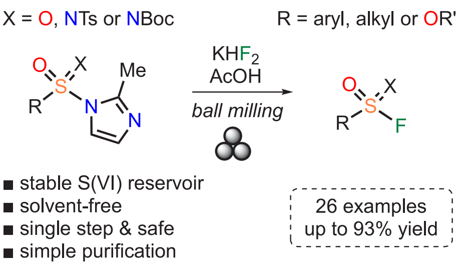
Synthesis of Sulfonyl, Sulfonimidoyl, and Sulfoxyl Fluorides under Solvent-Free Mechanochemical Conditions in a Mixer Mill by Imidazole-to-Fluorine Exchange

Marco T. Passia,[‖] Mostafa M. Amer,[‖] Joachim Demaerel, and Carsten Bolm*

ABSTRACT: A sustainable, mechanochemical procedure for the synthesis of sulfur(VI) fluorides starting from readily available sulfur(VI) 2-methylimidazoles as stable S(VI) precursors has been developed. The transformation proceeds with potassium bifluoride (KHF_2) as the fluorine source in the presence of acetic acid (AcOH) in a mixer mill under solvent-free conditions. The corresponding sulfonyl, sulfonimidoyl, and sulfoxyl fluorides are formed in good to excellent yields. Compared with the solution-based counterpart, the reaction times are shorter. This environmentally benign mechanochemical approach exhibits significant ecological advantages and requires less resources for the optimized purification by simple silica plug filtration.



KEYWORDS: *Ball mill, Mechanochemistry, Sulfonyl fluoride, Sulfonimidoyl fluoride, Sulfoxyl fluoride*

■ INTRODUCTION

Organosulfur motifs are embedded in many natural products and constitute the core of many pharmacophores and agrochemicals.[1−6] Because of their great importance, much effort has been devoted toward their syntheses. Examples of *N*-containing organosulfur derivatives include sulfoximines and sulfonimidamides, which have various unique features, such as chemical and metabolic stabilities, good hydrophilicity, and hydrogen bond donor and acceptor capabilities.[7−19]

Over the past decade, the interest in synthetic mechanochemistry has grown immensely.[20−36] In fact, mechanochemistry can help to reduce the amount of solvent, shorten the reaction time, and overcome solubility restrictions to provide an environmentally benign and efficient synthetic methodology with intrinsic sustainability.[31] Additionally, alternative reaction pathways and diverging selectivities can be achieved by mechanochemically induced reactions.[21,36] In light of the abovementioned benefits of mechanochemical protocols and the general importance of organosulfur skeletons, we felt encouraged to continue our efforts in merging both fields. Recently, we reported several studies in which sustainable mechanochemical methodologies in sulfur chemistry were applied. These studies have enabled us to synthesize a wide range of sulfur-containing compounds from a very different perspective.[37−46]

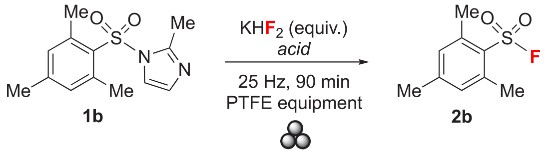
Since Sharpless and co-workers introduced the concept of "sulfur−fluoride exchange" (SuFEx) chemistry in 2014,[47] sulfur(VI) fluorides have received considerable attention in the field of synthetic and medicinal chemistry.[47−59] A variety of preparative applications was reported, including the use of sulfur(VI) fluorides as fluorinating and ^{18}F-radiolabeling agents.[48−54] In medicinal chemistry, SuFEx applications include protease inhibition, protein labeling, and drug target discovery.[55,56] In addition, polymerizations have been reported.[57−59] In light of these important breakthroughs, our recent report on the synthesis of sulfur(VI) fluorides from sulfonyl imidazoles[60] made us wonder if this solution-based process could also be performed under more environmentally benign solvent-free conditions. To our delight, we can now report an unprecedented mechanochemical approach to the aforementioned products, which proceeds under very mild conditions in a mixer mill with potassium bifluoride (KHF_2) as a safe and inexpensive fluoride source in the presence of simple acetic acid (AcOH).

■ RESULTS AND DISCUSSION

Preliminary tests were performed by milling 1-(*p*-toluenesulfonyl)-2-methylimidazole (**1a**) (0.2 mmol) with potassium bifluoride (3.0 equiv) and acetic acid (3.0 equiv) in a polytetrafluoroethylene (PTFE)-jar (V = 20 mL) with one PTFE-coated stainless steel milling ball (9 mm Ø) in a mixer mill at a frequency of 25 Hz for 60 min. This reaction led to only trace amounts of the expected product **2a**. The same result was observed when acetic acid was replaced by citric acid

(3.0 equiv; for more details see the Supporting Information). With 3.0 equiv of tartaric acid, a sticky off-white gum that was difficult to handle during workup was obtained. The addition of silica gel or acidified silica with sulfuric acid (indented to serve as a grinding auxiliary) hampered the product formation, as well, and none of **2a** was observed. Assuming that the low yields were related to the relatively high volatility of product **2a**, the starting material was switched from **1a** to 1-(mesitylsulfonyl)-2-methylimidazole (**1b**). Confirming our hypothesis, sulfonyl fluoride **2b** was obtained in 78% yield. This result was achieved by the milling of **1b** (0.227 mmol) with potassium bifluoride (2.6 equiv) and acetic acid (2.6 equiv) at a frequency of 25 Hz for only 90 min in the same PTFE milling device as described before (Table 1, entry 1).

Table 1. Optimization of the Mechanochemical Formation of Sulfonyl Fluoride 2b[a]



entry	KHF$_2$ (equiv)	acid (equiv)	deviation from standard conditions	yield of **2b** (%)[b]
1	2.6	AcOH (2.6)		78
2[c]	2.6	AcOH (2.6)		78
3	2.6	citric acid (2.6)		14
4[c]	1.4	AcOH (1.4)		70
5[c]	1.8	AcOH (1.8)		78
6[c]	1.4	AcOH (1.8)		79
7[c]	1.4	AcOH (1.8)	1 Y-ZrO$_2$ ball (10 mm)[d]	85
8[c]	1.4	AcOH (1.8)	30 Y-ZrO$_2$ balls (5 mm)[d]	82
9[c]	1.4	AcOH (2.5)	1 Y-ZrO$_2$ ball (10 mm)[d]	**93**
10[c]	1.2	AcOH (1.8)	1 Y-ZrO$_2$ ball (10 mm)[d]	87

[a]Reaction conditions: **1b** (0.227 mmol), KHF$_2$, and the additive were placed in a PTFE jar ($V = 20$ mL) with one PTFE-coated stainless steel milling ball (9 mm Ø). The milling container was placed in the fume hood before the acid was added and then promptly closed. (Caution: HF may be formed by adding the acid to KHF$_2$!) Then, the reaction mixture was milled at 25 Hz for 90 min. [b]Yield after silica plug filtration. [c]Silica gel addition after reaction completion and additional milling for 5 min. [d]Use of a Y-ZrO$_2$- instead of PTFE-coated milling ball.

The addition of a small amount of silica gel (200 mg for a 0.2 mmol scale reaction) to the crude product mixture after 90 min and continuing the milling for an additional period of 5 min led to **2b** in a comparable yield (Table 1, entry 2). This variation of the original protocol proved helpful for product extraction and purification, as well as quenching the excess of KHF$_2$ and the formed HF. Replacement of the acetic acid by citric acid had a detrimental effect on the reaction outcome and provided **2b** in only 14% yield (Table 1, entry 3). In this experiment, an insoluble gumlike crude mixture was obtained after the milling process, which suggests a polymerization of the reaction partners. When both the amount of KHF$_2$ and the one of AcOH were reduced from 2.6 equiv to 1.4 equiv, the yield of **2b** dropped to 70% (Table 1, entry 4). Further variations (Table 1, entries 5 and 6) showed that under those conditions a combination of 1.4 equiv of KHF$_2$ and 1.8 equiv of AcOH was optimal, which led to **2b** in 79% yield.

Next, the impact of the ball material was tested. To our delight, the yield of **2b** increased to 85% when the initially used PTFE-coated stainless steel milling ball was substituted by an Yttrium-stabilized ZrO$_2$ ball (10 mm Ø) (Table 1, entry 7). This result suggested that the density of the ball material affected the product formation. Almost the same yield of **2b** (82%) was obtained when 30 ZrO$_2$ balls of 5 mm diameter were applied (Table 1, entry 8). By staying with the single ZrO$_2$ ball and varying the reagent amounts, it was revealed that a 1.4 and 2.5 equiv combination of KHF$_2$ and AcOH, respectively, was optimal, which provided **2b** in 93% yield after milling at a frequency of 25 Hz for 90 min (Table 1, entries 7, 9, and 10).

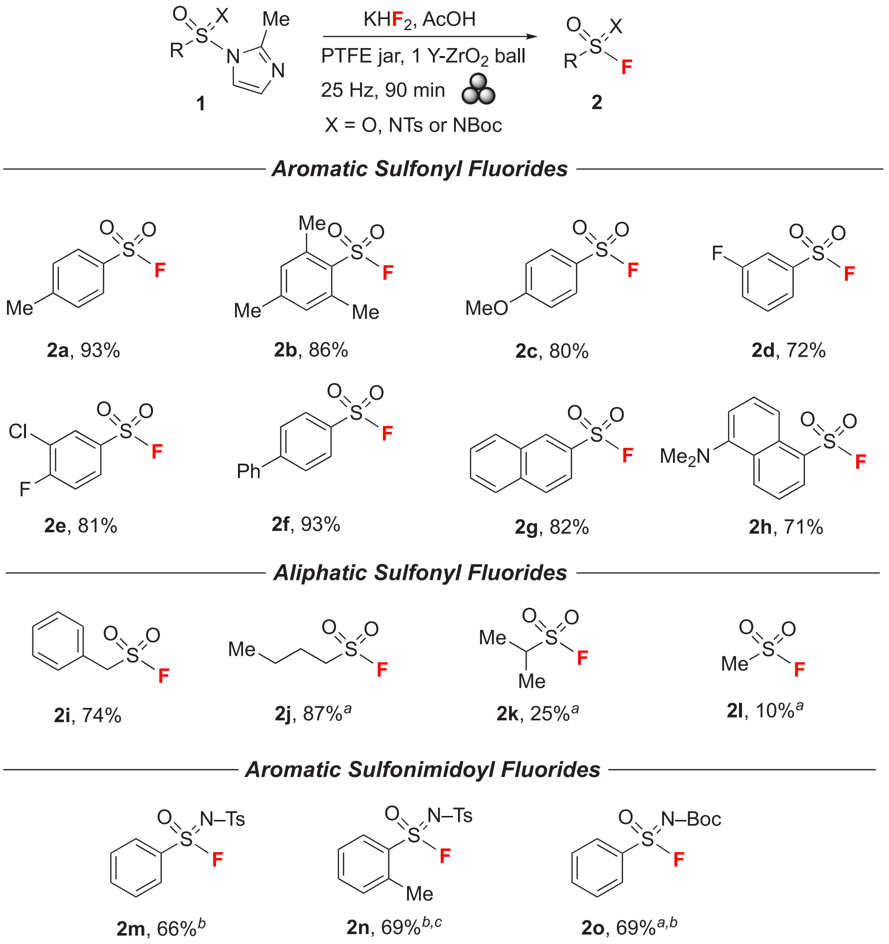
Under the optimized conditions (Table 1, entry 9), the substrate scope was investigated (Scheme 1). A variety of sulfonyl and sulfonimidoyl imidazoles afforded the corresponding fluorinated products **2a**–**o** in moderate to excellent yields. For example, substrates with *S*-aryl groups led to products **2a**–**h** in yields ranging from 71% to 93% (Scheme 1, top). Neither steric nor electronic factors induced by aryl substituents significantly affected the reaction outcome. Considering the high product volatility, the good yields of 3-fluoro and 3-chloro-4-fluoro-substituted derivatives **2d** (72%) and **2e** (81%), respectively, are noteworthy. For the same reason, the preparation of aliphatic sulfonyl fluorides (Scheme 1, middle) required a very careful workup. If that point was taken into account, benzyl sulfonyl fluoride (**2i**) and *n*-butyl sulfonyl fluoride (**2j**) were obtained in yields of 74% and 87%, respectively. Isopropyl sulfonyl fluoride (**2k**) and methyl sulfonyl fluoride (**2l**) could also be prepared, although the yields (25% and 10%) remained poor, presumably also in this case, because of their high volatility. In addition, in the last three products (**2j**–**l**), remaining solvent impurities could not fully be removed.

Transformations of sulfonimidoyl imidazoles to their corresponding fluorides worked well, too. In these reactions, which were demonstrated by the preparation of **2m**–**o**, the milling time had to be increased to 2 × 90 min, and the reagent quantities were increased to 2.0 equiv of KHF$_2$ and 3.0 equiv of AcOH (Scheme 1, bottom). Through the application of these modified reaction conditions, *N*-tosylated sulfonimidoyl fluorides **2m** and **2n** were obtained in 66% and 69% yield, respectively. For **2n**, 30% of the unreacted starting material was easily recovered by silica plug filtration. Because of the mild reactive medium, the acid-labile *N*-Boc group was retained in the preparation of sulfonimidoyl fluoride **2o**, which was isolated in 69% yield.

Compared with our previously reported method,[60] this protocol displays a number of advantages. First, the mechanochemical activation allows the reaction to proceed in the absence of any solvents or grinding auxiliary, thereby yielding the fluorinated products in good to high yields. Second, the reaction times are significantly shorter (90 min) than those of the solvent-based protocol. Third, the product purification method was optimized, and only very small quantities of solvent and silica are required, which further increases the sustainability and reduces the environmental impact of the method.

We aimed at an extension of the mechanochemical fluorination protocol to the synthesis of sulfoxyl fluorides **4**, and the required sulfoxyl imidazole precursors **3a**–**k** were prepared in a single step from 1,1-sulfonylbis(2-methylimida-

Scheme 1. Mechanochemical Syntheses of Sulfonyl and Sulfonimidoyl Fluoride 2



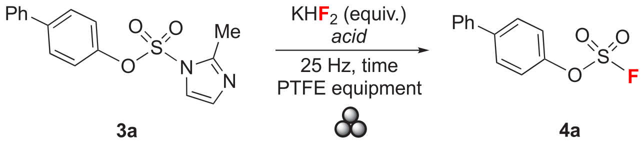
[a]Yield corrected because of remaining solvent impurities. [b]Modified conditions: 2 × 90 min milling at 25 Hz with 2.0 equiv of KHF_2 and 3.0 equiv of AcOH. [c]Recovered starting material **1n**: 30%.

zole) (for experimental details, see the Supporting Information).

As summarized in Table 2, with **3a** as the model substrate, none of the expected product **4a** was formed under the previously optimized conditions for the preparation of sulfonyl fluorides (Table 1, entry 9). Variations of the amounts of KHF_2 and AcOH also did not lead to a mechanochemical fluorination of **3a** to provide **4a** in a ball mill (Table 2, entry 2; for details and the full optimization study, see the Supporting Information). Hence, we turned our attention to a mechanochemical transformation under elevated temperature.[61−67] For those experiments, a stainless steel jar was used. First, a "heat and beat" strategy[65−67] was attempted that included a preheating of the milling vessel (T = 100 °C) prior to the milling and a repetition of this heat/beat cycle. The two experiments differed in the repetition number (1 versus 4) of the heat/beat cycle at a temperature of 100 °C and the reaction time [Table 2, entries 3 (60 min) and 4 (120 min)]. Under those conditions, sulfoxyl fluoride **4a** was formed, but the yield remained poor (38%). A better result (50% of **4a**) was achieved when a mixture of **3a**, KHF_2 (2.0 equiv), and AcOH (3.0 equiv) was milled in a stainless steel jar with one stainless steel ball (10 mm Ø) at a frequency of 25 Hz for 60 min at a temperature of roughly 80 °C (Table 2, entry 5). For the instrumental setup, we followed a protocol by Ito, Kubota, and co-workers[61] by using an adjustable heatgun with a preset temperature of 150 °C, which was fixed at a distance of ca. 1 cm from the jar (for the experimental details, see the Supporting Information). Performing an analogous experiment at a preset temperature of 250 °C with a milling frequency of 30 Hz and extending the reaction time from the previously used 60 to 90 min improved the product formation and finally allowed for the isolation of **4a** in 65% yield (Table 2, entry 6).

Using the newly optimized conditions, sulfoxyl fluorides **4** could be synthesized in moderate to good yields (Scheme 2). For example, if the *S*-aryloxy group was 4-substituted, the yields of the resulting products (**4a**−**e**) ranged from 39 to 81%. Surprisingly, a *tert*-butyl group in this position was not tolerated, and **4f** could not be obtained at all. Considering that the best yield (81%) was achieved in the formation of methoxy-substituted **4b**, electron-donating groups appeared to be beneficial. Although the yield of **4e** was only moderate (39%), it was remarkable that the 4-amino group was tolerated. Substrates **3** with *S*-3,4-dimethylphenyloxy and *S*-3-iodophenyloxy substituents reacted well, too, to provide the corresponding products in yields of 66% (for **4g**) and 45% (for **4h**), respectively. Finally, *S*-naphthyloxy derivatives **3i-k** were applied, and also in these cases, the expected sulfoxyl fluorides were obtained, although the yields remained moderate for all three products (**4i**, 24%; **4j**, 49%; and **4k**, 49%). Presumably because of the required elevated temperature of the mechanosynthesis protocol, several unidentified

Table 2. Optimization of the Mechanochemical Synthesis of Sulfoxyl Fluoride 4a[a]



entry	KHF_2 (equiv)	AcOH (equiv)	deviation from standard conditions	T (min)	yield of **4a** (%)[b]
1	1.4	2.5		90	0
2	2.0	3.0		90	0
3[c]	1.4	2.5	1 × 100 °C (heat and beat)	60	trace
4[c]	1.4	2.5	4 × 100 °C (heat and beat)	120	38
5[c]	2.0	3.0	150 °C (preset heatgun)	60	50
6[c]	2.0	3.0	250 °C (preset heatgun), 30 Hz	90	65

[a] Reaction conditions: **3a** (0.2 mmol) and KHF_2 was added into a PTFE jar (V = 20 mL) with one Y-ZrO_2 milling ball (10 mm Ø). The milling container was placed in the fume hood before the acid was added and then promptly closed. (Caution: HF may be formed by adding the acid to KHF_2!) The mixture was milled at 25 Hz for the corresponding time period. [b] After column chromatography. [c] Use of a stainless steel (SS) jar (V = 10 mL) and one SS milling ball (10 mm Ø); for further experimental details, see the Supporting Information.

side products were observed, and thus, flash column chromatography was necessary for product isolation and purification. Although the synthesis of sulfoxyl fluorides was accomplished under solvent-free mechanochemical conditions, the solution-based protocol remains the favorable methodology in terms of higher product yields of these compounds.[60]

CONCLUSIONS

We developed a mechanochemical synthesis of sulfur(VI) fluorides using a mixer mill. A wide range of sulfonyl 2-methylimidazoles were converted to the corresponding sulfonyl fluorides in moderate to good yields. Under slightly modified conditions, sulfonimidoyl and sulfoxyl fluorides are accessible, too. We are convinced that this green and sustainable method for the synthesis of sulfur(VI) fluorides will be appreciated by both academia and industry.

Details of general procedures, solution-based studies, and calculations of E-factors (PDF)

AUTHOR INFORMATION

Corresponding Author

Carsten Bolm − *Institute of Organic Chemistry, RWTH Aachen University, 52074 Aachen, Germany;* orcid.org/0000-0001-9415-9917; Email: Carsten.Bolm@oc.rwth-aachen.de

Authors

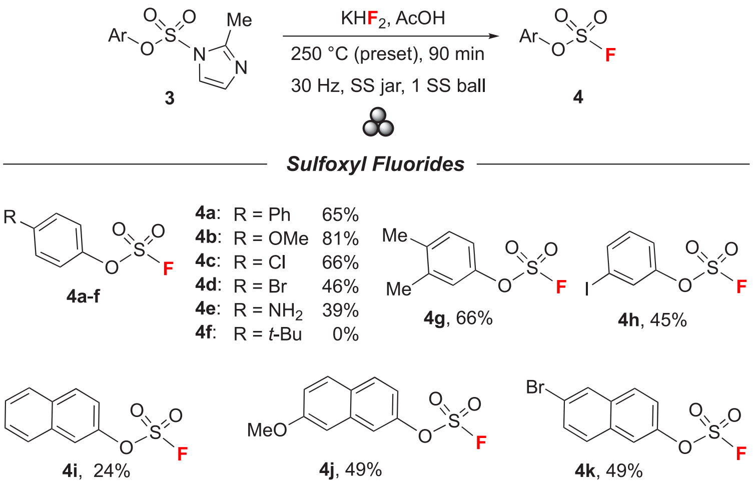
Marco T. Passia − *Institute of Organic Chemistry, RWTH Aachen University, 52074 Aachen, Germany;* orcid.org/0000-0001-8369-165X
Mostafa M. Amer − *Institute of Organic Chemistry, RWTH Aachen University, 52074 Aachen, Germany; Egyptian Petroleum Research Institute, 11727 Cairo, Egypt*
Joachim Demaerel − *Institute of Organic Chemistry, RWTH Aachen University, 52074 Aachen, Germany; Molecular Design and Synthesis, Department of Chemistry, KU Leuven, 3001 Leuven, Belgium;* orcid.org/0000-0003-3685-7535

‖M.T.P. and M.M.A. contributed equally. C.B. directed the project. M.T.P., M.M.A., and J.D. designed the study, and M.T.P and M.M.A. performed the experiments and drafted the manuscript and the Supporting Information. C.B. finalized the written summaries. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

Scheme 2. Mechanochemical Formations of Sulfoxyl Fluorides 4



■ ACKNOWLEDGMENTS

We acknowledge RWTH Aachen University for infrastructure and for research funding.

■ REFERENCES

(1) Ilardi, E. A.; Vitaku, E.; Njardarson, J. T. Data-mining for sulphur and fluorine: An evaluation of pharmaceuticals to reveal opportunities for drug design and discovery: Miniperspective. *J. Med. Chem.* **2014**, *57*, 2832−2842.

(2) Scott, K. A.; Njardarson, J. T. Analysis of US FDA-Approved Drugs Containing Sulfur Atoms. *Top. Curr. Chem.* **2018**, *376*, 5.

(3) Wang, N.; Saidhareddy, P.; Jiang, X. Construction of sulphur containing moieties in the total synthesis of natural products. *Nat. Prod. Rep.* **2020**, *37*, 246−275.

(4) Nguyen, T. B. Recent Advances in Organic Reactions Involving Elemental Sulfur. *Adv. Synth. Catal.* **2017**, *359*, 1066−1130.

(5) Lamberth, C.; Walter, H.; Kessabi, F. M.; Quaranta, L.; Beaudegnies, R.; Trah, S.; Jeanguenat, A.; Cederbaum, F. The Significance of Organosulfur Compounds in Crop Protection: Current Examples from Fungicide Research. *Phosphorus, Sulfur, and Silicon* **2015**, *190*, 1225−1235.

(6) Lamberth, C. Sulfur chemistry in crop protection. *J. Sulfur Chem.* **2004**, *25*, 39−62.

(7) Lücking, U. New Opportunities for the Utilization of the Sulfoximine Group in Medicinal Chemistry from the Drug Designer's Perspective. *Chem.—Eur. J.* **2022**, *28*, e202201993.

(8) Lücking, U. Neglected sulfur(vi) pharacophores in drug discovery: exploration of novel chemical space by the interplay of drug design and method development. *Org. Chem. Front.* **2019**, *6*, 1319−1324.

(9) Frings, M.; Bolm, C.; Blum, A.; Gnamm, C. Sulfoximines from a medicinal chemist's perspective: physicochemical and in vitro parameters relevant for drug discovery. *Eur. J. Med. Chem.* **2017**, *126*, 225−245.

(10) Mäder, P.; Kattner, L. Sulfoximines as rising stars in modern drug discovery? Current status and perspective on an emerging functional group in medicinal chemistry. *J. Med. Chem.* **2020**, *63*, 14243−14275.

(11) Han, Y.; Xing, K.; Zhang, J.; Tong, T.; Shi, Y.; Cao, H.; Yu, H.; Zhang, Y.; Liu, D.; Zhao, L. Application of sulfoximines in medicinal chemistry from 2013 to 2020. *Eur. J. Med. Chem.* **2021**, *209*, 112885.

(12) Tilby, M. J.; Willis, M. C. How do we address neglected sulfur pharmacophores in drug discovery? *Exp. Opinion Drug Develop.* **2021**, *16*, 1227−1231.

(13) Bizet, V.; Kowalczyk, R.; Bolm, C. Fluorinated sulfoximines: syntheses, properties and applications. *Chem. Soc. Rev.* **2014**, *43*, 2426−2438.

(14) Hosseinian, A.; Fekri, L. Z.; Monfared, A.; Vessally, E.; Nikpassand, M. Transition-metal-catalyzed C−N cross-coupling reactions of N-unsubstituted sulfoximines: a review. *J. Sulfur Chem.* **2018**, *39*, 674−698.

(15) Andresini, M.; Tota, A.; Degennaro, L.; Bull, J. A.; Luisi, R. Synthesis and Transformations of NH-Sulfoximines. *Chem.−Eur. J.* **2021**, *27*, 17293−17321.

(16) Ghosh, P.; Ganguly, B.; Das, S. N−H and C−H Functionalization of Sulfoximine: Recent Advancement and Prospects. *Asian J. Org. Chem.* **2020**, *9*, 2035−2082.

(17) Zheng, W.; Chen, X.; Chen, F.; He, Z.; Zeng, Q. Syntheses and Transformations of Sulfoximines. *Chem. Rec.* **2021**, *21*, 396−416.

(18) Izzo, F.; Schäfer, M.; Lienau, P.; Ganzer, U.; Stockman, R.; Lücking, U. Exploration of Novel Chemical Space: Synthesis and in vitro Evaluation of N−Functionalized Tertiary Sulfonimidamides. *Chem.−Eur. J.* **2018**, *24*, 9295−9304.

(19) Nandi, G. C.; Arvidsson, P. I. Sulfonimidamides: Synthesis and Applications in Preparative Organic Chemistry. *Adv. Synth. Catal.* **2018**, *360*, 2976−3001.

(20) James, S. L.; Adams, C. J.; Bolm, C.; Braga, D.; Collier, P.; Friščić, T.; Grepioni, F.; Harris, K. D. M.; Hyett, G.; Jones, W.; Krebs, A.; Mack, J.; Maini, L.; Orpen, A. G.; Parkin, I. P.; Shearouse, W. C.; Steed, J. W.; Waddell, D. C. Mechanochemistry: opportunities for new and cleaner synthesis. *Chem. Soc. Rev.* **2012**, *41*, 413−447.

(21) Hernández, J. G.; Bolm, C. Altering Product Selectivity by Mechanochemistry. *J. Org. Chem.* **2017**, *82*, 4007−4019.

(22) Do, J.-L.; Friščić, T. Mechanochemistry: A Force of Synthesis. *ACS Cent. Sci.* **2017**, *3*, 13−19.

(23) Howard, J. L.; Cao, Q.; Browne, D. L. Mechanochemistry as an emerging tool for molecular synthesis: what can it offer? *Chem. Sci.* **2018**, *9*, 3080−3094.

(24) Bolm, C.; Hernández, J. G. Mechanochemistry of Gaseous Reactants. *Angew. Chem., Int. Ed.* **2019**, *58*, 3285−3299.

(25) Friščić, T.; Mottillo, C.; Titi, H. M. Mechanochemistry for Synthesis. *Angew. Chem., Int. Ed.* **2020**, *59*, 1018−1029.

(26) Pickhardt, W.; Grätz, S.; Borchardt, L. Direct Mechanocatalysis: Using Milling Balls as Catalysts. *Chem.−Eur. J.* **2020**, *26*, 12903−12911.

(27) Porcheddu, A.; Colacino, E.; De Luca, L.; Delogu, F. Metal-Mediated and Metal Catalyzed Reactions Under Mechanochemical Conditions. *ACS Catal.* **2020**, *10*, 8344−8394.

(28) Pérez-Venegas, M.; Juaristi, E. Mechanochemical and Mechanoenzymatic Synthesis of Pharmacologically Active Compounds: A Green Perspective. *ACS Sustainable Chem. Eng.* **2020**, *8*, 8881−8893.

(29) Egorov, I. E.; Santra, S.; Kopchuk, D. S.; Kovalev, I. S.; Zyryanov, G. V.; Majee, A.; Ranu, B. C.; Rusinov, V. L.; Chupakhin, O. N. Ball milling: an efficient and green approach for asymmetric organic syntheses. *Green Chem.* **2020**, *22*, 302−315.

(30) Kubota, K.; Ito, H. Mechanochemical Cross-Coupling Reactions. *Trends in Chem.* **2020**, *2*, 1066−1081.

(31) Ardila-Fierro, K. J.; Hernández, J. G. Sustainability Assessment of Mechanochemistry by Using the Twelve Principles of Green Chemistry. *ChemSusChem* **2021**, *14*, 2145−2162.

(32) Virieux, D.; Delogu, F.; Porcheddu, A.; García, F.; Colacino, E. Mechanochemical Rearrangements. *J. Org. Chem.* **2021**, *86*, 13885−13894.

(33) Leitch, J. A.; Browne, D. L. Mechanoredox Chemistry as an Emerging Strategy in Synthesis. *Chem.−Eur. J.* **2021**, *27*, 9721−9726.

(34) Wang, G.-W. Fullerene Mechanochemistry: Serendipitous Discovery of Dumb-Bell-Shaped C120 and Beyond. *Chin. J. Chem.* **2021**, *39*, 1797−1803.

(35) Xuan, M.; Schumacher, C.; Bolm, C.; Göstl, R.; Herrmann, A. The Mechanochemical Synthesis and Activation of Carbon-Rich π-Conjugated Materials. *Adv. Sci.* **2022**, *9*, 2105497.

(36) Cuccu, F.; De Luca, L.; Delogu, F.; Colacino, E.; Solin, N.; Mocci, R.; Porcheddu, A. Mechanochemistry: New Tools to Navigate the Uncharted Territory of "Impossible" Reactions. *ChemSusChem* **2022**, *15*, e202200362.

(37) Schöbel, J.-H.; Liang, W.; Wöll, D.; Bolm, C. Mechanochemical Synthesis of 1,2,6-Thiadiazine 1-Oxides from Sulfonimidamides and The Fluorescence Properties of the Products. *J. Org. Chem.* **2020**, *85*, 15760−15766.

(38) Van Bonn, P.; Bolm, C.; Hernández, J. G. Mechanochemical Palladium-Catalyzed Carbonylative Reactions Using $Mo(CO)_6$. *Chem.−Eur. J.* **2020**, *26*, 2576−2580.

(39) Schumacher, C.; Fergen, H.; Puttreddy, R.; Truong, K.-N.; Rinesch, T.; Rissanen, K.; Bolm, C. N-(2,3,5,6-Tetrafluoropyridyl)-sulfoximines: synthesis, X-ray crystallography, and halogen bonding. *Org. Chem. Front.* **2020**, *7*, 3896−3906.

(40) Schöbel, J. H.; Elbers, P.; Truong, K.-N.; Rissanen, K.; Bolm, C. 1,2-Benzothiazine Derivatives from Sulfonimidamides by Metal-Catalyzed Annulation Reactions in Solution and under Solvent-Free Mechanochemical Conditions. *Adv. Synth. Catal.* **2021**, *363*, 1322−1329.

(41) Krauskopf, F.; Truong, K.- N.; Rissanen, K.; Bolm, C. 2,3-Dihydro-1,2,6-thiadiazine 1-Oxides by Biginelli-Type Reactions with Sulfonimidamides under Mechanochemical Conditions. *Org. Lett.* **2021**, *23*, 2699−2703.

(42) Passia, M. T.; Schöbel, J.-H.; Lentelink, N.; Truong, K.-N.; Rissanen, K.; Bolm, C. Synthesis of trifluoromethyl-substituted 1,2,6-thiadiazine 1-oxides from sulfonimidamides under mechanochemical conditions. *Org. Biomol. Chem.* **2021**, *19*, 9470−9475.

(43) Kong, D.; Amer, M. M.; Bolm, C. Stainless steel-initiated chloro sulfoximidations of allenes under solvent-free conditions in a ball mill. *Green Chem.* **2022**, *24*, 3125−3129.

(44) Terhorst, S.; Jansen, T.; Langletz, T.; Bolm, C. Sulfonimidamides by Sequential Mechanochemical Chlorinations and Aminations of Sulfinamides. *Org. Lett.* **2022**, *24*, 4109−4113.

(45) Kong, D.; Ma, D.; Wu, P.; Bolm, C. Mechanochemical Solvent-Free N-Sulfenylations of Sulfoximines and Sulfonimidamides. *ACS Sustain. Chem. Eng.* **2022**, *10*, 2863−2867.

(46) Amer, M. M.; Hommelsheim, R.; Schumacher, C.; Kong, D.; Bolm, C. Electro-mechanochemical approach towards chloro sulfoximidations of allenes under solvent-free conditions in a ball mill. *Faraday Discuss.* **2023**, *241*, 79−90.

(47) 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.

(48) Abdul Fattah, T.; Saeed, A.; Albericio, F. Recent advances towards sulfur (VI) fluoride exchange (SuFEx) click chemistry. *J. Fluorine Chem.* **2018**, *213*, 87−112.

(49) Chinthakindi, P. K.; Arvidsson, P. I. Sulfonyl Fluorides (SFs): More Than Click Reagents? *Eur. J. Org. Chem.* **2018**, *2018*, 3648−3666.

(50) Revathi, L.; Ravindar, L.; Leng, J.; Rakesh, K. P.; Qin, H.-L. Synthesis and Chemical Transformations of Fluorosulfates. *Asian J. Org. Chem.* **2018**, *7*, 662−682.

(51) 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.

(52) 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*, 9571−9574.

(53) Matesic, L.; Wyatt, N. A.; Fraser, B. H.; Roberts, M. P.; Pham, T. Q.; Greguric, I. Ascertaining the suitability of aryl sulfonyl fluorides for [^{18}F]radiochemistry applications: A systematic investigation using microfluidics. *J. Org. Chem.* **2013**, *78*, 11262−11270.

(54) Inkster, J. A. H.; Liu, K.; Ait-Mohand, S.; Schaffer, P.; Guérin, B.; Ruth, T. J.; Storr, T. Sulfonyl Fluoride-Based Prosthetic Compounds as Potential ^{18}F Labelling Agents. *Chem.—Eur. J.* **2012**, *18*, 11079−11087.

(55) Narayanan, A.; Jones, L. H. Sulfonyl fluorides as privileged warheads in chemical biology. *Chem. Sci.* **2015**, *6*, 2650−2659.

(56) Jones, L. H. Emerging Utility of Fluorosulfate Chemical Probes. *ACS Med. Chem. Lett.* **2018**, *9*, 584−586.

(57) Xiao, X.; Zhou, F.; Jiang, J.; Chen, H.; Wang, L.; Chen, D.; Xu, Q.; Lu, J. Highly efficient polymerization *via* sulfur(VI)-fluoride exchange (SuFEx): novel polysulfates bearing a pyrazoline−naphthylamide conjugated moiety and their electrical memory performance. *Polym. Chem.* **2018**, *9*, 1040−1044.

(58) Yang, C.; Flynn, J. P.; Niu, J. Facile Synthesis of Sequence-Regulated Synthetic Polymers Using Orthogonal SuFEx and CuAAC Click Reactions. *Angew. Chem., Int. Ed.* **2018**, *57*, 16194−16199.

(59) Wang, H.; Zhou, F.; Ren, G.; Zheng, Q.; Chen, H.; Gao, B.; Klivansky, L.; Liu, Y.; Wu, B.; Xu, Q.; Lu, J.; Sharpless, K. B.; Wu, P. SuFEx-Based Polysulfonate Formation from Ethenesulfonyl Fluoride−Amine Adducts. *Angew. Chem., Int. Ed.* **2017**, *56*, 11203−11208.

(60) Passia, M. T.; Demaerel, J.; Amer, M. M.; Drichel, A.; Zimmer, S.; Bolm, C. Acid-Mediated Imidazole-to-Fluorine Exchange for the Synthesis of Sulfonyl and Sulfonimidoyl Fluorides. *Org. Lett.* **2022**, *24*, 8802−8805.

(61) Seo, T.; Toyoshima, N.; Kubota, K.; Ito, H. Tackling Solubility Issues in Organic Synthesis: Solid-State Cross-Coupling of Insoluble Aryl Halides. *J. Am. Chem. Soc.* **2021**, *143*, 6165.

(62) Gao, Y.; Feng, C.; Seo, T.; Kubota, K.; Ito, H. Efficient access to materials-oriented aromatic alkynes *via* the mechanochemical Sonogashira coupling of solid aryl halides with large polycyclic conjugated systems. *Chem. Sci.* **2022**, *13*, 430−438.

(63) Takahashi, R.; Seo, T.; Kubota, K.; Ito, H. Palladium-Catalyzed Solid-State Polyfluoroarylation of Aryl Halides Using Mechanochemistry. *ACS Catal.* **2021**, *11*, 14803−14810.

(64) Kubota, K.; Endo, T.; Uesugi, M.; Hayashi, Y.; Ito, H. Solid-State C-N CrossCoupling Reactions with Carbazoles as Nitrogen Nucleophiles Using Mechanochemistry. *ChemSusChem* **2022**, *15*, e202102132.

(65) Cao, Q.; Crawford, D. E.; Shi, C.; James, S. L. Greener Dye Synthesis: Continuous, Solvent-Free Synthesis of Commodity Perylene Diimides by Twin-Screw Extrusion. *Angew. Chem., Int. Ed.* **2020**, *59*, 4478−4483.

(66) Rensch, T.; Fabig, S.; Grätz, S.; Borchardt, L. Mechanochemically-Assisted Synthesis of Polyimides. *ChemSusChem* **2022**, *15*, e202101975.

(67) Kong, D.; Bolm, C. Stainless steel-initiated thiosulfonylations of unactivated alkenes under solvent-free conditions in a mixer mill. *Green Chem.* **2022**, *24*, 6476−6480.