Communication

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Direct and Regioselective C—H Oxidative Difluoromethylation of Heteroarenes

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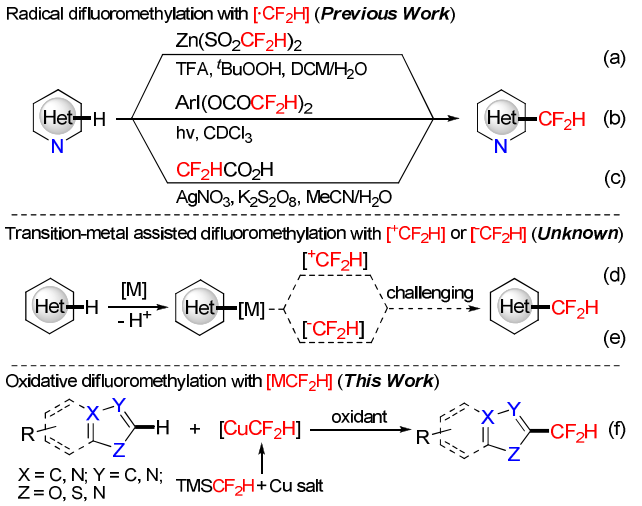
Supporting Information Placeholder

ABSTRACT: The difluoromethyl group (CF_2H) has great interest in the area of medicinal chemistry. However, the investigation of molecules scaffolds containing this group has been hampered by the limitation of synthetic methods for the introduction of CF_2H into heteroarenes. Herein we disclose a new strategy for the direct introduction of difluoromethyl group into heteroarenes via the copper mediated C—H oxidative difluoromethylation of heteroarenes with $TMSCF_2H$. This mild and regioselective method enables the convenient synthesis of a range of difluoromethylated heteroarenesin high yields. The usage of 9,10-phenanthrenequinone (PQ) as an oxidant is critical to the success of this new difluoromethylation reaction.

It is well-recognized that the introduction of fluoroalkyl groups into heteroarenes frequently has a dramatic impact on their physical, chemical, and biological properties.[1] Consequently, the fluorinated heteroarenes have attached increasing interest in the drug discovery.[2] Among them, the difluoromethylated heteroarenes such as thiazopyr (herbicide),[3a] fluxapyroxad (fungicide),[3b] and deracoxib (anti-inflammatory drug)[3c] have shown promising biological activities, probably because the difluoromethyl group (CF_2H) is normally considered as a lipophilic and metabolically stable hydrogen-bond donor.[4] Traditional approaches to difluoromethylated heteroarenes mainly include deoxyfluorination of heteroaromatic aldehydes,[5] difluorination of benzylic C—H bonds,[6] construction of heteroaromatic systems from CF_2H-containing building blocks,[7] and transformation of CF_2R-containing heteroarene precursors.[8] Recently, the transition-metal-assisted difluoromethylation of heteroaromatic compounds (halides,[9] boronic acids,[10] zinc reagents,[11] and diazonium salts[12]) have been developed for the synthesis of difluoromethylated heteroarenes. But these protocols rely on the prefunctionalized substrates.

Over the past decade, the direct transformation of ubiquitous C—H bonds has emerged as a straightforward and atom-economical functionalization method.[13] In 2012, Baran and co-workers reported a direct C—H difluoromethylation of heteroarenes with $Zn(SO_2CF_2H)_2$ through a radical pathway (Scheme 1a).[14a] Very recently, Maruoka[14b] and Nielsen[14c] disclosed the radical difluoromethylation of heteroarenes using $ArI(OCOCF_2H)_2$ (Scheme 1b) or CF_2HCO_2H (Scheme 1c) as the CF_2H sources respectively. However, these radical processes mainly focused on the *N*-containing heteroaromatic substrates (pyridines, pyrroles, pyrimidines, pyrazines, purines, etc.), and in some cases a mixture of regioisomers were formed. Thus, the development of new C—H regioselective difluoromethylation of other heteroaromatic compounds (*O*- or *S*-containing heterocycles) is highly desirable.

Scheme 1.C—H Difluoromethylation of Heteroarenes

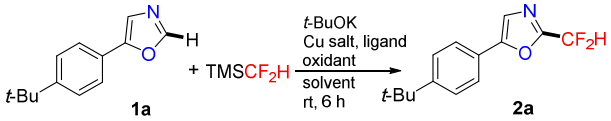


Normally, the transition-metal assisted C—H functionalization involves the first formation of the metal intermediate and followed by reaction with electrophilic[15] or nucleophilic[16] coupling partners. However, to the best of our knowledge, the transition-metal assisted C—H difluoromethylation has not been reported yet. We reasoned that the following two problems might make C—H difluoromethylation challenging: (1) the lack of practical electrophilic difluoromethylating reagents[17] hampered the development of electrophilic coupling pathway (Scheme 1d); (2) the relative instability of CF_2H anion[18] resulted in the difficult of the transmetalation of metal intermediates with nucleophilic difluoromethylating reagents (Scheme 1e). As difluoromethyl metal complexes (L_nMCF_2H, M = Zn, Ag, Cu) are involved in difluoromethylation reactions,[9a-c,f,i,12] we envisioned that the cross-

coupling of heteroarenes and L_nMCF_2H under oxidative conditions might be feasible. In continuation of our research interest in oxidative fluoroalkylation reactions,[19] we disclose here the oxidative C─H difluoromethylation of heteroarenes with [$CuCF_2H$] complexes generated *in situ* from $TMSCF_2H$ and copper salt (Scheme 1f). This protocol provides a convenient and regioselective access to a variety of difluoromethylated *N*- and/or *O*(*S*)-containing heteroarenes, which are difficultly obtained by radical difluoromethylation.

We initiated our studies by exploring the oxidative difluromethylation of oxazoles. The oxazole motif is widely found in pharmaceuticals.[20] However, no method is available for the direct introduction of -CF_2H group into oxazoles. Thus, we chose 5-(4-(*tert*-butyl)phenyl)oxazole (**1a**) as the model substrate to optimize the reaction conditions (Table 1). The oxidative difluoromethylation reaction was firstly conducted with **1a** and $TMSCF_2H$ in the presence of CuCl, phen(1,10-phenanthroline), and an oxidant (DTBP (di-*tert*-butyl peroxide) or Ag_2CO_3). To our disappointment, the reactions failed to deliver the desired product **2a** (entries 1 and 2). Only trace of **2a** was detected in the absence of phen (entry 3). Further screening of the oxidants showed that the oxidant was crucial and only 9,10-phenanthrenequinone (PQ) could promote the desired reaction in 45% yield (entry 6).The use of different copper salts revealed that CuCN was optimal (entries 7-10). Subsequently, switching DMF to NMP or DMA resulted in higher yields (entries 11 and 12). When the reaction was performed at lower or higher temperature, no better results were achieved (entries 13 and 14). To our surprise, the addition of phen led to a significantly diminished yield (entry 15). Finally, the yield of **2a** was improved to 89% by increasing the amounts of $TMSCF_2H$, *t*-BuOK, CuCN, and PQ (entry 16).

Table 1. Optimization of Reaction Conditions[a]

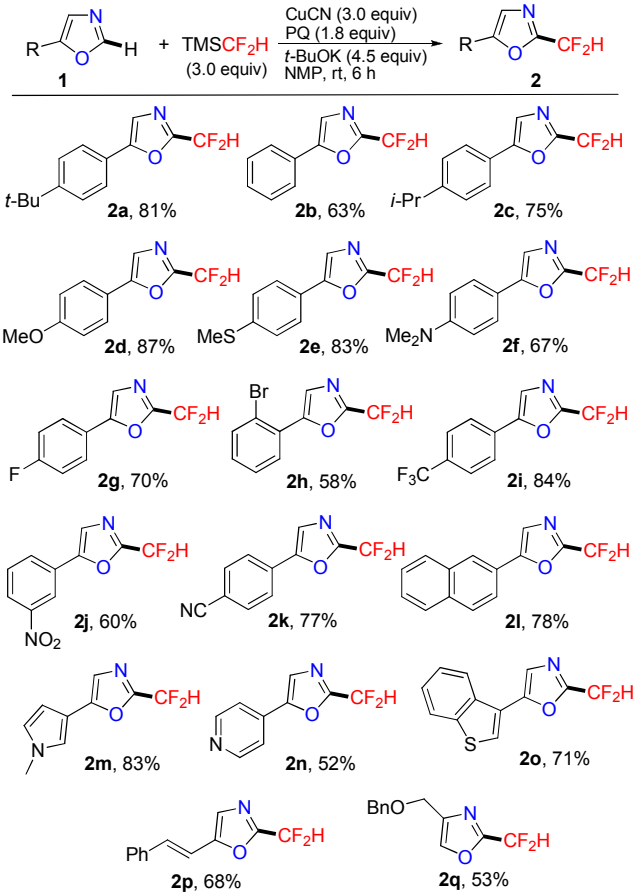


entry	Cu salt	ligand	oxidant	solvent	yield(%)[b]
1	CuCl	phen	DTBP	DMF	0
2	CuCl	phen	Ag_2CO_3	DMF	0
3	CuCl	—	DTBP	DMF	trace
4	CuCl	—	Ag_2CO_3	DMF	0
5	CuCl	—	$PhI(OAc)_2$	DMF	trace
6	CuCl	—	PQ	DMF	45
7	CuI	—	PQ	DMF	38
8	CuTc	—	PQ	DMF	39
9	CuCN	—	PQ	DMF	54
10	CuSCN	—	PQ	DMF	46
11	CuCN	—	PQ	NMP	75
12	CuCN	—	PQ	DMA	63
13[c]	CuCN	—	PQ	NMP	68
14[d]	CuCN	—	PQ	NMP	71
15	CuCN	phen	PQ	NMP	18
16[e]	CuCN	—	PQ	NMP	89

[a]Reaction conditions: **1a** (0.1 mmol), $TMSCF_2H$ (0.2mmol), *t*-BuOK (0.3mmol), Cu salt (0.2 mmol), ligand (0.2 mmol), oxidant (0.12mmol), solvent (2.0 mL), under Ar, rt, 6 h. [b]Yields determined by ^{19}F NMR spectroscopy using trifluoromethylbenzene as an internal standard. [c]0 °C. [d]50 °C. [e]$TMSCF_2H$ (0.3mmol), *t*-BuOK (0.45mmol), CuCN (0.3 mmol), PQ (0.18mmol).

With the optimized reaction conditions in hand, we then evaluated the scope of copper-mediated direct difluoromethylation of oxazoles (Table 2). The mild reaction conditions allow the tolerance of electronically diverse functionalities, including alkyl, methoxy, methylthio, dimethylamino, halide, trifluoromethyl, nitro, and cyano substituents (**1c-1k**). 5-Naphthyloxazole **1l** underwent this transformation smoothly, affording **2l** in high yield. Importantly, oxazoles (**1m-o**) bearing a heteroaryl ring were suitable to give the desired products (**2m-o**) in good yields and excellent chemoselectivites. Besides aryl substituted oxazoles, alkenyl and alkyl substituted oxazoles (**1p** and **1q**) could also be employed in this protocol.

Table 2. Substrate Scope of C─H Difluoromethylation of Oxazoles[a]

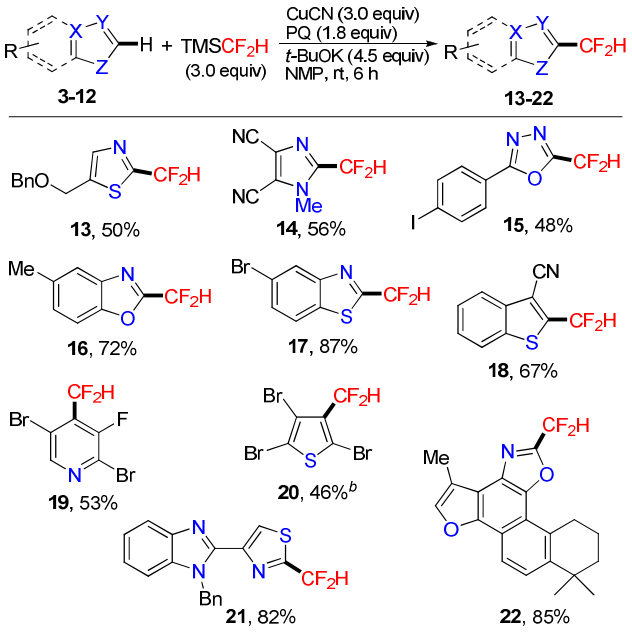


[a]Reaction conditions: **1** (0.2mmol), $TMSCF_2H$ (0.6mmol), CuCN (0.6 mmol), *t*BuOK (0.9mmol), 9,10-phenanthrenequinone (0.36 mmol), NMP (4.0 mL), under Ar, rt, 6 h, isolated yields.

This oxidative C─H difluoromethylation was extended to other heteroarenes. As shown in Table 3, a series of heteroarenes including thiazole (**3**), imidazole (**4**), 1,3,4-oxadiazole (**5**), benzo[*d*]oxazole (**6**), benzo[*d*]thiazole (**7**), benzo[*b*]thiophene (**8**), pyridine (**9**), and thiophene (**10**) were all compatible to afford the corresponding difluoromethylated products **13-20**. It was noteworthy that the CF_2H group was regioselectively attached to the more acidic carbon of the heteroaromatic ring. In the cases of imidazole (**4**), benzo[*b*]thiophene (**8**), pyridine (**9**), and thiophene

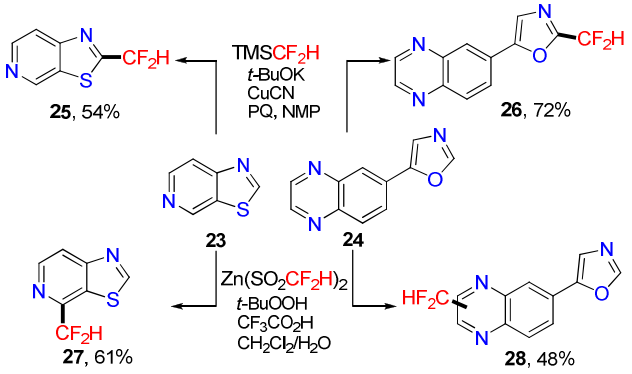
(**10**), the substitution of electron-withdrawing groups is necessary for these transformations. Remarkably, this procedure is also applicable for the late-stage C–H difluoromethylation of biologically relevant compounds. For example, thiabendazole (fungicide and parasiticide)[21] derivative **11** was converted to product **21** in 82% yield. Furthermore, neosalvianen (natural product isolated from *Salvia miltiorrhiza*)[22] analog **12** underwent this oxidative difluoromethylation reaction to give compound **22** in 85% yield. Unfortunately, other types of heteroarenes including caffeine, pyrimidine, and 1,3,5-triazine only afforded trace amounts of the desired products.

Table 3. C–H Difluoromethylation of Other Heteroarenes[a]



[a]Reaction conditions: **3-12** (0.2mmol), $TMSCF_2H$ (0.6mmol), CuCN (0.6 mmol), *t*-BuOK (0.9mmol), 9,10-phenanthrenequinone (0.36 mmol), NMP (4.0 mL), under Ar, rt, 6 h, isolated yields. [b]Yields determined by ^{19}F NMR spectroscopy using trifluoromethylbenzene as an internal standard.

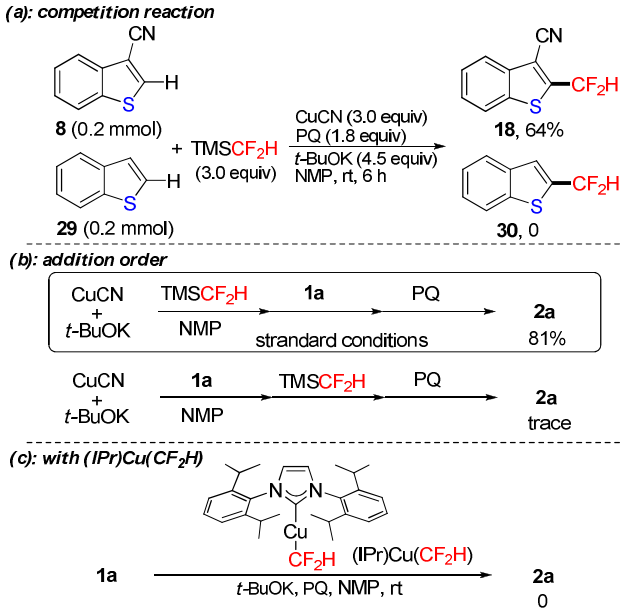
Scheme 2.Comparison withOxidative and Radical C–H Difluoromethylation



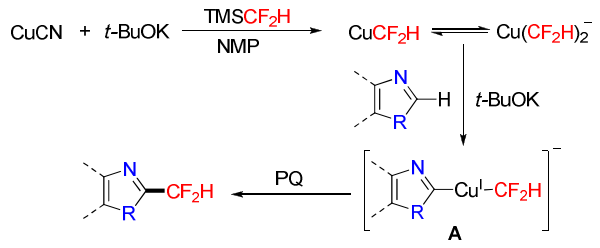
To further understand the scope and limitation of this protocol, the C-H difluorometylation of the same heteroarenes under this oxidative and Baran's radical[14a] reaction conditions was investigated. As shown in Scheme 2, the oxidative difluoromethylation of thiazolo[5,4-*c*]pyridine (**23**) and 5-(quinoxalin-6-yl)oxazole (**24**) bearing several potential reactive sites took place exclusively on the more acidic carbon of azole rings, affording the difluoromethylated products **25** and **26**. On the other hand, compounds **23** and **24** underwent radical difluoromethylation to give products **27** and **28**, in which the CF_2H group was connected to the more electron-poor carbon adjacent to the nitrogen atoms of the heteroarenes. These results clearly demonstrated the complementarity and orthogonality of oxidative and radical difluoromethylation reactions.

To gain insight into the reaction mechanism of the C-H oxidative difluoromethylation, a competition reaction was conducted with equivalent amount of compounds **8** and **29** (Scheme 3a). The difluoromethylation of **8** took place exclusively to afford product **18** in 64% yield, and no conversion was observed for less acidic substrate **29**. This experimental result showed that the deprotonation of the acidic C-H bond of herteroarene with base was crucial to the oxidative difluoromethylation. Furthermore, the addition order of the substrates was important for this reaction. Under the standard procedures, $TMSCF_2H$, **1a**, and PQ must be successively added to the mixture of *t*-BuOK and CuCN in NMP (Scheme 3b). If **1a** was added before $TMSCF_2H$, only trace of **2a** was observed. These result demonstrated that difluoromethylcopper complex must be generated firstly. Finally, the oxidative coupling of **1a** with the isolated $(IPr)Cu(CF_2H)$[9i] failed to give the desired product **2a** (Scheme 3c). We assumed that the bulky IPr ligand might deactivate the $CuCF_2H$ specie for this reaction, which was consistent with the experimental observation (Table 1, entry 15). On the basis of the above experimental results and reported mechanisms for similar reactions,[19e,23] a preliminary reaction mechanism was proposed (Scheme 4). First, treatment of $TMSCF_2H$ with *t*-BuOK and CuCN gave $CuCF_2H$ and $Cu(CF_2H)_2^-$.[9b,c] Then, deprotonation of hereroarene with *t*-BuOK and transmetalation delivered intermediate **A**. Finally, oxidation of intermediate **A** with PQ[24] followed by reductive elimination afforded the desired product.

Scheme 3.Mechanistic Investigation



Scheme 4.Proposed Reaction Mechanism



In conclusion, we have developed a copper-mediated oxidative C─H difluoromethylation of a variety of heteroarenes including oxazloe, thiazole, imidazole, 1,3,4-oxadiazole, benzo[*d*]oxazole, benzo[*d*]thiazole, benzo[*b*]thiophene, pyridine, thiophene, and thiazolo[5,4-*c*]pyridine. This protocol provides a new method for selective synthesis of the difluoromethylated heteroarenes that were not accessible by the reported reactions.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Detailed experimental procedures and spectra data for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1)(a) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (b) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (c) Meanwell, N. A. *J. Med. Chem.* **2011**, *54*, 2529. (d) Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.;Meanwell, N. A. *J. Med. Chem.* **2015**, *58*, 8315.

(2) (a)Fustero, S.; Sanchez-Rosello, M.; Barrio, P.; Simon-Fuentes, A. *Chem. Rev.* **2011**, *111*, 6984. (b) Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; delPozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014**, *114*, 2432. (c) Vitale, A.; Bongiovanni, R.; Ameduri,B. *Chem. Rev.* **2015**, *115*, 8835. (d) Zhou, Y.; Wang, J.; Gu, Z.; Wang, S.; Zhu, W.; Acena,J. L.; Soloshonok,V. A.; Izawa, K.; Liu, H. *Chem. Rev.* **2016**, *116*, 422.

(3) (a) Page, M. J.; Ma, Y.; Qi, H.; Healy, E.; Trolinger, J. *J. Agric. Food Chem.* **1997**, *45*, 3095. (b) Chen, X.; Dong, F.; Xu, J.; Liu, X.; Wu, X.; Zheng, Y. *J. Agric. Food Chem.* **2016**, *64*, 8935. (c) Penning,T. D.; Talley,J. J.; Bertenshaw,S. R.; Carter,J. S.; Collins,P. W.; Doctor,S.; Graneto,M. J.; Lee,L. F.; Malecha,J. W.; Miyashiro,J. M.; Rogers,R. S.; Rogier,D. J.; Yu,S. S.; Anderson,G. D.; Burton,E. G.; Cogburn,J. N.; Gregory,S. A.; Koboldt,C. M.; Perkins,W. E.; Seibert, K.; Veenhuizen,A. W.; Zhang, Y. Y.; Isakson,P. C.*J. Med.Chem.***1997**, *40*, 1347.

(4) (a) Erickson, J. A.; McLoughlin, J. I. *J. Org. Chem.***1995**, *60*, 1626. (b) Caminati, W.; Melandri, S.; Moreschini, P.; Favero, P. G. *Angew.Chem., Int. Ed.***1999**, *38*, 2924. (c) Jones, C. R.; Baruah, P. K.; Thompson, A. L.; Scheiner, S.;Smith, M. D. *J. Am. Chem. Soc.***2012**, *134*, 12064. (d) Prakash, G. K. S.; Krishnamoorthy, S.; Ganesh, S. K.; Kulkarni,A.; Haiges, R.; Olah, G. A. *Org. Lett.* **2014**, *16*, 54. (e) Sessler,C. D.; Rahm,M.; Becker,S.; Goldberg,J. M.; Wang, F.; Lippard, S. J. *J. Am. Chem. Soc.***2017**, *139*, 9325.

(5) (a) Dishington, A.; Feron, J. L.; Gill, K.; Graham, M. A.; Hollingsworth, I.; Pink,J. H.; Roberts, A.; Simpson, I.; Tatton, M. *Org. Lett.* **2014**, *16*, 6120. (b) Ivonin, S. P.; Kurpil', B. B.; Bezdudny, A. V.; Volochnyuk, D. M.; Grygorenko, O. O. *J. Fluorine Chem.* **2015**, *176*,78.

(6) (a) Xia, J.-B.; Zhu, C.; Chen, C. *J. Am. Chem. Soc.* **2013**,*135*, 17494.(b) Xu, P.; Guo, S.; Wang, L.; Tang, P.*Angew. Chem., Int. Ed.* **2014**, *53*, 5955.

(7) (a) Mykhailiuk, P. K. *Angew. Chem., Int. Ed.* **2015**, *54*, 6558.(b) Wu, J.; Xu, W.; Yu, Z.-X.; Wang, J. *J. Am. Chem. Soc.* **2015**, *137*, 9489.(c) Okusu, S.; Tokunaga, E.; Shibata, N .*Org. Lett.* **2015**, *17*, 3802. (d) Rong, J.; Deng, L.; Tan, P.; Ni, C.; Gu, Y.; Hu, J. *Angew. Chem., Int. Ed.* **2016**, *55*, 2743.

(8) (a) Gui, J.; Zhou, Q.; Pan, C.-M.; Yabe, Y.; Burns, A. C.; Collins, M. R.; Ornelas, M. A.; Ishihara, Y.; Baran, P. S. *J. Am. Chem. Soc.* **2014**, *136*, 4853. (b) Belhomme, M.-C.; Poisson, T.;Pannecoucke, X. *J. Org. Chem.* **2014**, *79*, 7205.(c) Shi, H.; Braun, A.; Wang, L.; Liang, S. H.; Vasdev, N.; Ritter, T. *Angew. Chem., Int. Ed.* **2016**, *55*, 10786. (d) McAtee, R. C.; Beatty, J. W.; McAtee, C. C.; Stephenson, C. R. J. *Org. Lett.* **2018**, *20*, 3491.

(9) (a) Prakash, G. K. S.; Krishnan, H. S.; Jog, P. V.; Iyer, A. P.; Olah, G. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 12090. (b) Fier, P. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2012**, *134*, 5524. (c) Jiang, X.-L.; Chen, Z.-H.; Xu, X.-H.; Qing, F.-L. *Org. Chem. Front.* **2014**, *1*, 774.(d) Gu, Y.; Leng, X.-B.; Shen, Q. *Nat. Commun.* **2014**,*5*, 5405. (e) Xu, L.; Vicic, D. A. *J. Am. Chem. Soc.* **2016**, *138*, 2536. (f) Serizawa, H.; Ishii, K.;Aikawa, K.;Mikami, K. *Org. Lett.* **2016**, *18*, 3686. (g) Aikawa, K.; Serizawa, H.; Ishii, K.;Mikami, K. *Org. Lett.* **2016**, *18*, 3690. (h) Lu, C.; Gu, Y.; Wu, J.; Gu, Y.; Shen, Q. *Chem. Sci.* **2017**, *8*, 4848. (i) Bour, J. R.; Kariofillis, S. K.; Sanford, M. S. *Organometallics* **2017**, *36*, 1220. (j) Lu, C.; Lu, H.; Wu, J.; Shen, H. C.; Hu, T.; Gu, Y.; Shen, Q. *J. Org. Chem.* **2018**, *83*, 1077. (k) Xu, C.; Guo, W.-H.; He, X.;Guo, Y.-L.; Zhang, X.-Y.; Zhang, X. *Nat. Commun.* **2018**,*9*, 1170.

(10) (a) Feng, Z.; Min. Q.-Q.; Zhang, X. *Org. Lett.* **2016**, *18*, 44. (b) Deng, X.-Y.; Lin, J.-H.; Xiao, J.-C. *Org. Lett.* **2016**, *18*, 4384. (c) Feng, Z.; Min. Q.-Q.; Fu, X.-P.; An, L.; Zhang, X. *Nat. Chem.* **2017**,*9*, 918. (d) Sheng, J.; Ni, H.-Q.;Bian, K.-J.; Li, Y.; Wang, Y.-N.; Wang, X.-S. *Org. Chem. Front.* **2018**, *5*, 606.

(11) Miao, W.; Zhao, Y.; Ni, C.; Gao, B.; Zhang, W.; Hu, J. *J. Am. Chem. Soc.* **2018**, *140*, 880.

(12) Matheis, C.; Jouvin, K.; Goossen, L. J. *Org. Lett.* **2014**, *16*, 5984.

(13) For selected reviews, see: (a) Lyons,T.W.; Sanford,M. S. *Chem.Rev.* **2010**, *110*, 1147. (b) Yeung,C. S.; Dong,V. M. *Chem. Rev.* **2011**, *111*, 1215. (c) Ackermann, L. *Chem. Rev.* **2011**,*111*, 1315. (d) Liu, C.; Yuan, J.; Gao, M.; Tang, S.; Li, W.; Shi, R.; Lei, A. *Chem. Rev.* **2015**, *115*, 12138. (e) Zhu, R.-Y.; Farmer, M.E.; Chen, Y.-Q.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2016**, *55*, 10578. (f) Hartwig, J. F. *J. Am. Chem. Soc.* **2016**, *138*, 2.(g) Yang, Y.; Lan, J.; You, J. *Chem. Rev.* **2017**, *117*, 8787.

(14) (a) Fujiwara, Y.; Dixon, J. A.; Rodriguez, R. A.; Baxter, R. D.; Dixon, D. D.; Collins, M. R.; Blackmond, D. G.; Baran, P. S. *J. Am. Chem. Soc.* **2012**, *134*, 1494. (b) Sakamoto, R.;Kashiwagi, H.;Maruoka, K. *Org. Lett.* **2017**, *19*, 5126. (c) Tung, T. T.; Christensen, S. B.; Nielsen, J. *Chem. Eur. J.* **2017**, *23*, 18125.

(15) For selected examples, see: (a) Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 2300. (b) Hull, K. L.; Anani, W. Q.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 7134. (c) Wang, X.; Truesdale, L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 3648. (d) Tran, L. D.; Popov, I.; Daugulis, O. *J. Am. Chem. Soc.* **2012**, *134*, 18237.

(16) For selected examples, see: (a) Giri, R.; Maugel, N.; Li, J.-J.; Wang, D.-H.; Breazzano, S. P.; Saunders, L. B.; Yu, J.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 3510. (b) Hull, K. L.; Anani, W. Q.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 11904. (c) Zhang, S.-Y.; He, G.; Zhao, Y.; Wright, K.; Nack, W. A.; Chen, G. *J. Am. Chem. Soc.* **2012**, *134*, 7313. (d) Shang, M.; Sun, S.-Z.; Wang, H.-L.; Laforteza, B. N.; Dai, H.-X.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2014**, *53*, 10439.

(17) Most of the electrophilic difluoromethylation reactions involve difluorocarbene intermediates. The direct transfer of CF_2H group through electrophilic approaches is rare. For reviews, see: (a)Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 8214. (b) Lu, Y.; Liu, C.; Chen, Q.-Y. *Curr. Org. Chem.* **2015**, *19*, 1638. (c) Rong, J.; Ni, C.; Hu, J.

Asian J. Org. Chem. **2017**, *6*, 139. (d) Yerien, D. E.;Barata-Vallejo, S.;Postigo, A. *Chem. Eur. J.* **2017**, *23*, 14676.

(18) The difluoromethylanion is prone to α-elimination, see: (a) Burton, D. J.; Hartgraves, G. A. *J. Fluorine Chem.* **2007**, *128*, 1198. (b) Hu, J.; Zhang, W.; Wang, F. *Chem. Commun.* **2009**, 7465.

(19) (a) Chu, L.; Qing, F. L. *Acc.Chem. Res.* **2014**, *47*, 1513. (b) Chu, L.; Qing, F. L. *J. Am. Chem. Soc.* **2010**, *132*, 7262. (c) Chen, C.; Xie, Y.; Chu, L.; Wang, R.-W.; Zhang, X.; Qing, F.-L. *Angew. Chem., Int. Ed.* **2012**, *51*, 2492. (d)Chu, L.; Qing, F.-L. *J.Am. Chem. Soc.* **2012**, *134*, 1298. (e) Chu, C.;Chu, L.; Qing, F. L. *J. Am. Chem. Soc.* **2012**, *134*, 12454. (f) Liu, J.-B.; Chen, C.; Chu, L.; Chen, Z.-H.; Xu, X.-H.; Qing, F.-L. *Angew. Chem., Int. Ed.* **2015**, *54*, 11839.

(20) (a) Wipf, P. *Chem. Rev.* **1995** ,*95*, 2125. (b) Jin, Z. *Nat. Prod. Rep.* **2006**, *23*, 464.

(21) Schiffmann, R.; Neugebauer, A.; Klein, C. D. *J. Med. Chem.* **2006**, *49*, 511.

(22) Don, M.-J.; Shen, C.-C.; Lin, Y.-L.; Syu, W.-J.; Ding, Y.-H.; Sun, C.-M. *J. Nat. Prod.* **2005**, *68*, 1066.

(23) Yang, F.; Xu, Z.; Wang, Z.; Yu, Z.; Wang, R. *Chem. Eur. J.* **2011**, *17*, 6321.

(24) (a) Speier, G.; Tyeklár, Z.; Tóth, P.; Speier, E.; Tisza, S.; Rockenhauer, A.; Whalen, A. M.; Alkire, N.; Pierpont, C. G. *Inorg. Chem.* **2001**, *40*, 5653. (b) Roy, S.; Sarkar, B.; Bubrin, D.; Niemeyer, M.; Záliš, S.; Lahiri, G. K.; Kaim, W. *J.Am. Chem. Soc.* **2008**, *130*, 15230.