Green Chemistry

PAPER

View Article Online
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Cite this: *Green Chem.*, 2025, **27**, 1771

Solid-state aromatic nucleophilic fluorination: a rapid, practical, and environmentally friendly route to N-heteroaryl fluorides†

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A simple mechanochemical protocol for solid-state aromatic nucleophilic fluorination using potassium fluoride (KF) and quaternary ammonium salts was developed. This solid-state fluorination is fast and a variety of N-heteroaryl halides can be efficiently fluorinated within 1 h. Notably, highly polar and high-boiling solvents, which are often toxic and difficult to remove during purification, are not required for this protocol. Moreover, all the synthetic operations can be carried out under ambient conditions without complicated setups involving inert gases. The practical advantages of this mechanochemical protocol suggest potentially widespread applications for the preparation of valuable fluorine-containing molecules in a more efficient, cost-effective, and environmentally friendly manner than existing solution-based protocols.

Received 16th December 2024,
Accepted 3rd January 2025

DOI: 10.1039/d4gc06362g

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1. This work advances the field of green chemistry by introducing a solid-state mechanochemical protocol for aromatic nucleophilic fluorination that eliminates the need for toxic, high-boiling solvents, which are typically difficult to remove and environmentally harmful. The newly developed method operates under ambient conditions, without requiring complex setups or inert gases, making it more energy-efficient and reducing the overall environmental footprint compared to traditional solution-based fluorination processes.

2. The specific achievement of this work is the development of a fast, solid-state nucleophilic aromatic fluorination method using a cost-effective combination of potassium fluoride and quaternary ammonium salts. This enables the efficient synthesis of a wide range of aromatic fluorides, which are crucial structural motifs in pharmaceuticals, agrochemicals, organic materials, and biological imaging agents. Notably, this approach eliminates the need for toxic, high-boiling solvents such as dimethylsulfoxide (DMSO), significantly reducing the environmental impact associated with their use and disposal. Using the *E*-factor evaluation, a metric for quantitatively assessing the environmental impact of chemical processes, it was found that this solid-state fluorination method is substantially more eco-friendly than conventional solution-based approaches.

3. A notable limitation of this method is the requirement for elevated temperatures to achieve efficient fluorination. However, we are confident that this study serves as an important proof of concept, demonstrating the feasibility of sustainable, solvent-free aromatic nucleophilic fluorination *via* mechanochemical methods. As a follow-up project, we aim to develop a room-temperature version of the aromatic nucleophilic fluorination under mechanochemical conditions, which represents the ultimate goal of our research.

Introduction

Aromatic fluorides are crucial structural motifs in pharmaceuticals, agrochemicals, organic materials, and biological imaging agents.[1,2] An increasing number of fluorine-containing biologically active molecules have been developed for pharmaceutical and agrochemical applications (Fig. 1A),[3] and to date, several useful procedures for the formation of C_{aryl}–F

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† Electronic supplementary information (ESI) available. See DOI: https://doi.org/10.1039/d4gc06362g

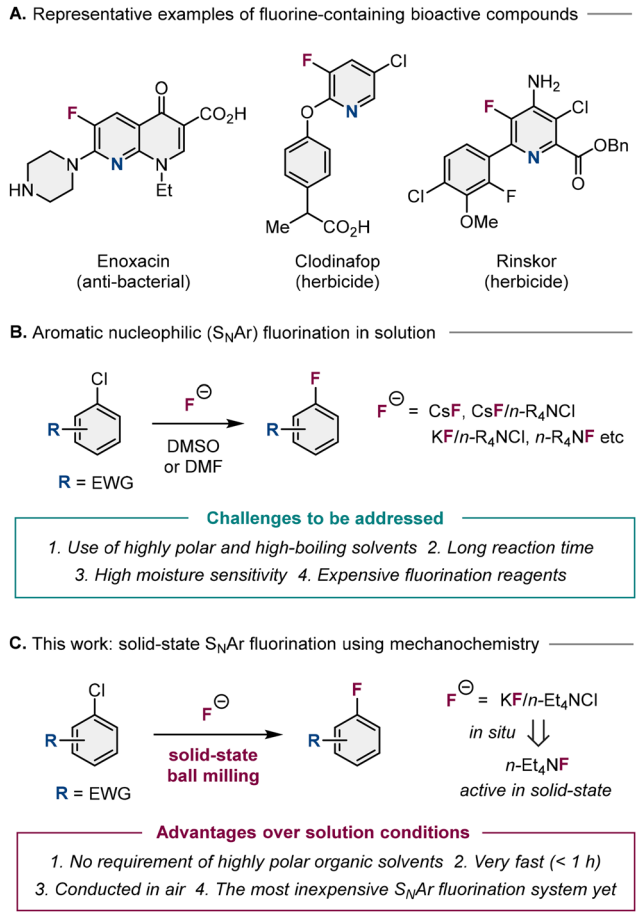


Fig. 1 Aromatic nucleophilic (S_NAr) fluorination for the synthesis of N-heteroaryl fluorides.

bonds have been reported.[1,2] One common approach for the formation of C_{aryl}–F bonds are aromatic nucleophilic (S_NAr) fluorination reactions, which use fluoride salts, *i.e.*, reagents that are widely used in industrial-process chemistry (Fig. 1B).[4–6] Traditionally, cesium fluoride (CsF) has been employed as a nucleophilic fluorination reagent at high temperatures.[6] Since then, a combination of potassium fluoride (KF) and tetrabutylammonium chloride (*n*-Bu_4NCl) has emerged as a more cost-effective alternative to CsF for S_NAr fluorinations.[6–9] More recently, Sanford has reported that the use of anhydrous tetramethylammonium fluoride (Me_4NF) allows the reaction temperature of the S_NAr fluorination to be lowered to room-temperature.[10]

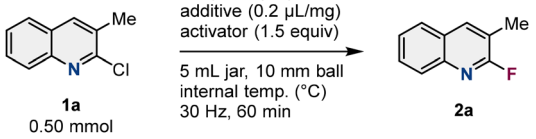
Despite this recent progress, S_NAr fluorination chemistry still suffers from the following well-documented limitations (Fig. 1B):[6] (1) a large amount of highly polar and high-boiling organic solvents, such as dimethyl sulfoxide (DMSO) or *N*,*N*-dimethyl formamide (DMF), which are difficult to remove during purification, are required. This makes the solution-based process wasteful and both time- and energy-consuming. In particular, DMF is a highly toxic solvent, and its use has been restricted in the European Union since 2023 on account of especially the hazards it poses to reproductive health;[11] (2) the solution-based conditions require long reaction times (typically >24 h); (3) the solution-based reactions are highly moisture-sensitive, as water both attenuates the nucleophilicity of the fluoride and leads to hydrolysis byproducts; and (4) highly reactive but expensive fluorination reagents (*e.g.*, CsF or Me_4NF) are often required for the efficient formation of C–F bonds. Therefore, the exploration of reliable, efficient, low-cost, time-saving, and environmentally friendly methods for S_NAr fluorination represents an important challenge in synthetic chemistry.

Recently, mechanochemical synthesis using ball milling has emerged as a more sustainable and efficient alternative to traditional solution-based approaches.[12,13] This method allows organic reactions to be conducted using minimal amounts of solvent, and in most cases, all synthetic operations can be conducted under ambient conditions. Inspired by the attractive features of mechanochemistry, we envisioned that a mechanochemical protocol could allow the development of highly efficient solid-state S_NAr fluorination reactions that overcome the aforementioned shortcomings associated with solution-based fluorination reactions (Fig. 1C). Elegant examples of mechanochemical fluorination have already been reported, but most of them are electrophilic fluorination protocols, and mechanochemical S_NAr fluorination remained unexplored.[14]

Results and discussion

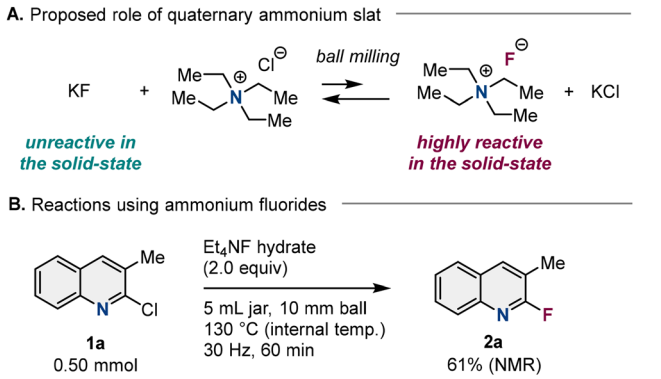
All mechanochemical reactions were conducted in a Retsch MM400 mill [stainless-steel milling jar (5 mL); 30 Hz; stainless-steel ball (diameter: 10 mm)] and were performed under ambient conditions. First, we investigated the S_NAr fluorination of 2-fluoroquinoline derivative **1a** with KF to give **2a** (Table 1). In order to carry out the reaction at high temperature, we used a commercially available temperature-controllable heat gun, which was placed directly above the ball-milling jar (for details, see the ESI†).[13g] The reaction was conducted with the heat gun preset to 250 °C, and the internal temperature of the reaction mixture (130 °C) was determined by thermography immediately after opening the milling jar (for details, see the ESI†). The mechanochemical reaction did not yield the fluorination product (**2a**) (<1%; Table 1, entry 1) under the applied conditions. To accelerate the mechanochemical S_NAr fluorination, we conducted the reaction in the presence of liquid additives (Table 1, entries 2–5).[15] Although polar solvents such as DMSO and DMF, which are commonly used in solution-based conditions,[6] were tested, **2a** was not obtained (Table 1, entries 2–4). A reaction using toluene was also unsuccessful (Table 1, entry 5). Surprisingly, the addition of *n*-Bu_4NCl, which is commonly used as a phase-transfer reagent under solution-based conditions,[6–9] dramatically accelerated the solid-state S_NAr fluorination to form **2a** in 88% yield (Table 1, entry 6). The combination of *n*-Bu_4NCl and DMSO was not as effective (72%; Table 1, entry 7). Next, other quaternary ammonium salts were examined (Table 1, entries

Table 1 Optimization study[a]



Entry	Additive	Activator	Temp. (°C)	Yield of **2a**[b] (%)
1	None	None	130	<1
2	DMSO	None	130	<1
3	DMF	None	130	<1
4	DMA	None	130	<1
5	Toluene	None	130	<1
6	None	*n*-Bu_4NCl	130	88
7	DMSO	*n*-Bu_4NCl	130	72
8	None	Me_4NCl	130	<1
9	None	Et_4NCl	130	>99 (85)
10	None	*n*-Pr_4NCl	130	89
11	None	*n*-Bu_4NBr	130	7
12	None	Ph_4PCl	130	6
13	None	Et_4NCl	100	<1
14	None	Et_4NCl	40	<1

[a] Conditions: **1a** (0.5 mmol), KF (1.00 mmol), liquid additive (0.20 μL mg^{-1}), activator (0.75 mmol) in a stainless-steel ball-milling jar (5 mL) with a stainless-steel ball (diameter: 10 mm). [b] Determined based on ^{19}F NMR spectroscopy. Isolated yields are given in parenthesis.



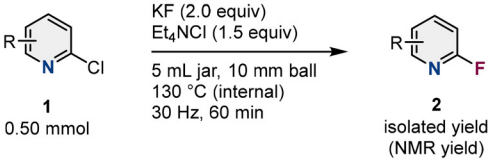
Scheme 1 Proposed active species for the solid-state S_NAr fluorination reactions.

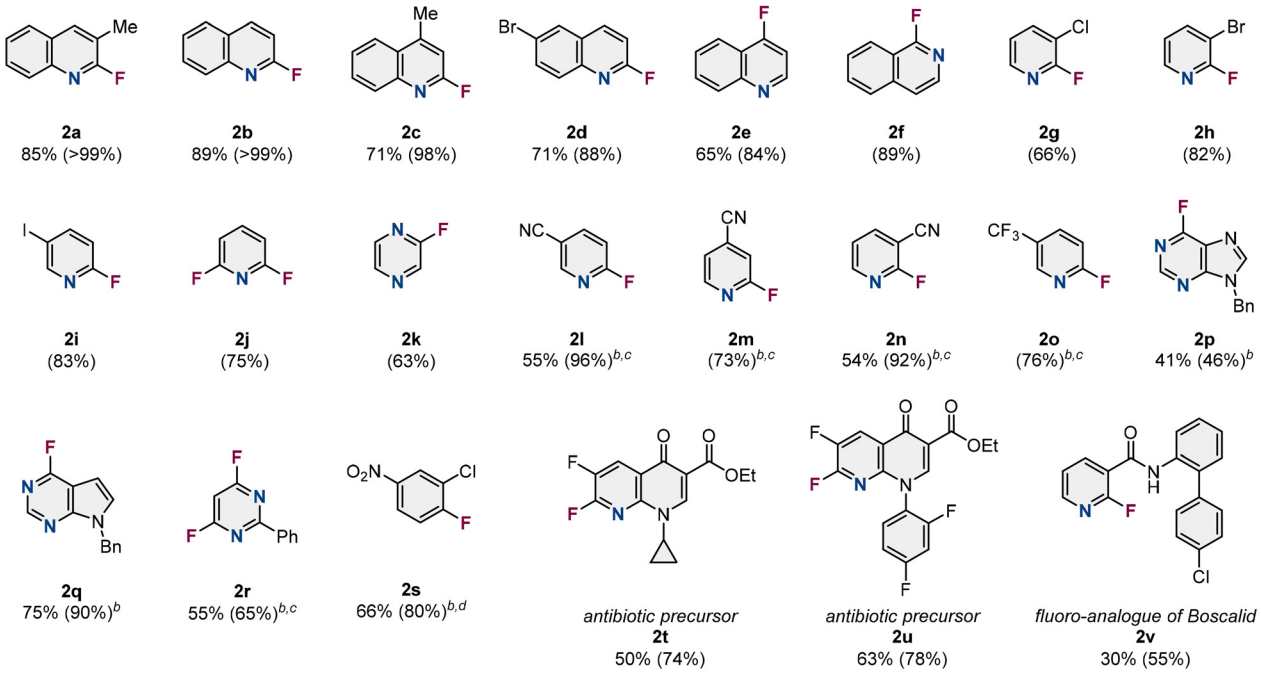
8–11). We found that the presence of an alkyl substituent on the ammonium salt affects the reactivity and the use of Et_4NCl provided **2a** quantitatively (Table 1, entry 9). Importantly, Et_4NCl is much cheaper than the *n*-Bu_4NCl reagent that is commonly employed in solution-based reactions.[16] The reaction using *n*-Bu_4NBr gave a poor result (7%; Table 1, entry 11), suggesting that the correct counter anion is also important to achieve high efficiency. The use of Ph_4PCl did not promote the fluorination (6%; Table 1, entry 12). Next, we investigated the effect of the reaction temperature. Successively lowering the reaction temperature to 100 °C and 40 °C did not result in any reaction (Table 1, entries 13 and 14). Ultimately, we identified the optimized solid-state conditions as using an inexpensive KF/Et_4NCl moisture-insensitive system without the requirement for any highly polar organic solvents (*e.g.*, DMSO or DMF), thereby successfully addressing the aforementioned issues associated with typical solution-based protocols.

We assumed that an anion exchange between KF and Et_4NCl occurs to form the more reactive ion pair tetraethylammonium fluoride (Et_4NF) under the applied solid-state conditions, thereby improving the reaction efficiency (Scheme 1A).[6–9] To test this hypothesis, the reaction of **1a** using pre-formed Et_4NF was investigated (Scheme 1B). Because anhydrous Et_4NF is not commercially available and difficult to prepare, commercial Et_4NF hydrate was used. We found that the reaction proceeded to give **2a** in 61% yield under our mechanochemical conditions. Although the yield was relatively low, which can probably be attributed to the presence of water,[6] this result suggests that Et_4NF is most likely the active fluorinating species in the present system. Under conventional solution-based conditions, quaternary ammonium salts act as phase-transfer reagents that improve the solubility of fluoride sources in organic solvents.[9] Here, we found a different role for quaternary ammonium salts under mechanochemical conditions, *i.e.*, they can tune and enhance the reactivity of fluoride anions in the solid-state reaction environment, thus enabling highly efficient S_NAr fluorination reactions (Scheme 1A).

Next, we explored the substrate scope under the optimized conditions (Table 2). 2-Chloroquinoline derivatives (**1a–1d**) underwent the solid-state S_NAr fluorination to give the corresponding products (**2a–2d**) in high yield (71–99%). The reaction of 4-chloroquinoline (**1e**) also proceeded efficiently to form **2e** in 84% yield. This method also allows the synthesis of 1-fluoroisoquinoline (**2f**) in 89% yield. Next, we investigated the substrate scope of pyridine derivatives. We found that the reactions of 2-chloropyridines (**1g–1i**) with halogen groups selectively provided the 2-fluoropyridines (**2g–2i**) in good yield (66–83%). 2-Chloropyrazine (**1k**) also underwent the fluorination to give **2k** in moderate yield (63%). For the reactions involving electron-deficient pyridines (**1l–1o**), adenine (**1p**), deazapurine (**1q**), and a pyrimidine (**1r**) derivative, the use of a smaller jar (1.5 mL) and ball (diameter: 7 mm) was crucial in order to achieve high yields of the corresponding products (**2l–2r**) (for details, see the ESI†). This mechanochemical approach is furthermore applicable to the electron-deficient benzene derivative **1s**, which provided S_NAr fluorination product **2s** in 80% yield. Next, the robustness of the developed protocol was demonstrated *via* the efficient solvent-free S_NAr fluorination of various bioactive molecules and their building blocks (**1t–1o**). The fluorination of **1t** and **1u**, synthetic intermediates for fluoroquinolone-based antimicrobial agents, proceeded smoothly to deliver the desired products (**2t** and **2u**) in good yield (74% and 78%, respectively). The synthesis of a fluoro-analogue of Boscalid (**2u**), which is a carboxyamide-based fungicide, was accomplished in moderate yield (55%). Overall, the substrate scope of our newly developed reaction was found to be broad and comparable to established solution-based approaches.[6–9]

Table 2 Substrate scope[a]



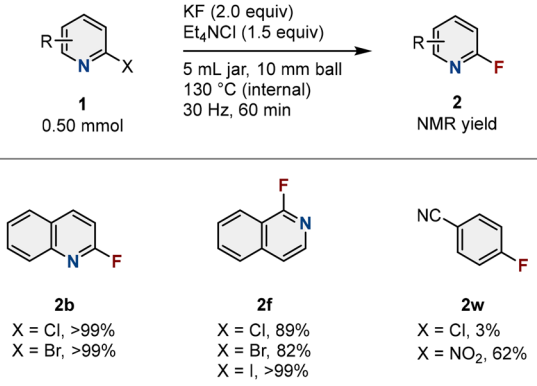


[a] Unless otherwise noted, all mechanochemical reactions were conducted in a Retsch MM400 mill (stainless-steel milling jar (5 mL); 30 Hz; stainless-steel balls (diameter: 10 mm)). Conditions: **1** (0.5 mmol), KF (2.0 mmol), Et_4NCl (0.75 mmol) in a stainless-steel ball-milling jar (5 mL) with a stainless-steel ball (diameter: 10 mm), heat gun set to 250 °C, ball milling (30 Hz) for 60 min. NMR yields were determined based on a ^{19}F NMR analysis with an internal standard and are given in parentheses. [b] A stainless-steel ball-milling jar (1.5 mL) with a stainless-steel ball (diameter: 7 mm) was used. [c] Reaction time: 30 min. [d] Reaction time: 45 min.

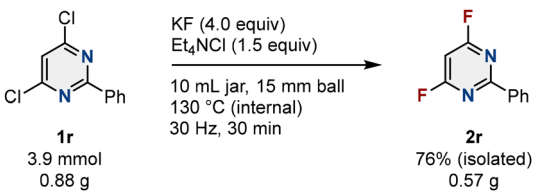
Subsequently, we investigated the solid-state reactions of substrates with different halide leaving groups (Table 3). We found that this method is not limited to arylchlorides, *i.e.*, the reaction of arylbromides and aryliodides afforded the corresponding fluorination products (**2b** and **2f**) in excellent yield (82–99%). The use of a nitro group as a leaving group in a simple cyanobenzene substrate facilitates the mechanochemical S_NAr fluorination to give **2w** in good yield (62%), while the corresponding chloride showed poor reactivity. This trend in reactivity is identical to the reported solution-based conditions.[10]

The utility of this protocol was demonstrated by conducting a scaled-up reaction (Scheme 2). The reaction of **1r** on the 3.9 mmol scale was carried out in a 10 mL stainless-steel

Table 3 Effect of leaving groups[a]



[a] For details of the reaction conditions, see the ESI.†

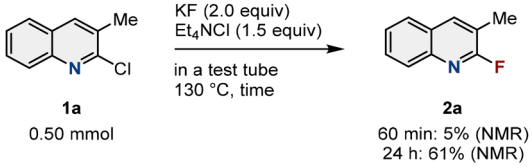


Scheme 2 Scaled-up reaction of **1r**. For details of the reaction conditions, see the ESI.†

milling jar using a stainless-steel ball (diameter: 15 mm), which provided **2r** in 76% isolated yield without any loss of yield compared to the small-scale reaction. This result emphasizes the practical utility of the protocol.

Control experiments were performed using a test tube as a reaction vessel to confirm the effectiveness of the ball-milling process (Scheme 3). The S_NAr fluorination of **1a** was carried out under solvent-free neat conditions using a test tube with a stirring bar at 130 °C. We found that the test-tube reaction showed almost no conversion to **2a** after 60 min (5% yield), while the mechanochemical reaction furnished **2a** quantitatively after 60 min. Even after 24 h, the yield of the stirred test-tube reaction was still merely moderate (61%). This result clearly shows that strong mechanical agitation imparted by the ball-milling process is essential to achieve the remarkable efficiency of the solid-state S_NAr fluorination.

To quantify the environmental benefits of this solid-state mechanochemical approach, we compared the *E*-factor of the present solid-state conditions to those of previously reported representative solution-based conditions found in the literature (Table 4). The *E*-factor is an index for the quantitative evaluation of the environmental impact of a chemical process.[17] For our solid-state S_NAr fluorination, the *E*-factor is 2.6 (Table 4, entry 1), whereas the *E*-factors of representative solution-based methods reported by Bland[9c] and Sanford[10a] are 18.7 and 33.5, respectively (Table 4, entries 2 and 3). This difference is mainly due to the absence of bulk solvents under our solid-state conditions. According to these results, the present solid-state S_NAr fluorination approach is substantially more eco-friendly than conventional solution-based approaches. However, it should also be noted here that the current workup/purification procedure is not optimal from a sustainability perspective. Even though this was not the focus of this study, it must be taken into account when developing industrial mechanochemical protocols.

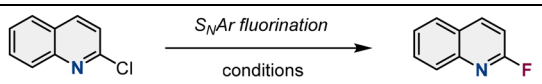


1a
0.50 mmol

2a
60 min: 5% (NMR)
24 h: 61% (NMR)

Scheme 3 Reaction in a test tube with a magnetic stirring bar under solvent-free neat conditions. For details of the reaction conditions, see the ESI.†

Table 4 Comparison of *E*-factors[a]



1b **2b**

Entry	Conditions	*E*-factor
1	KF, nBu$_4$NCl, in DMSO (0.5 M), 130 °C, 24 h	18.7
2	Me$_4$NF, in DMF (0.2 M), rt, 24 h	33.5
3	This work: KF, nEt$_4$NCl, ball milling, 130 °C, 1 h	2.6

[a] For details of the *E*-factor calculations, see the ESI.†

Conclusions

In this study, we have developed the first solid-state protocol for S_NAr fluorinations of N-heteroaryl halides using a combination of KF and Et$_4$NCl. Remarkably, the reactions of a variety of substrates were completed within 1 h to give the desired fluorinated aromatic compounds in good to high yield. Our protocol is much quicker than previous solution-based methods (typically >24 h) and neither depends on significant quantities of highly polar solvents, which are often not easy to remove and can be highly toxic, nor complicated moisture-free reaction setups that use inert gases. We propose that the active fluorinating reagent under the solid-state conditions is *in situ*-formed Et$_4$NF. To the best of our knowledge, this is the most inexpensive S_NAr fluorination system reported to date (for details, see the ESI†). Given these benefits, our mechanochemical approach has the potential to inspire the development of industrially relevant, solvent-free fluorination technologies.

Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was supported by the Japan Society for the Promotion of Science (JSPS) *via* KAKENHI grants 24H00453, 24H01050, 24H01832, 22H00318, and 22K18333; by the JST *via* CREST grant JPMJCR19R1; by FOREST grant JPMJFR201I; and by the Institute for Chemical Reaction Design and Discovery (ICReDD), which was established by the World Premier International Research Initiative (WPI), MEXT, Japan. We thank Mr Reon Hisazumi for his help in cross-checking experiments.

References

1 J. Wang, M. Sańchez-Rosello, J. L. Aceña, C. delPozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok and H. Liu, *Chem. Rev.*, 2014, **114**, 2432.
2 (*a*) S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320; (*b*) A. Haupt, *Organic and inorganic fluorine chemistry*, De Gruyter, Berlin, Boston, 2021;

(*c*) E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly and N. A. Meanwell, *J. Med. Chem.*, 2015, **58**, 8315.

3 (*a*) T. Fujiwara and D. O'Hagan, *J. Fluorine Chem.*, 2014, **167**, 16; (*b*) P. Jeschke, *Pest Manage. Sci.*, 2010, **66**, 10; (*c*) M. Braun and J. Eicher, *Prog. Fluorine Sci. Ser.*, 2017, **3**, 7.

4 D. J. Adams and J. H. Clark, *Chem. Soc. Rev.*, 1999, **28**, 225.

5 P. A. Champagne, J. Desroches, J. D. Hamel, M. Vandamme and J. F. Paquin, *Chem. Rev.*, 2015, **115**, 9073.

6 Y. Y. See, M. T. Morales-Colón, D. C. Bland and M. S. Sanford, *Acc. Chem. Res.*, 2020, **53**, 2372.

7 Y. Sasson, S. Negussie, M. Royz and N. Mushkin, *Chem. Commun.*, 1996, 297.

8 (*a*) H. R. Sun and S. G. DiMagno, *J. Am. Chem. Soc.*, 2005, **127**, 2050; (*b*) H. Sun and S. G. DiMagno, *Angew. Chem., Int. Ed.*, 2006, **45**, 2720.

9 (*a*) L. J. Allen, J. M. Muhuhi, D. C. Bland, R. Merzel and M. S. Sanford, *J. Org. Chem.*, 2014, **79**, 5827; (*b*) M. A. Cismesia, S. J. Ryan, D. C. Bland and M. S. Sanford, *J. Org. Chem.*, 2017, **82**, 5020; (*c*) L. J. Allen, S. H. Lee, Y. Cheng, P. S. Hanley, J. M. Muhuhi, E. Kane, S. L. Powers, J. E. Anderson, B. M. Bell, G. A. Roth, M. S. Sanford and D. C. Bland, *Org. Process Res. Dev.*, 2014, **18**, 1045; (*d*) C. M. Hong, A. M. Whittaker and D. M. Schultz, *J. Org. Chem.*, 2021, **86**, 3999.

10 (*a*) S. D. Schimler, S. J. Ryan, D. C. Bland, J. E. Anderson and M. S. Sanford, *J. Org. Chem.*, 2015, **80**, 12137; (*b*) S. D. Schimler, M. A. Cismesia, P. S. Hanley, R. D. J. Froese, M. J. Jansma, D. C. Bland and M. S. Sanford, *J. Am. Chem. Soc.*, 2017, **139**, 1452; (*c*) S. D. Schimler, R. D. J. Froese, D. C. Bland and M. S. Sanford, *J. Org. Chem.*, 2018, **83**, 11178; (*d*) M. T. Morales-Colón, Y. Y. See, S. J. Lee, P. J. H. Scott, D. C. Bland and M. S. Sanford, *Org. Lett.*, 2021, **23**, 4493; (*e*) S. J. Lee, M. T. Morales-Colón, A. F. Brooks, K. J. Wright, P. J. H. Scott and M. S. Sanford, *J. Org. Chem.*, 2021, **86**, 14121.

11 (*a*) J. Sherwood, F. Albericio and B. G. de la Torre, *ChemSusChem*, 2024, **17**, e202301639; (*b*) A. Gescher, *Chem. Res. Toxicol.*, 1993, **6**, 245.

12 For selected reviews on the use of ball-milling for organic synthesis, see: (*a*) S. L. James, C. J. Adams, C. Bolm, D. Braga, P. Collier, T. Friščić, F. Grepioni, K. D. M. Harris, G. Hyett, W. Jones, A. Krebs, J. Mack, L. Maini, A. G. Orpen, I. P. Parkin, W. C. Shearouse, J. W. Steed and D. C. Waddell, *Chem. Soc. Rev.*, 2012, **41**, 413; (*b*) G.-W. Wang, *Chem. Soc. Rev.*, 2013, **42**, 7668; (*c*) J.-L. Do and T. Friščić, *ACS Cent. Sci.*, 2017, **3**, 13; (*d*) J. G. Hernández and C. Bolm, *J. Org. Chem.*, 2017, **82**, 4007; (*e*) T.-X. Métro, J. Martinez and F. Lamaty, *ACS Sustainable Chem. Eng.*, 2017, **5**, 9599; (*f*) T. K. Achar, A. Bose and P. Mal, *Beilstein J. Org. Chem.*, 2017, **13**, 1907; (*g*) O. Eguaogie, J. S. Vyle, P. F. Conlon, M. A. Gîlea and Y. Liang, *Beilstein J. Org. Chem.*, 2018, **14**, 955; (*h*) J. L. Howard, Q. Cao and D. L. Browne, *Chem. Sci.*, 2018, **9**, 3080; (*i*) J. Andersen and J. Mack, *Green Chem.*, 2018, **20**, 1435; (*j*) C. Bolm and J. G. Hernández, *Angew. Chem., Int. Ed.*, 2019, **58**, 3285; (*k*) T. Friščić, C. Mottillo and H. M. Titi, *Angew. Chem., Int. Ed.*, 2020, **59**, 1018; (*l*) K. Kubota and H. Ito, *Trends Chem.*, 2020, **2**, 1066; (*m*) A. Porcheddu, E. Colacino, L. De Luca and F. Delogu, *ACS Catal.*, 2020, **10**, 8344; (*n*) J. A. Leitch and D. L. Browne, *Chem. – Eur. J.*, 2021, **27**, 9721; (*o*) K. J. Ardila-Fierro and J. G. Hernández, *ChemSusChem*, 2021, **14**, 2145; (*p*) V. Martinez, T. Stolar, B. Karadeniz, I. Brekalo and K. Užarević, *Nat. Rev. Chem.*, 2023, **7**, 51; (*q*) K. Kubota, *Bull. Chem. Soc. Jpn.*, 2023, **96**, 913; (*r*) N. Fantozzi, J.-N. Volle, A. Porcheddu, D. Virieux, F. García and E. Colacino, *Chem. Soc. Rev.*, 2023, **52**, 6680.

13 For selected examples of organic transformations using ball milling from our group, see: (*a*) K. Kubota, T. Seo, K. Koide, Y. Hasegawa and H. Ito, *Nat. Commun.*, 2019, **10**, 111; (*b*) Y. Pang, T. Ishiyama, K. Kubota and H. Ito, *Chem. – Eur. J.*, 2019, **25**, 4654; (*c*) K. Kubota, R. Takahashi and H. Ito, *Chem. Sci.*, 2019, **10**, 5837; (*d*) T. Seo, T. Ishiyama, K. Kubota and H. Ito, *Chem. Sci.*, 2019, **10**, 8202; (*e*) T. Kubota, Y. Pang, A. Miura and H. Ito, *Science*, 2019, **366**, 1500; (*f*) T. Seo, K. Kubota and H. Ito, *J. Am. Chem. Soc.*, 2020, **142**, 9884; (*g*) T. Seo, N. Toyoshima, K. Kubota and H. Ito, *J. Am. Chem. Soc.*, 2021, **143**, 6165; (*h*) T. Seo, K. Kubota and H. Ito, *Angew. Chem., Int. Ed.*, 2023, **62**, e202311531; (*i*) T. Seo, K. Kubota and H. Ito, *J. Am. Chem. Soc.*, 2023, **145**, 6823.

14 For selected examples of mechanochemical fluorination reactions, see: (*a*) Z. Zhao, S. Ikawa, S. Mori, Y. Sumii, H. Adachi, T. Kagawa and N. Shibata, *ACS Sustainable Chem. Eng.*, 2024, **12**, 3565; (*b*) J. L. Howard, Y. Sagatov, L. Repusseau, C. Schotten and D. L. Browne, *Green Chem.*, 2017, **19**, 2798; (*c*) J. L. Howard, Y. Sagatov and D. L. Browne, *Tetrahedron*, 2018, **74**, 3118–3123; (*d*) J. G. Hernández, K. J. Ardila-Fierro, D. Barišić and H. Geneste, *Beilstein J. Org. Chem.*, 2022, **18**, 182; (*e*) S. Min, B. Park, J. Nedsaengtip and S. H. Hong, *Adv. Synth. Catal.*, 2022, **364**, 1975; (*f*) D. Krištofíková, Ma. Mečiarová, E. Rakovský and R. Šebesta, *ACS Sustainable Chem. Eng.*, 2020, **8**, 14417; (*g*) X. Wang, X. Zhang, L. Xue, Q. Wang, F. You, L. Dai, J. Wu, S. Kramer and Z. Lian, *Angew. Chem., Int. Ed.*, 2023, **62**, e202307054.

15 P. Ying, J. Yu and W. Su, *Adv. Synth. Catal.*, 2021, **363**, 1246.

16 Retail price of Et_4Cl in Feb 2024: ca. US $185 per mol (TCI Chemicals); retail price of *n*-Bu_4Cl in Feb 2024: ca. US $643 per mol (TCI Chemicals).

17 (*a*) R. A. Sheldon, *Green Chem.*, 2007, **9**, 1273; (*b*) V. K. Singh, A. Chamberlain-Clay, H. C. Ong, F. León, G. Hum, M. Y. Par, P. Daley-Dee and F. García, *ACS Sustainable Chem. Eng.*, 2021, **9**, 1152.

