OL | Organic Letters

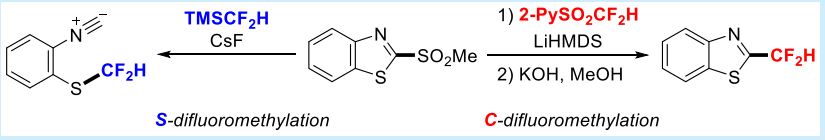
pubs.acs.org/OrgLett Letter

Divergent S- and C-Difluoromethylation of 2-Substituted Benzothiazoles

Xiu Wang,‡ Wenchao Ye,‡ Taige Kong, Chenlu Wang, Chuanfa Ni, and Jinbo Hu*

Cite This: *Org. Lett.* 2021, 23, 8554–8558 Read Online

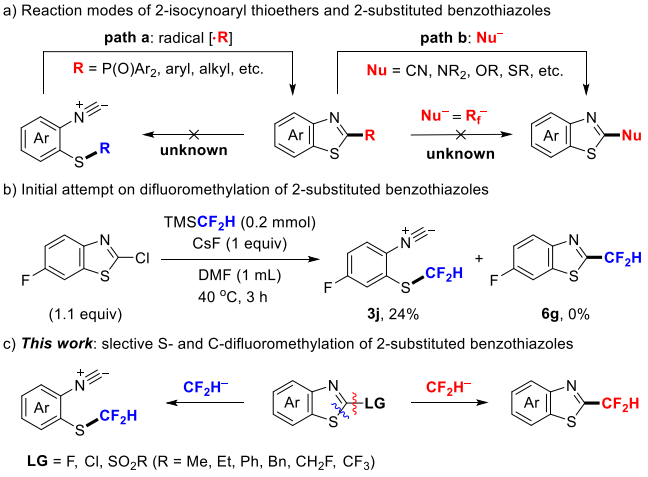
ACCESS | Metrics & More | Article Recommendations | Supporting Information



ABSTRACT: Two unprecedented and complementary synthetic strategies for S- and C-difluoromethylation of 2-substituted benzothiazoles have been developed by taking advantage of the remarkably different reactivity of CF_2H^- and 2-$PySO_2CF_2^-$ nucleophiles. A variety of structurally diverse difluoromethyl 2-isocyanophenyl sulfides and 2-difluoromethylated benzothiazoles were synthesized with these two new synthetic protocols.

Isocyanides are versatile synthetic building blocks for the synthesis of nitrogen-containing molecules.[1] Their wide applications in multicomponent reactions,[2] transition-metal-catalyzed isocyanide insertions,[3] and radical cascade reactions[4,5] provide efficient access to an array of pharmaceutically relevant molecules. In particular, 2-isocyanoaryl thioethers could be used as radical acceptors in radical cyclization reactions to construct 2-substituted benzothiazoles (Scheme 1a, path a),[6] which are prevalently existing in various naturally occurring compounds and drugs.[7] However, despite the remarkable progress in the cyclization of 2-isocyanoaryl thioethers to 2-substituted benzothiazoles,[6] its reverse process, namely, the ring-opening reaction of 2-substituted benzothiazoles to give 2-isocyanoaryl thioethers, still remains unknown.

Scheme 1. Transformations of 2-Isocyanoaryl Thioethers and 2-Substituted Benzothiazoles



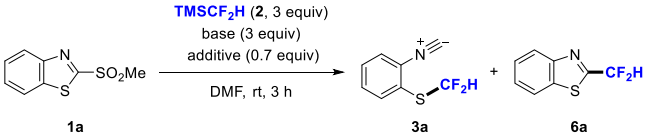
To date, the known reaction mode of 2-substituted benzothiazoles is the nucleophilic aromatic substitution (S_NAr) at the C-2 position with a series of C-, N-, O- and S-nucleophiles (Scheme 1a, path b).[8] However, to the best of our knowledge, the S_NAr reaction between a fluoroalkyl nucleophile and a 2-substituted benzothiazole has never been reported. Difluoromethyl group (CF_2H) can serve as a lipophilic hydrogen bond donor, and a bioisostere of OH or SH functionality.[9] In this context, we initially attempted the S_NAr-type nucleophilic difluoromethylation of 2-substituted benzothiazoles with (difluoromethyl)trimethylsilane[10] ($TMSCF_2H$, **2**). To our surprise, the expected product 2-difluoromethyl benzothiazole (**6g**) was not observed, and instead, difluoromethyl 2-isocyanophenyl sulfide (**3j**) was obtained in 24% yield (Scheme 1b). It is likely that an unprecedented S-difluoromethylation-ring-opening elimination tandem occurred.[11] This unexpected result intrigued us to investigate the nucleophilic difluoromethylation of 2-substituted benzothiazoles, especially the selectivity between S_NAr and aromatic ring opening reactions (Scheme 1c).

At the onset of our investigation, we chose 2-methanesulfonyl benzothiazole **1a** as a model substrate and $TMSCF_2H$ (**2**) as the difluoromethyl anion precursor, and the reaction conditions were screened (Table 1). When a mixture of **1a** (0.2 mmol), **2** (3 equiv), CsF (3 equiv) in DMF were stirred at room temperature, neither ring-opening product **3a** nor S_NAr product **6a** was observed (entry 1). It is interesting that when

Received: September 24, 2021
Published: October 20, 2021

https://doi.org/10.1021/acs.orglett.1c03267
Org. Lett. 2021, 23, 8554–8558

Table 1. Optimization of the Reaction Conditions of Ring-Opening S-Difluoromethylation of Benzothiazole 1a



1a 3a 6a

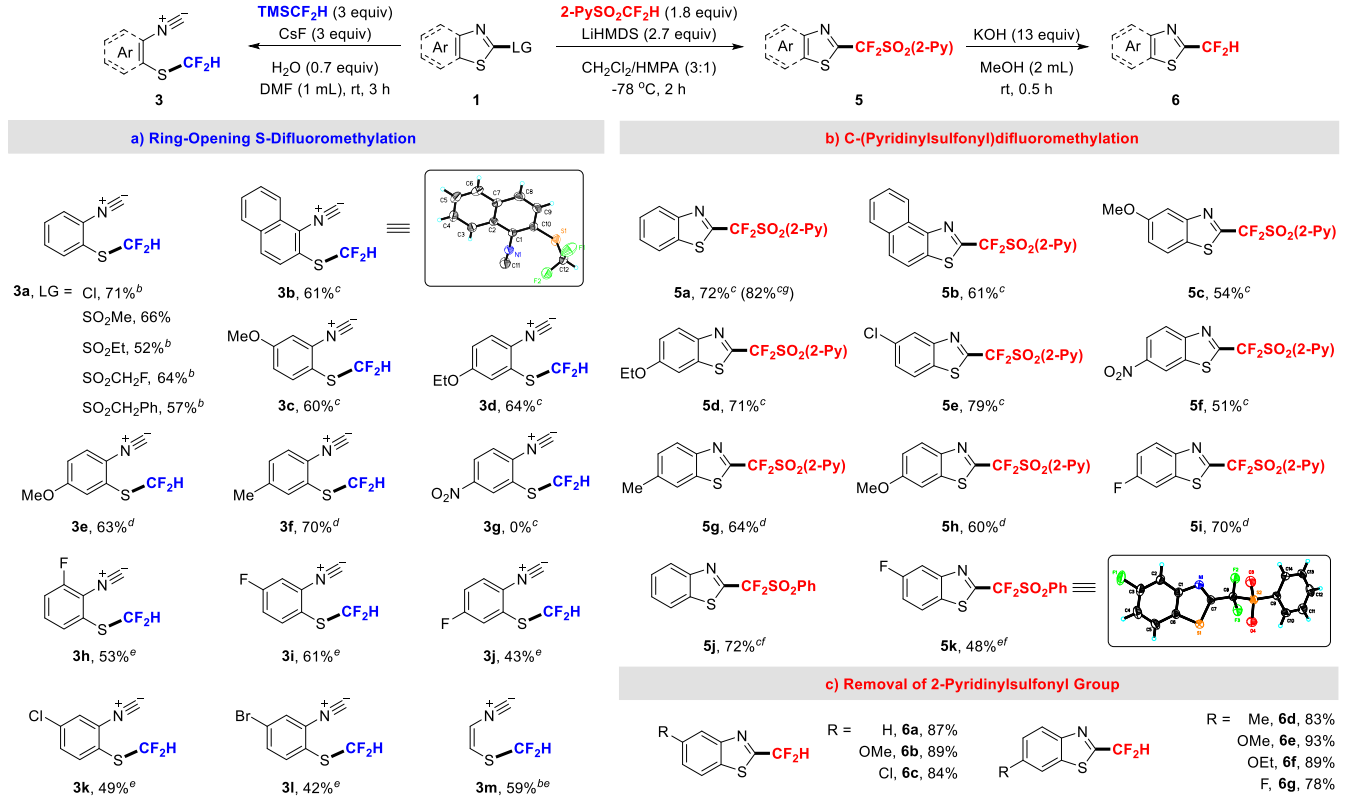
			yield (%)[b]	
entry[a]	base	additive	3a	6a
1	CsF	none	0	0
2	CsF	H_2O	70 (66)	0
3	CsF	MeOH	53	0
4	TBAT	H_2O	33	0
5	KF	H_2O	6	0
6	K_2CO_3	H_2O	14	0
7	CsOH	H_2O	9	0

[a]Reaction conditions: **1a** (0.2 mmol, 1 equiv), **2** (0.6 mmol, 3 equiv), base (3 equiv), additive (0.7 equiv), DMF (1 mL), rt, 3 h. [b]Yields were determined by ^{19}F NMR spectroscopy using $PhCF_3$ as an internal standard, and the isolated yield was shown in parentheses.

0.7 equiv of water was added, 70% yield of the ring-opening product **3a** was formed (entry 2). To figure out the role of water, we replaced water with another proton source methanol, and found that **3a** was formed in slightly lower yield (53%; entry 3). Furthermore, when a mixture of **3a** (0.2 mmol), $TMSCF_2H$ (3 equiv), CsF (3 equiv) and DMF (1 mL) was stirred at room temperature for 3 h in the absence of water, compound **3a** completely decomposed (Scheme S1 in Supporting Information). These results indicate that water serves as a proton source and quenches the unreacted difluoromethyl anion (forming CH_2F_2), which diminishes the decomposition of **3a**. The amount of water was carefully screened, and 0.7 equiv of water was identified as optimal for the reaction (Table S2 in Supporting Information). In addition to CsF, other Lewis base activators such as TBAT, KF, K_2CO_3, and CsOH were tested, but all showed lower efficiency than CsF in activating the Si−CF_2H bond cleavage in DMF at room temperature (entries 4−7). Notably, in all cases, no formation of S_NAr-type C-difluoromethylation product **6a** was observed during the current ring-opeing S-difluoromethylation reaction (Table 1).

With the standard reaction conditions in hand (Table 1, entry 2), the substrate scope of the ring-opening S-difluoromethylation reaction with $TMSCF_2H$ was investigated (Scheme 2a). First, the leaving group ability of different groups at C-2 position of **1** was examined (LG = Cl, SO_2Me, SO_2Et, SO_2CH_2F, and SO_2CH_2Ph), and in call cases the reaction proceeded smoothly, affording product **3a** in moderate to good yields. Second, we chose 2-(methanesulfonyl)naphthothiazole as a substrate in the reaction, and product **3b** was obtained in 61% yield. The structure of **3b** was confirmed by its single crystal X-ray analysis. Third, benzothiazoles bearing electron-donating groups (such as methyl, methoxyl and ethoxyl) are amenable to the present ring-opening S-difluoromethylation reaction, with the corresponding products **3c**-**3f** being formed in 60−70% yields. However, no desired product **3g** was

Scheme 2. Divergent S- and C-Difluoromethylation of 2-Substituted Benzothiazoles[a]



[a]Isolated yields. [b]Yields were determined by ^{19}F NMR spectroscopy using trifluorotoluene as an internal standard. [c]LG = SO_2Me. [d]LG = SO_2Ph. [e]LG = Cl; 2.0 equiv of H_2O were used in S-difluoromethylation. [f]$PhSO_2CF_2H$ was used instead of 2-$PySO_2CF_2H$, THF (1.2 mL) was used instead of CH_2Cl_2. [g]6 mmol scale reaction.

https://doi.org/10.1021/acs.orglett.1c03267
Org. Lett. 2021, 23, 8554−8558

detected when a nitrated benzothiazole was subjected to the standard reaction conditions. Fourth, in cases of 2-chlorobenzothiazoles, the halogen substituents (such as F, Cl and Br) on the aromatic ring were compatible with the reaction conditions (see **3h**-**3l**). Finally, 2-chlorothiazole was also able to participate in the reaction, and target product **3m** was formed in 59% yield (determined by NMR).

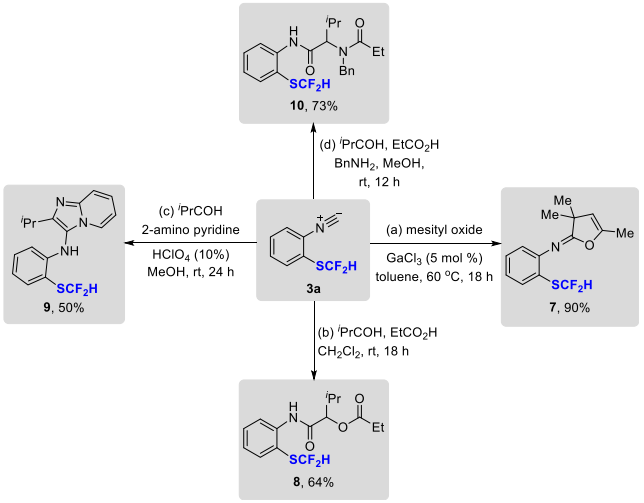
Encouraged by the aforementioned ring-opening S-difluoromehtylation of 2-substituted benzothiazoles with $TMSCF_2H$, we further applied other fluorinated nucleophiles in the reaction with 2-substituted benzothiazoles. Difluoromethyl 2-pyridyl sulfone (2-$PySO_2CF_2H$), a reagent developed by us, is now commercially available and widely used for fluoroalkylation and fluoroolefination reactions.[12] We were surprised to find, when 2-(methanesulfonyl)benzothiazole **1a** reacted with 2-$PySO_2CF_2^-$ (derived from 2-$PySO_2CF_2H$ and LiHMDS) in CH_2Cl_2/ HMPA at −78 °C for 2 h, no ring-opening S-(2-pyridinesulfonyl)difluoromethylation product was formed, but S_NAr-type C-(2-pyridinesulfonyl)difluoromethylation product **5a** was obtained in 72% isolated yield (see Table S3 in Supporting Information and Scheme 2b). This result suggests that different α-fluoro carbanions show remarkably different reactivity (chemoselectivity) in their reactions with 2-substituted benzothiazoles.

Next, we examined the generality of the current S_NAr-type C-(2-pyridinesulfonyl)difluoromethylation of **1** (Scheme 2b). First, the reaction was not sensitive to leaving groups at C-2 position of benzothiazoles **1**. When chloro, methanesulfonyl, and benzenesulfonyl groups were used as the leaving groups, the S_NAr-type C-fluoroalkylation reactions proceeded smoothly to yield the corresponding products in 48−79% yields (**5a**−**5k**). The current C-fluoroalkylation reaction was applied in gram-scale synthesis, and product **5a** was obtained in 82% isolated yield (1.6 g). Second, the reaction was able to tolerate different substituents on **1**, including methyl, methoxyl, ethyoxyl, chloro, and nitro groups (**5c**−**5i**). Third, when we replaced 2-$PySO_2CF_2H$ with $PhSO_2CF_2H$, the S_NAr-type C-benzenesulfonyl difluoromethylation products **5j** and **5k** were also successfully formed in 72% and 48% yields, respectively. With products **5** in hand, we performed the base-promoted selective desulfonylation to transform **5** to difluoromethylated compounds **6** (Scheme 2c, also see details in Table S4 in Supporting Information). In the presence of KOH (13 equiv) in methanol at room temperature, **5** were readily converted into **6** within 30 min in 78−93% yields (Scheme 2c). Given the results shown in Scheme 2, it is intriguing that the remarkably different reactivity of CF_2H^- and 2-$PySO_2CF_2^-$ have enabled two complementary synthetic strategies for highly chemoselective S- and C-difluoromethylation of 2-substituted benzothiazoles **1**.

To demonstrate the synthetic utility of the current synthetic protocol, we applied **3a** as a valuable building block in multicomponent reactions. First, **3a** was used in a $GaCl_3$-catalyzed [4 + 1] cycloaddition with mesityl oxide, which afforded SCF_2H-substituted unsaturated lactone derivative **7** in 90% yield (Scheme 3a).[13] Furthermore, **3a** was also applied in Passerini, Gröbcke−Blackburn−Bienaymé, and Ugi reactions, giving products **8**−**10** in moderate to good yields (Scheme 3b−d).

In summary, we have successfully developed two unprecedented and complementary synthetic strategies for divergent S- and C-difluoromethylation of 2-substituted benzothiazoles by taking advantage of the remarkably different reactivity of CF_2H^- and 2-$PySO_2CF_2^-$ nucleophiles. A variety of structurally diverse difluoromethyl 2-isocyanophenyl sulfides **3** and 2-difluoromethylated benzothiazoles **6** were synthesized with these two new synthetic protocols. Our study uncovers the unique reactivity of CF_2H^-, which promises to stimulate further development of new difluoromethylation reactions.

Scheme 3. Synthetic Applications of 3a



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c03267.

Full characterization, copies of all spectral data, crystallographic data of CCDC 2031759 (**3b**) and CCDC 2031760 (**5k**), and experimental procedures (PDF)

Accession Codes

CCDC 2031759−2031760 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

Jinbo Hu − *Key Laboratory of Organofluorine Chemistry, Center for Excellence in Molecular Synthesis, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, Shanghai 200032, China;* orcid.org/0000-0003-3537-0207; Email: jinbohu@sioc.ac.cn

Authors

Xiu Wang − *Key Laboratory of Organofluorine Chemistry, Center for Excellence in Molecular Synthesis, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, Shanghai 200032, China*

Wenchao Ye − *Key Laboratory of Organofluorine Chemistry, Center for Excellence in Molecular Synthesis, Shanghai Institute of Organic Chemistry, University of Chinese*

https://doi.org/10.1021/acs.orglett.1c03267
Org. Lett. 2021, 23, 8554−8558

Academy of Sciences, Chinese Academy of Sciences, Shanghai 200032, China

Taige Kong − *Key Laboratory of Organofluorine Chemistry, Center for Excellence in Molecular Synthesis, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, Shanghai 200032, China*

Chenlu Wang − *Key Laboratory of Organofluorine Chemistry, Center for Excellence in Molecular Synthesis, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, Shanghai 200032, China*

Chuanfa Ni − *Key Laboratory of Organofluorine Chemistry, Center for Excellence in Molecular Synthesis, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, Shanghai 200032, China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.1c03267

Author Contributions

‡X.W. and W.Y. contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the National Key Research and Development Program of China (2016YFB0101200), the National Natural Science Foundation of China (21632009), the Key Programs of the Chinese Academy of Sciences (KGZD-EW-T08), the Key Research Program of Frontier Sciences of CAS (QYZDJ-SSW-SLH049), and the fellowship of China Postdoctoral Science Foundation (2020M671273).

■ REFERENCES

(1) (a) Zhang, B.; Studer, A. Recent advances in the synthesis of nitrogen heterocycles via radical cascade reactions using isonitriles as radical acceptors. *Chem. Soc. Rev.* **2015**, *44*, 3505−3521. (b) Lei, J.; Huang, J.; Zhu, Q. Recent progress in imidoyl radical-involved reactions. *Org. Biomol. Chem.* **2016**, *14*, 2593−2602. (c) Giustiniano, M.; Basso, A.; Mercalli, V.; Massarotti, A.; Novellino, E.; Tron, G. C.; Zhu, J. To each his own: isonitriles for all flavors. Functionalized isocyanides as valuable tools in organic synthesis. *Chem. Soc. Rev.* **2017**, *46*, 1295−1357. (d) Song, B.; Xu, B. Metal-catalyzed C−H functionalization involving isocyanides. *Chem. Soc. Rev.* **2017**, *46*, 1103−1123.

(2) (a) Dömling, A. Recent Developments in Isocyanide Based Multicomponent Reactions in Applied Chemistry. *Chem. Rev.* **2006**, *106*, 17−89. (b) Domling, A.; Wang, W.; Wang, K. Chemistry and Biology of Multicomponent Reactions. *Chem. Rev.* **2012**, *112*, 3083−3135. (c) Cioc, R. C.; Ruijter, E.; Orru, R. V. A. Multicomponent reactions: advanced tools for sustainable organic synthesis. *Green Chem.* **2014**, *16*, 2958−2975. (d) Wang, Q.; Wang, D.-X.; Wang, M.-X.; Zhu, J. Still Unconquered: Enantioselective Passerini and Ugi Multicomponent Reactions. *Acc. Chem. Res.* **2018**, *51*, 1290−1300.

(3) (a) Lang, S. Unravelling the labyrinth of palladium-catalysed reactions involving isocyanides. *Chem. Soc. Rev.* **2013**, *42*, 4867−4880. (b) Boyarskiy, V. P.; Bokach, N. A.; Luzyanin, K. V.; Kukushkin, V. Y. Metal-Mediated and Metal-Catalyzed Reactions of Isocyanides. *Chem. Rev.* **2015**, *115*, 2698−2779.

(4) (a) Yi, H.; Zhang, G.; Wang, H.; Huang, Z.; Wang, J.; Singh, A. K.; Lei, A. Recent Advances in Radical C−H Activation/Radical Cross-Coupling. *Chem. Rev.* **2017**, *117*, 9016−9085. (b) Liu, Y.; Li, S.-J.; Chen, X.-L.; Fan, L.-L.; Li, X.-Y.; Zhu, S.-S.; Qu, L.-B.; Yu, B. Mn(III)-Mediated Regioselective 6-endo-trig Radical Cyclization of *o*-Vinylaryl Isocyanides to Access 2-Functionalized Quinolines. *Adv. Synth. Catal.* **2020**, *362*, 688−694.

(5) (a) Rong, J.; Deng, L.; Tan, P.; Ni, C.; Gu, Y.; Hu, J. Radical Fluoroalkylation of Isocyanides with Fluorinated Sulfones by Visible-Light Photoredox Catalysis. *Angew. Chem., Int. Ed.* **2016**, *55*, 2743−2747. (b) Li, D.; Mao, T.; Huang, J.; Zhu, Q. Denitrogenative Imidoyl Radical Cyclization: Synthesis of 2-Substituted Benzoimidazoles from 1-Azido-2-isocyanoarenes. *Org. Lett.* **2017**, *19*, 3223−3226. (c) Liu, Y.; Chen, X.-L.; Zeng, F.-L.; Sun, K.; Qu, C.; Fan, L.-L.; An, Z.-L.; Li, R.; Jing, C.-F.; Wei, S.-K.; Qu, L.-B.; Yu, B.; Sun, Y.-Q.; Zhao, Y.-F. Phosphorus Radical-Initiated Cascade Reaction to Access 2-Phosphoryl-Substituted Quinoxalines. *J. Org. Chem.* **2018**, *83*, 11727−11735.

(6) (a) Yang, W. C.; Wei, K.; Sun, X.; Zhu, J.; Wu, L. Cascade C(sp^3)−S Bond Cleavage and Imidoyl C−S Formation: Radical Cyclization of 2-Isocyanoaryl Thioethers toward 2-Substituted Benzothiazoles. *Org. Lett.* **2018**, *20*, 3144−3147. (b) Yuan, Y.; Dong, W.; Gao, X.; Xie, X.; Zhang, Z. Sodium Sulfite-Involved Photocatalytic Radical Cascade Cyclization of 2-Isocyanoaryl Thioethers: Access to 2-CF_2/CF_3-Containing Benzothiazoles. *Org. Lett.* **2019**, *21*, 469−472. (c) Liu, Y.; Chen, X.-L.; Sun, K.; Li, X.-Y.; Zeng, F.-L.; Liu, X.-C.; Qu, L.-B.; Zhao, Y.-F.; Yu, B. Visible-Light Induced Radical Perfluoroalkylation/Cyclization Strategy to Access 2-Perfluoroalkylbenzothiazoles/Benzoselenazoles by EDA Complex. *Org. Lett.* **2019**, *21*, 4019−4024.

(7) (a) Yang, W.; Li, B.; Zhang, M.; Wang, S.; Ji, Y.; Dong, S.; Feng, J.; Yuan, S. Metal-free photo-induced radical C−P and C−S bond formation for the synthesis of 2-phosphoryl benzothiazoles. *Chin. Chem. Lett.* **2020**, *31*, 1313−1316. (b) Aiello, S.; Wells, G.; Stone, E. L.; Kadri, H.; Bazzi, R.; Bell, D. R.; Stevens, M. F. G.; Matthews, C. S.; Bradshaw, T. D.; Westwell, A. D. Synthesis and Biological Properties of Benzothiazole, Benzoxazole, and Chromen-4-one Analogues of the Potent Antitumor Agent 2-(3,4-Dimethoxyphenyl)-5-fluorobenzothiazole (PMX 610, NSC 721648). *J. Med. Chem.* **2008**, *51*, 5135−5139. (c) Le Bozec, L.; Moody, C. J. Naturally Occurring NitrogenSulfur Compounds. The Benzothiazole Alkaloids. *Aust. J. Chem.* **2009**, *62*, 639−647.

(8) (a) Kadoya, S.; Takamura, I.; Suzuki, N.; Dohmori, R. Synthetic Chemotherapeutic Agents. II. Synthesis of 2-Substituted Thiazolo [5, 4-f] quinoline Derivatives. *Chem. Pharm. Bull.* **1976**, *24*, 136−146. (b) Ueno, Y.; Kojima, A.; Okawara, M. A Convenient And General Synthesis of Alkane Sulfinic Acids. *Chem. Lett.* **1984**, *13*, 2125−2128. (c) Cressier, D.; Prouillac, C.; Hernandez, P.; Amourette, C.; Diserbo, M.; Lion, C.; Rima, G. Synthesis, antioxidant properties and radioprotective effects of new benzothiazoles and thiadiazoles. *Bioorg. Med. Chem.* **2009**, *17*, 5275−5284. (d) Hrobárik, P.; Hrobáriková, V.; Sigmundová, I.; Zahradník, P.; Fakis, M.; Polyzos, I.; Persephonis, P. Benzothiazoles with Tunable Electron-Withdrawing Strength and Reverse Polarity: A Route to Triphenylamine-Based Chromophores with Enhanced Two-Photon Absorption. *J. Org. Chem.* **2011**, *76*, 8726−8736. (e) Stella, A.; Segers, K.; DeJonghe, S.; Vanderhoydonck, B.; Rozenski, J.; Anné, J.; Herdewijn, P. Synthesis and Antibacterial Evaluation of a Novel Series of 2-(1,2-Dihydro-3-oxo-3*H*-pyrazol-2-yl)benzothiazoles. *Chem. Biodiversity* **2011**, *8*, 253−265. (f) Kamps, J. J. A. G.; Belle, R.; Mecinović, J. Hydroxylamine as an oxygen nucleophile: substitution of sulfonamide by a hydroxyl group in benzothiazole-2-sulfonamides. *Org. Biomol. Chem.* **2013**, *11*, 1103−1108. (g) Toda, N.; Asano, S.; Barbas, C. F. Rapid, Stable, Chemoselective Labeling of Thiols with Julia−Kocieński-like Reagents: A Serum-Stable Alternative to Maleimide-Based Protein Conjugation. *Angew. Chem., Int. Ed.* **2013**, *52*, 12592−12596. (h) Söderström, M.; Zamaratski, E.; Odell, L. R. BF_3·SMe_2 for Thiomethylation, Nitro Reduction and Tandem Reduction/SMe Insertion of Nitrogen Heterocycles. *Eur. J. Org. Chem.* **2019**, *2019*, 5402−5408. (i) Ma, X.; Yu, J.; Yan, R.; Yan, M.; Xu, Q. Promoting Effect of Crystal Water Leading to Catalyst-Free Synthesis of Heteroaryl Thioether from Heteroaryl Chloride, Sodium Thiosulfate Pentahydrate, and Alcohol. *J. Org. Chem.* **2019**, *84*, 11294−11300.

(9) (a) Martínez, M. D.; Luna, L.; Tesio, A. Y.; Feresin, G. E.; Duran, F. J.; Burton, G. Antioxidant properties in a non-polar environment of difluoromethyl bioisosteres of methyl hydroxycinnamates. *J. Pharm. Pharmacol.* **2016**, *68*, 233−244. (b) Sessler, C. D.; Rahm, M.; Becker, S.; Goldberg, J. M.; Wang, F.; Lippard, S. J. CF_2H, a Hydrogen Bond Donor. *J. Am. Chem. Soc.* **2017**, *139*, 9325−9332. (c) Zafrani, Y.; Sod-Moriah, G.; Yeffet, D.; Berliner, A.; Amir, D.; Marciano, D.; Elias, S.; Katalan, S.; Ashkenazi, N.; Madmon, M.; Gershonov, E.; Saphier, S. CF_2H, a Functional Group-Dependent Hydrogen-Bond Donor: Is It a More or Less Lipophilic Bioisostere of OH, SH, and CH_3? *J. Med. Chem.* **2019**, *62*, 5628−5637.

(10) Chen, D.; Ni, C.; Zhao, Y.; Cai, X.; Li, X.; Xiao, P.; Hu, J. Bis(difluoromethyl)-trimethylsilicate Anion: A Key Intermediate in Nucleophilic Difluoromethylation of Enolizable Ketones with Me_3SiCF_2H. *Angew. Chem., Int. Ed.* **2016**, *55*, 12632−12636.

(11) The aromatic ring-opening reaction between a nucleophile and a benzothiazole has never been reported. We notice that aromatic ring-opening of 3-chloro-1,2-benzisothiazole and fused thiophenes have been documented in literature; see: (a) Carrington, D. E. L.; Clarke, K.; Scrowston, R. M. 1.2-Benzisothiazoles. Part I. Reaction of 3-Chloro-I, 2-benzisothiazole with Nucleophiles. *J. Chem. Soc. C* **1971**, 3262−3265; *J. Chem. Soc. C* **1971**, 3903−3906. (b) Carrington, D. E. L.; Clarke, K.; Scrowston, R. M. 1.2-Benzisothiazoles. Part II. Reaction of 3-Chloro-1, 2-benzisothiazole with Carbanions. *J. Chem. Soc. C* **1971**, 3903−3906. (c) Hill, B.; De Vleeschauwer, M.; Houde, K.; Belley, M. Aromatic Ring Opening of Fused Thiophenes via Organolithium Addition to Sulfur. *Synlett* **1998**, *1998*, 407−410. (d) Belley, M.; Douida, Z.; Mancuso, J.; Vleeschauwer, M. C. Aromatic Ring-Opening of 2-Fluorobenzothiophenes by Alkylitlhiums. *Synlett* **2005**, 247−250.

(12) For selected examples of synthetic applications of 2-$PySO_2CF_2H$: (a) Zhao, Y.; Huang, W.; Zhu, L.; Hu, J. Difluoromethyl 2-Pyridyl Sulfone: A New gem-Difluoroolefination Reagent for Aldehydes and Ketones. *Org. Lett.* **2010**, *12*, 1444−1447. (b) Zhao, Y.; Gao, B.; Hu, J. From Olefination to Alkylation: In-Situ Halogenation of Julia-Kocienski Intermediates Leading to Formal Nucleophilic Iodo- and Bromodifluoromethylation of Carbonyl Compounds. *J. Am. Chem. Soc.* **2012**, *134*, 5790−5793. (c) Miao, W.; Zhao, Y.; Ni, C.; Gao, B.; Zhang, W.; Hu, J. Iron-Catalyzed Difluoromethylation of Arylzincs with Difluoromethyl 2-Pyridyl Sulfone. *J. Am. Chem. Soc.* **2018**, *140*, 880−883. (d) Miao, W.; Ni, C.; Xiao, P.; Jia, R.; Zhang, W.; Hu, J. Nickel-Catalyzed Reductive 2-Pyridination of Aryl Iodides with Difluoromethyl 2-Pyridyl Sulfone. *Org. Lett.* **2021**, *23*, 711−715. (e) Thornbury, R. T.; Toste, F. D. Palladium-Catalyzed Defluorinative Coupling of 1-Aryl-2,2-Difluoroalkenes and Boronic Acids: Stereoselective Synthesis of Monofluorostilbenes. *Angew. Chem., Int. Ed.* **2016**, *55*, 11629−11632. (f) Zhou, Q.; Ruffoni, A.; Gianatassio, R.; Fujiwara, Y.; Sella, E.; Shabat, D.; Baran, P. S. Direct Synthesis of Fluorinated Heteroarylether Bioisosteres. *Angew. Chem., Int. Ed.* **2013**, *52*, 3949−3952.

(13) Chatani, N.; Oshita, M.; Tobisu, M.; Ishii, Y.; Murai, S. A $GaCl_3$-Catalyzed [4 + 1] Cycloaddition of α,β-Unsaturated Carbonyl Compounds and Isocyanides Leading to Unsaturated γ-Lactone Derivatives. *J. Am. Chem. Soc.* **2003**, *125*, 7812−7813.

https://doi.org/10.1021/acs.orglett.1c03267
Org. Lett. 2021, 23, 8554−8558