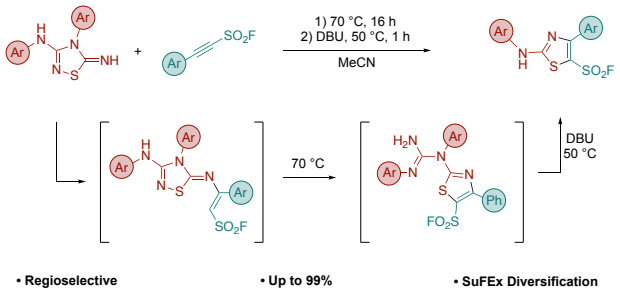
The Synthesis of Sulfonyl Fluoride Functionalized 2-Aminothiazoles using a Diversity Oriented Clicking Strategy

Joshua Kop, Carol Hua and Christopher J. Smedley*

* **Christopher J. Smedley** – Medicinal Chemistry, Monash Institute of Pharmaceutical Sciences, Monash University, Parkville, VIC 3052, Australia. https://orcid.org/0000-0001-5110-2574. E-mail: chris.smedley@monash.edu.

Joshua Kop – Medicinal Chemistry, Monash Institute of Pharmaceutical Sciences, Monash University, Parkville, VIC 3052, Australia.

Carol Hua – School of Chemistry, The University of Melbourne, Parkville, 3010 Victoria, Australia. https://orcid.org/0000-0002-4207-9963



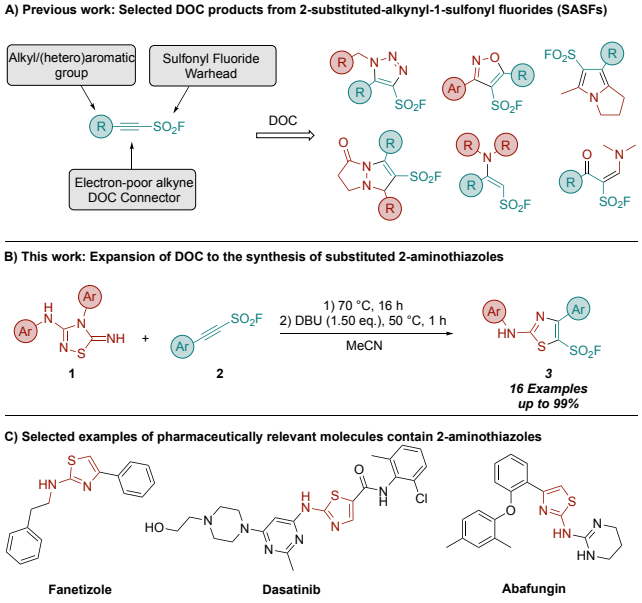
ABSTRACT: We present the synthesis of 16 unprecedented sulfonyl fluoride functionalized 2-aminothiazoles in good to excellent yields. The transformation is simple to perform, tolerant of a wide range of functionality and regioselective for a single product. Additionally, we showcase the diversification of the novel 2-aminothiazoles through SuFEx click chemistry. Finally, we propose a plausible stepwise reaction mechanism.

Diversity Oriented Clicking (DOC) is a powerful strategy for the synthesis of complex molecular frameworks featuring the valuable S—F functionality.[1–3] DOC combines classical click chemistry techniques, such as Huisgen cycloadditions,[4–6] with next generation Sulfur-Fluoride Exchange (SuFEx) chemistry (a technology which creates molecular connections via substitution of S—F for S—O and S—N bonds) to achieve "*diversity with ease*".[7–12] DOC was initially demonstrated using the 2-Substituted-Alkynyl-1-Sulfonyl Fluoride (SASF) molecular spring-loaded connectors, which can undergo a variety of selective click reactions, including cycloadditions[1] and 1,4-Michael additions.[2] This approach generated a structurally diverse library of sulfonyl fluoride-containing heterocycles and β-substituted alkenyl sulfonyl fluoride, which could be further diversified through late-stage SuFEx modifications. More recently, we applied SASF connectors in a novel series of addition reactions with DMSO and DMF to synthesize two unique, highly functionalized classes of olefins.[3]

The utility of the DOC strategy is underscored by the identification of several lead compounds with valuable biological properties. Notably, a number of compounds from the seminal DOC paper exhibited antibacterial activity against MRSA (USA300),[1] while several Michael addition products emerged as potent inhibitors of human neutrophil elastase (hNE).[2] These findings highlight the potential of DOC in drug discovery and development.

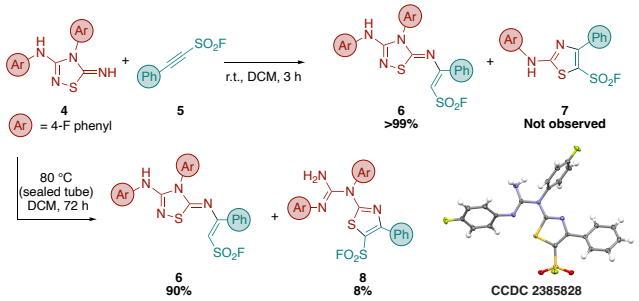
The 2-aminothiazole group has emerged as a promising scaffold in medicinal chemistry and drug discovery, found in many pharmaceutically relevant small molecules.[13–16] Examples include Fanetizole, an anti-inflammatory agent;[14] Dasatinib, an anti-tumor agent via Src inhibition and Abafungin, an antimicrobial agent.[15,16] Additionally, 2-aminothiazoles serve as versatile building blocks for accessing more complex structures.[17,18]

Scheme 1. Diversity Oriented Clicking of 2-substituted-alkynyl-1-sulfonyl fluorides (SASFs)



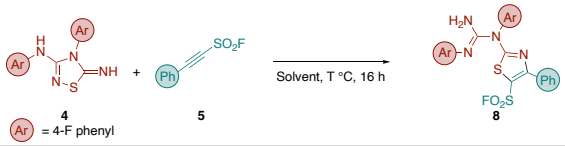
Given the prevalence of the 2-aminothiazole core, we sought to develop a clickable *N*-substituted 2-aminothiazole that could serve as a connective hub for further derivatization. Kostryukov *et al.* reported the use of 5-imino-*N*,4-diaryl-4,5-dihydro-1,2,4-thiadiazol-3-amines as masked 1,3-dipoles in 1,3 dipolar cycloaddition reactions with acetylenic 1,3-dipolarphiles at room temperature.[19] The transformation resulted in the formation of a library of 2-aminothiazoles. Based on previous literature, the authors proposed the reaction proceeded through a concerted manner via a hypervalent sulfurane intermediate.[20,21] We envisioned SASFs could be applied in a similar reaction to access sulfonyl fluoride functionalized 2-aminothiazoles that can be further diversified through late-stage SuFEx click chemistry.

Scheme 2. Initial reaction tests



Using **4** and **5** as model substrates, we began our initial investigations by applying conditions similar to those used by Kostryukov *et al*[19] (Scheme 2). Stirring equimolar quantities of **4** and **5** in CH_2Cl_2 at room temperature for 3 h resulted in the complete consumption of both starting materials. However, NMR and LCMS analysis of the product indicated that it was not the 2-aminothiazole but rather the 1,4-addition product **6**, as evidenced by the presence of the alkenyl proton in the ^{1}H NMR. We envisioned it may still be possible to achieve the desired 2-aminothiazole using more forcing conditions. Therefore, we heated equimolar equivalents of **4** and **5** in a sealed tube at 80 °C for 72 h. LCMS analysis indicated that, in addition to the 1,4-addition product, another product (**8**) with the same mass was present in a 9:1 ratio (**6**:**8**) and none of the desired 2-aminothiazole was observed. Following NMR analysis, the new product was hypothesized to be a guanidine intermediate (**8**). The structure of **8** was corroborated through single crystal X-ray crystallography. Following this unexpected result, we decided to optimize formation of the intermediate **8** (Table 1). Performing the reaction at 80 °C in THF saw no improvement in the yield of **8** (9%). However, both MeCN and 1,4-dioxane gave excellent yields of the guanidine product **8** (93 and 95% respectively) whilst toluene gave a moderate yield of 59%. Moving forward with MeCN, due to its lower boiling point and its more favourable hazard profile, it was observed that the reaction could be performed at 70 °C with no real effect on the yield but lowering further to 50 °C led to a decreased yield of 36%.

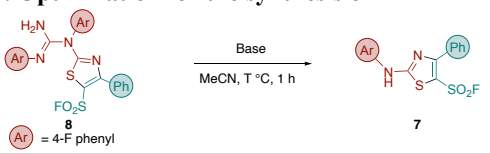
Table 1. Optimization for the synthesis of 8



Entry[a]	Solvent	T (°C)	Yield (%)[b]
1	THF	80	9
2	MeCN	80	93
3	1,4-Dioxane	80	95
4	Toluene	80	59
5	MeCN	70	99
6	MeCN	50	36

[a]Reactions performed on 0.25 mmol of **4**, 0.25 mmol of **5** in the stipulated solvent and temperature for 16 h. [b]Isolated yields.

Table 2. Optimization for the synthesis of 7



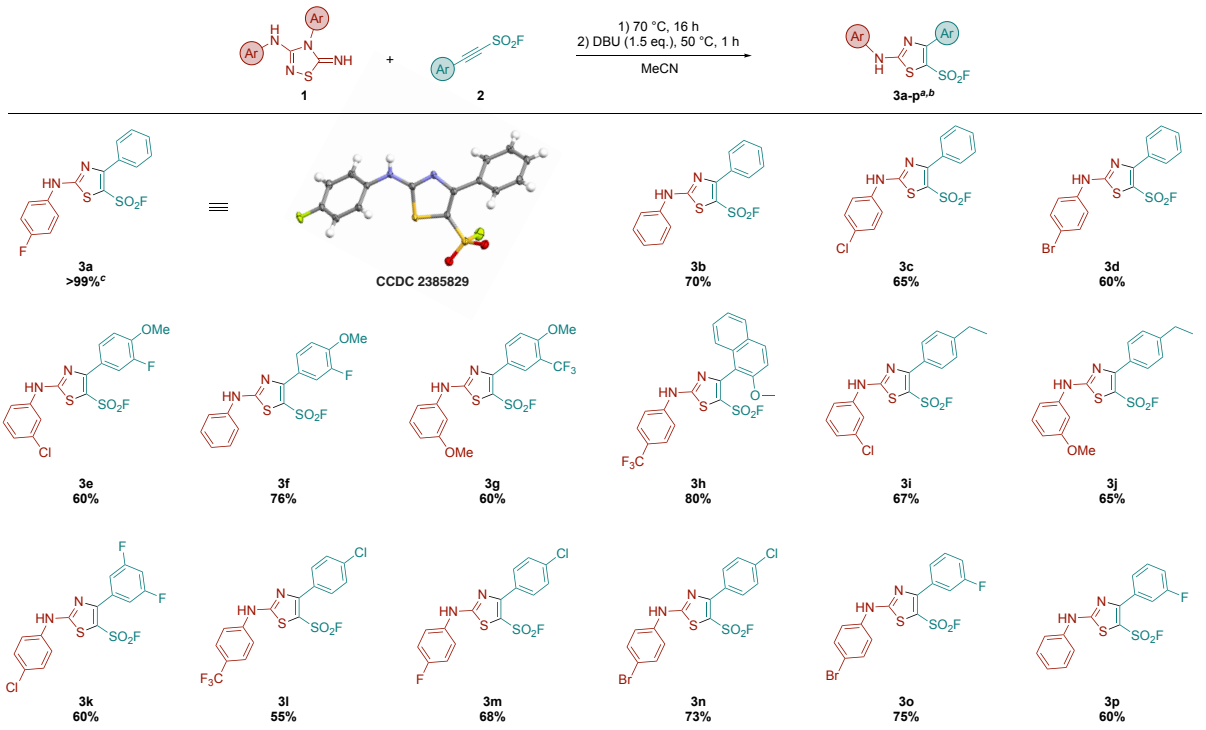
Entry[a]	Base (eq.)	T (°C)	Yield (%)[b]
1	Et_3N (1.00 eq.)	r.t.	n.r.
2	Et_3N (1.00 eq.)	50	n.r.
3	Et_3N (1.00 eq.)	80	n.r.
4	DBU (1.00 eq.)	50	66
5	DBU (1.50 eq.)	50	>99

[a]Reactions performed on 0.10 mmol of **8** in the stipulated solvent and temperature for 16 h. [b]Isolated yields.

With the optimized conditions in hand for the intermediate **8**, our attention next turned to facilitating formation of the desired 2-aminothiazole **7** from the guanidine product **8** through the release of *N*-(4-fluorophenyl)cyanamide (Table 2). We hypothesized that in order to facilitate this transformation a base would be required. Therefore, we stirred **8** with 1.00 eq. Et_3N at room temperature, 50 °C and 80 °C. However, no new products were observed indicating a stronger base may be required. Pleasingly DBU at 50 °C proved effective and the desired thiazole was isolated in a 66% yield along with unconverted starting material. Increasing the equivalents of DBU to 1.50 eq. led to full conversion of starting material to product and was isolated in excellent yield (>99%). With both optimised conditions in hand, it proved possible to combine them to perform the reaction one pot without any detriment to the yield of **8** and the following condition were identified: heating **4** and **5** at 70 °C in MeCN for 16 h followed by cooling to 50 °C and the addition of 1.50 eq. of DBU and stirring for 1 hour.

With the optimized one-pot conditions for the 2-aminothiazole product established, we shifted our focus to exploring the substrate scope of the reaction (Scheme 3). The substrate scope of the reaction was first investigated by reacting 2-phenylethyne-1-sulfonyl fluoride with a range of 5-imino-*N*,4-diaryl-4,5-dihydro-1,2,4-thiadiazol-3-amines (**1**) yielding 2-aminothiazoles **3a**-**3d** in good to excellent yields (60-99%). Next, a selection of substituted SASFs were tested in the reaction. The reaction performed well with a selection of electron rich SASFs to give the corresponding 2-aminothiazoles (**3e**-**3j**) in good to excellent yields (60-80%). Notably, this also includes the sterically hindered 2-methoxynaphthyl SASF to give **3h** in an impressive 80% yield. Next, electron-deficient SASFs were used, also proving successful and yielding 2-aminothiazoles **3k**-**3p** with yields ranging from 55 to 75%. The transformation also proved to be suitable for 5-imino-*N*,4-diaryl-4,5-dihydro-1,2,4-

Scheme 3. Substrate scope of reaction

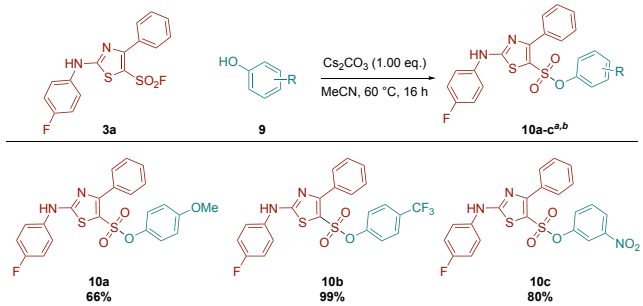


[a]Reactions performed on 0.25 mmol of **1**, 0.25 mmol of **2** in MeCN (1.00 mL) heated at 70 °C for 16 h and then 1 h at 50 °C with DBU (0.38 mmol). [b]Isolated yields. [c]Reaction performed on 0.10 mmol of **1** and 0.10 mmol of **2**.

thiadiazol-3-amines bearing a variety of functional groups, including halo, haloalkyl and methoxy.

To demonstrate the utility of these products, we attempted SuFEx chemistry on product **3a** (Scheme 4). Interestingly, the SuFEx reaction on these products proved more challenging than anticipated both accelerated SuFEx click chemistry (ASCC)[22] and using Cs_2CO_3 at room temperature were unsuccessful. We postulated that the electron-rich nature of the 2-aminothiazole ring deactivates the electrophilic sulfur making S-F exchange more challenging. Pleasingly, the more forcing conditions of Cs_2CO_3 and the desired phenol in MeCN heating at 60 °C for 16 h gave the desired sulfonate products (**10a-10c**) in excellent yields (66-99%).

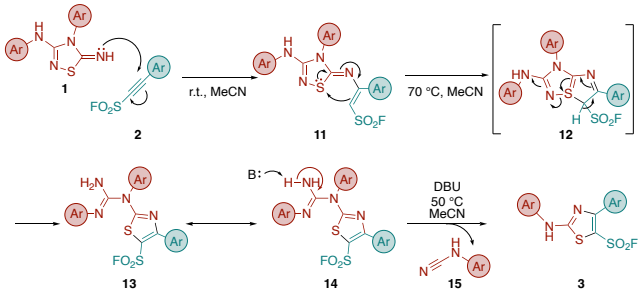
Scheme 4. SuFEx reactions of 3a



[a]Reactions performed on 0.10 mmol of **3a**, 0.10 mmol of **9** and 0.10 mmol of Cs_2CO_3 in MeCN (0.50 mL) heated at 60 °C for 16 h. [b]Isolated yields.

Finally, we propose that the mechanism to the desired thiazole **3** proceeds through a multi-step mechanism in a stepwise cycloaddition and elimination (Scheme 5). First 1,4-Michael addition of 5-imino-*N*,4-diaryl-4,5-dihydro-1,2,4-thiadiazol-3-amine **1** into the SASF **2** occurs to give the isolated intermediate **11**, which when heated undergoes an intramolecular cycloaddition forming the proposed unstable hypervalent sulfurane **12**. Intermediate **12** then undergoes ring opening to form the isolated guanidine intermediate **13**. The addition of DBU facilitates deprotonation and release of thecyanamide byproduct **15** to give the desired thiazole **3** in perfect regioselectivity.

Scheme 5. Proposed mechanistic pathway



In conclusion, this novel transformation of the SASF hubs reinforces DOC as a powerful tool for achieving "*diversity with ease*." First, we have developed a straightforward approach for the synthesis of 16 unprecedented sulfonyl fluoride functionalized *N*-substituted 2-aminothiazoles with up to 99% yield through reacting the SASF hubs with a range of 5-imino-*N*,4-diaryl-4,5-dihydro-1,2,4-thiadiazol-3-amines. Next, we

demonstrate the capacity of the *N*-substituted 2-aminothiazole product to be rapidly diversified through late-stage SuFEx modification. Lastly, a plausible stepwise reaction is proposed. This advancement highlights the potential for streamlined processes and improved outcomes within DOC, paving the way for more efficient and effective applications.

Author Contributions

C.J.S conceived and supervised the project. J.K and C.J.S performed synthetic experiments and analyses. C.H performed X-ray crystallography. C.J.S wrote the manuscript, and all authors approved the final draft.

Acknowledgements

C.J.S thanks the Australian Research Council (ARC) for a Discovery Early Career Research Fellowship (DECRA, DE240100449). Thanks to Monash University for infrastructure and Dr William O'Malley spectroscopy support.

References

(1) Smedley, C. J.; Li, G.; Barrow, A. S.; Gialelis, T. L.; Giel, M.-C.; Ottonello, A.; Cheng, Y.; Kitamura, S.; Wolan, D. W.; Sharpless, K. B.; Moses, J. E. Diversity Oriented Clicking (DOC): Divergent Synthesis of SuFExable Pharmacophores from 2-Substituted-Alkynyl-1-Sulfonyl Fluoride (SASF) Hubs. *Angew. Chem. Int. Ed.* **2020**, *59,* 12460–12469.

(2) Cheng, Y.; Li, G.; Smedley, C. J.; Giel, M.-C.; Kitamura, S.; Woehl, J. L.; Bianco, G.; Forli, S.; Homer, J. A.; Cappiello, J. R.; Wolan, D. W.; Moses, J. E.; Sharpless, K. B. Diversity Oriented Clicking Delivers β-Substituted Alkenyl Sulfonyl Fluorides as Covalent Human Neutrophil Elastase Inhibitors. *Proc. Natl. Acad. Sci. U.S.A.* **2022**, *119*, e2208540119.

(3) Smedley, C. J. A Diversity Oriented Clicking Strategy: The Stereoselective Synthesis of Highly-Functionalised Olefins from 2-Substituted-Alkynyl-1-Sulfonyl Fluorides. *Chem. Commun.* **2022**, *58*, 11316–11319.

(4) Huisgen, R. Kinetics and Mechanism of 1,3-Dipolr Cycloadditions. *Angew. Chem. Int. Ed.* **1963**, *2*, 633–645.

(5) Moses, J. E.; Moorhouse, A. D. The Growing Applications of Click Chemistry. *Chem Soc Rev.* **2007**, *36*, 1249–1262.

(6) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. Click Chemistry: Diverse Chemical Function from a Few Good Reactions. *Angew. Chem. Int. Ed.* **2001**, *40*, 2004–2021.

(7) Dong, J.; Krasnova, L.; Finn, M. G.; Sharpless, K. B. Sulfur(VI) Fluoride Exchange (SuFEx): Another Good Reaction for Click Chemistry. *Angew. Chem. Int. Ed.* **2014**, *53*, 9430–9448.

(8) Barrow, A. S.; Smedley, C. J.; Zheng, Q.; Li, S.; Dong, J.; Moses, J. E. The Growing Applications of SuFEx Click Chemistry. *Chem. Soc. Rev.* **2019**, *48*, 4731–4758.

(9) Li, S.; Wu, P.; Moses, J. E.; Sharpless, K. B. Multidimensional SuFEx Click Chemistry: Sequential Sulfur(VI) Fluoride Exchange Connections of Diverse Modules Launched From An SOF_4 Hub. *Angew. Chem. Int. Ed.* **2017**, *56*, 2903–2908.

(10) Giel, M.-C.; Zhang, S.; Hu, Q.; Ding, D.; Tang, Y.; Hong, Y. Synthesis of a β-Arylethenesulfonyl Fluoride-Functionalized AIEgen for Activity-Based Urinary Trypsin Detection. *ACS Appl Bio Mater.* **2022**, *5*, 4321–4326.

(11) Homer, J. A.; Xu, L.; Kayambu, N.; Zheng, Q.; Choi, E. J.; Kim, B. M.; Sharpless, K. B.; Zuilhof, H.; Dong, J.; Moses, J. E. Sulfur Fluoride Exchange. *Nat. Rev. Methods Primers* **2023**, *3*, 58.

(12) Giel, M.-C.; Smedley, C. J.; Moses, J. E. *Science of Synthesis: Click Chemistry* (Ed.: F. P. J. T. Rutjes); Thieme Chemistry, **2021**; pp. 435-484.

(13) Azzali, E.; Girardini, M.; Annunziato, G.; Pavone, M.; Vacondio, F.; Mori, G.; Pasca, M. R.; Costantino, G.; Pieroni, M. 2-Aminooxazole as a Novel Privileged Scaffold in Antitubercular Medicinal Chemistry. *ACS Med. Chem. Lett.* **2020**, *11*, 1435–1441.

(14) Li, P.; Yang, S.-F.; Fang, Z.-L.; Cui, H.-R.; Liang, S.; Tian, H.-Y.; Sun, B.-G.; Zeng, C.-C. An Efficient One-Pot Synthesis of 2-Aminothiazoles via Electrochemically Oxidative α-C-H Functionalization of Ketones with Thioureas. *J. Environ. Chem. Eng.* **2022**, *10*, 107487.

(15) Das, D.; Sikdar, P.; Bairagi, M. Recent Developments of 2-Aminothiazoles in Medicinal Chemistry. *Eur. J. Med. Chem.* **2016**, *109*, 89–98.

(16) Jakopin, Ž. 2-Aminothiazoles in Drug Discovery: Privileged Structures or Toxicophores? *Chem. Biol. Interact.* **2020**, *330*, 109244.

(17) Kaupp, G.; Amer, F. A.; Metwally, M. A.; Abdel-Latif, E. Versatile 2-Aminothiazoles, Building Blocks for Highly Functionalised Heterocycles. *J. Heterocycl. Chem.* **2003**, *40*, 963–971.

(18) Imtiaz, S.; Ahmad war, J.; Banoo, S.; khan, S. α-Aminoazoles/Azines: Key Reaction Partners for Multicomponent Reactions. *RSC Adv.* **2021**, *11*, 11083–11165.

(19) Kostryukov, S. G.; Masterova, Yu. Yu.; Pugacheva, E. Yu. On Reactions of 5-Imino-N,4-Diaryl-4,5-Dihydro-1,2,4-Thiadiazol-3-Amines with Phenylethynyl Sulfones. *Russ. J. Org. Chem.* **2022**, *58*, 219–225.

(20) Akiba, K.; Ochiumi, M.; Tsuchiya, T.; Inamoto, N. Formation of 2-Arylaminothiazoles by 1,3-Dipolar Cycloaddition of "Hector's Base" with Acetylenes. *Tetrahedron Lett.* **1975**, *16*, 459–462.

(21) Yamamoto, Y.; Tsuchiya, T.; Ochiumi, M.; Arai, S.; Inamoto, N. A Mechanistic Study on the Reaction of Imiothidiazolines with Activated Acetylenes: Competitive Pathway through Hypervalent Sulfurane and Zwitterion. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 211–218.

(22) Smedley, C. J.; Homer, J. A.; Gialelis, T. L.; Barrow, A. S.; Koelln, R. A.; Moses, J. E. Accelerated SuFEx Click Chemistry For Modular Synthesis. *Angew. Chem. Int. Ed*., **2022**, *61*, e20212375.