RSC Mechanochemistry

ROYAL SOCIETY OF CHEMISTRY

PAPER

View Article Online
View Journal | View Issue

Cite this: *RSC Mechanochem.*, 2026, **3**, 265

Sustainable mechanochemical synthesis of functionalisable fluorinated scaffolds for drug discovery using green LAG

Adam G. Buchanan,[a] Elizabeth T. Areola,[a] Maryam Farrukh Butt,[a] Yan Kiu Lee,[a] Jasper Murphy,[b] Annie E. Taylor,[b] Avninder S. Bhambra[b] and George W. Weaver *[a]

Fluoroarenes have become widely recognised as useful building blocks in medicinal chemistry, and manipulation of these compounds can be achieved readily using nucleophilic aromatic substitution (S_NAr) to introduce a diverse range of functionality for drug development. A more sustainable mechanochemical approach to S_NAr of fluoroarenes using planetary ball milling with a range of aliphatic and aromatic amines as nucleophiles has been investigated with 20 examples described. An efficient set of milling conditions using liquid assisted grinding (LAG) employing the bio-solvent Cyrene or water, and short reaction times (30 minutes) has been developed. Yields were consistently higher when using Cyrene or water as LAG agent rather than DMF. The method provides a useful alternative to the dipolar aprotic solvents DMF and DMSO and high temperatures commonly used in S_NAr. Ethyl acetate is employed in the extractive work-up, but is recyclable and considered a green solvent. The method reduces or obviates bulk reaction solvent and aqueous waste streams containing dipolar aprotic solvents.

Received 8th August 2025
Accepted 14th December 2025

DOI: 10.1039/d5mr00100e

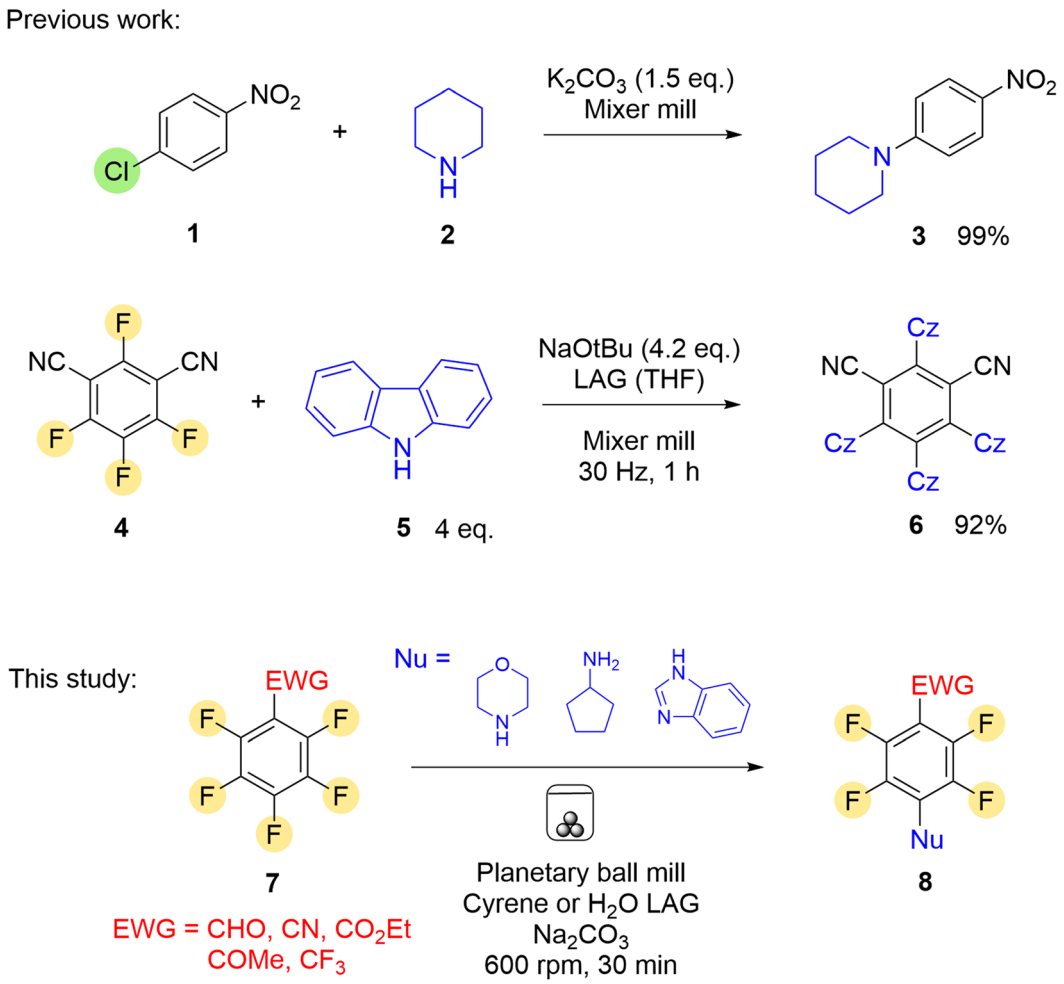
rsc.li/RSCMechanochem

Introduction

As part of our ongoing programme to develop new compounds active against a number of neglected tropical diseases we required fluorinated arenes substituted with amine or nitrogen heterocyclic groups.[1] Such compounds can be elaborated into drug scaffolds by manipulation of the initial arene substituent and/or further substitution of fluorine by S_NAr reaction, for example by *ortho* substitution and cyclocondensation onto aldehyde, ketone or nitrile groups.[2] This approach offers an alternative route to fluorinated drug scaffolds which are more usually prepared by late-stage fluorination or by incorporation of reactants containing strategically placed fluorine atoms. Fluorine's small size, high electronegativity, and electrostatic interactions frequently improves drug performance making it key to modern drug development,[3] while its leaving-group ability allows for further synthetic manipulation of fluorinated scaffolds enabling unique substitution patterns to be achieved. Fluorine can be introduced either by electrophilic or nucleophilic reactions, but the former often involve the use of highly reactive or expensive fluorinating agents.[4] Per- and poly-fluoroarenes can now synthesised using nucleophilic fluorination using fluoride ion (halex reaction) without the need for fluorine gas or reactive reagents derived from F_2.[5] We have thus exploited S_NAr reactions of per- or poly-fluorinated arenes in the construction of novel heterocycles and drug scaffolds.[6] S_NAr allows the addition of nucleophiles that have proven to be ideal structural motifs in the synthesis of pharmaceutical compounds without the need for transition metal catalysis.[7] However, these reactions often require the use of harmful dipolar aprotic solvents, and with the introduction of stricter legislation in recent times with regards to the handling of these solvents, there is an increasing need for a more environmentally friendly way of conducting these reactions. The aim of this work was to investigate the viability of ball milling to promote S_NAr reactions, whilst moving away from the use of harmful solvents and towards more sustainable methods using green solvents for liquid-assisted grinding (LAG). Mechanochemistry has become key to recent approaches to develop more sustainable chemical synthesis.[8] Recent mechanochemical approaches to S_NAr include Andersen and Starbuck's[9] work using ball milling to promote S_NAr in halonitrobenzenes **1** with amines to form **3** (Scheme 1) but showed temperatures up to 100 °C were required, while Leitch, Smallman and Browne[10] reported a study on the synthesis of the organophotocatalyst 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4CzIPN) **6** using tetrafluoroisophthalonitrile **4** and carbazole **5**. They showed that substitution of the four fluorines in **4** with carbazole occurred with yields of up to 92% when using NaO*t*Bu as base, and pre-milling the NaO*t*Bu and carbazole before the addition of the tetrafluoroisophthalonitrile **4**. The reaction employed

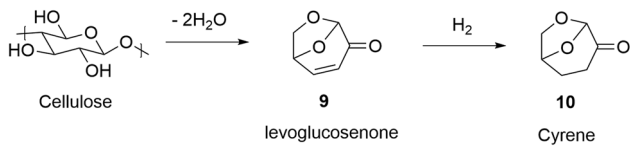
[a]*Department of Chemistry, Loughborough University, Epinal Way, Loughborough, Leicestershire, LE11 3TU, UK. E-mail: g.w.weaver@lboro.ac.uk*

[b]*Leicester School of Allied Health Sciences, De Montfort University, The Gateway, Leicester, LE1 9BH, UK*



Scheme 1 Previous mechanochemical S_NAr reactions and the current study using green LAG.

THF for LAG which leads to a higher convection rate and better mass transport often improving the yield of reactions. S_NAr reactions are conventionally conducted using toxic dipolar aprotic solvents such as dimethylformamide (DMF) or dimethyl sulfoxide (DMSO), that add significant disposal costs to synthetic protocols. We wished to explore the use of water, or bio-based solvents, such as Cyrene[11] **10** to promote greener S_NAr transformations. Cyrene is synthesised (Scheme 2) by hydrogenation of levoglucosenone **9**, a dehydration product of cellulose derived glucose, and whilst renewable hydrogen generation is not currently economically viable, it is possible, meaning that Cyrene is classified as a bio-solvent, and a viable substitute for toxic and non-renewable petrochemical-derived solvents. We also wished to develop lower energy demanding S_NAr reactions that can be readily conducted in a short time, rather than the prolonged high temperature reaction commonly encountered (typically >12 h, ~100 °C). The target compounds were chosen for their desirable properties as building blocks for medicinal scaffolds. Although per- and poly-fluoroalkyl substances (PFAS) are considered environmentally persistent and harmful, the corresponding fluoroarenes are more readily degraded due to their propensity to undergo easy S_NAr reaction. Recent work by Gouverneur[12] has highlighted how mechanochemical processing with potassium phosphate can be used to degrade PFAS materials while recovering fluoride as KF and K_2PFO_3 for reuse.



Scheme 2 Preparation of bio-solvent Cyrene from cellulose derived glucose.

Results and discussion

Initial studies using a YKL-0.4L planetary ball mill (Fig. 1a) with reactions conducted in 100 mL stainless steel jars found the use of steel ball bearings of different sizes: 5.68 g (3), 3.28 g (2) and 2.14 g (5) led to the best recovery of material, so these conditions were employed in the S_NAr reactions using a 30-minute reaction time and a rotational frequency of 600 rpm. Method optimisation experiments are described in the SI. Three

Fig. 1 Planetary ball mills used in this study: Changsha Yonglekang YKL-0.4L mill (left) and Fritsch Pulverisette 7 micro mill (right).

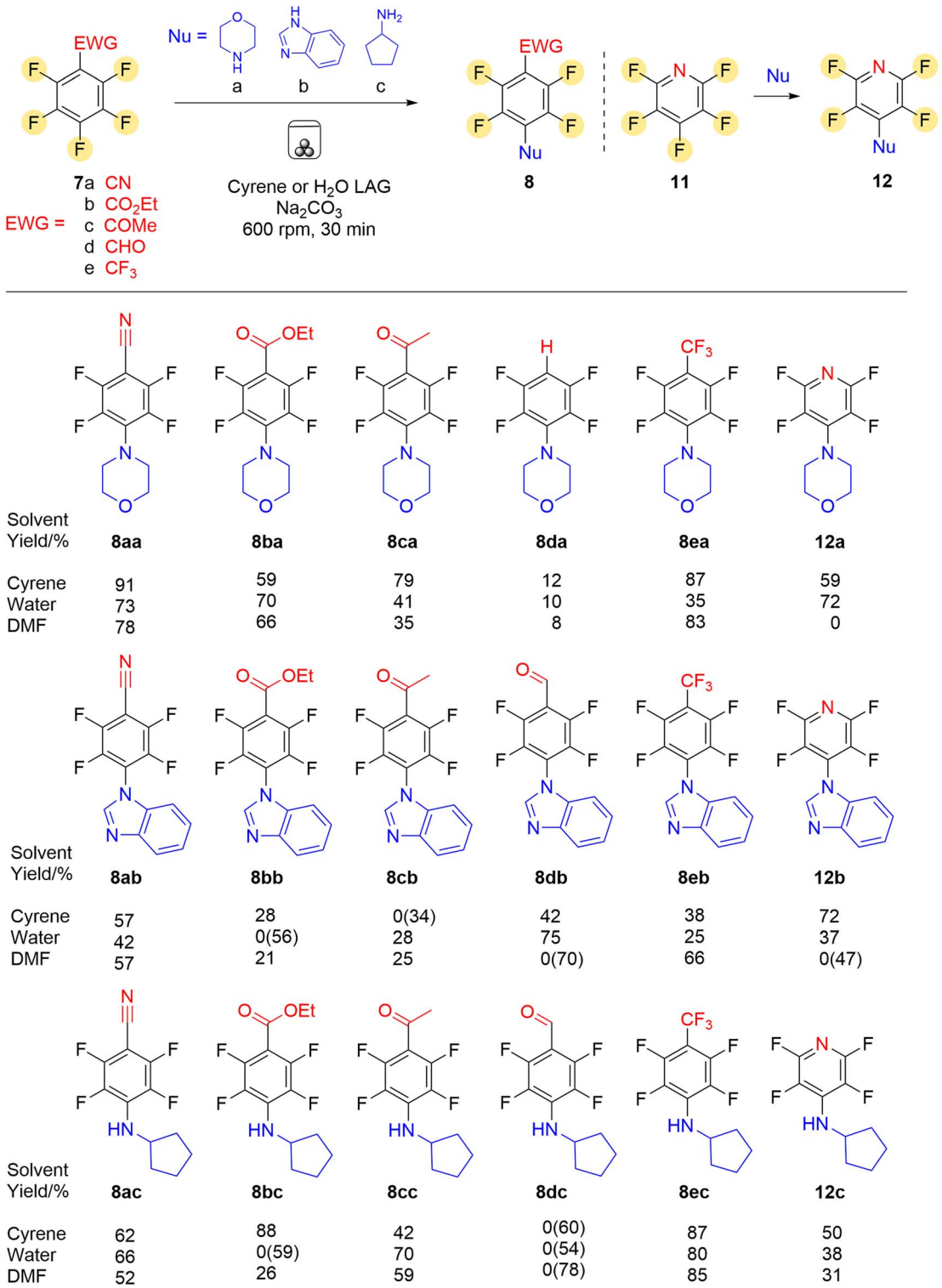
different solvents were employed: Cyrene or water would be compared to DMF as greener aprotic and protic solvents for LAG. Use of an aqueous solvent would allow partial dissolution of the sodium carbonate base employed to neutralise the HF formed as a by-product in the reaction. Reactions were conducted on a 5 mmol scale with 0.25 mL of LAG agent used in each case.

Perfluorinated aromatic compounds **7a–e** (Scheme 3) with electron-withdrawing substituents were chosen to increase the likelihood of *para* substitution in the S_NAr reaction,[13] and to test if poly-substitution would occur under ball milling as often multiple substitution can occur under conventional S_NAr methods. Three nitrogen based nucleophiles were used in the study, two aliphatic and one aromatic amine. Morpholine was chosen as a typical aliphatic secondary amine which is often present in drug molecules as a protonatable water solubilising substituent and is an effective nucleophile in S_NAr.[14] Benzimidazole and cyclopentylamine were chosen to test the lower nucleophilicity of a nitrogen heterocycle compared to a primary amine, and for their pharmaceutically desirable properties. Morpholine was reacted with five different perfluorinated aromatics with electron withdrawing substituents **7a–e**, or with pentafluoropyridine **11** as a heterocyclic substrate, with the three chosen solvents (Scheme 2). The results of the reaction set are shown in row 1, with all reactions giving the desired mono-substituted *para* isomers **8(a–e)a** and **12a** as confirmed by ^{19}F NMR spectrscopy, except for the formation of compound **12a** when using DMF as LAG agent. There was no evidence of di-substitution occurring. All reactions were conducted on a synthetically useful 5 mmol scale with reproducible results (minimum of two repetitions or reactions repeated by different coworkers). The lack of reaction of pentafluoropyridine **11** in DMF was repeatable, and it is not clear why this substrate failed to react with morpholine in the presence of DMF. A control reaction with **7a** and morpholine was conducted with no LAG agent. This showed the reaction still to proceed, but not to completion in the same time. Nitrile **8aa** was formed in a lower 52% yield after purification.

None of the compounds **8(a–e)a** and **12a** have been previously reported synthesised by mechanochemical methods. Compounds **8aa**[15] and **12a**[16] have been prepared in solution, but required prolonged reactions times (*e.g.* **8aa**, 60 h in refluxing THF or 12 h in boiling MeCN). We found **8ba** and **8ca** were formed in solution in THF in only 36% and 52% respectively after 75 h at room temperature. The ball milling method here afforded **8aa** in 91% yield and **12a** in 70% in only 30 minutes. **8ea** has been prepared previously in 60% isolated yield in THF using a magnesium amide reagent under Schlenk conditions.[17] Milling with Cyrene as LAG agent and only sodium carbonate as both base and grinding agent gave **8ea** in 87% yield with no need for inert atmosphere conditions. Compounds **8ba** and **8ca** were synthesised for the first time, with water and Cyrene giving the highest yields, 70% and 79% respectively, as LAG agents. In the reaction of pentafluorobenzaldehyde **7d** the expected 4-substituted aldehyde product was not obtained, and 2,3,5,6-tetrafluorophenyl morpholine **8da** was isolated instead. Addition of morpholine at the *para* position was confirmed by the two signals of an AA′BB′ spin pattern in the ^{19}F NMR spectrum but no aldehyde proton signal was visible in the ^{1}H NMR spectrum. A triplet of triplets signal at 6.70 (J 10 and 3 Hz) indicated a single aromatic proton coupling to two pairs of fluorine atoms. Additionally no carbonyl signal was present in the IR spectrum and a mass ion was detected at m/z 236 corresponding to a molecular formula of $C_{10}H_9F_4NO$ for the decarbonylated compound **8da**. This likely formed (Scheme 4) by addition of morpholine at the *para* position of **7d** as first expected, forming **13**.

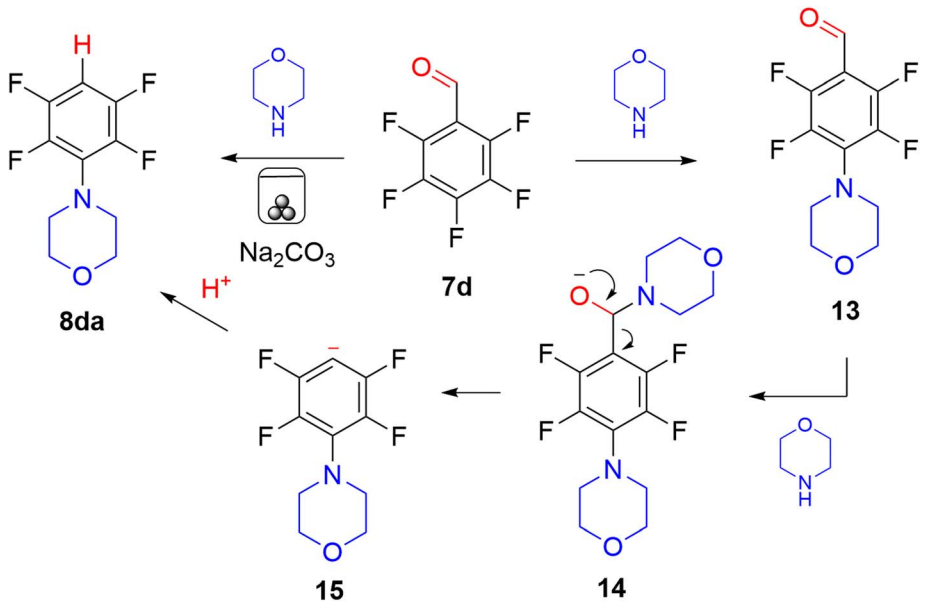
This however undergoes further reaction at the aldehyde centre by addition of a second molecule of morpholine, to form an intermediate **14** which then undergoes Haller Bauer type cleavage[18] to form a fluorine stabilised aromatic anion **15** which protonates to give **8da**. We have observed similar diacylation reaction of perfluorobenzaldehydes previously.[2]

After the initial success with the morpholine set of reactions, benzimidazole was then used to investigate whether aromatic nitrogen heterocycles could be introduced by mechanochemical S_NAr. Often strong bases such NaH are required to form the



Scheme 3 Mechanochemical S_NAr reaction of perfluoroarenes with products formed and LAG agent % yields (isolated yields reported; values in parenthesis refer to starting material recovered).

heterocyclic anion to ensure sufficient nucleophilicity, but all reactions in the ball mill were successful with both Cyrene or water proving effective as LAG agents. The reactions produced the mono-substituted *para* derivatives in moderate to good yields (Scheme 3: **8(a–e)b** and **12b**). Reaction with pentafluorobenzaldehyde **7d** was successful with a good yield of **8db** (75%) (δ_H 10.35 for the aldehydic proton) obtained with water as LAG agent. Use of Cyrene afforded a moderate yield of 42%, but none of the deacylated product was detected. Expect in the case of **8eb** yields were better using Cyrene or water rather

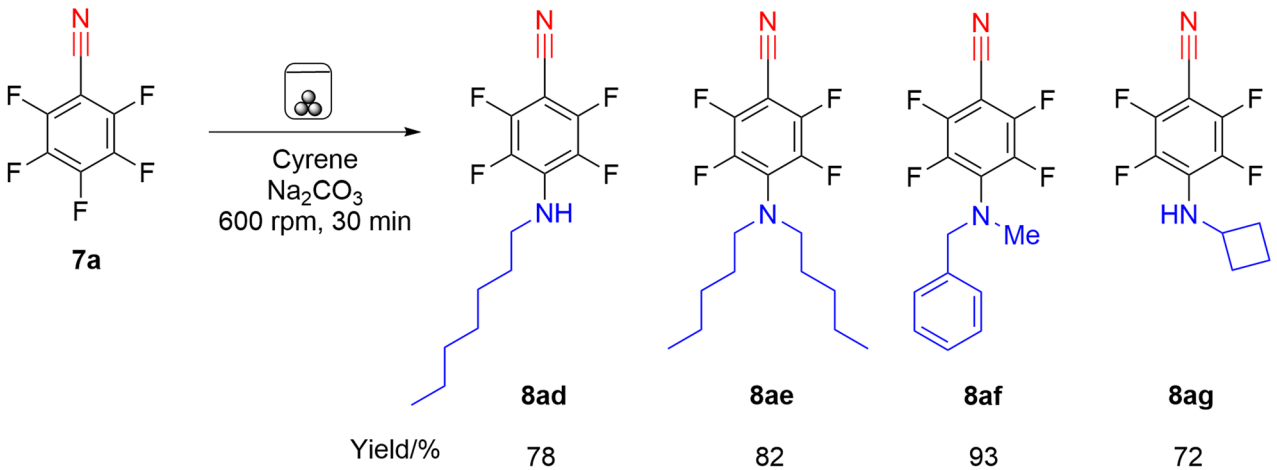


Scheme 4 Proposed mechanism for the formation of deacylated product **8da**.

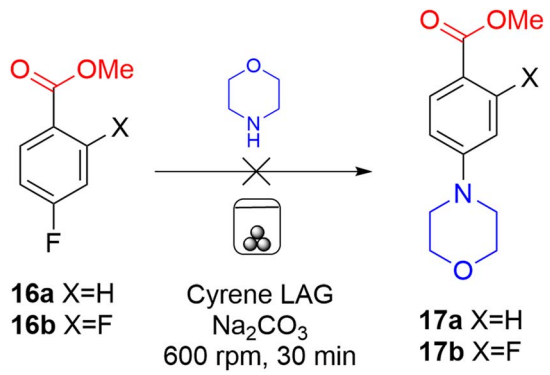
than DMF as solvent. No instances of di-substitution were observed which is often an issue in solution based S_NAr chemistry. Compounds **8ab**, **8eb** and **12b** have been synthesised by conventional solution methods previously[19] as part of a study on polar crystal engineering exploiting π–π interactions, but used bulk THF as solvent and long reaction times (48 h). Aldehyde **8db** was prepared previously by us as a precursor to biologically active benzothiophenes.[1c]

Cyclopentylamine was the third nucleophile to be investigated for mechanochemial reaction with the set of fluoroarenes. Due to the compounds role as drug scaffold precursors, amines were prioritised as being desirable nucleophiles. The novel compounds **8ac**, **8bc**, **8cc**, **8ec** and **12c** were successfully synthesised in moderate to high yields with Cyrene or water outperforming DMF as LAG agents in terms of yield. The reaction between pentafluorobenzaldehyde **7d** and cyclopentylamine was unsuccessful with all three solvents investigated, with two repetitions attempted for each solvent. TLC analysis of the crude products showed complex mixtures that could not be separated using column chromatography. None of the product **8dc** was isolated. Possible side reactions could have occurred between the amine and the aldehyde such as imine formation or deacylation. With DMF as LAG agent a high recovery (78%) of **7d** was recovered indicating a slow reaction rate in this solvent. There was no indication of imine formation between the amine and the ketone group of Cyrene.

Considering the Kamlet–Abboud–Taft (KAT) parameters[20] of the solvents used, both Cyrene and water have greater π* values (0.93 and 1.08 respectively) than DMF (0.88), and should better stabilise dipolar interactions in the transition state for addition of the nucleophile. These reactions are likely to proceed by a two-step addition–elimination mechanism, although there is



Scheme 5 Reactions of perfluorobenzonitrile **7a** with hindered amines in an agate milling jar.



Scheme 6 Attempted reactions of mono- and di-fluorobenzoates with morpholine.

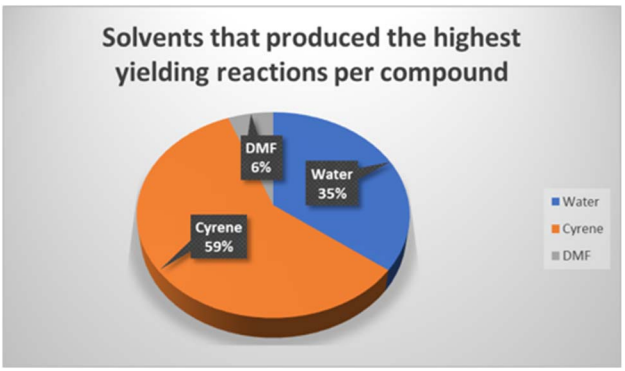
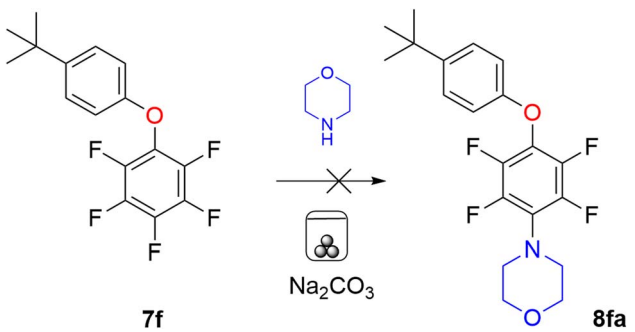


Fig. 2 Highest yielding reactions by LAG agent.

increasing evidence that many S_NAr reactions are concerted processes.[7] Hydrogen Bond Accepting (HBA) solvent Cyrene can also interact with the NH bond of the amines increasing nucleophilicity, while water being also a hydrogen bond donor (HBA-D) solvent should also assist in stabilising the departing fluoride ion. Alcohols, such as bio-ethanol, could also be effective LAG agents, but we did not investigate these as we have found ethanol can add to perfluoroarenes under basic conditions to form ethoxy substituted by-products. Additionally Cyrene (b.p. 227 °C) is stable up to 195 °C and is non-toxic and biodegradable. DMF (b.p 153 °C) begins to decompose above 100 °C forming carbon monoxide and dimethylamine, and this is likely to occur under the high frictional forces of the ball mill. We have previously detected dimethylamino containing by-products in S_NAr reactions using DMF.

With the optimised conditions employing Cyrene as LAG agent we then investigated reactions of nitrile **7a** with more hindered primary and secondary amines (Scheme 5) and also employed agate milling jars and balls in a Fritsch Pulverisette 7 planetary micro mill (Fig. 1b) as an alternative to steel which has the advantage of not introducing potentially harmful metal particulates into the drug precursors. These amines also reacted successfully in high yield (72–93%) on a 2 mmol scale.

With perfluorinated arenes **7a–e** shown to react successfully under milling conditions, mono- and di-fluorinated benzoates **16a** and **16b** (Scheme 6) were investigated as less reactive arenes with morpholine as nucleophile. Cyrene was employed for LAG but both reactions were unsuccessful, with only starting material recovered in each case. No evidence for the formation of **17a** or **17b**, or the corresponding *ortho* isomers, was obtained. No reaction was also observed between morpholine and 4-fluorobenzonitrile. Chloronitrobenzene **1**, discussed above (Scheme 1), required a reaction temperature of 100 °C, and even though fluorine as nucleofuge[21] in **16** should increase reaction rate relative to chlorine, it appears the ester group is not sufficiently activating to allow reaction under the current milling conditions. The temperature of the jars in the ball mill increase by around 10 °C due to friction, but this did not influence reaction rate sufficiently to allow reaction.



Scheme 7 Attempted reaction of morpholine with electron donor substituted fluoroarene **7f**.

We also studied the potential reaction of a fluoroarene **7f** bearing an electron donating group (*t*-butylphenoxy) with morpholine (Scheme 7), but no reaction occurred under the conditions successful for arenes **7a–e**. Only starting material **7f** was isolated in a high recovery of 76%. This result matches solution phase reactions of perfluoroarenes with electron donating substituents that require more forcing conditions to undergo S_NAr and which, in some cases, lead to *meta* substitution.[13] Further investigations into reactions with less activated substrates, and the effects of temperature are in progress.

An estimation of the energy consumption of the milling method compared to conventional heating was made. The YKL0.4L ball mill used operated at 750 W and allowed four reactions to be completed simultaneously in 30 minutes. Energy consumption was determined to be approximately 0.09 kWh per reaction compared to 6.6 kWh for conventional thermal reactions (reflux for 12 h). The method developed reduces energy usage as well as minimising solvent waste and disposal costs. The green solvent Cyrene was shown to be the most effective LAG agent affording the highest yields (Fig. 2) in 59% of reactions, with water also proving superior to DMF.

The simplicity of the method should allow easy translation to continuous production methods such as twin-screw extrusion (TSE).[22]

Conclusions

In conclusion, a more sustainable mechanochemical approach to conduct S_NAr of fluorinated aromatics with nitrogen

nucleophiles has been developed. Cyrene or water were shown to be more effective LAG agents than DMF and the method provides a viable alternative to conventional solution phase S_NAr reactions using dipolar aprotic solvents. Ethyl acetate is employed in the extractive work-up, but is recyclable and considered a green solvent. The method reduces or removes bulk reaction solvent waste and aqueous streams contaminated with dipolar aprotic solvents. A library of twenty (fifteen novel) functionalisable scaffolds has been prepared with the compounds being used in the synthesis of new screening candidates for drug development.

Author contributions

AGB and ETA developed the experimental method, synthesised compounds and obtained characterisation data, MFB, CL, JM, and AET synthesised compounds and obtained characterisation data. ASB supervised the project and designed target compounds. GWW conceived and supervised the project and wrote the manuscript. All authors have reviewed the manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

Supplementary information (SI): all supporting experimental data, including synthetic procedures, analytical and spectroscopic characterisation data, and copies of ^{1}H, ^{19}F and ^{13}C NMR spectra. See DOI: https://doi.org/10.1039/d5mr00100e.

Acknowledgements

We thank the Royal Society of Chemistry (Research Enablement Grant E21-3753888107) and both Lougborough and De Montfort Universities for support.

References

1 (*a*) L. B. Tulloch, H. Tawell, A. E. Taylor, M. L. Lima, A. Dawson, S. Carvalho, R. J. Wall, V. Corpas-Lopez, G. Dey, J. Duggan, L. G. Magalhaes, L. S. Torrie, L. Frame, D. Robinson, S. Patterson, M. Tinti, G. W. Weaver, W. J. Robinson, M. Cal, M. Kaiser, P. Maeser, P. Sjö, B. Perry, M. Kelly, A. F. Francisco, A. S. Bhambra and S. Wyllie, *Sci. Transl. Med.*, 2025, **17**, eadu4564, DOI: 10.1126/scitranslmed.adu4564; (*b*) E. Taylor, M. Hering, M. R. J. Elsegood, S. J. Teat, G. W. Weaver, R. R. J. Arroo, M. Kaiser, P. Maeser and A. S. Bhambra, *Bioorg. Med. Chem. Lett.*, 2024, **109**, 129825; (*c*) A. S. Bhambra, M. Edgar, M. R. J. Elsegood, Y. Li, G. W. Weaver, R. R. J. Arroo, V. Yardley, H. Burrell-Saward and V. Krystof, *Eur. J. Med. Chem.*, 2016, **108**, 347–353.

2 H. W. Tawell, W. Robinson, Y. Li, G. J. Tizzard, S. J. Coles, A. S. Bhambra, M. Edgar and G. W. Weaver, *RSC Adv.*, 2025, **15**, 12843.

3 (*a*) E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly and N. A. Meanwell, *J. Med. Chem.*, 2015, **58**, 8315–8359; (*b*) K. Müller, C. Faeh and F. Diederich, *Science*, 2007, **317**, 1881.

4 (*a*) N. Rozatian and D. R. W. Hodgson, *Chem. Commun.*, 2021, **57**, 683; (*b*) R. Szpera, D. F. J. Moseley, L. B. Smith, A. J. Sterling and V. Gouverneur, *Angew. Chem., Int. Ed.*, 2019, **58**, 14824–14848.

5 A. Pleschkea, A. Marholda, M. Schneidera, A. Kolomeitsevb and G.-V. Röschenthaler, *J. Fluorine Chem.*, 2004, **125**, 1031–1038.

6 (*a*) S. Riaz, M. Edgar, M. R. J. Elsegood, L. Horsburgh, S. J. Teat, T. G. Warwick and G. W. Weaver, *Cryst. Growth Des.*, 2019, **19**, 5237–5248; (*b*) J. Ponce González, M. Edgar, M. R. J. Elsegood and G. W. Weaver, *Org. Biomol. Chem.*, 2011, **9**, 2294–2305.

7 (*a*) M. Shigeno, K. Hayashi, O. Sasamoto, R. Hirasawa, T. Korenaga, S. Ishida, K. Nozawa-Kumada and Y. Kondo, *J. Am. Chem. Soc.*, 2024, **146**, 32452–32462; (*b*) L. Finck and M. Oestr, *Chem.–Eur. J.*, 2021, **27**, 11061–11064; (*c*) S. Rohrbach, A. J. Smith, J. Hao Pang, D. L. Poole, T. Tuttle, S. Chiba and J. A. Murphy, *Angew. Chem., Int. Ed.*, 2019, **58**, 16383–16388.

8 (*a*) X. Liu, Y. Li, L. Zeng, X. Li, N. Chen, S. Bai, H. He, Q. Wang and C. Zhang, *Adv. Mater.*, 2022, **34**, 2108327; (*b*) R. T. O'Neill and R. Boulatov, *Nat. Rev. Chem.*, 2021, **5**, 148–167; (*c*) T. Friščić, C. Mottillo and H. Titi, *Angew. Chem., Int. Ed.*, 2019, **59**, 1018–1029; (*d*) J. L. Howard, Q. Cao and D. L. Browne, *Chem. Sci.*, 2018, **9**, 3080–3094.

9 J. M. Andersen and H. F. Starbuck, *J. Org. Chem.*, 2021, **86**, 13983–13989.

10 J. Leitch, H. Smallman and D. Browne, *J. Org. Chem.*, 2021, **86**, 14095–14101.

11 (*a*) N. A. Stini, P. L. Gkizis and C. G. Kokotos, *Green Chem.*, 2022, **24**, 6435; (*b*) T. Brouwer and B. Schuur, *ACS Sustain. Chem. Eng.*, 2020, **8**, 14807–14817; (*c*) F. Gao, R. Bai, F. Ferlin, L. Vaccaro, M. Li and Y. Gu, *Green Chem.*, 2020, **22**, 6240–6257; (*d*) J. E. Camp, *ChemSusChem*, 2018, **11**, 3048–3055.

12 L. Yang, Z. Chen, C. A. Goult, T. Schlatzer, R. S. Paton and V. Gouverneur, *Nature*, 2025, **640**, 100–106.

13 (*a*) R. D. Chambers, *Fluorine in Organic Chemistry*, Blackwell, Oxford, 2004; (*b*) G. M. Brooke, *J. Fluorine Chem.*, 1997, **86**, 1–76; (*c*) R. D. Chambers and C. R. Sargent, *Adv. Heterocycl. Chem.*, 1981, **28**, 1–71.

14 J. Alarcón-Espósito, R. Tapia, R. Contreras and P. Campodónico, *RSC Adv.*, 2015, **5**, 99322–99328.

15 M. Cargill, K. Linton, G. Sandford, D. Yufit and J. Howard, *Tetrahedron*, 2010, **66**, 2356–2362.

16 G. Podolan, P. Jungk, D. Lentz, R. Zimmer and H. Reissig, *Adv. Synth. Catal.*, 2015, **357**, 3215–3228.

17 L. J. Bole, L. Davin, A. R. Kennedy, R. McLellan and E. Hevia, *Chem. Commun.*, 2019, **55**, 4339–4342.

18 (*a*) A. Haller and E. Bauer, *Comptes Rendus*, 1908, **147**, 824; (*b*) G. Mehta and R. V. Venkateswaran, *Tetrahedron*, 2000,

56, 1399–1422; (*c*) A. K. Barbour, M. W. Buxton, P. L. Coe, R. Stephens and J. C. Tatlow, *J. Chem. Soc.*, 1961, 808–817.
19 H. Althagbi, J. Lane, G. Saunders and S. Webb, *J. Fluorine Chem.*, 2014, **166**, 88–95.
20 (*a*) J. Sherwood, J. Granelli, C. R. McElroy and J. H. Clark, *Molecules*, 2019, **24**, 2209; (*b*) P. G. Jessop, D. A. Jessop, D. Fu and L. Phan, *Green Chem.*, 2012, **14**, 1245–1259; (*c*) M. J. Kamlet, J. L. Abboud and R. W. Taft, *J. Am. Chem. Soc.*, 1977, **99**, 6027–6038.
21 N. A. Senger, B. Bo, Q. Cheng, J. R. Keeffe, S. Gronert and W. Wu, *J. Org. Chem.*, 2012, **77**, 9535–9540.
22 (*a*) J. A. Leitch, P. Richardson and D. L. Browne, *Chimia*, 2023, **77**, 339–345; (*b*) J. Andersen, H. Starbuck, T. Current, S. Martin and J. Mack, *Green Chem.*, 2021, **23**, 8501–8509.