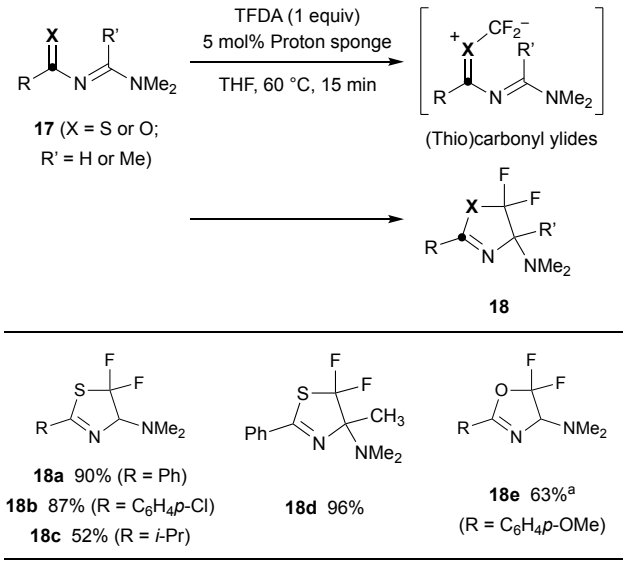
Scheme 9 Synthesis of ring-fluorinated thienothiophenes and thienofurans via abnormal [4 + 1] cycloaddition.



Scheme 10 Synthesis of dibenzothienothienofurans.

2.4 Reactions with *N*-(thioacyl)amidines and *N*-acylamidines: Introduction of –CF_2– and –CF= groups

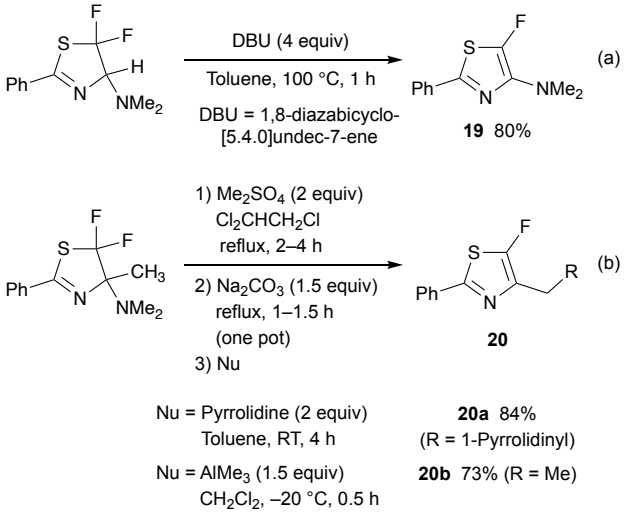
Inspired by the [2 + 1] cycloaddition depicted in Scheme 9, which formed thiirane rings, [4 + 1] cycloaddition was next examined for five-membered ring construction. The sulfur or oxygen atom of *N*-thioacyl- or *N*-acylamidines **17** reacted with difluorocarbene generated from TFDA and a proton sponge catalyst, providing the corresponding [4 + 1] cycloaddition products **18** via thiocarbonyl or carbonyl ylide formation followed by 5-*endo-trig* cyclization, respectively (Scheme 11, –CF_2– introduction).[40]



[a] ^{19}F NMR yield.

Scheme 11 Synthesis of ring-fluorinated thiazolines and oxazolines via [4 + 1] cycloaddition.

The obtained difluorinated thiazolines and oxazolines are useful intermediates for the synthesis of ring-fluorinated thiazoles and oxazoles, which are promising components of pharmaceuticals and agrochemicals. Dehydrofluorination (Scheme 12a) and a Hofmann elimination/S_N2'-type reaction sequence (Scheme 12b) facilitated the aromatization of these intermediates, leading to the corresponding aminated and alkylated 5-fluorothiazoles **19** and **20**, respectively (–CF= introduction).



Scheme 12 Synthesis of ring-fluorinated thiazoles.

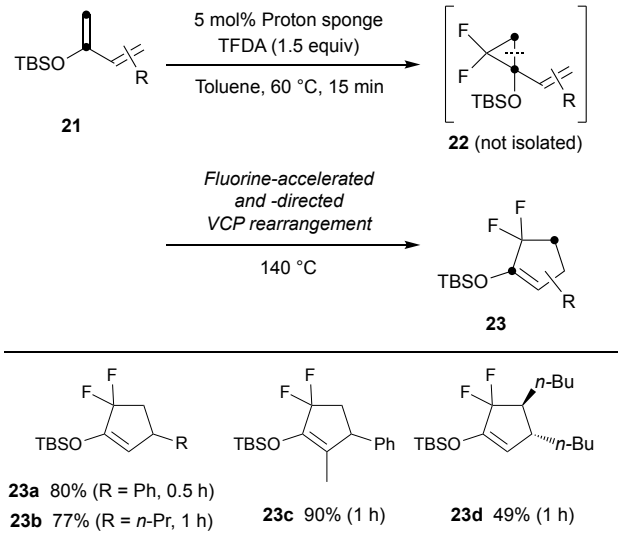
2.5 Reactions with silyl dienol ethers: Introduction of –CF_2– and –CF= groups

Difluorocyclopropanes, which can be prepared by treatment of alkenes with difluorocarbene, have a highly strained ring system,

which renders them potential intermediates for the synthesis of organofluorine compounds. In particular, the carbon–carbon bond distal to the difluoromethylene moiety is elongated[11a] due to the presence of electronegative fluorine substituents (Bent's rule),[41] which leads to regioselective ring expansion (vide supra, §2.3).

The difluorocyclopropanation of silyl dienol ethers **21**, which are prone to undergo hydrolysis, was only achieved when using TFDA at low temperatures (Scheme 13). Thus, upon treatment with difluorocarbene generated from TFDA and a proton sponge catalyst, silyl ethers **21** prepared from α,β-unsaturated ketones underwent difluorocyclopropanation, which proceeded selectively on the electron-rich alkene moiety to afford the corresponding difluoro(vinyl)cyclopropanes **22**.[42] The obtained cyclopropanes **22** were heated to 160 °C without isolation, affording difluorinated five-membered silyl enol ethers **23** via vinylcyclopropane–cyclopentene (VCP) rearrangement,[43,44] which was accelerated and directed by the enhanced strain of the difluorocyclopropane ring. Thus regioselective bond cleavage occurred to afford the products, where the carbon alignment was altered from the starting silyl dienol ethers **21** (*abnormal* [4 + 1] cycloaddition, –CF_2– introduction).

The produced silyl enol ethers **23** were transformed to a wide variety of fluorinated cyclopentanone derivatives **24**, including 3-fluorinated 2-hydroxycyclopent-2-en-1-one **24e**, whose oxygenated cyclopentenone skeleton is found in cyclotene,[45] a food additive with a caramel-like flavor (Fig. 3). Notably, the metal-free synthesis of **23** was achieved as an alternative to the nickel(II)-catalyzed synthesis of the same compounds previously accomplished by our group.[46]



TBS = Si*t*-BuMe_2.

Scheme 13 Synthesis of α,α-difluorocyclopentanone-derived silyl enol ethers via abnormal [4 + 1] cycloaddition.

To change the reactivity of free difluorocarbene, its transition metal complexes are powerful alternatives as intermediates for the synthesis of fluorinated compounds.[47] The same silyl dienol ethers **21** underwent *normal* [4 + 1] cycloaddition with difluorocarbene under copper(I) catalysis to afford the isomeric products **25** (β,β-difluorocyclopentanone-derived silyl enol ethers, Scheme 14, –CF_2– introduction).[48] It seems likely that the copper difluorocarbene complex generated in situ from $BrCF_2CO_2Na$ is sufficiently electrophilic to react with **22**, generating an alkylcopper species that is, in turn, nucleophilic and undergoes a 5-*endo-trig* cyclization like that shown in Scheme 11, leading to the corresponding products. The formation of the key copper difluorocarbene complex was supported by HRMS analysis in its aminolysis form.[49]

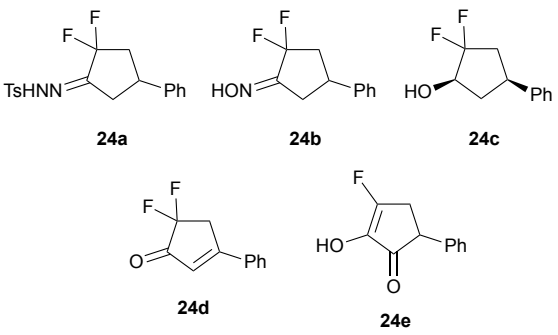
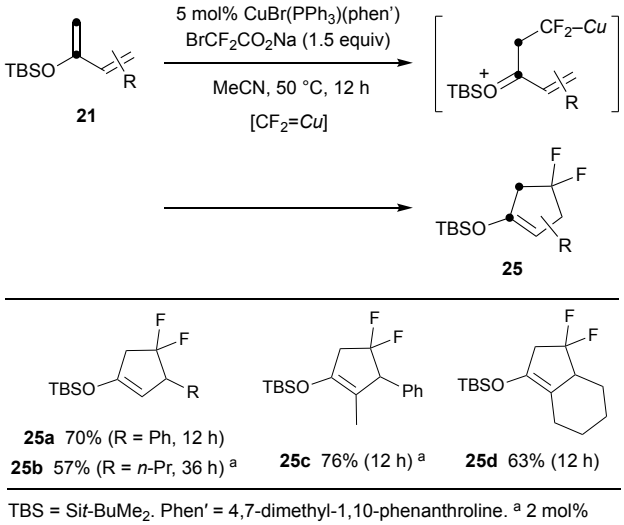


Fig. 3 α,α-Difluorinated and β-fluorinated cyclopentanone derivatives synthesized from **23**.

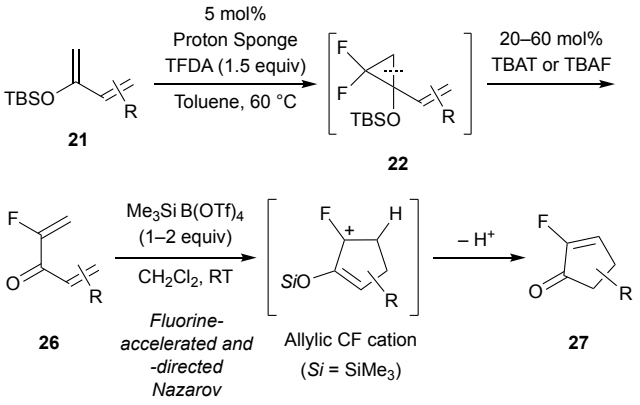


TBS = Si*t*-BuMe_2. Phen' = 4,7-dimethyl-1,10-phenanthroline. [a] 2 mol% $CuBr(PPh_3)$(phen').

Scheme 14 Synthesis of β,β-difluorocyclopentanone-derived silyl enol ethers via normal [4 + 1] cycloaddition.

Similar to the –CF_2– introduction (Scheme 13), the –CF= introduction (Scheme 15) was achieved using difluorocyclopropane intermediates **22** by adopting *fluorine-accelerated* and *-directed* Nazarov cyclizations of α-fluorovinyl vinyl ketones **26**. Vinylic difluorocyclopropanes **22**, which were obtained from **21** and TFDA in the presence of a proton sponge catalyst at 60 °C, were transformed into α-fluorovinyl vinyl ketones **26**. Subsequent Lewis acid-promoted Nazarov cyclizations proceeded regioselectively to yield the desired α-fluorocyclopentenones **27**.[38] Fluorine substituents stabilize α-carbocations by donating its unshared electron pair to the vacant p orbital of the cationic center (+M effect).[50] It seems that the α-carbocation stabilizing effect i) accelerates the cyclization of **26** ~~**27**~~ and ii) facilitates the regioselective deprotonation.

Of note, proton sponge is more advantageous as a catalyst for activation of TFDA. Thus, the proton sponge catalyst afforded difluorocyclopropanes **22** in good yields, whereas the NHC catalysts in Schemes 3, 5 and 6 afforded lower yields of **22** and substantial amounts of starting **21**.[38]



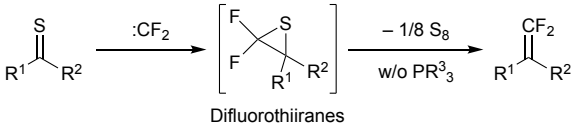
TBS = Si*t*-BuMe$_2$. TBAT = *n*-Bu$_4$N$^+$ $^-$SiF$_2$Ph$_3$. TBAF = *n*-Bu$_4$N$^+$ F$^-$.

Scheme 15 Synthesis of α-fluorocyclopentenones via Nazarov cyclization.

2.6 Reactions with thioketones and dithioesters: Introduction of CF_2= group

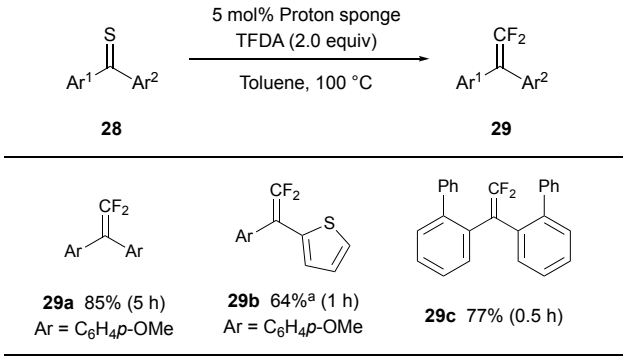
The Barton–Kellogg reaction is applicable to the synthesis of sterically hindered alkenes.[51] In this reaction, thioketones are typically treated with diazo compounds to generate thiiranes, [52] which provide the corresponding alkenes upon treatment with phosphines as reducing agents.[53]

Thus, the Barton–Kellogg-type synthesis of 1,1-difluoroalkenes via difluorothiiranes was investigated (Scheme 16). As previously shown in Schemes 9 and 13, the fluorine-substituted three-membered rings have enhanced strain, which was expected to facilitate spontaneous desulfurization of thiiranes.[54]



Scheme 16 Route to 1,1-difluoroalkenes through difluorothiiranes.

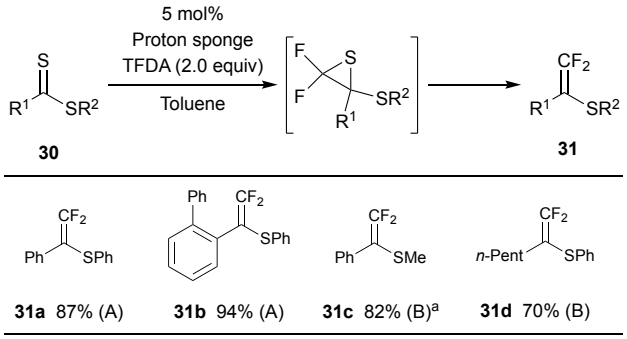
When diarylthioketones **28** were treated with TFDA in the presence of a proton sponge catalyst (Scheme 17), the desired diaryl difluoroalkenes **29** were obtained without requiring the use of phosphines.[55] This difluoromethylidenation was successfully applied to hindered diarylthioketones, yielding the corresponding difluoroalkenes bearing two sterically demanding aryl groups, which are less accessible via Wittig-type difluoromethylidenations.



[a] ^{19}F NMR yield.

Scheme 17 Synthesis of diarylated 1,1-difluoroalkenes via difluoromethylidenation.

Next, dithioesters **30** were treated with TFDA in the presence of a proton sponge catalyst (Scheme 18)[56] to produce the desired sulfanylated 1,1-difluoroalkenes **31**. For the synthesis of 1,1-difluoroalkenes, Wittig-type difluoromethylidenations have long been utilized with difluoromethylene ylides. However, dithioesters are much less reactive to nucleophilic ylides. Thus, the systematic synthesis of sulfanylated 1,1-difluoroalkenes has not been explored to date.[57] By contrast, the difluorocarbene-mediated Barton–Kellogg-type difluoromethylidenation is electrophilic, that is, complementary to the nucleophilic Wittig-type methods and thus provides a general route to sulfanylated 1,1-difluoroalkenes.



A: TFDA was added over 5 min, 60 °C (0.5 h) then 100 °C (0.5 h); B TFDA was added over 1 min, 110 °C (0.5 h). [a] ^{19}F NMR yield.

Scheme 18 Synthesis of sulfanylated 1,1-difluoroalkenes via difluoromethylidenation.

Conclusions

Despite being known for a long time, difluorocarbene has not been fully utilized in organic synthesis. For the generation of appropriate difluorocarbene species under mild conditions, (i)

difluorocarbene sources, (ii) organocatalysts and (iii) metals for complexation should be appropriately selected depending on the acceptor substrates. Their reactions with a variety of substrates lead to a broad diversity of products, including *O*-/*S*-difluoromethylated compounds, ring-fluorinated hetero/carbocycles and difluoroalkenes, which are potential pharmaceuticals, agrochemicals, and functional materials.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

1 (a) J.-P. Bégué and D. Bonnet-Delpon, *Bioorganic and Medicinal Chemistry of Fluorine*, Wiley, Hoboken, 2008; (b) W. K. Hagmann, *J. Med. Chem.*, 2008, **51**, 4359; (c) K. L. Kirk, *Org. Proc. Res. Development*, 2008, **12**, 305; (d) J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok and H. Liu, *Chem. Rev.*, 2014, **114**, 2432; (e) Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J. L. Aceña, V. A. Soloshonok, K. Izawa and H. Liu, *Chem. Rev.*, 2016, **116**, 422; (f) J. Han, A. M. Remete, L. S. Dobson, L. Kiss, K. Izawa, H. Moriwaki, V. A. Soloshonok and D. O'Hagan, *J. Fluorine Chem.*, 2020, **239**, 109639.

2 (a) F. Babudri, G. M. Farinola, F. Naso and R. Ragni, *Chem. Commun.*, 2007, 1003; (b) M. L. Tang and Z. Bao, *Chem. Mater.*, 2011, **23**, 446; (c) M. Hird, *Chem. Soc. Rev.*, 2007, **36**, 2070.

3 B. Kohl, E. Sturm, J. Senn-Bilfinger, W. A. Simon, U. Krueger, H. Schaefer, G. Rainer, V. Figala and K. Klemm, *J. Med. Chem.*, 1992, **35**, 1049.

4 G. Sun, W. Jin, L. Zuon and H. Xie, PCT Int. Appl. WO 9518790, 1995.

5 J. C. Kips, G. F. Joos, R. A. Peleman and R. A. Pauwels, *Clin. Exp. Allergy*, 1993, **23**, 518.

6 K. Morita, K. Ide, Y. Hayase, T. Takahashi and Y. Hayashi, *Agric. Biol. Chem.*, 1987, **51**, 1339.

7 M. Henriksson, E. Homan, L. Johansson, J. Vallgarda, M. Williams, E. A. Bercot, C. H. Fotsch, A. Li, G. Cai, R. W. Hungate, C. C. Yuan, C. Tegley, D. J. St. Jean, Jr., N. Han, Q. Huang, Q. Liu, M. D. Bartbeger, G. A. Moniz, M. J. Frizzle and T. L. Marshall, PCT Int. Appl. WO WO2007061661A2, 2007.

8 C. Fäh, L. A. Hardegger, L. Baitsch, W. B. Schweizer, S. Meyer, D. Bur and F. Diederich, *Org. Biomol. Chem.*, 2009, **7**, 3947.

9 K. Iguchi, S. Kaneta, C. Tsune and Y. Yamada, *Chem. Pharm. Bull.*, 1989, **37**, 1173.

10 S. Takahashi, Y. Domon, Y. Kitano and T. Shinozuka, PCT Int. Appl. WO 2014142221A1, 2014.

11 (a) W. R. Dolbier and M. A. Battiste, *Chem. Rev.*, 2003, **103**, 1071; (b) D. L. S. Brahms and W. P. Dailey, *Chem. Rev.*, 1996, **96**, 1585; (c) C. Ni and J. Hu, *Synthesis*, 2014, **46**, 842.; (d) W. Zhang and Y. Wang, *Tetrahedron Lett.*, 2018, **59**, 1301.

12 (a) J. M. Birchall, G. W. Cross and R. N. Haszeldine, *Proc. Chem. Soc.*, 1960, 81; (b) L. H. Knox, E. Velarde, S. Berger, D. Cuadriello, P. W. Landis and A. D. Cross, *J. Am. Chem. Soc.*, 1963, **85**, 1851; (c) C. Beard, N. H. Dyson and J. H. Fried, *Tetrahedron Lett.*, 1966, **7**, 3281; (d) P. D. O'Shea, C.-y. Chen, W. Chen, P. Dagneau, L. F. Frey, E. J. J. Grabowski, K. M. Marcantonio, R. A. Reamer, L. Tan, R. D. Tillyer, A. Roy, X. Wang and D. Zhao, *J. Org. Chem.*, 2005, **70**, 3021. See also: (e) Y. Chang and C. Cai, *Chem. Lett.*, 2005, **34**, 1440; (f) K. Oshiro, Y. Morimoto and H. Amii, *Synthesis*, 2010, **2010**, 2080.

13 (a) P. B. Sargeant, *J. Org. Chem.*, 1970, **35**, 678; (b) H. Millauer, W. Schwertfeger and G. Siegemund, *Angew. Chem. Int. Ed.*, 1985, **24**, 161.

14 (a) T. G. Miller and J. W. Thanassi, *J. Org. Chem.*, 1960, **25**, 2009; (b) T. Y. Shen, S. Lucas and L. H. Sarett, *Tetrahedron Lett.*, 1961, **2**, 43; (c) B. R. Langlois, *J. Fluorine Chem.*, 1988, **41**, 247; (d) A. Fuss and V. Koch, *Synthesis*, 1990, **1990**, 604; (e) A. Fuss and V. Koch, *Synthesis*, 1990, **1990**, 681.

15 (a) L. Zhang, J. Zheng and J. Hu, *J. Org. Chem.*, 2006, **71**, 9845; (b) G. Guerrini, G. Ciciani, F. Bruni, S. Selleri, C. Guarino, F. Melani, M. Montali, S. Daniele, C. Martini, C. Ghelardini, M. Norcini, S. Ciattini and A. Costanzo, *J. Med. Chem.*, 2010, **53**, 7532.

16 J. Zheng, Y. Li, L. Zhang, J. Hu, G. J. Meuzelaar and H.-J. Federsel, *Chem. Commun.*, 2007, 5149.

17 (a) W. Zhang, F. Wang and J. Hu, *Org. Lett.*, 2009, **11**, 2109 (corrigendum: (b) W. Zhang, F. Wang and J. Hu, *Org. Lett.*, 2013, **15**, 5613); (b) G. K. S. Prakash, Z. Zhang, F. Wang, C. Ni and G. A. Olah, *J. Fluorine Chem.*, 2011, **132**, 792.

18 (a) D. Seyferth, J. Y.-P. Mui, M. E. Gordon and J. M. Burlitch, *J. Am. Chem. Soc.*, 1965, **87**, 681; (b) D. Seyferth, S. P. Hopper and K. V. Darragh, *J. Am. Chem. Soc.*, 1969, **91**, 6536; (c) D. Seyferth and S. P. Hopper, *J. Org. Chem.*, 1972, **37**, 4070. See also: (d) I. Nowak and M. J. Robins, *Org. Lett.*, 2005, **7**, 721.

19 D. Seyferth, H. Dertouzos, R. Suzuki and J. Y.-P. Mui, *J. Org. Chem.*, 1967, **32**, 2980.

20 L. Li, C. Ni, Q. Xie, M. Hu, F. Wang and J. Hu, *Angew. Chem. Int. Ed.*, 2017, **56**, 9971.

21 F. Wang, T. Luo, J. Hu, Y. Wang, H. S. Krishnan, P. V. Jog, S. K. Ganesh, G. K. S. Prakash and G. A. Olah, *Angew. Chem. Int. Ed.*, 2011, **50**, 7153.

22 F. Wang, W. Zhang, J. Zhu, H. Li, K.-W. Huang and J. Hu, *Chem. Commun.*, 2011, **47**, 2411.

23 Y. Zafrani, G. Sod-Moriah and Y. Segall, *Tetrahedron*, 2009, **65**, 5278.

24 P. S. Fier and J. F. Hartwig, *Angew. Chem. Int. Ed.*, 2013, **52**, 2092.

25 J. Zheng, J.-H. Lin, J. Cai and J.-C. Xiao, *Chem. Eur. J.*, 2013, **19**, 15261.

26 For other recent difluorocarbene precursors, see: (a) F. Wang, W. Huang and J. Hu, *Chi. J. Chem.*, 2011, **29**, 2717; (b) C. S. Thomoson and W. R. Dolbier, Jr., *J. Org. Chem.*, 2013, **78**, 8904; (c) G. Liu, X. Wang, X.-H. Xu, X. Lu, E. Tokunaga, S. Tsuzuki and N. Shibata, *Org. Lett.*, 2013, **15**, 1044; (d) C.-B. Yue, J.-H. Lin, J. Cai, C.-P. Zhang, G. Zhao, J.-C. Xiao and H. Li, *RSC Adv.*, 2016, **6**, 35705; (e) G.-K. Liu, X. Li, W.-B. Qin, X.-S. Peng, H. N. C. Wong, L. Zhang and X. Zhang, *Chem. Commun.*, 2019, **55**, 7446.

27 (a) R. J. Terjeson, J. Mohtasham, D. H. Peyton and G. L. Gard, *J. Fluorine Chem.*, 1989, **42**, 187; (b) F. Tian, V. Kruger, O.

Bautista, J.-X. Duan, A.-R. Li, W. R. Dolbier, Jr. and Q.-Y. Chen, *Org. Lett.*, 2000, **2**, 563; (c) W. R. Dolbier, Jr., F. Tian, J.-X. Duan, A.-R. Li, S. Ait-Mohand, O. Bautista, S. Buathong, J. Marshall Baker, J. Crawford, P. Anselme, X. H. Cai, A. Modzelewska, H. Koroniak, M. A. Battiste and Q.-Y. Chen, *J. Fluorine Chem.*, 2004, **125**, 459.
28 K. Fuchibe, R. Takayama, T. Aono, J. Hu, T. Hidano, H. Sasagawa, M. Fujiwara, S. Miyazaki, R. Nadano and J. Ichikawa, *Synthesis*, 2018, **50**, 514.
29 (a) J. T. Welch, *Tetrahedron*, 1987, **43**, 3123; (b) F. Leroux, P. Jeschke and M. Schlosser, *Chem. Rev.*, 2005, **105**, 827; (c) N. A. Meanwell, *J. Med. Chem.*, 2011, **54**, 2529.
30 (a) S. Kaneko, T. Yamazaki and T. Kitazume, *J. Org. Chem.*, 1993, **58**, 2302; (b) J. A. Erickson and J. I. McLoughlin, *J. Org. Chem.*, 1995, **60**, 1626; (c) Y. Zafrani, S. Saphier and E. Gershonov, *Future Med. Chem.*, 2020, **12**, 361.
31 (a) A. F. M. Barton, *Handbook of Solubility Parameters and Other Cohesion Parameters*, CRC press, 1983; (b) J. N. Israelachvili, *Intermolecular and Surface Forces: with Applications to Colloidal and Biological Systems*, Academic Press Inc., London, 1985; (c) L. E. Kiss, I. Kövesdi and J. Rábai, *J. Fluorine Chem.*, 2001, **108**, 95; (d) Y. Zafrani, G. Sod-Moriah, D. Yeffet, A. Berliner, D. Amir, D. Marciano, S. Elias, S. Katalan, N. Ashkenazi, M. Madmon, E. Gershonov and S. Saphier, *J. Med. Chem.*, 2019, **62**, 5628.
32 K. Fuchibe, Y. Koseki, H. Sasagawa and J. Ichikawa, *Chem. Lett.*, 2011, **40**, 1189.
33 X. Cai, K. Wu and W. R. Dolbier, Jr., *J. Fluorine Chem.*, 2005, **126**, 479.
34 K. Fuchibe, Y. Koseki, T. Aono, H. Sasagawa and J. Ichikawa, *J. Fluorine Chem.*, 2012, **133**, 52.
35 J. P. Chupp, D. M. Hemmerly and J. J. Freeman, *J. Org. Chem.*, 1993, **58**, 245.
36 E. Nawrot and A. Jonczyk, *J. Fluorine Chem.*, 2006, **127**, 943.
37 K. Fuchibe, M. Bando, R. Takayama and J. Ichikawa, *J. Fluorine Chem.*, 2015, **171**, 133.
38 K. Fuchibe, R. Takayama, T. Yokoyama and J. Ichikawa, *Chem. Eur. J.*, 2017, **23**, 2831.
39 K. Fuchibe, I. Mukohara, A. Yamada, D. Miyazaki, R. Takayama and J. Ichikawa, *Org. Lett.*, 2022, **24**, 169.
40 K. Fuchibe, Y. Morota, T. Miura and J. Ichikawa, *Chem. Lett.*, in press.
41 (a) W. Henderson, in *Main Group Chemistry*, Vol. 3 (Ed: W. Henderson), The Royal Society of Chemistry, London, 2000; (b) I. V. Alabugin, S. Bresch, G. P. dos Gomes, *J. Phys. Org. Chem.*, 2015, **28**, 147.
42 R. Takayama, K. Fuchibe and J. Ichikawa, *ARKIVOC*, 2018, 72.
43 (a) M. Ramaiah, *Synthesis*, 1984, **1984**, 529; (b) T. Hudlický, T. M. Kutchan and S. M. Naqvi, *Org. React.*, 1985, **33**, 247; (c) H. N. C. Wong, M. Y. Hon, C. W. Tse, Y. C. Yip, J. Tanko and T. Hudlicky, *Chem. Rev.*, 1989, **89**, 165; (d) J. E. Baldwin, *Chem. Rev.*, 2003, **103**, 1197.
44 D. Orr, J. M. Percy, T. Tuttle, A. R. Kennedy and Z. A. Harrison, *Chem. Eur. J.*, 2014, **20**, 14305.
45 Y. Naoshima, M. Yamaguchi, M. Kawai, I. Ichimoto and H. Ueda, *Agric. Biol. Chem.*, 1974, **38**, 2273.
46 T. Aono, H. Sasagawa, K. Fuchibe and J. Ichikawa, *Org. Lett.*, 2015, **17**, 5736.
47 For the use of transition metal difluorocarbene complexes in organic synthesis, see: (a) T. M. Trnka, M. W. Day and R. H. Grubbs, *Angew. Chem. Int. Ed.*, 2001, **40**, 3441; (b) Y. Takahira and Y. Morizawa, *J. Am. Chem. Soc.*, 2015, **137**, 7031; (c) J. Zheng, J.-H. Lin, L.-Y. Yu, Y. Wei, X. Zheng and J.-C. Xiao, *Org. Lett.*, 2015, **17**, 6150; (d) Z. Feng, Q.-Q. Min and X. Zhang, *Org. Lett.*, 2016, **18**, 44; (e) M. Goswami, B. de Bruin and W. I. Dzik, *Chem. Commun.*, 2017, **53**, 4382; (f) X.-P. Fu, X.-S. Xue, X.-Y. Zhang, Y.-L. Xiao, S. Zhang, Y.-L. Guo, X. Leng, K. N. Houk and X. Zhang, *Nat. Chem.*, 2019, **11**, 948; (g) K. Mori, M. Akiyama, K. Inada, Y. Imamura, Y. Ishibashi, Y. Takahira, K. Nozaki and T. Okazoe, *J. Am. Chem. Soc.*, 2021, **143**, 20980.
48 K. Fuchibe, T. Aono, J. Hu and J. Ichikawa, *Org. Lett.*, 2016, **18**, 4502.
49 For the structures of mono- and multinuclear transition metal difluorocarbene complexes in organic synthesis, see for example: (a) ref 47a; (b) X.-Y. Deng, J.-H. Lin and J.-C. Xiao, *Org. Lett.*, 2016, **18**, 4384.
50 (a) B. E. Smart, *Organofluorine Chemistry, Principles and Commercial Applications*, Plenum Press, New York, 1994; (b) K. Uneyama, *Organofluorine Chemistry*, Blackwell Publishing, Oxford, 2006.
51 For example, see: (a) G. Kim, M. Y. Chu-Moyer, S. J. Danishefsky and G. K. Schulte, *J. Am. Chem. Soc.*, 1993, **115**, 30; (b) N. Ruangsupapichat, M. M. Pollard, S. R. Harutyunyan and B. L. Feringa, *Nat. Chem.*, 2011, **3**, 53; (c) M. Yang, J. Li and A. Li, *Nat. Commun.*, 2015, **6**, 6445.
52 (a) M. Sander, *Chem. Rev.*, 1966, **66**, 297; (b) M. Saito and J. Nakayama, *Science of Synthesis*, 2007, **39**, 589.
53 (a) R. M. Kellogg, A. P. Schaap, E. T. Harper and H. Wynbert, *J. Org. Chem.*, 1968, **33**, 2902; (b) R. M. Kellogg and S. Wassenaar, *Tetrahedron Lett.*, 1970, **11**, 1987; (c) Z. Wang, in *Comprehensive Organic Name Reactions and Reagents*, John Wiley & Sons, Inc. (Ed: Z. Wang), Hoboken, 2009, pp 249–253.
54 G. Mloston, J. Romanski and H. Heimgartner, *Heterocycles*, 1999, **50**, 403.
55 K. Fuchibe, A. Yamada, K. Hachinohe, K. Matsumoto and J. Ichikawa, *Bull. Chem. Soc. Jpn.*, 2021, **94**, 2451.
56 R. Takayama, A. Yamada, K. Fuchibe and J. Ichikawa, *Org. Lett.*, 2017, **19**, 5050.
57 J. H. Choi and I. H. Jeong, *Tetrahedron Lett.*, 2008, **49**, 952.

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