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[3,3]-Sigmatropic Rearrangement of Aryl Fluoroalkyl Sulfoxides with Alkyl Nitriles

Mengjie Hu,[a,b] Jia-Ni He,[a,b] Yanping Liu,[a] Taotao Dong,[a] Mengyuan Chen,[a] Chao Yan,[a] Yulu Ye,[a] and Bo Peng*[a]

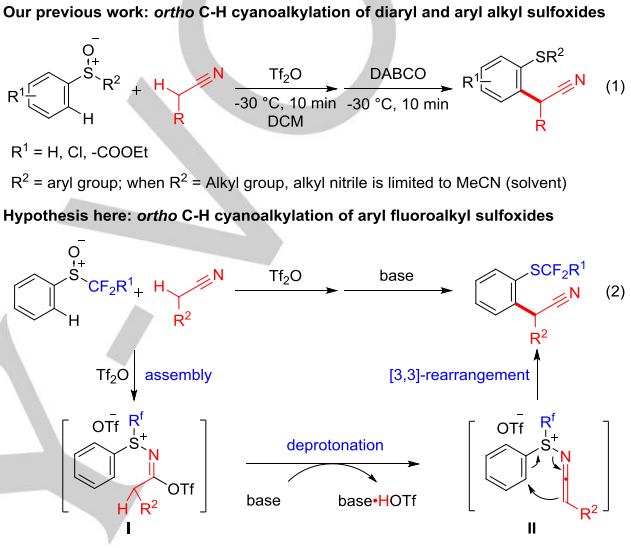
Dedication ((optional))

Abstract: Herein we report the *ortho*-cyanoalkylation of aryl fluoroalkyl sulfoxides with alkyl nitriles. The reaction proceeds through an "assembly/deprotonation" triggered [3,3]-rearrangement and allows the incorporation of two valuable functional groups including the cyano group and difluoromethylthio group into arenes. As a consequence, a wide range of *ortho*-cyanoalkylated difluoromethylthio arenes were produced with high efficiency under mild and environmentally friendly conditions. Remarkably, the reaction proceeds smoothly with the electron-donating group substituted arenes which can be challenging to the reaction of non-fluoroalkyl sufloxides. This beneficial effect can be attributed to the unique electronegativity of fluoroalkyl substituents.

Introduction

Cyanoalkylated arenes and their derivatives are often found as structural motifs in drugs[1] and bioactive compounds[2]. The cyano group can also be readily converted into other functional groups (FGs) such as carboxylic acids, amides, aldehydes, amines, and ketones.[3] Furthermore, cyanoalkylated arenes are useful precursors to an array of N-heterocycles including thiozoles, oxazolines, tetrazoles, imidazoles, and triazoles.[4] On the other hand, the difluoromethylthio group is generally considered as a highly lipophilic weak hydrogen bonding donor and thus plays critical roles in many pharmaceuticals[5], agrochemicals[6] and bioactive compounds[7]. Therefore, the cyanoalkylated arene and the difluoromethylthio group are highly desirable in both the synthetic chemistry and drug discovery process.[8,9]

In recent years, we have been interested in exploring the use of "assembly" protocol for the development of aromatic [3,3]-rearrangements.[10,11] For example, we have recently demonstrated a metal-free *ortho*-cyanoalkylation of aryl sulfoxides through an "assembly/deprotonation" triggered [3,3]-rearrangement, which allows the synthesis of α-aryl nitriles in a redox-neutral manner (Scheme 1, eq 1).[10a] Inspired by that work, we wondered whether the reaction pattern can be applicable to aryl fluoroalkyl sulfoxides that would produce *ortho*-cyanoalkylated difluoromethylthio arenes by incorporating two valuable functional groups into arenes simultaneously (eq 2).



Scheme 1. Our previous work and hypothesis here.

According to our previous studies, the hypothesized reaction would consist of three major stages: (1) Tf_2O initiated electrophilic assembly of aryl fluoroalkyl sulfoxide with alkyl nitrile forms an imine-sulfonium intermediate **I**; (2) Base promoted deprotonation of **I** generates a ketenimine-sulfonium species **II**; (3) Intermedaite **II** undergoes [3,3]-rearrangement and rearomatization to afford the final product. Since the [3,3]-rearrangement would proceed rapidly with the congestion release of ketenimine moiety of **II**,[10a] the success of the reaction would rely on the other two critical steps including the "assembly" and "deprotonation" steps. It should be noted that the *ortho*-cyanoalkylation of aryl perfluoroalkyl sulfoxides with alkyl nitriles has also been reported by Magnier and coworkers.[12] In that case, only anhydride (Tf_2O) was used for the coupling process. However, the reported base-free protocol merely resulted in the deterioration of aryl sulfoxide (Table 1, entry 4).

Results and Discussion

To test our hypothesis, we examined the reaction of aryl fluoroalkyl sulfoxide **1a** with alkyl nitrile **2a** (Table 1). To our delight, the reaction afforded the desired *ortho*-cyanoalkylated product **3aa** with modest yield (48%) under the reported conditions previously used for *ortho*-cyanoalkylation of non-fluoroalkyl sulfoxides (Tf_2O, -30 °C, 10 min; DABCO, -30 °C, 10 min)[10a] (Table 1, entry 1). Simply prolonging the reaction time (t^1)

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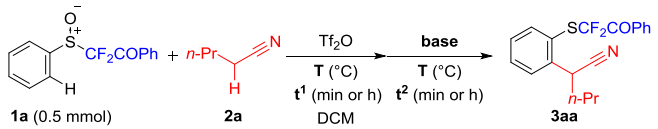
Table 1. Optimization of reaction conditions[a]



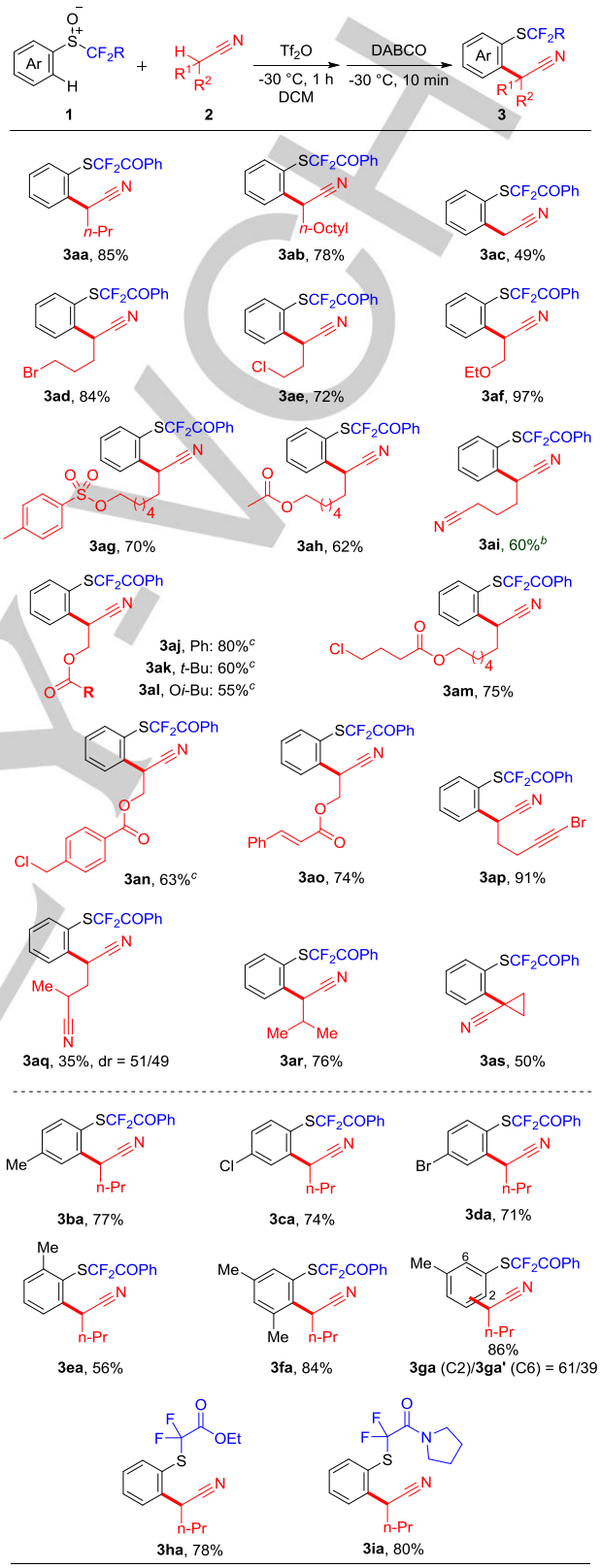
1a (0.5 mmol) **2a** **3aa**

entry	base	T (°C)	t [1]	t [2]	yield (%)[b]
1	DABCO	-30	10 min	10 min	48
2	DABCO	-30	1 h	10 min	85
3	DABCO	-30	6 h	10 min	62
4	none	-30	1 h	10 min	0
5	pyridine	-30	1 h	10 min	trace
6	DIPEA	-30	1 h	10 min	68
7	DBU	-30	1 h	10 min	16
8	DABCO	-20	1 h	10 min	80
9	DABCO	-40	1 h	10 min	75
10	DABCO	-30	1 h	1 h	78
11	DABCO	-30	1 h	6 h	77

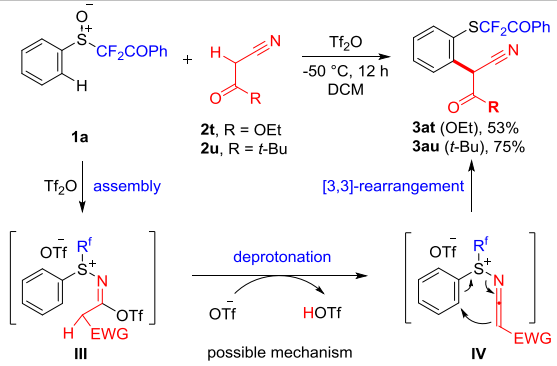
[a] Reaction conditions: **1a** (0.5 mmol), **2b** (1.5 equiv) and Tf_2O (1.5 equiv), DCM (0.17 M), T(°C), t^1 (min or h); then base (2.0 equiv), T(°C), t^2 (min or h). [b] Isolated yield.

for the electrophilic assembly of **1a** with **2a** could significantly improve the yield of **3aa** (entry 2). The best yield (85%) was obtained when 1 h (t^1) was applied. However, further prolonging t^1 to 6 h resulted in a lower yield (62%). This was probably due to the deterioration of in situ-assembled imine-sulfonium intermediate **I** when longer "assembly" time (t^1) was used (Scheme 1, eq 2). Further screen of bases demonstrated that DABCO was more suitable than other organic bases such as pyridine, Hünig's base, and DBU. A slightly increase or drop in reaction temperature could not further improve the yield of **3aa** (entries 7 and 8). Moreover, 10 minutes (t^2) was found to be adequate for the "deprotonation" step by comparing the results of the use of 1 h and 6 h (entries 9 and 10). Therefore, the "deprotonation" process is similar to that of non-fluoroalkyl sulfoxides that we have previously studied.[10a] Eventually, the optimum conditions (Tf_2O, -30 °C, 1 h; DABCO, -30 °C, 10 min) was identified for the reaction (entry 2).

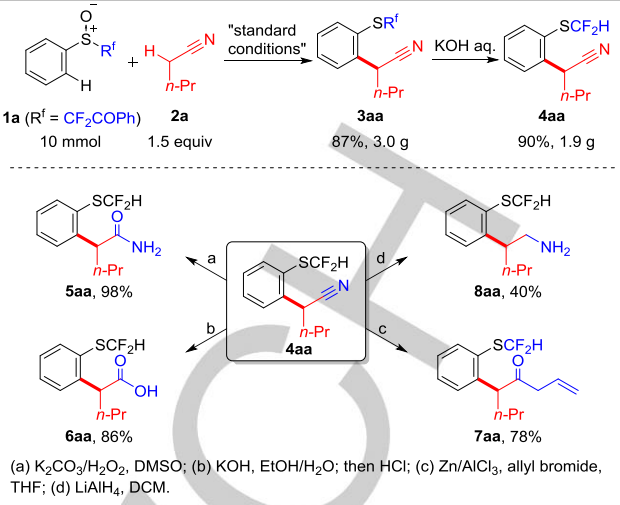
With the best conditions in hand, we examined the generality of the reaction with an array of alkyl nitriles **2** (Scheme 2). To our delight, a wide range of alkyl nitriles **2a**-**2s** were found to be suitable for the reaction. Regardless of the length of alkyl chains at α-position of alkyl nitriles (**2a** and **2b**), the reactions afforded cyanoalkylated products **3aa** and **3ab** in good yields (85% and 78%, respectively). However, acetonitrile **2c** as the simplest alkyl nitrile furnished **3ac** in a relatively low yield (49%). Remarkably, the reaction exhibited excellent functional group compatibility. Functional groups including alkyl halides/pseudohalides (**3ad**, **3ae**, **3am**, **3an**, **3ap**, and **3ag**), ethers (**3af**), esters (**3ah**, **3aj**-**3ao**) and internal alkynes (**3ap**) were all well tolerated in the reaction. It is worthy to note that highly electrophilic functional groups such as benzylic chloride (**3an**), α, β-unsaturated ester (**3ao**) and alkynyl bromide (**3ap**) were also compatible with the reaction conditions. This result was impressive since these tolerated functionalities can be challenging for conventional aromatic cyanoalkylation reactions.[8] Accordingly, the excellent functional group compatibility makes



Scheme 2. Scope of alkyl nitriles. [a] Unless otherwise noted, the reaction was performed under optimized conditions. [b] 3.0 equiv of nitrile **2i** was used. [c] The mixture of **1a** and **2** (**2j**-**l** and **2n**) was stirred under -50 °C for 12 h before the addition of DABCO.



Scheme 3. Reactions of aryl fluoroalkyl sulfoxide1a with activated alkyl nitriles.



Scheme 4. Gram-scale reaction and further elaboration of products.

the reaction complementary to other known methods. In addition, stereo-hindered substrates such as β-methyl substituted alkyl nitrile (**2r**), and cyclopropane nitrile (**2s**) also proved suitable for the reaction although **3as** bearing a new quaternary carbon center was obtained in a relatively low yield (50%). Encouraged by the obtained results, we further studied the scope of aryl sulfoxides **1** (Scheme 2, bellow the dashed line). Gratifyingly, different from non-fluoroalkyl sulfoxides that have been studied previously,[10a] aryl fluoroalkyl sulfoxides bearing electron donating groups on phenyl rings (**1b**, **1e**, **1f**, and **1g**) could also produce the desired cyanoalkylated products (**3ba**, **3ea**, **3fa**, **3ga**) in good yields. In addition, stereo-hindered *ortho*-substituted aryl sulfoxides **1e** was also suitable for the reaction. This is remarkable since the corresponding *ortho*-methyl aryl non-fluoroalkyl sulfoxides have proved unfeasible for this type of rearrangement. We suspected that the enlarged scope of aryl substituents could benefit from the increased electronegative effect of fluoroalkyl groups which would facilitate the electrophilic assembly of aryl fluoroalkyl sulfoxides with alkyl nitriles to form imine-sulfonium intermediate **I** (Scheme 1, eq 2). Remarkably, in addition to the benzoyl group (**1a**-**1g**,), ester or amide groups (**1h** and **1i**) substituted fluoroalkyl sulfoxides also produced the desired products **3ha** and **3ia** with high efficiency. These two functional groups provided a versatile platform for further elaboration of the products.

Interestingly, alkyl nitriles **2t** and **2u** bearing an electron-withdrawing group at α-position displayed a different reactivity (Scheme 3). Even in absence of bases, these active alkyl nitriles could be coupled with aryl fluoroalkyl sulfoxide **1a** leading to cyanoalkylated products **3at** and **3au** in modest to good yields. This result was probably due to the enhanced acidity of α-proton of in situ-generated imine-sulfonium intermediate **III**, which could readily be deprotonated by counter anion to give the rearrangement precursor, namely ketenimine-sulfonium intermediate **IV**. This result also reflects the importance of base in the reaction of simple alkyl nitriles (Table 1, entry 4).

To demonstrate the practicability of the reaction, a gram-scale reaction of **1a** and **2a** was performed under the optimum conditions (Scheme 4). The reaction at gram-scale still afforded **3aa** in good yield (87%). The benzoyl group of **3aa** could be readily removed under a reported basic conditions.[13] As mentioned in the introduction, the cyano group was indeed readily converted to other functionalities such as amide (**5aa**), carboxylic acid (**6aa**), ketone (**7aa**) and amine (**8aa**) through simple hydrolysis, nucleophilic addition, and reduction, respectively. The diverse elaboration of cyano group demonstrated the utility of the reaction.

Conclusions

In summary, we have developed an efficient [3,3]-rearrangement of aryl fluoroalkyl sulfoxides with alkyl nitriles that allows the synthesis of valuable *ortho*-cyanoalkylated difluoromethylthio arenes. In contrast with non-fluoroalkyl sulfoxides that we studied previously, the aryl fluoroalkyl sulfoxides owns a broader scope of aryl sulfoxides. This can be attributed to the electronegative effect of fluoroalkyl group. The notable features of the reaction include mild conditions, exclusive selectivity, the use of readily available and environmental friendly reagents, and the broad substrate scope for both coupling partners. Applications of the method and further exploiting the rearrangement triggered by the "assembly/deprotonation" sequence are underway in our laboratory.

Experimental Section

General procedure for the synthesis of ortho-cyanoalkylated difluoromethylthio arenes 3. To a mixture of aryl sulfoxide (**1**, 0.5 mmol) and alkyl nitrile (**2**, 0.75 mmol) in DCM (3 mL) was added Tf_2O (126 μL, 0.75 mmol) under -30 °C. After stirring for 1 h, DABCO (112 mg, 1.0 mmol) was added to the mixture under the same temperature. The mixture was then stirred for another 10 min. After that, the mixture was passed through a short silica gel column and concentrated under vacuum. The resulting residue was further purified by column chromatography over silica gel eluting with a gradient of EtOAc/Petroleum ether (0−50%) to afford **3**.

Preparation of 2-(2-((difluoromethyl)thio)phenyl)pentanenitrile (4aa). To a solution of **3aa** (2.1 g, 8.7 mmol) in PhMe (45 mL) was added H_2O (2.2 g, 121.8 mmol) at room temperature. The reaction mixture was gradually warmed to 100 °C and stirred for 2 h. After cooling to room temperature, the mixture was dissolved in EtOAc and washed with H_2O. The organic layer was separated, dried over Na_2SO_4, and concentrated. The resulting residue was further purified by column chromatography over silica gel eluting with a gradient of EtOAc/Petroleum ether (10−25%) to afford **4aa** in 90% (1.9 g).

Preparation of 2-(2-((difluoromethyl)thio)phenyl)pentanamide (5aa). To a solution of **4aa** (121 mg, 0.5 mmol) in DMSO (1 mL) were sequentially added H_2O_2 (30% aq., 140 μL) and K_2CO_3 (14 mg, 0.1 mmol) at 25 °C. After stirring for 12 hours, the mixture was diluted with H_2O,

extracted with DCM and dried over Na_2SO_4. Then the mixture was filtrated and concentrated under vacuum. The resulting residue was further purified by column chromatography over silica gel eluting with a gradient of EtOAc/Petroleum ether (10−33%) to afford **5aa** in 98% (127 mg).

Preparation of 2-(2-((difluoromethyl)thio)phenyl)pentanoic acid (6aa). To a solution of KOH (278 mg, 5 mmol) in EtOH (2 mL) and H_2O (0.5 mL) was added **4aa** (121 mg, 0.5 mmol). The mixture was stirred under reflux for 20 hours. After cooling to room temperature, the mixture was diluted with H_2O, acidified to pH = 1~2 (con. HCl), extracted with $CHCl_3$ and dried over Na_2SO_4. Then the mixture was filtrated and concentrated under vacuum. The resulting residue was further purified by column chromatography over silica gel eluting with a gradient of MeOH/DCM (0−6%) to afford **6aa** in 86% (112 mg).

Preparation of 5-(2-((difluoromethyl)thio)phenyl)oct-1-en-4-one (7aa). To a mixture of **4aa** (121 mg, 0.5 mmol), allyl bromide (91 mg, 0.75 mmol) and Zn (powder, 131 mg, 2.0 mmol) in THF (2.0 mL) was added anhydrous $AlCl_3$ (27 mg, 0.2 mmol) at -15 °C under N_2 atmosphere. The mixture was stirred for 3 h at the same temperature. Then to the mixture was added HCl (1.0 M, 5 mL) dropwise. After stirring for another 30 min, the mixture was neutralized with $NaHCO_3$ (sat.), extracted with DCM. The organic layer was separated, dried over Na_2SO_4, and concentrated. The resulting residue was further purified by column chromatography over silica gel eluting with a gradient of EtOAc/Petroleum ether (5−10%) to afford **7aa** in 78% (110.3 mg).

Preparation of 2-(2-((difluoromethyl)thio)phenyl)pentan-1-amine (8aa). To a solution of $LiAlH_4$ (1 M in THF, 1 mL) in diethyl ether (1 mL) was added a solution of **4aa** (121 mg, 0.5 mmol) in diethyl ether (0.5 mL) dropwise for 1 hour at 0 °C under N_2 atmosphere. Then the mixture was gradually warmed to room temperature. After stirring for 24 hours, to the mixture was added NaOH (10% aq., 2 mL). The mixture was stirred for 12 hours, then extracted with EtOAc, filtrated through Kieselguhr and dried over Na_2SO_4. After that the mixture was filtrated and concentrated under vacuum. The resulting residue was further purified by column chromatography over silica gel eluting with a gradient of MeOH/DCM (0−6%) to afford **8aa** in 40% (49 mg).

Acknowledgments ((optional))

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Keywords: rearrangement • cyanoalkylation • difluoromethylthio group • sulfoxide • C-H functionalization

[1] P. J. Harrington, E. Lodewijk, *Org. Process Res. Dev.* **1997**, *1,* 72–76.

[2] a) S. Dei, M. N. Romanelli, S. Scapecchi, E. Teodori, A. Chiarini, F. Gualtieri, *J. Med. Chem.* **1991**, *34*, 2219–2225; b) K. Mitani, S. Sakurai, T Suzuki, K. Morikawa, E. Koshinaka, H. Kato, Y. Ito, T. Fujita, *J. Med. Chem.* **1988**, *36*, 4121–4135; c) L. J. Theodore, W. Nelson, *J. Org. Chem.* **1987**, *52*, 1309–1315.

[3] a) H. -Y. Xiong, T. Besset, D. Cahard, X. Pannecoucke, *J. Org. Chem.* **2015**, *80*, 4204–4212; b) V. Cadierno, J. Francos, J. Gimeno, *Chem. Eur. J.* **2008**, *14*, 6601–6605; c) Z. Shao, S. Fu, M. Wei, S. Zhou, Q. Liu, *Angew. Chem. Int. Ed*. **2016**, *55* 1465–14657; d) B. Skillinghaug, C. Sköld, J. Rydfjord, F. Svensson, M. Behrends, J. Sävmarker, P. J. R. Sjöberg, M. Larhed, *J. Org. Chem.* **2014**, *79*, 12018–12032.

[4] K. Friedrich, K. Wallenfels, The Chemistry of the Cyano Group, (Eds.: A. I. Meyers, J. C. Sircar), Wiley-Interscience, New York, **1970**, pp. 341-421.

[5] L. Yagupolskii, I. Maletina, K. Petko, D. Fedyuk, R. Handrock, S. Shavaran, B. Klebanov, S. Herzig, *J. Fluorine Chem.* 2001, *109*, 87–94.

[6] a) J. J. Fourie, I. G. Horak, V de la. Puente Redondo, *Sarcoptes scabiei. Vet. Rec.*, **2010**, *167*, 442–445; b) K. Morita, K. Ide, Y. Hayase, T. Takahashi, Y. Hayashi, *Agric. Biol. Chem.* **1987**, *51*, 1339–1343.

[7] a) Z. Huang, O. Matsubara, S. Jia, E. Tokunaga, N. Shibata, *Org. Lett.* **2017**, *19*, 934–937; b) S. Okui, N. Kyomura, T. Fukuchi, K. Okano, L. He, A. Miyauchi, *US Pat., 7* 371 768, 2008.

[8] For selected examples of synthesizing cyanoalkylated nitriles: a) J. Choi, G. C. Fu, *J. Am. Chem. Soc.* **2012**, *134*, 9102–9105; b) R. Shang, D.-S. Ji, L. Chu, Y. Fu, L. Liu, *Angew. Chem., Int. Ed.* **2011**, *50*, 4470–4474; c) D. A. Culkin, J. F. Hartwig, *J. Am Chem. Soc.* **2002**, *124*, 9330–9331; d) J. You, J. G. Verkade, *Angew. Chem., Int. Ed.* **2003**, *42*, 5051–5053.

[9] For selected exmaples of incorporating difluoromethylthio group into arenes: a) H.-Y. Xiong, X. Pannecoucke, T. Besset, *Chem. Eur. J.* **2016**, *22*, 16734–16749; b) D. Zhu, X. Shao, X. Hong, L. Lu, Q. Shen, *Angew. Chem. Int. Ed.* **2016**, *55*, 15807–15811; c) L. Jiang, T. Ding, W. Yi, X. Zeng, W. Zhang, *Org. Lett.* **2018**, *20*, 2236–2240; d) J. Li, D. Zhu, L. Lv, C.-J. Li, *Chem. Sci.* **2018**, *9*, 5781–5786.

[10] a) L. Shang, Y. Chang, F. Luo, J.-N. He, X. Huang, L. Zhang, L. Kong, K. Li, B. Peng, *J. Am. Chem. Soc.* **2017**, *139*, 4211–4217; b) F. Luo, Y. Lu, M. Hu, J. Tian, L. Zhang, W. Bao, C.Yan, X. Huang, Z.-X. Wang, B. Peng, *Org. Chem. Front.* **2018**, *5*, 1756–1762; c) L. Zhang, J.-N. He, Y. Liang, M. Hu, L. Shang, X. Huang, L. Kong, Z.-X. Wang, B. Peng, *Angew. Chem. Int. Ed.* **2019**, *58*, 5316–5320; d) J. Tian, F. Luo, C. Zhang, X. Huang, Y. Zhang, L. Zhang, L. Kong, X. Hu, Z.-X. Wang, B. Peng, *Angew. Chem. Int. Ed.* **2018**, *57*, 9078–9082; e) X. Huang, Y. Zhang, C. Zhang, L. Zhang, Y. Xu, L. Kong, Z.-X. Wang, B. Peng, *Angew. Chem. Int. Ed.* **2019**, *58*, 5956–5961; f) W. Zhao, X. Huang, Y. Zhan, Q. Zhang, D. Li, Y. Zhang, L.Kong, B. Peng, *Angew. Chem. Int. Ed.* **2019**, DOI: 10.1002/ange.201909019

[11] For reviews on *ortho*-functionalization of aryl sulfoxides, see: a) D. Kaiser, I. Klose, R. Oost, J. Neuhaus, N. Maulide, *Chem. Rev.* **2019**, *119*, 8701–8780; b) T. Yanagi, K. Nogi, H. Yorimitsu, *Tetrahedron Lett.* **2018**, *59*, 2951–2959; c) H. Yorimitsu, *Chem. Rec.* **2017**, *17*, 1156–1167; d) A. P. Pulis, D. J. Procter, *Angew. Chem. Int. Ed.* **2016**, *55*, 9842–9860; e) A. Shafir, *Tetrahedron Lett.* **2016**, *57*, 2673–2682; f) X.Huang, S. Klimczyk, N. Maulide, *Synthesis.* **2012**, *44*, 175–183.

[12] a) Y. Macé, C. Urban, C. Pradet, J-C. Blazejewski, E. Magnier, *Eur. J. Org. Chem.* **2009**, 5313–5316; b) B. Pégot, C. Urban, P. Diter, E. Magnier, *Eur. J. Org. Chem.* **2013**, 7800–7808.

[13] L. A.Paquette, G. D.Maynard, *J. Org. Chem.* **1989**, *54*, 5054-5063.

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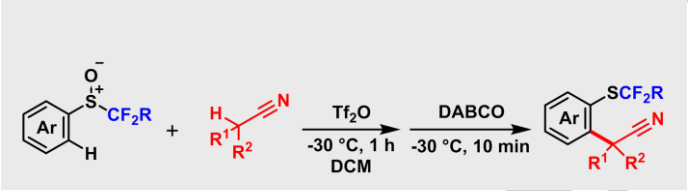

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Rearrangement*

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