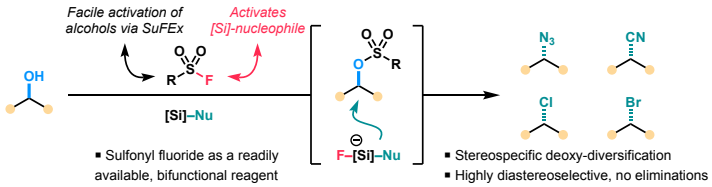
SuFEx-Enabled Direct Deoxy-Diversification of Alcohols

Amaechi Shedrack Odoh, Courtney Keeler, † Byoungmoo Kim*

Department of Chemistry, Clemson University, Clemson, South Carolina 29634, United States.



ABSTRACT: We introduce a new use of sulfonyl fluoride as a bifunctional reagent that facilitates the one-step deoxy-diversification of complex alcohol libraries. Our reaction design features a Sulfur(VI) Fluoride Exchange (SuFEx) mediated activation of alcohols and fluoride-induced activation of silicon-bound nucleophiles. This method enables the direct conversion of alcoholic C–O bonds in complex molecules into diverse analogs via C–C, C–N, C–Cl, and C–Br bond formation while suppressing any elimination side-products.

The prevalence of hydroxy motifs in structurally diverse biomolecules and chemical feedstocks has inspired heightened interest in advancing synthetic strategies for the deoxygenative functionalization of alcohols.[1-4] Such campaigns have enabled the diversification of alcohol-bearing natural products into new analogs with enhanced biological properties,[5,6] and facilitated the generation of versatile intermediates that simplify the synthesis of bioactive molecular targets (Figure 1A).[7-9]

Pivotal to the development of deoxy-functionalization protocols is the strategic transformation of a hydroxy group into a more potent leaving group prior to substitution with nucleophiles (Figure 1B). In this regard, the use of phosphorus reagents as activators has led to the development of prominent deoxy-functionalizations such as the Mitsunobu[10–12] and Appel[13,14] reactions, and, more recently, a Ph_3P/ICH_2CH_2I mediated deoxy-functionalization by Xiao and co-workers.[15,16] However, these transformations generate stoichiometric amounts of phosphonium oxide byproducts that render product isolation quite laborious and require the use of hazardous reagents, such as tetrahalomethanes and azodicarboxylates. Although sulfonyl chlorides are alternative alcohol activators, they require two synthetic steps to achieve deoxy-functionalization. Also, the activation step necessitates aqueous workup or chromatographic purification, which is wasteful and decreases synthetic efficiency.[17] As an alternative approach, radical deoxy-functionalization strategies have emerged as a powerful tool that offers complementary scope and improved yields.[4,18] However, the activation stage generates carbon-centered radicals that often undergo non-stereospecific radical coupling with poor stereocontrol. As a result, the quest for more universal, safe, and operationally convenient alternatives remains a pressing goal.

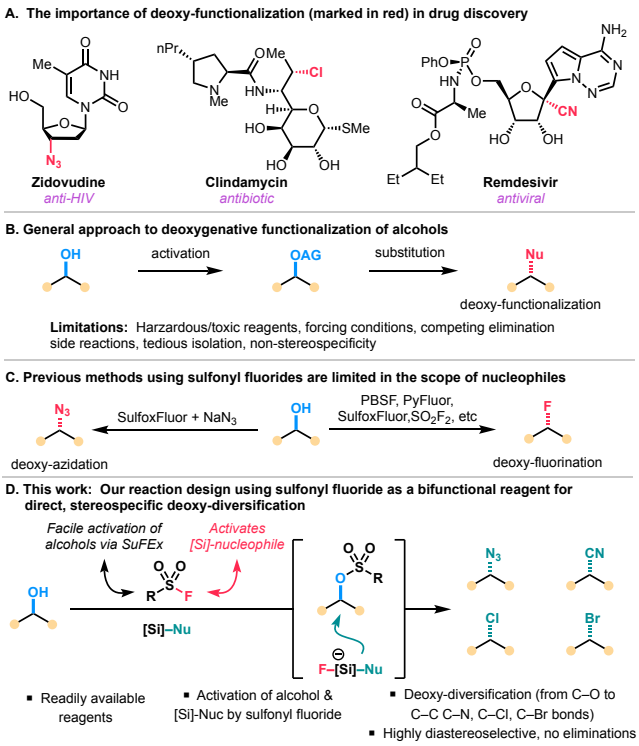


Figure 1. Deoxy-functionalization of alcohols: Applications in drug discovery and synthetic strategies

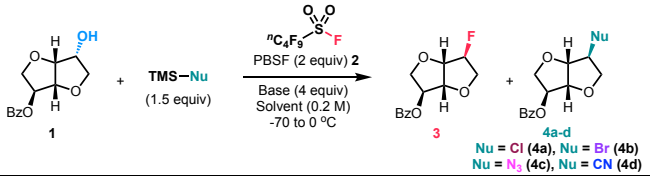
In conceptualizing a new unified strategy that could enable diverse deoxy-functionalization, we were drawn to the well-known Sulfur(VI) Fluoride Exchange (SuFEx) click chemistry, which utilizes sulfonyl fluorides (R-S^{VI}-F) as a key reagent for the creation of several covalent linkages.[19–22] Sulfonyl fluorides are attractive reagents due to their remarkable hydrolytic stability compared to sulfonyl chlorides.[21] Although SuFEx

reactions with aliphatic alcohols are far less developed than with aromatic alcohols, the SuFEx reactions of aliphatic alcohols have led to the development of efficient deoxy-fluorinations[23–25] and deoxy-azidation[26] (Figure 1C). While the use of sulfonyl fluorides in deoxy-fluorinations offers unique advantages over classic reagents like PhenoFluor,[27] DAST,[28] XtalFluor,[29] and Deoxo-fluor,[30] a versatile SuFEx-based protocol capable of facilitating deoxy-functionalization using a diverse array of nucleophiles remains underdeveloped.[31] The realization of such protocol would enable late-stage diversification of complex alcohols and expedite access to analogs of bioactive molecules.[32,33]

With this objective in mind, we present a one-step deoxy-functionalization that employs sulfonyl fluoride as a bifunctional reagent that carries out two roles in a cascade manner – SuFEx-mediated activation of alcohols[19,21] and fluoride-induced activation of silicon-bound nucleophiles (Figure 1D). Herein, the fluoride anion generated from the SuFEx activation of alcohols facilitates an *in situ* activation of a silicon-bound nucleophile via the formation of a favorable silicon-fluoride bond,[34] thereby facilitating a chemoselective substitution on the sulfonate ester intermediate. This sequence of activation allows us to employ a diverse range of silyl reagents as nucleophiles towards stereospecific deoxy-functionalization across various substrates. Importantly, the use of *in situ* generated fluoride for the activation of silicon-bound nucleophiles contributes to an overall atom-economic process by eliminating the need for an external Lewis base activator, thereby streamlining the synthetic pathway and enhancing efficiency.

Our investigation began with identifying a SuFExable reagent that can quantitatively promote rapid alcohol activation while yielding a reactive sulfonate ester that is amenable to seamless functionalization with a diverse array of nucleophiles. A survey of existing literature pointed us toward the commercially available PBSF (**2**) as an ideal candidate due to its common usage in industry, high reactivity, cost-effectiveness, and utility in the deoxy-fluorination of alcohols.[24,35,36] For the optimization of deoxy-diversification, we began with deoxy-chlorination. We found that the desired deoxy-chloro product **4a** was obtained in 50% isolated yield when alcohol **1** was reacted with TMS-Cl in the presence of **2** and MTBD (Table 1, entry 1). In addition, we observed that commencing the reaction at -70 °C is crucial for the success of this transformation, as control experiment suggested that at this starting temperature, the nucleophilicity of the fluoride anion is tamed to accommodate effective sequestration by the silyl reagent. (Table 1, compare entry 1 and 2). Furthermore, conducting the reaction with a 2:1 volume ratio of THF and DCM was paramount for minimizing the generation of deoxy-fluorination side-product **3** (Table 1, entries 1, 3-4) and enhancing deoxy-chlorination, deoxy-bromination and deoxy-azidation (Table 1, entries 6, 8 and 13, respectively). For deoxy-cyanation, conducting the reaction solely in THF yielded maximal selectivity for deoxy-cyano product **4d** (Table 1, entry 17). Also, the reactions displayed distinct compatibility between the identity of the base and nucleophile employed. While DBU proved optimal for deoxy-halogenation (Table 1, entries 6 and 8), TMG was more effective for both deoxy-azidation and deoxy-cyanation (Table 1, entries 13 and 17).

Table 1. Reaction optimization for the deoxy-diversification of alcohols.[a]



Entry	TMS–Nu	Base	Solvent	**3** (%)[b]	**4** (%)[b]
1[c]	TMS–Cl	MTBD	THF	30	50
2[d]	TMS–Cl	MTBD	THF	96	nd[e]
3	TMS–Cl	MTBD	DCM	34	48
4	TMS–Cl	MTBD	THF/DCM (2:1)	16	78
5	TMS–Cl	TMG	THF/DCM (2:1)	31	36
6	**TMS–Cl**	**DBU**	**THF/DCM (2:1)**	**11**	**80**
7	TMS–Cl	DBN	THF/DCM (2:1)	04	63
8	**TMS–Br**	**DBU**	**THF/DCM (2:1)**	**10**	**81**
9	TMS–Br	MTBD	THF/DCM (2:1)	28	51
10	TMS–Br	TMG	THF/DCM (2:1)	36	38
11	TMS–N_3	DBU	THF/DCM (2:1)	48	41
12	TMS–N_3	MTBD	THF/DCM (2:1)	31	33
13	**TMS–N_3**	**TMG**	**THF/DCM (2:1)**	**nd[e]**	**96**
14	TMS–CN	DBU	THF/DCM (2:1)	95	nd[e]
15	TMS–CN	MTBD	THF/DCM (2:1)	83	07
16	TMS–CN	TMG	THF/DCM (2:1)	40	31
17[c]	**TMS–CN**	**TMG**	**THF**	**39**	**53**

[a] Unless noted otherwise, reactions were conducted on a 0.2 mmol scale using alcohol (1.0 equiv), PBSF (2.0 equiv), base (4.0 equiv), TMS-Nu (1.5 equiv), and solvent (1 mL); reagents were added at -70 °C and the reaction mixture was allowed to gently warm up to 0 °C while stirring for 12 h. [b] Isolated yields; products were furnished as single isomers based on ^{1}H NMR analysis of the crude reaction mixture. [c] Reaction time was 24 h. [d] Reagents were added at 0 °C, and the mixture was stirred at 0 °C for 1 h. [e] Not detected by ^{1}H NMR analysis of the crude reaction mixture. (PBSF = perfluorobutanesulfonyl fluoride; TMS = trimethylsilyl; MTBD = 7-Methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene; TMG = 1,1,3,3-tetramethylguanidine; DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene; DBN = 1,5-Diazabicyclo(4.3.0)non-5-ene)

Under our optimized conditions, the desired substitution products were furnished with inversion of configuration as single isomers, which were confirmed by ^{1}H NMR analysis of crude reaction mixtures and the X-ray structure of **4b** (see Figure S12 and S13 in the supporting information). Also, notably, no elimination side-product was observed. These observations suggest that the nucleophilic substitutions proceed via an S_N2 pathway and that any ionization pathway is highly unlikely.

With the optimized conditions in hand, we embarked on elaborating the substrate scope using structurally diverse primary and secondary alcohols derived from natural products and biomolecules. We are pleased to report that sugar-derived secondary alcohols (**1** and **5**), hydroxy proline (**7**), and epi-androsterone (**9**) readily underwent deoxy-diversification with inversion of configuration to furnish the corresponding products in moderate to excellent yields (up to 96% isolated yield)

without any elimination side-products (Figure 2). Furthermore, the transformation displayed good scalability given that 95% isolated yield of the azide **4c** was obtained as a single isomer starting from 1 mmol of alcohol **1** (see the supporting information).

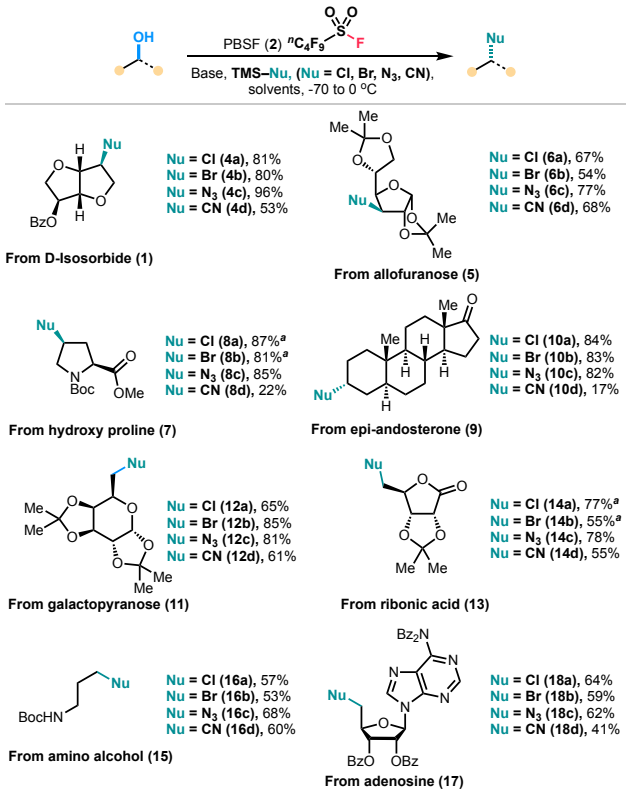


Figure 2. Deoxy-diversification of secondary and primary alcohols (see procedure in the supporting information). Isolated yields are reported. Products were furnished as single isomers based on ^{1}H NMR analysis of the crude reaction mixture. [a]2 equivalents of DBU was used.

We noted that the deoxy-cyanation of alcohol **7** and **9** were sluggish and low isolated yields were obtained for the corresponding cyano-product **8d** and **10d** (22% and 17% yield, respectively). We observed near quantitative recovery of their unreacted sulfonate esters, suggesting that the nucleophilicity of the cyanide anion is dampened, perhaps due to the presence of stoichiometric quantities of conjugate Brønsted acid in the reaction medium.

Primary alcohols derived from sugars (**11** and **13**), amino alcohol (**15**), and adenosine nucleoside (**17**) readily underwent deoxy-diversification to furnish the corresponding products in good to excellent yields (up to 85% isolated yield, Figure 2). While trace amounts of elimination side-products (<10% by ^{1}H NMR analysis) were observed in some cases of deoxy-halogenation (see compound **8a, 8b, 14a,** and **14b** in Figure 2), the undesired pathway was completely suppressed by employing two equivalents of DBU instead of four equivalents. Overall, the high yields and extensive accommodation of a diverse class of biomolecules accentuate our protocol's versatility and synthetic potential for the efficient late-stage diversification of complex molecules and natural products.

We also conducted a series of control experiments to gain insights into the underlying reaction mechanism (Figure 3). Fundamental of the SuFEx reaction relies on fluoride's ability to transition from a stable covalent S–F bond to a good leaving group. Previous reports have suggested that this transition can be initiated via coordination with acidic species (such as H^+ and R_3Si^+) or accelerated by Lewis basic catalysts (such as tertiary amines, amidines, and phosphazenes).[19–21,35,37,38] Building upon these considerations, we embarked on a mechanistic investigation using NMR spectroscopy to ascertain whether a silyl reagent such as TMS–Cl could initiate the SuFEx process with **2** under our standard condition (Figure 3A). We observed that in the absence of DBU, the ^{19}F NMR spectrum of the reaction mixture revealed no discernible alteration in the chemical shifts of **2**. Concurrently, the ^{1}H NMR spectrum showed unreacted compound **1** and the absence of deoxy-functionalization intermediate or product (Figure S1 and S2 in the supporting information). These findings collectively suggest a lack of apparent interaction between **2** and TMS–Cl. We then probed the possibility of S–F bond activation by DBU via the formation of a sulfonyl ammonium fluoride salt with **2**.[19] Combining **2** and DBU in a 1:1 molar ratio exhibited no observable change in the ^{1}H and ^{19}F NMR spectra, underscoring a lack of evident interaction (Figure 3B and Figure S3). Next, we considered whether the reaction proceeds via an initial deprotonation or H-bonding activation of alcohol **1** by DBU (Figure 3C). Titrating 2.0 equivalents of DBU with alcohol **1** resulted in a collective upfield displacement of the ^{1}H NMR signals belonging to alcohol **1**, which reasonably suggest the formation of alkoxide-amidinium complex **19** (Figure S4 – S7 in the supporting information).[39] Finally, our focus shifted to unraveling the role of the silicon reagent. Under our standard condition, alcohol **1** reacted with **2**, DBU and TMS–Cl to furnish the corresponding deoxy-fluorination and deoxy-chlorination products in a 17:83 molar ratio as determined by ^{1}H NMR analysis of the crude reaction mixture (Figure 3D). However, when TMS–Cl was replaced with benzyl triethylammonium chloride, the product selectivity was reversed, where products **3** and **4a** were generated in a 60:40 molar ratio, respectively (Figure 3D). This outcome strongly attests to the pivotal role of silicon as a fluoride scavenger, which enables deoxy-functionalization with the nucleophile of choice.

Taken together, our experiments are consistent with the following reaction mechanism (Figure 3E). First, hydroxy group of the alcohol undergoes reversible deprotonation by a Brønsted base.[35,40] Subsequently, the conjugate acid activates the S–F bond within **2** via H-bond interaction, and the activated entity combines with the alkoxide to generate the corresponding sulfonate ester and a fluoride anion. Alternatively, it is plausible that the alkoxide is nucleophilic enough to promote the SuFEx process and liberate the fluoride anion without the H-bond interaction. In turn, the fluoride anion engages with the silicon-bound nucleophile, which facilitates a S_N2 reaction on the sulfonate ester, furnishing the deoxy-functionalized product.

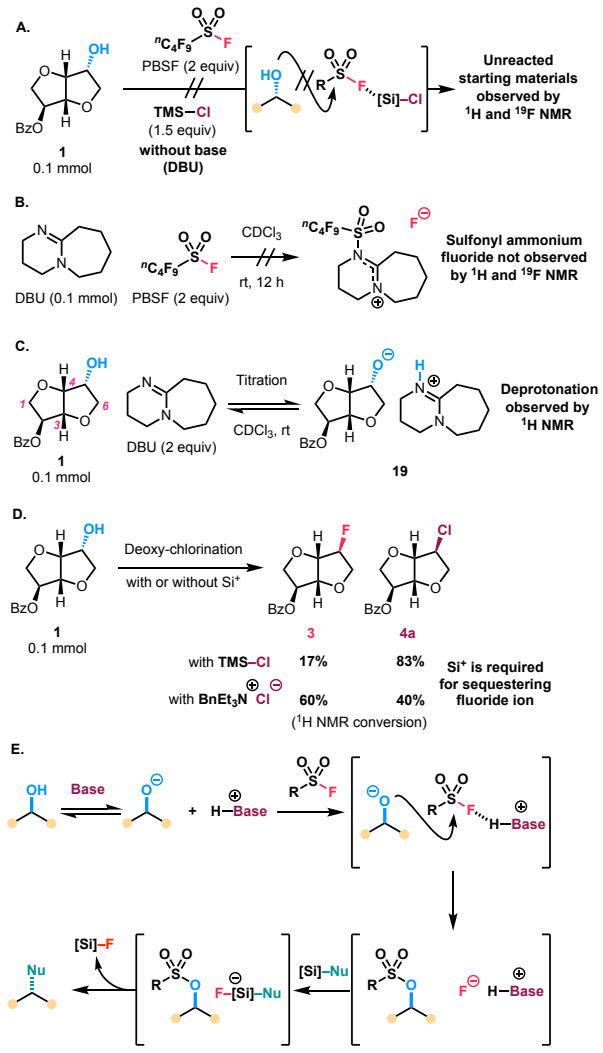


Figure 3. Control experiments and plausible reaction mechanism. (A) Reaction of alcohol **1** with **2** and TMS-Cl under standard condition without base. (B) Combining **2** and DBU in $CDCl_3$ showed no change in ^1H and ^{19}F NMR spectra. (C) Titration of DBU into a solution of alcohol **1** lead a collective upfield displacement of ^1H NMR signals. (D) Replacement of TMS-Cl with $BnEt_3NCl$ led to deoxy-fluorination as the major pathway, indicating the role TMS as a fluoride trap. (E) Proposed mechanism of the SuFEx-mediated deoxy-diversification.

In conclusion, we have developed a unified strategy for robust, operationally simple, and versatile deoxy-diversification of complex alcohols into several analogs via C–C, C–N, C–Cl, and C–Br bond formation. Mechanistic studies are consistent with the proposed cascade reaction pathway that combines SuFEx reaction and fluoride-induced activation of silicon-bound nucleophiles. This work demonstrates its synthetic utility for the late-stage modification of complex molecules.

ASSOCIATED CONTENT

Data Availability Statement: The data underlying this study are available in the published article and its Supporting Information.

Supporting Information: The supporting information is available free of charge via the Internet at http://pubs.acs.org. The supporting information includes Experimental procedures, NMR spectra and crystallographic data (PDF). FAIR Data is available as Supporting Information for this Publication and includes the primary NMR FID files for compounds **1**, **4a-d**, **6a-d**, **8a-d**, **10a-d**, **12a-d**, **14a-d**, **15**, **16a-d**, **17**, **18a-d**, **and 22**.

Accession Codes: CCDC 2320979-2320980 contain the supplementary crystallographic data for this paper. Available free of charge at 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

*Email: byoungk@clemson.edu

Present Addresses

Courtney Keeler – †Department of Chemistry, University of Georgia, Athens, GA 30602

Author Contributions

A.S.O.: Conceptualization, synthesis, compound characterization, writing, and revision
C.K.: Synthesis and compound characterization under the guidance of A.S.O.
B.K.: conceptualization, writing, and revision.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

B.K. gratefully acknowledge the financial support from Clemson University. B.K. thanks Prof. Daniel C. Whitehead (Clemson University) for mentorship and helpful discussions. B.K. and C.K. gratefully acknowledge the financial support from NSF, Division of Chemistry, award CHE-2050042 (2021-2024). The authors would like to acknowledge Dr. Colin McMillen (Clemson University) for helping us acquire X-ray crystallographic data and Dr. Rakesh Sachdeva (Clemson University) for helping us acquire HRMS data.

REFERENCES

(1) Chen, J.; Lin, J.-H.; Xiao, J.-C. Dehydroxylation of Alcohols for Nucleophilic Substitution. *Chem. Commun.* **2018**, *54* (51), 7034–7037.

(2) Huy, P. H.; Hauch, T.; Filbrich, I. Lewis Base Catalyzed Nucleophilic Substitutions of Alcohols. *Synlett* **2016**, *27* (19), 2631–2636.

(3) Stach, T.; Dräger, J.; Huy, P. H. Nucleophilic Substitutions of Alcohols in High Levels of Catalytic Efficiency. *Org. Lett.* **2018**, *20* (10), 2980–2983.

(4) Anwar, K.; Merkens, K.; Aguilar Troyano, F. J.; Gómez-Suárez, A. Radical Deoxyfunctionalisation Strategies. *Eur. J. Org. Chem.* **2022**, *2022* (26), e202200330.

(5) Li, G.; Lou, H.-X. Strategies to Diversify Natural Products for Drug Discovery. *Med. Res. Rev.* **2018**, *38* (4), 1255–1294.

(6) Boström, J.; Brown, D. G.; Young, R. J.; Keserü, G. M. Expanding the Medicinal Chemistry Synthetic Toolbox. *Nat. Rev. Drug Discov.* **2018**, *17* (10), 709–727.

(7) Morton, D.; Leach, S.; Cordier, C.; Warriner, S.; Nelson, A. Synthesis of Natural-Product-Like Molecules with Over Eighty Distinct Scaffolds. *Angew. Chem. Int. Ed.* **2009**, *48* (1),

(8) Schreiber, S. L. Molecular Diversity by Design. *Nature* **2009**, *457* (7226), 153–154.

(9) Wang, F.; Xu, X. Y.; Wang, F. Y.; Peng, L.; Zhang, Y.; Tian, F.; Wang, L. X. An Improved and Economical Process for the Manufacture

of the Key Intermediate of Aliskiren, a New Potent Renin Inhibitor. *Org. Process Res. Dev.* **2013**, *17* (11), 1458–1462.
(10) Beddoe, R. H.; Sneddon, H. F.; Denton, R. M. The Catalytic Mitsunobu Reaction: A Critical Analysis of the Current State-of-the-Art. *Org. Biomol. Chem.* **2018**, *16* (42), 7774–7781.
(11) Swamy, K. C. K.; Kumar, N. N. B.; Balaraman, E.; Kumar, K. V. P. P. Mitsunobu and Related Reactions: Advances and Applications. *Chem. Rev.* **2009**, *109* (6), 2551–2651.
(12) Mitsunobu, O.; Yamada, M. Preparation of Esters of Carboxylic and Phosphoric Acid via Quaternary Phosphonium Salts. *Bull. Chem. Soc. Jpn.* **1967**, *40* (10), 2380–2382.
(13) de Andrade, V.; de Mattos, M. New Reagents and Synthetic Approaches to the Appel Reaction. *Curr. Org. Synth.* **2015**, *12* (3), 309–327.
(14) Appel, R. Tertiary Phosphane/Tetrachloromethane, a Versatile Reagent for Chlorination, Dehydration, and P N Linkage. *Angew. Chem. Int. Ed.* **1975**, *14* (12), 801–811.
(15) Xiang, Y.-J.; Liu, S.; Zhou, J.; Lin, J.-H.; Yao, X.; Xiao, J.-C. Dehydroxylative Sulfonylation of Alcohols. *J. Org. Chem.* **2023**, *88* (7), 4818–4828.
(16) Chen, J.; Lin, J. H.; Xiao, J. C. Halogenation through Deoxygenation of Alcohols and Aldehydes. *Org. Lett.* **2018**, *20* (10), 3061–3064.
(17) Constable, D. J. C.; Dunn, P. J.; Hayler, J. D.; Humphrey, G. R.; Leazer, Jr., J. L.; Linderman, R. J.; Lorenz, K.; Manley, J.; Pearlman, B. A.; Wells, A.; et al. Key Green Chemistry Research Areas—a Perspective from Pharmaceutical Manufacturers. *Green Chem.* **2007**, *9* (5), 411–420.
(18) Intermaggio, N. E.; Millet, A.; Davis, D. L.; MacMillan, D. W. C. Deoxytrifluoromethylation of Alcohols. *J. Am. Chem. Soc.* **2022**, *144* (27), 11961–11968.
(19) Lee, C.; Cook, A. J.; Elisabeth, J. E.; Friede, N. C.; Sammis, G. M.; Ball, N. D. The Emerging Applications of Sulfur(VI) Fluorides in Catalysis. *ACS Catal.* **2021**, *11* (11), 6578–6589.
(20) 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* (17), 4731–4758.
(21) 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* (36), 9430–9448.
(22) Epifanov, M.; Foth, P. J.; Gu, F.; Barrillon, C.; Kanani, S. S.; Higman, C. S.; Hein, J. E.; Sammis, G. M. One-Pot 1,1-Dihydrofluoroalkylation of Amines Using Sulfuryl Fluoride. *J. Am. Chem. Soc.* **2018**, *140* (48), 16464–16468.
(23) Nielsen, M. K.; Ugaz, C. R.; Li, W.; Doyle, A. G. PyFluor: A Low-Cost, Stable, and Selective Deoxyfluorination Reagent. *J. Am. Chem. Soc.* **2015**, *137* (30), 9571–9574.
(24) Nielsen, M. K.; Ahneman, D. T.; Riera, O.; Doyle, A. G. Deoxyfluorination with Sulfonyl Fluorides: Navigating Reaction Space with Machine Learning. *J. Am. Chem. Soc.* **2018**, *140* (15), 5004–5008.
(25) Guo, J.; Kuang, C.; Rong, J.; Li, L.; Ni, C.; Hu, J. Rapid Deoxyfluorination of Alcohols with N -Tosyl-4-chlorobenzenesulfonimidoyl Fluoride (SulfoxFluor) at Room Temperature. *Chem. – A Eur. J.* **2019**, *25* (30), 7259–7264.
(26) Guo, J.; Wang, X.; Ni, C.; Wan, X.; Hu, J. SulfoxFluor-Enabled Deoxyazidation of Alcohols with NaN3. *Nat. Commun.* **2022**, *13* (1), 2752.
(27) Sladojevich, F.; Arlow, S. I.; Tang, P.; Ritter, T. Late-Stage Deoxyfluorination of Alcohols with PhenoFluor. *J. Am. Chem. Soc.* **2013**, *135* (7), 2470–2473.
(28) Middleton, W. J. New Fluorinating Reagents. Dialkylaminosulfur Fluorides. *J. Org. Chem.* **1975**, *40* (5), 574–578.
(29) Beaulieu, F.; Beauregard, L.-P.; Courchesne, G.; Couturier, M.; LaFlamme, F.; L'Heureux, A. Aminodifluorosulfinium Tetrafluoroborate Salts as Stable and Crystalline Deoxofluorinating Reagents. *Org. Lett.* **2009**, *11* (21), 5050–5053.
(30) Lal, G. S.; Pez, G. P.; Pesaresi, R. J.; Prozonic, F. M.; Cheng, H. Bis(2-Methoxyethyl)Aminosulfur Trifluoride: A New Broad-Spectrum Deoxofluorinating Agent with Enhanced Thermal Stability. *J. Org. Chem.* **1999**, *64* (19), 7048–7054.
(31) 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* (4).
(32) An, J.; Denton, R. M.; Lambert, T. H.; Nacsa, E. D. The Development of Catalytic Nucleophilic Substitution Reactions: Challenges, Progress and Future Directions. *Org. Biomol. Chem.* **2014**, *12* (19), 2993.
(33) Grigalunas, M.; Brakmann, S.; Waldmann, H. Chemical Evolution of Natural Product Structure. *J. Am. Chem. Soc.* **2022**, *144* (8), 3314–3329.
(34) Walsh, R. Bond Dissociation Energy Values in Silicon-Containing Compounds and Some of Their Implications. *Acc. Chem. Res.* **1981**, *14* (8), 246–252.
(35) Vorbrüggen, H. The Conversion of Primary or Secondary Alcohols with Nonaflyl Fluoride into Their Corresponding Inverted Fluorides. *Synthesis* **2008**, No. 8, 1165–1174.
(36) Bennua-Skalmowski, B.; Vorbrüggen, H. A Facile Conversion of Primary or Secondary Alcohols with N-Perfluorobutane-Sulfonyl Fluoride/1,8-Diazabicyclo[5.4.0]Undec-7-Ene into Their Corresponding Fluorides. *Tetrahedron Lett.* **1995**, *36* (15), 2611–2614.
(37) Barrow, A.; Moses, J. Synthesis of Sulfonyl Azides via Lewis Base Activation of Sulfonyl Fluorides and Trimethylsilyl Azide. *Synlett* **2016**, *27* (12), 1840–1843.
(38) Gembus, V.; Marsais, F.; Levacher, V. An Efficient Organocatalyzed Interconversion of Silyl Ethers to Tosylates Using DBU and p -Toluenesulfonyl Fluoride. *Synlett* **2008**, *2008* (10), 1463–1466.
(39) Pérez-Casas, C.; Yatsimirsky, A. K. Detailing Hydrogen Bonding and Deprotonation Equilibria between Anions and Urea/Thiourea Derivatives. *J. Org. Chem.* **2008**, *73* (6), 2275–2284.
(40) Wang, Y.; Cao, Z.; Li, Q.; Lin, G.; Zhou, J.; Tian, P. Activating Pronucleophiles with High p K a Values: Chiral Organo-Superbases. *Angew. Chem. Int. Ed.* **2020**, *59* (21), 8004–8014.