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Difluoroacetic Acid as a New Reagent for Direct C-H Difluoromethylation of Heteroaromatic Compounds

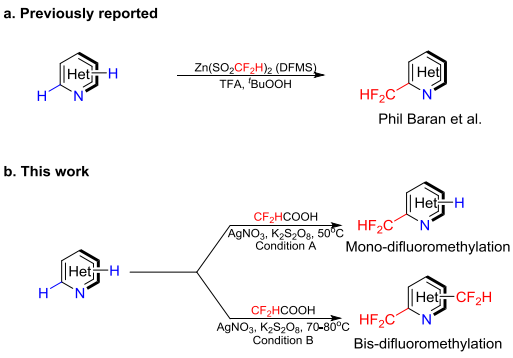
Truong Thanh Tung, Søren Brøgger Christensen and John Nielsen*

Abstract: A technically simple procedure for direct C-H difluoromethylation of heteroaromatic compounds using off-the-shelf difluoroacetic acid as the difluoromethylating reagent has been developed. Mono-difluoromethylation versus bis-difluoromethylation is controlled as the result of the reaction temperature. The reactions described here enable access to the late-stage C–H mono- and bis-difluoromethylation for preparation of tool compounds for chemical biology and provide access to this hitherto untapped substituent for drug discovery.

Approximately 20-25 % of marketed drugs contain fluorine atoms revealing that this particular element plays a pivotal role in modern drug discovery and development.[1,2] Introduction of fluorine atoms in lead compounds enhance the druggability by transforming the physicochemical properties as well as habitually improving both chemical and metabolic stability.[1,3] Whereas fluorine atoms and trifluoromethyl groups have been introduced in a large number of drugs,[1,2] the difluoromethyl (CF_2H) moiety is much less in common. Three examples are roflumilast [for treatment of asthma and chronic obstructive pulmonary disease (COPD)],[2] pantoprazole [for treatment of gastroesophageal reflux disease (GERD)] and eflornithine [for treatment of sleeping disease (trypanosimiasis)].[3d,4] In the cases of roflumilast and pantoprazole, the introduction of the difluoromethyl moiety improved the pharmacokinetic properties enabling the use of the drug in the clinic. In contrast, the ability of the two fluorine atoms to function as leaving groups makes difluoroornithine (eflornithine) an electrophilic suicide inhibitor of ornithine decarboxylase.[3d]

The presumption that the difluoromethyl group is a hydrophobic hydrogen donor being a bioisoster of hydroxy, amino and sulfanyl groups has inspired studies of the effect of replacing these groups with difluoromethyl moieties.[5,6] However, these studies have been hampered by the limited number of synthetic routes available for the introduction of the CF_2H into heteroaromatic compounds.[7-9] Thus, a technically simple, convenient and direct synthetic method would enable medicinal chemists, biologists, and pharmacologists to investigate the properties of such bioisosters.

The most well-known strategy for the introduction of a difluoromethyl group on aromatic rings is deoxyfluorination of aldehydes using (diethylamino)sulfur trifluoride (DAST) and its derivatives.[10] However, the low functional group compatibility of these methods has limited its broad application in practice. Currently, synthetic chemists pay great attention to the development of novel metal-catalyzed difluoromethylation reactions.[9] Nevertheless, these reactions rely on substitution of a halogen atom,[11,12a-f] a boronic acid,[12g,h] a triflyloxy group[11b] or diazonium salt[12i] with the difluoromethylated sources, respectively. The preparation of difluoromethylated compounds via silver-catalyzed decarboxylation of α-fluoroarylacetic acids[12j], α,α-difluoroarylacetic acids[12k] were also reported.[12l] To date, only one method for innate C-H functionalization of *N*-containing heteroaromatic with the difluoromethyl radicals has been reported deploying zinc difluoromethanesulfinate (DFMS) in stoichiometric amounts as the key difluoromethylating reagent (**Scheme 1**).[13,14] However, this procedure is mainly focused on mono-difluoromethylation. The use of DFMS does not enable the selectivity, controllability of bis-difluoromethylation toward mono-difluoromethylation and *vice versa*.



Scheme 1. Previous approaches to direct difluoromethylation and current discovery of direct mono- and one-step bis-difluoromethylation.

Herein, we wish to report the direct and innate C-H functionalization and mono-selective introduction of one difluoromethyl moiety into heteroaromatic compounds using difluoroacetic acid as the difluoromethyl radical source. The methodology furthermore offers for the first time the opportunity to introduce two difluoromethyl moieties in a controllable manner by varying the reaction conditions.

As part of a recent project on the design and synthesis of fusaric acid analogues,[15] we recently applied the Minisci reaction to introduce alkyl groups to the pyridine ring via a well-established

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radical process.[16,17] To our delight, in the presence of difluoroacetic acid, a difluoromethylated derivative was obtained by a silver(I)/persulfate-catalyzed reaction (**Table 1**, entry 2). This exciting discovery encouraged us to develop and optimize a new protocol for difluoromethylation of heteroaromatic rings using off-the-shelf difluoroacetic acid and to further investigate the scope and limitations of this novel reaction.

The conditions listed in **Table 1** were screened. A ratio of 0.5 equivalent of silver(I) nitrate ($AgNO_3$) and 5 equivalent of the oxidant potassium persulfate ($K_2S_2O_8$) afforded the best yields (**Table 1**, entry 3). Decomposition was observed if higher ratios of $K_2S_2O_8$ and $AgNO_3$ were used (**Table 1**, entry 4). Heating is required as demonstrated by a yield of less than 5 % if the reaction is run at room temperature (**Table 1**, entry 5).

Table 1. Optimization of reaction conditions.

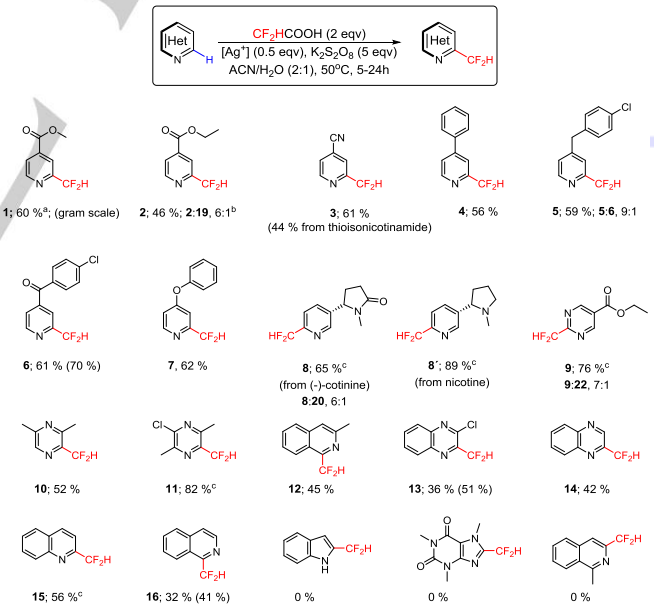
Entry	Solvent (+H_2O)[a]	[Ag^+][b]	Oxidation (equiv.)[c]	Add.[d]	T °C	Yield (%)[e]
1	ACN	$AgNO_3$	$K_2S_2O_8$(1)	-	50	13
2	ACN	$AgNO_3$	$K_2S_2O_8$(3)	-	50	50
3	**ACN**	**$AgNO_3$**	**$K_2S_2O_8$(5)**	**-**	**50**	**71**
4	ACN	$AgNO_3$	$K_2S_2O_8$(7)[f]	-	50	55
5	ACN	$AgNO_3$	$K_2S_2O_8$(5)	-	rt[g]	<5
6	Acetone	$AgNO_3$	$K_2S_2O_8$(5)	-	50	10
7	DCM	AgNO3	$K_2S_2O_8$(5)	-	rt-40	n.r[h]
8	EtOH	$AgNO_3$	$K_2S_2O_8$(5)	-	rt-50	n.r
9	MeOH	$AgNO_3$	$K_2S_2O_8$(5)	-	rt-50	n.r
10	Dioxane	$AgNO_3$	$K_2S_2O_8$(5)	-	rt-50	n.r
11	DMF	$AgNO_3$	$K_2S_2O_8$(5)	-	rt-50	n.r
12	ACN	$AgNO_3$	*t*BuOOH(1-5)	-	rt	n.r
13	ACN	$AgNO_3$	*t*BuOOH(1-5)	-	50	<5
14	ACN	$AgNO_3$	$(NH_4)_2S_2O_8$(1-5)	-	50	11
15	ACN	$AgNO_3$	H_2O_2(1-5)	-	50	<5
16	ACN	AgDFA[i]	$K_2S_2O_8$(5)	-	50	7
17	ACN	$AgClO_4$	$K_2S_2O_8$(5)	-	50	12
18	ACN	AgF	$K_2S_2O_8$(5)	-	50	32
19	ACN	AgOTf	$K_2S_2O_8$(5)	-	50	27
20	ACN	$AgNO_3$	$K_2S_2O_8$(5)	$FeSO_4$	50	30
21	ACN	-	$K_2S_2O_8$(5)	$FeSO_4$	50	n.r
22	ACN	$AgNO_3$	$K_2S_2O_8$(5)	Cu_2SO_4	50	21
23	ACN	-	$K_2S_2O_8$(5)	Cu_2SO_4	50	n.r

[a]2:1 (v/v). [b]0.5 equivalent of $AgNO_3$ gives the best conversion rate in our studies. [c]equivalents are given in parentheses. [d]0.1 equivalent when using as addictive to $AgNO_3$ and 0.5 equivalent when using as catalyst. [e]Yields are based on ^{19}F-NMR using 4-fluorobenzoic acid as internal standard. [f]Decomposition and yield reduction was observed (by complicated TLC chromatograms with many inseparable spots and complicated UPLC-MS) when increasing the amount of $K_2S_2O_8$ to over 5 equiv. [g]r.t, room temperature. [h]n.r, no reaction. [i]$AgOCOCF_2H$, in situ prepared by the reaction of Ag_2CO_3 and CF_2HCOOH.

Acetonitrile was found to be the optimum solvent. The use of EtOH, MeOH, DCM, dioxane or DMF (**Table 1**, entries 7-11) resulted in no reaction and a poor yield was obtained with acetone (**Table 1**, entry 6). Attempts to use other oxidants than $K_2S_2O_8$ such as *t*BuOOH, H_2O_2 or $(NH_4)_2S_2O_8$ also afforded a poor yield (**Table 1**, entries 12-15).

The use of different silver salts (**Table 1**, entries 16-19) revealed that $AgNO_3$ provided the highest yield. Other metals salts such as iron(II) sulfate or copper(I) sulfate were tested and found to be inferior (**Table 1**, entries 20-23). These observations made us adopt the reaction conditions showed in entry 3, **Table 1** as the preferred standard conditions for the mono-difluoromethylation.

Mono-difluoromethylation of a number of *N*-heteroaromatic substrates including some commonly appearing in pharmaceutically interesting heteroaromatic scaffolds like pyridine, pyrimidine, pyrazine, quinoline, quinoxaline and selected natural products was successfully performed (**Scheme 2**). The standard reaction conditions in general afforded a product, in which one difluoromethyl group was regioselectively attached to the ring in the position neighboring the nitrogen atom (C-2). The selectivity of the substitution was also observed when heterocyclic scaffold contained multiple potentially reactive positions. Moreover, the reaction is compatible with the presence of halogen atoms in the molecule (compounds **5**, **6**, **11**, **13**, **Scheme 2**). The practicality and scalability of the reaction was demonstrated by the preparation of compound **1** from 1 g of methyl isonicotinate using lower amount of $AgNO_3$ (20 mol%) and $K_2S_2O_8$ (2.5 equiv., **Scheme 2**). In case of **8**, **8´**, **9**, **11**, **15**, the low yields obtained when using the standard reaction condition. However, a significant improvement of the yield was observed by adding H_2SO_4 to support the protonation process (See SI). Some limitations of the present procedure are illustrated by the finding that indole, caffeine and 1-methylisoquinoline did not react under the standard conditions.



Scheme 2. Scope of the mono-difluoromethylation using standard reaction conditions. Yields are isolated yield. ^{19}F-NMR yields are given in parentheses. [a]1 gram scale, $AgNO_3$ 0.2 equivalent and $K_2S_2O_8$ 2.5 equiv., 6 % of mono-C3-CF_2H as minor product was isolated, 22 % of starting material recovered. [b]Ratios are based on ^{19}F-NMRs. [c]10 mol% of H_2SO_4 was added to standard reaction condition (see SI).

Under the standard reaction conditions, difluoromethylation of quinoline afforded the monosubstituted derivative 2-

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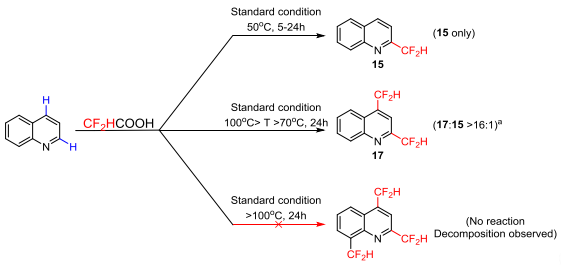
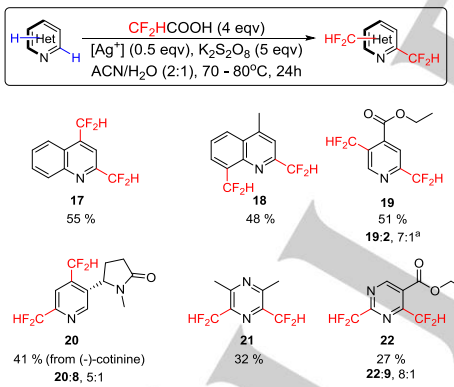
(difluoromethyl)quinoline as the dominant product (**15**, **Scheme 2**). In contrast, the use of DFMS resulted in formation of 2,4-bis(difluoromethyl)quinoline.[13] Noteworthy, during the synthesis of compounds **2**, **8** and **9** (**Scheme 2**), bis-difluoromethylated products were observed in minor amounts. Encouraged by these observations, we investigated if a one-step disubstitution of quinoline could be accomplished using difluoroacetic acid as reagent and $AgNO_3$ as catalyst applying more forceful reaction conditions. Indeed, increasing the reaction temperature to 70 °C or slightly higher, successfully afforded **17** as the major product in one-step from quinoline (mono-bis, 1:16, **Scheme 3**). Thus, the present reaction not only enables selective monosubstitution but intensified reaction conditions empower a one-step disubstitution. With these new reaction conditions in hand, several heteroaromatic systems were successfully bis-difluoromethylated as listed in **Scheme 4**.



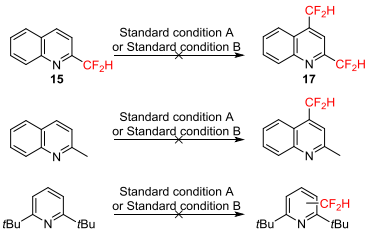
Scheme 3. Controllability of the mono- and bis- difluoro-methylation of quinoline. No tri-substitution/decomposition when temperature increasing to above 100 °C. Boiling point of CF_2HCOOH is 132-134 °C. [a]Ratio is based on ^{19}F-NMR.



Scheme 4. Scope of the one-step bis-difluoromethylation using standard reaction conditions. Yields are isolated yield. [a]Ratios are based on ^{19}F-NMRs.

Mono-difluoromethylation occurs at the electron poor carbon atom neighboring the nitrogen atom (**Scheme 2**) indicating that a nucleophilic difluoromethyl radical reacts with the heterocycles. This assumption also deliniates the substitution pattern in the bis-difluoromethylated quinoline molecule, where the second difluoromethyl group is attached to the electron deficient (*i. e.* the C-4 position) to form **17** (**Scheme 3**).

Noteworthy, the products arising from the bis-difluoromethylation always contain one of the difluoromethyl moieties at the C-2 position. In several cases (**Scheme 4**), small amounts of the C-2 mono-difluoromethylated product were observed along with bis-difluoromethylated product. In general, the second difluoromethyl radical preferentially reacts with the electron deficient carbon in the heteroaromatic ring. During the bis-difluoromethylation of 4-methylquinoline, in which the C-4 position is blocked by a methyl group, the second difluoromethyl group is installed at the C-8 (**18**, **Scheme 4**). Since C-8 is not an electron deficient position, this represents an exception from the general observed rules. This unexpected product might be formed via reaction of the radical intermediate generated after the initial reaction installing the first difluoromethyl moiety with a second difluoromethyl radical. A study of the resonance structures of this intermediate reveals that it is possible to rationalize a plausible resonance structure with the radical at C-8.[18] The assumption that the second alkylation occurs by the reaction of an intermediate formed after the first alkylation is supported by the observation that compound **15** cannot be converted into **17** (**Scheme 5**) whereas conversion of quinoline into **17** occurs smoothly by a one-step reaction (**Scheme 3**). In addition, no reaction occurs when blocking C-2 in the compounds tested (**Scheme 5**). Thus, we believed that the introduction of the first difluoromethyl moiety at C-2 under the reinforced reaction conditions (higher temperature, > 70 °C) leads to formation of an intermediate, which reacts with the second difluoromethyl radical affording formation of the disubstituted product. Overall, the site-selectivity of second difluoromethyl radical depends on availability of electron deficient positions and the substitution pattern in the heteroaromatic ring.



Scheme 5. Limitation and mechanistic studies of mono/bis-difluoromethylation. No reaction was observed when C-2 blocked.

Interestingly, in the case of ethyl 4-nicotinate, the second difluoromethyl group was introduced into the electron deficient C-5 position (compound **19**) and not at C-6. Apparently, the electron withdrawing effect of the carbonyl group overrules the directing effects of the nitrogen on C-6. In the report by Fujiwara et al.[13] 2,6-difluoromethylation of isonicotinamide is the dominating product when DFMS is used as the reagent. The different product distribution indicates dissimilar reaction pathways. One explanation could be that two independent alkylations occur when using DFMS.[13] Using the present reactions conditions, the 2,6-difluoromethylated product is only formed if the 3,5-dimethylpyrazine was transformed to the corresponding bis-difluoromethylated product (**21**) in a one-pot procedure.

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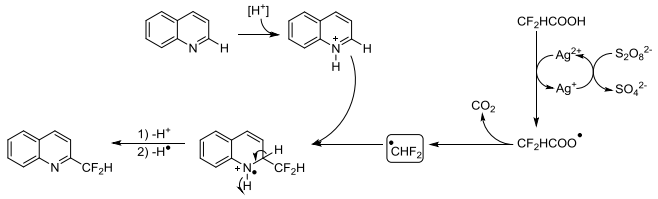
Attempt to perform tri-substitution by increasing the reaction temperature to above 100 °C solely resulted in decomposition (**Scheme 3**).

Based on our observation and the recent mechanistic studies,[12g,12h,19,20] we propose the mechanism depicted in **Scheme 6** for mono-difluoromethylation of quinoline. Specifically, we proposed that the formation of difluoromethyl radical is evoked by silver-catalyzed oxidative decarboxylation of difluoroacetic acid and subsequent addition to the heteroaromatic ring.



Scheme 6. Plausible mechanism for mono-difluoromethylation. Proposed mechanism for mono-difluoromethylation of quinoline.[21]

In conclusion, we have discovered that difluoroacetic acid can be used as a new reagent for innate C-H difluoromethylation of heteroaromatic compounds. The procedure presented is technically simple, scalable, inexpensive, controllable and a direct C-H activation synthetic methodology for preparation of both mono- and bis-difluoromethylated derivatives of *N*-containing heteroaromatics. Remarkably, the present protocol employs the easily accessible and off-the-shelf difluoroacetic acid as starting material. Furthermore, the late-stage one-step access to bis-difluoromethylated products is novel and has enabled synthesis of several compounds, which were not available using previously reported reaction conditions. Since the protocol makes a broad number of difluoromethylated derivatives of heteroaromatic compounds available, this report enables preparation of previous inaccessible tool compounds for biological assays and predictably important lead structures for drug discovery. Intensive studies on the mechanism as well as expanding the scope of this reaction are currently being performed in our lab.

Acknowledgements

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Keywords: difluoromethylation • difluoroacetic acid • bis-difluoromethylation • radicals

[1] A. Vulpetti, C. Dalvit, *Drug. Discov. Today*. **2012**, *17*, 890-897.

[2] J. Wang, M. Sánchez-Roselló, J.L. Aceña, C.D. Pozo, A.E. Sorochinsky, S. Fustero, V.A. Soloshonok, H. Liu, *Chem. Rev*. **2014**, *114*, 2432-2506.

[3] a) E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly, N. A. Meanwell, *J. Med. Chem.* **2015**, 58, 8315-8359; b) I. Ojima in *Fluorine in Medicinal Chemistry and Chemical Biology*, (Eds.: I. Ojima), Wiley-VCH, Weinheim, **2009**; c) S. Purser, P. R. Peter, S. Swallow, V. Gouverneur, Chem. Soc. Rev. **2008**, 37, 320-330; d) K. Müller, C. Faeh, F. Diederich, *Science*. **2007**, *317*, 1881-1886; (d) R. Poulin; L. Lu; B. Ackermann; P. Bey; A. E. Pegg, *J. Biol. Chem.* **1992**, 267, 150-158.

[4] There are six other drugs containing CF_2H: zardaverine, D0870, RS 71684, flucythrinate, foridon and devacoxib. However, It should be noted that roflumilast, pantoprazole, zardaverine, RS 71684 and flucythrinate are actually containing -OCF_2H not carbon-bonded -CF_2H.

[5] N.A. Meanwell, *J. Med. Chem.* **2011**, *54*, 2529-2591.

[6] a) G.W. Rewcastle, S.A. Gamage, J.U. Flanagan, R. Frederick, W.A. Denny, B.C. Baguley, P. Kestell, R. Singh, J.D. Kendall, E.S. Marshall, C.L. Lill, W.J. Lee, S. Kolekar, C.M Buchanan, S.M. Jamieson, P.R. Shepherd, *J. Med. Chem*. **2011**, *54*, 7105-7126. b) Y. Zafrani, D. Yeffet, G. Sod-Moriah, A. Berliner, D. Amir, D. Marciano, E. Gershonov, S. Saphier, *J. Med. Chem.* **2017**, 60, 797–804.

[7] T. Furuya, C. Kuttruff, T. Ritter, *Curr. Opin. Drug Disc. Dev.* **2008**, *11*, 803−819.

[8] T. Liang, C. N. Neumann, T. Ritter, *Angew. Chem. Int. Ed*. **2013**, *52*, 8214–8264.

[9] For recent review see: J. Rong, C. Ni, J. Hu, *Asian J. Org. Chem.* **2017**, 6, 139; and references therein.

[10] a) L. N. Markovski, V. E. Pahinnik, A. V. Kirsanov, *Synthesis*. **1973**, 787−789; b) T. Umemoto, R. P. Singh, Y. Xu, N. Saito, *J. Am. Chem. Soc.* **2010**, 132, 18199.

[11] a) Y. Gu, X. Leng, Q. Shen, Nat. Commun. 2014, 5, 5405; b) L. Xu, D.A. Vicic, *J. Am. Chem. Soc*. **2016**,*138*, 2536-2539.

[12] For recent methods of difluoromethylation of Aryl Halides see: a) H. Serizawa, K. Ishii, K. Aikawa, K. Mikami, *Org. Lett.* **2016**, *18*, 3686–3689; b) K. Aikawa, H. Serizawa, K. Ishii, K. Mikami, *Org. Lett.* **2016**, *18*, 3690–3693; c) G. K. Prakash, S. K. Ganesh, J. P. Jones, A. Kulkarni, K. Masood, J. K. Swabeck, G. A. Olah, *Angew. Chem. Int. Ed.* **2012**, 51, 12090-12094. d) P. S. Fier, J. F. Hartwig, *J Am Chem Soc*. **2012**, 134, 5524-5527. e) R.B. James, K.K. Stavros, S.S. Melanie, *Organometallics*. **2017**, 36, 1220. f) C. Lu, Y. Gu, J. Wu, Y. Gub, Q. Shen, *Chem. Sci.*, **2017**, 8, 4848. Difluoromethylation of Aryl boronic acid: g) Z. Feng, Q. Min, X. Zhang, *Org. Lett*. **2016**, *18*, 44–47; h) Z. Feng, Q. Min, X. Fu, L. An, X. Zhang, *Nat. Chem.* **2017**, 9, 918. Sandmeyer difluoromethylation of (hetero-)arenediazonium salts see: i) C. Matheis, K. Jouvin, L. J. Goossen, *Org Lett*, **2014**, 16, 5984-5987. Preparation of difluoromethylated compounds via silver-catalyzed decarboxylation of α-fluoroarylacetatic acids and α,α-difluoroarylacetic acids see: j) S. Mizuta, I. S. R. Stenhagen, M. ODuill, J. Wolstenhulme, A. K. Kirjavainen, S. J. Forsback, M. Tredwell, G. Sandford, P. R. Moore, M. Huiban, S. K. Luthra, J. Passchier, O. Solin, V. Gouverneur, *Org. Lett.* **2013**, 15, 2648; k) F. Chen, A. S. K. Hashmi, *Org. Lett.* **2016**, 18, 2880-2882. l) There is one method for silver-catalyzed C-H trifluoromethylation of arenes using trifluoroacetic acid: G. Shi, C. Shao, S. Pan, J. Yu, Y. Zhang, *Org. Lett.* **2015**, 17, 38.

[13] Y. Fujiwara, J.A. Dixon, R.A. Rodriguez, R.D. Baxter, D.D Dixon, M.R. Collins, D.G. Blackmond, P.S. Baran, *J. Am. Chem. Soc*. **2012**, *134*, 1494-1497.

[14] Y. Fujiwara, J. A. Dixon, F. O'Hara, E. D. Funder, D. D. Dixon, R. A. Rodriguez, R. D. Baxter, B. Herlé, N. Sach, M. R. Collins, Y. Ishihara, P. S. Baran, *Nature*. **2012**, 492, 95-99; and references therein.

[15] T.T. Tung, T.H. Jakobsen, T.T. Dao, A.T. Fuglsang, M. Givskov, S.B. Christensen, J. Nielsen, *Eur. J. Med. Chem*. **2016**, *126*, 1011-1020.

[16] a) F. Minisci, R. Bernardi, F. Bertini, R. Galli, M. Perchinummo, *Tetrahedron*. **1971**, *27*, 3575–3579; b) F. Minisci, E. Vismara, F. Fontana *Heterocycles*. **1989**, 28, 489-519.

[17] A. J. Duncton, *Med. Chem. Commun.* **2011**, 2, 1135−1161.

[18] See page s15 in supporting information for full proposed mechanism.

[19] (a) N. R. Patel, R. A. Flowers II, *J. Am. Chem. Soc.* **2013**, 135, 4672; (b) N. R. Patel, R. A. Flowers II, *J. Org. Chem*. **2015**, 80, 5834-5841.

[20] R. D. Baxter, Y. Liang, X. Hong, T. A. Brown, R. N. Zare, K. N. Houk, P. S. Baran, D. G. Blackmond, *ACS Cent. Sci.* **2015**, 1, 456–46.

[21] See page S4 in ESI for full proposed mechanism.

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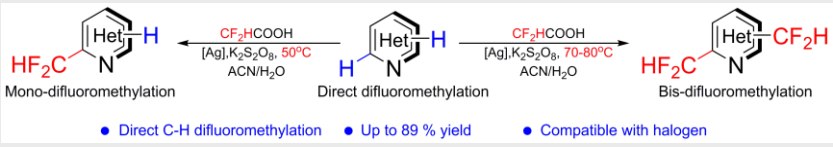

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