ChemComm

Chemical Communications

rsc.li/chemcomm

MECHANOREDOX CATALYSIS

BaTiO₃

RESONANT ACOUSTIC MIXING

ROYAL SOCIETY
OF CHEMISTRY

COMMUNICATION
Xavier Ottenwaelder, Tomislav Friščić *et al.*
Resonant acoustic mixing (RAM) for efficient mechanoredox
catalysis without grinding or impact media

Check for updates

Resonant acoustic mixing (RAM) for efficient mechanoredox catalysis without grinding or impact media†

Farshid Effaty, [ID] [ab] Lori Gonnet, [ID] [b] Stefan G. Koenig, [ID] [c] Karthik Nagapudi, [c] Xavier Ottenwaelder [ID] *[a] and Tomislav Friščić [ID] *[bd]

Resonant acoustic mixing (RAM) enables mechanoredox catalysis with BaTiO₃ as the piezoelectric catalyst on model diazonium coupling reactions. RAM proceeds without formal grinding or impact media, is faster than the analogous ball-milling strategy, and is readily scalable. X-ray diffraction and spectroscopy indicate that reusability of BaTiO₃ as a mechanoredox catalyst under ball-milling or RAM might be limited by boration.

Mechanochemical reactions by impact, stress or shear have emerged as powerful approaches for synthesis without bulk solvents.[1,2] Mechanochemistry also offers unexpected benefits, such as enhanced control over reaction selectivity, stoichiometry, as well as reactions or products that are difficult to achieve in solution.[3] An exciting opportunity in mechanosynthesis, introduced by the Ito group, is the use of a piezoelectric material, such as $BaTiO_3$, to catalyse electron-transfer reactions.[4] In such mechanoredox catalysis,[5] the mechanical impact from the grinding media (*e.g.*, milling balls) triggers the piezoelectric effect on the catalyst, enabling reaction progress. Grinding media, however, are generally found to complicate mechanochemical reaction design because of unwanted leaching, abrasion, and/or chipping.[6] Moreover, the complex motion of such media renders scaling-up difficult, requiring changes to instrument design and/or further trial-and-error screening of reaction parameters such as filling ratios, milling frequency, choice and number of milling balls.[7]

Resonant Acoustic Mixing (RAM, Fig. 1), a technology developed for media-free mixing and blending of sensitive materials,

such as explosives,[8] can enable mechanosynthesis without either bulk solvent or milling media. So far, RAM has been used for synthesis of cocrystals,[8,9] metal–organic frameworks, and for metal-catalysed coupling reactions.[10,11] In contrast to ball-milling, RAM reaction design is simplified by the absence of grinding media, and reactions are readily scalable.[11]

Here we show that, despite the lack of mechanical impact from milling media, RAM is amenable to piezoelectric catalysis. By using commercial cubic $BaTiO_3$ as catalyst, we establish single electron transfer (SET) borylation and arylation of diazonium salts,‡ scalable from *ca.* 0.1 gram to at least gram amounts (Fig. 1). When the catalyst is reused, a loss of activity is observed, but is smaller than under ball-milling. We tentatively attribute this activity loss to *in situ* $BaTiO_3$ boration.

Cubic $BaTiO_3$ was obtained from Sigma-Aldrich, with declared particle size < 100 nm (BET, $\geq 99\%$ purity trace metals basis), and was used as-is. As a model reaction we chose the borylation of aryldiazonium salts, with *p*-chlorobenzenediazonium tetrafluoroborate (**1a**) and bis(pinacolato)boron (**bpb**) as test substrates. Because this reaction pioneered mechanoredox catalysis,[4] it offers an opportunity to compare RAM and ball-milling protocols. Acoustic mixing was performed using a Resodyn LabRAM II instrument, with samples placed in glass vials mounted on in-house designed holders (Fig. 1A and B).[11] RAM of an equimolar mixture (0.3 mmol each) of **1a** and **bpb** at an acceleration of 90g (g = 9.81 m s^{-2}) led to no reaction, as revealed by ^{1}H-NMR analysis in DMSO-d$_6$. Addition of 300 mg (4.3 equivalents) of $BaTiO_3$, however, led to *ca.* 10% conversion to the anticipated product **2a** after 3 h. Similar results were seen when RAM was performed with a small amount of a non-polar liquid additive (ratio of the liquid volume to weight of solid reaction mixture $\eta = 0.25$ μL mg^{-1} [12]) such as hexanes (17%) or toluene (13%). Acetonitrile (MeCN) as the liquid additive at $\eta = 0.10$ μL mg^{-1} led to 92% NMR conversion to **2a** in 3 h, comparable to a 3 hour ball-milling protocol.[6]

Screening[13] of reaction times at $\eta = 0.25$ μL mg^{-1} indicated that reaction conversion increases for up to 2 h of RAM and

[a] Department of Chemistry and Biochemistry, Concordia University, Montreal, Canada. E-mail: dr.x@concordia.ca

[b] Department of Chemistry, McGill University, Montreal, Canada

[c] Genentech, Inc., One DNA Way, South San Francisco, CA 94080, USA

[d] School of Chemistry, University of Birmingham, Edgbaston, Birmingham, B15 2TT, UK. E-mail: t.friscic@bham.ac.uk
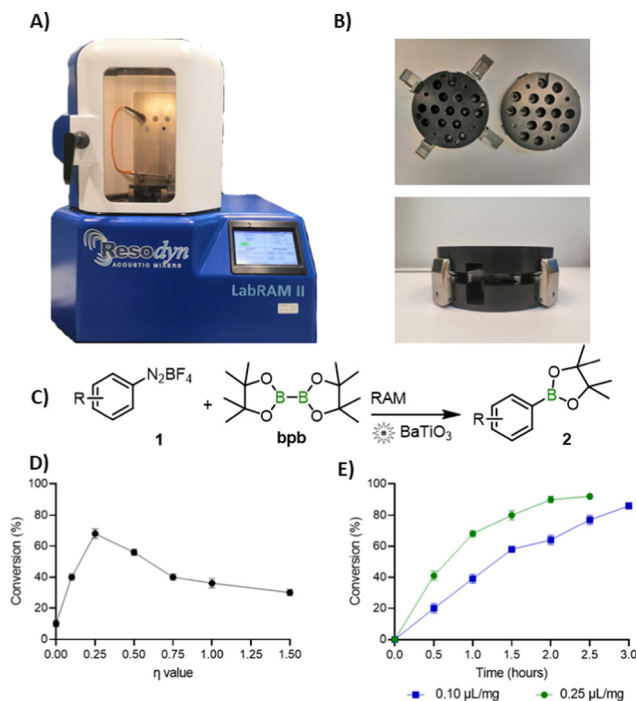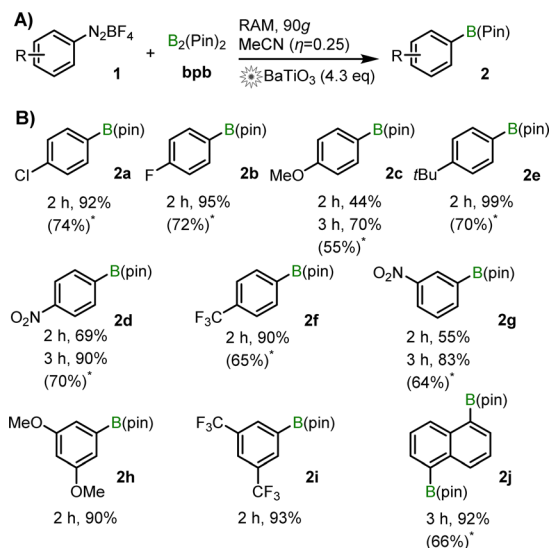
Fig. 1 (A) Resodyn LabRAM II instrument and (B) different views of the in-house designed RAM sample holder used in this work; (C) the mechanoredox diazonium borylation studied in this work; (D) η-dependent conversion for the borylation of p-chlorophenyldiazonium tetrafluoroborate (1a, R = p-Cl) with bpb after 1 hour RAM, and (E) time-dependent conversion for the reaction conducted at η = 0.10 and 0.25 µL mg^{-1}. All reactions were performed in triplicate, at 90g, using 0.3 mmol of 1a and 0.3 mmol of bpb in the presence of BaTiO$_3$ (300 mg, 4.3 eq. with respect to (1a) and MeCN liquid additive. The ^{1}H NMR yields were obtained upon dissolution of the crude product in DMSO-d$_6$.

Scheme 1 NMR yields of products 2a–2j bearing different substituents, with isolated yields in parentheses. Reaction conditions: 0.3 mmol 1a–1j, 0.3 mmol bpb (0.63 mmol for 1j), 1.29 mmol (4.3 equivalents) of BaTiO$_3$, MeCN (η = 0.25 µL mg^{-1}) at RAM acceleration of 90g for 2 or 3 h. *Isolated yields after column chromatography.

then levels off, which is noticeably shorter compared to 3 h reported for ball-milling (Fig. 1E). Attempts to further optimize the reaction through screening η-values between 0 and 1.5 µL mg^{-1} revealed maximum conversion (η_{max})[14] at η = 0.25 µL mg^{-1} (Fig. 1D). Conversion fell at lower accelerations, and at lower amounts of BaTiO$_3$. Consequently, all work was performed at 90g, using 4.3 equivalents of BaTiO$_3$ (see ESI†). The relevance of BaTiO$_3$ for the reaction was verified by conducting RAM with the same weight amount of Celite, sand, or NaCl. In each case, only trace of reaction was observed by ^{1}H NMR (below 5%).

The established RAM conditions were applicable to a range of aryldiazonium salts, with diverse positioning and nature of the aromatic ring substituent. In almost all cases, reactions proceeded with high ($>$80%) to excellent ($>$95%) yields within 2 h (Scheme 1). For substrates with unexceptional conversions after 2 h (e.g., 1c, 1d), the yield of product increased significantly upon extending the reaction time to 3 h, e.g., from 69% to 90% for 2d. For substrates 1a–1g, the NMR yields (70–99%) are significantly higher than reported by ball-milling (52–86%, see also ESI†).[4]

From the examples in Scheme 1, there is no clear trend between the electronic properties of arene and the yield of 2. For example, diazonium salts bearing two meta-substituents,
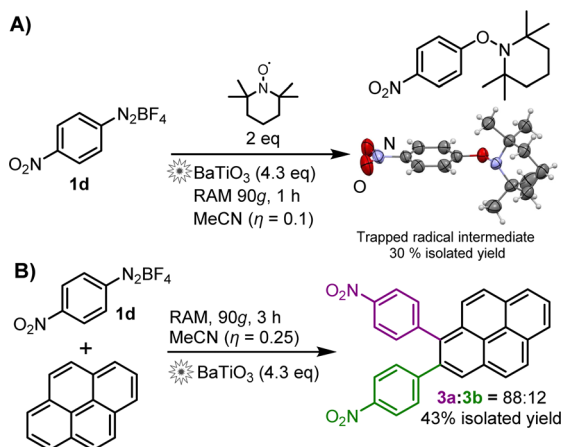
1h and 1i, both provide more than 90% NMR yields after 2 h of RAM, despite electronically very different groups (–OMe in 1h, –CF$_3$ in 2i). Overall, RAM-based mechanoredox catalysis provides access to a broad range of products with excellent yields, faster than previously reported for ball-milling. Efficiency of RAM opens access to ditopic substrates such as 1j, when using 2.1 equivalents of bpb. Here, 2j was obtained in 92% after 3 h, i.e., 96% yield per each pinacolato boron function (67% isolated yield).

We hypothesize that the RAM reaction mechanism is much the same as via ball-milling, i.e., follows a radical SET mechanism. This is supported by the reaction of 2d in the presence of BaTiO$_3$ and two equivalents of TEMPO radical scavenger (Scheme 2A). After 1 h, the expected[4] TEMPO-trapped radical intermediate was obtained in 30% yield, characterised by ^{1}H and ^{13}C NMR, as well as X-ray single-crystal diffraction.

Application of RAM to mechanoredox catalysis is not limited to borylation, as demonstrated by a successful pyrene arylation (Scheme 2B). RAM of pyrene and 1d proceeded readily over 3 h in the presence of MeCN (η = 0.25 µL mg^{-1}) and BaTiO$_3$ (4.3 equivalents) to produce a 88:12 mixture of 1- and 2-(4-nitrophenyl)pyrenes (3a, 3b) in 43% overall isolated yield.

Because BaTiO$_3$ is present in super-stoichiometric amounts, we also explored the possibility of re-using it. In a typical procedure, with 1a as the model reactant, RAM was conducted over 1 h, and BaTiO$_3$ was separated from the crude reaction mixture by extracting the organic materials with ethyl acetate (EtOAc), followed by centrifugation and drying, before being used in the next reaction cycle. Mass loss of BaTiO$_3$ between cycles ranged between 5 and 10%. Upon several such reactions, the yield of 2a per cycle steadily decreased, from 68% when using pristine BaTiO$_3$ to 11% after the fourth cycle (Table 1).

A)

B)

Scheme 2 (A) Radical-trapping reaction by RAM mechanoredox catalysis, using TEMPO as the radical scavenger. A molecule of the TEMPO-trapped reaction intermediate is shown using a thermal ellipsoid plot (50% probability) based on single crystal X-ray crystal structure analysis (CCDC deposition number 2205247†). (B) Pyrene arylation *via* BaTiO$_3$-catalysed RAM mechanoredox reaction; the **3a** : **3b** ratio was determined by ^{1}H-NMR spectroscopy in CDCl$_3$ solution.

Table 1 NMR yields of **2a** for 1 hour mechanoredox borylation of **1a** with **bpb** using recycled BaTiO$_3$, conducted by ball-milling or RAM^a

Cycle	Ball-milling NMR yield (%)	RAM NMR yield (%)
1	43	68
2	32	42
3	10	21
4	8	11

^{a} Reactions were performed for 1 h in the presence of MeCN as liquid additive (ball-milling at 30 Hz in a 10 mL zirconia jar and ball; RAM at 90g). ^{1}H NMR yields were obtained by dissolving the crude product in DMSO-d$_6$.

Loss of BaTiO$_3$ activity was also seen in ball-milling reactions (Table 1). A potential cause for the higher yields and improved retention of BaTiO$_3$ activity in RAM might be the gentler nature of acoustic mixing, evident from scanning electron microscopy (SEM) images of BaTiO$_3$ before and after reactions by RAM and by ball milling (Fig. 2A). Commercial BaTiO$_3$ was found to consist of spherical particles, tens of micrometers in size, that were significantly disrupted by ball-milling. By contrast, RAM led to little morphological change, but for a layer of finer material on the larger particles.

Further analysis of BaTiO$_3$ across multiple reaction cycles was carried out by powder X-ray diffraction (PXRD) and Fourier-transform infrared attenuated total reflectance spectroscopy (FTIR-ATR) (Fig. 2B and C, also ESI†).§[15] Analysis by PXRD revealed very little broadening of BaTiO$_3$ Bragg reflections after four runs under either RAM or ball-milling conditions, indicating that the loss of reactivity in either protocol is not due to crystal structure disruption. PXRD analysis of materials after the 3rd and 4th cycles revealed the appearance of new, low-intensity X-ray reflections distinct from those of BaTiO$_3$, suggesting the formation of a yet unidentified phase.

Surprisingly, FTIR-ATR spectra revealed the appearance of a new absorption band at 1050 cm^{-1} immediately after the first
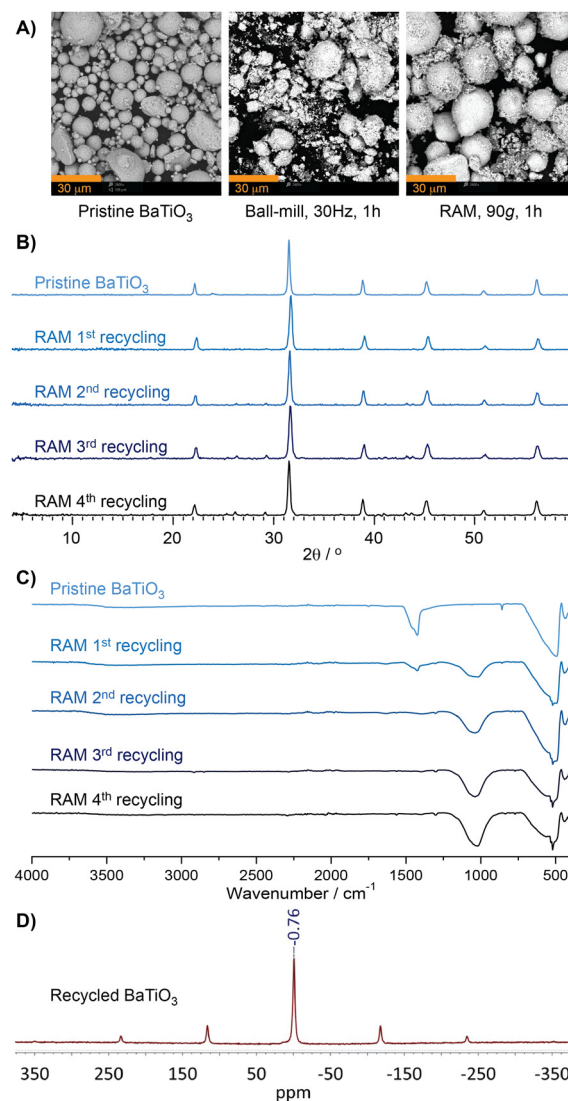
A)

Pristine BaTiO$_3$ Ball-mill, 30Hz, 1h   RAM, 90g, 1h

B)

C)

D)

Fig. 2 Investigation of recyclability of BaTiO$_3$ in mechanoredox catalysis by RAM and by ball-milling. (A) SEM images of BaTiO$_3$ particles: pristine, recycled from a ball-milling, and from a RAM process. (B) PXRD patterns for BaTiO$_3$ pristine and recycled from RAM reactions. (C) Comparison of FTIR-ATR spectra for BaTiO$_3$ pristine and recycled from RAM reactions. (D) ^{11}B ssNMR spectrum of BaTiO$_3$ recycled from a RAM mechanoredox reaction.

cycle. This new band, not seen for pristine BaTiO$_3$, is retained upon extensive washing with EtOAc, suggesting a strongly bound and/or inorganic species arising from the reaction mixture.

Moreover, thermogravimetric analysis (TGA) of recycled BaTiO$_3$, conducted in air up to 900 °C, did not reveal any loss of weight that would have been expected from adsorbed organic materials. Consequently, we speculate that the feature at 1050 cm^{-1} would be related to a boron species, as the infrared B–O and B–F stretching bands are found around 900–1100 cm^{-1}, depending on the chemical environment.[16] In order to verify the presence of boron, a washed sample of the BaTiO$_3$ after one cycle was analysed by ^{11}B solid-state NMR (ssNMR) spectroscopy, which revealed a signal centered at −0.76 pm with respect to F$_3$B·O(C$_2$H$_5$)$_2$ (Fig. 2D). The ^{11}B signal exhibited symmetry

consistent with a tetrahedral boron species, such as BO_4 or BF_4.[17] No boron signal was detected in pristine $BaTiO_3$ initially used for this reaction (see ESI†). $BaTiO_3$ analysis by X-ray photoelectron spectroscopy (XPS) was largely inconclusive due to the overlap of the B 1s and Ba $4p_{1/2}$ regions, but the growth of the peak around 193 eV suggests incorporation of boron (see ESI†).[18] Based on spectroscopy, we suggest that the loss of $BaTiO_3$ activity might be due to the incorporation and/or surface adsorption of boron species.¶[19]

Finally, we explored the potential to scale-up RAM-based mechanoredox reactions. Previous reports indicate that scaling-up RAM conditions can be simple and straightforward.[10] Here, the $BaTiO_3$-catalysed reaction between **1a** and **bpb** was immediately adapted from the initial scale of 150 mg reactants to 2 grams, while retaining the same relative amounts of $BaTiO_3$ and MeCN (see ESI†). Such linear scaling-up led to 80% conversion to **1b** within 2 h and >99% conversion after 3 h.

In summary, combining mechanoredox catalysis and RAM provides an attractive protocol that simultaneously avoids milling media, enables reactivity driven by the piezoelectric effect, and achieves excellent yields faster than a ball-milling process. While the effectiveness of $BaTiO_3$ as a catalyst drops upon repeated use, the loss of activity is smaller than under ball-milling. This loss appears to be due to inadvertent boration of $BaTiO_3$ by mechanochemical reaction components, which purports the need to develop more robust mechanoredox catalysts.

Conflicts of interest

There are no conflicts to declare.

Notes and references

‡ Diazonium salts should always be handled with care and reactions performed behind a glass shield.
§ The FTIR-ATR spectrum of pristine $BaTiO_3$ reveals a band at 1425 cm^{-1}, ascribed to small amounts of carbonate.[15] Upon mechanoredox catalysis, this band vanishes, and can also be removed by calcination in N_2 (see ESI†).

¶ Deactivation of $BaTiO_3$ by boron species would be consistent with a slower loss of catalyst activity reported for mechanoredox arylation reactions with furan.[4]

1 (a) S. L. James, C. J. Adams, C. Bolm, D. Braga, P. Collier, T. Friščić, F. Grepioni, K. D. M. Harris, G. Hyatt, W. Jones, A. Krebs, J. Mack, L. Maini, A. G. Orpen, I. P. Parkin, W. C. Shearouse, J. W. Steed and D. Waddell, *Chem. Soc. Rev.*, 2012, **41**, 413; (b) M. Pérez-Venegas and E. Juaristi, *ACS Sustainable Chem. Eng.*, 2020, **8**, 8881; (c) T. Friščić, C. Mottillo and H. M. Titi, *Angew. Chem., Int. Ed.*, 2020, **59**, 1018.
2 (a) O. Galant, G. Cerfeda, A. S. McCalmont, S. L. James, A. Porcheddu, F. Delogu, D. E. Crawford, E. Colacino and S. Spatari, *ACS Sustainable Chem. Eng.*, 2022, **10**, 1430; (b) K. J. Ardila-Fierro and J. G. Hernández, *ChemSusChem*, 2021, **14**, 2145; (c) F. Effaty, X. Ottenwaelder and T. Friščić, *Curr. Opin. Green Sustainable Chem.*, 2021, **32**, 100524; (d) W. Pickhardt, S. Grätz and L. Borchardt, *Chem. – Eur. J.*, 2020, **26**, 12903.
3 (a) J. G. Hernández and C. Bolm, *J. Org. Chem.*, 2017, **82**, 4007; (b) F. Cuccu, L. De Luca, F. Delogu, E. Colacino, N. Solin, R. Mocci and A. Porcheddu, *ChemSusChem*, 2022, **15**, e202100362; (c) R. F. Koby, T. P. Hanusa and N. D. Schley, *J. Am. Chem. Soc.*, 2018, **140**, 15934.
4 K. Kubota, Y. Pang, A. Miura and H. Ito, *Science*, 2019, **366**, 1500.
5 (a) Y. Pang, J. W. Lee, K. Kubota and H. Ito, *Angew. Chem., Int. Ed.*, 2020, **59**, 22570; (b) J. A. Leitch and D. L. Browne, *Chem. – Eur. J.*, 2021, **27**, 9721; (c) S. M. Zeitler, P. Chakma and M. R. Golder, *Chem. Sci.*, 2022, **13**, 4131; (d) C. Schumacher, J. G. Hernández and C. Bolm, *Angew. Chem., Int. Ed.*, 2020, **59**, 16357; (e) M. M. Amer, R. Hommelsheim, C. Schumacher, D. Kong and C. Bolm, *Faraday Discuss.*, 2022, DOI: 10.1039/D2FD00075J; (f) J. Jiang, S. Song, J. Guo, J. Zhou and J. Li, *Tetrahedron Lett.*, 2022, **98**, 153820; (g) Z. Ren, Y. Peng, H. He, C. Ding, J. Wang, Z. Wang and Z. Zhang, *Chin. J. Chem.*, 2023, **41**, 111; (h) K. Wang, C. Han, J. Li, J. Qiu, J. Sunarso and S. Liu, *Angew. Chem., Int. Ed.*, 2022, **61**, e202110429.
6 (a) D. Tan and F. García, *Chem. Soc. Rev.*, 2019, **48**, 2274; (b) T. Di Nardo and A. Moores, *Beilstein J. Org. Chem.*, 2019, **15**, 1217.
7 (a) A. Stolle, R. Schmidt and K. Jacob, *Faraday Discuss.*, 2014, **170**, 267; (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.
8 S. R. Anderson, D. J. Am Ende, J. S. Salan and P. Samuels, *Propellants, Explos., Pyrotech.*, 2014, **39**, 637.
9 (a) D. J. Am Ende, S. R. Anderson and J. S. Salan, *Org. Proc. Dev.*, 2014, **18**, 331; (b) K. Nagapudi, E. Y. Umanzor and C. Masui, *Int. J. Pharm.*, 2017, **521**, 337.
10 H. M. Titi, J.-L. Do, A. J. Howarth, K. Nagapudi and T. Friščić, *Chem. Sci.*, 2020, **11**, 7578.
11 L. Gonnet, C. B. Lennox, J.-L. Do, I. Malvestiti, S. G. Koenig, K. Nagapudi and T. Friščić, *Angew. Chem., Int. Ed.*, 2022, **61**, e202115030.
12 T. Friščić, S. L. Childs, S. A. A. Rizvi and W. Jones, *CrystEngComm*, 2009, **11**, 418.
13 P. A. Julien and T. Friščić, *Cryst. Growth Des.*, 2022, **22**, 5726.
14 L. Gonnet, T. H. Borchers, C. B. Lennox, J. Vainauskas, Y. Teoh, H. M. Titi, C. J. Barrett, S. G. Koenig, K. Nagapudi and T. Friščić, *Faraday Discuss.*, 2022, DOI: 10.1039/D2FD00131D.
15 M. Del Carmen, B. López, G. Fourlaris, B. Rand and F. L. Riley, *J. Am. Ceram. Soc.*, 1999, **82**, 1777.
16 D. Peak, G. W. Luther and D. L. Sparks, *Geochim. Cosmochim. Acta*, 2003, **67**, 2551.
17 K. J. D. MacKenzie and M. E. Smith, *Multinuclear solid-state NMR of inorganic materials*, Pergamon, Oxford, 2002.
18 B. R. Strohmeier, *Appl. Surf. Sci.*, 1989, **40**, 249.
19 (a) Y. Cao, P. Zhou, Y. Tu, Z. Liu, B. W. Dong, A. Azad, D. Ma, D. Wang, X. Zhang, Y. Yang, S. Da Jiang, R. Zhu, S. Guo, F. Mo and W. Ma, *iScience*, 2019, **20**, 195; (b) A. Sinhamahapatra, P. Pal, A. Tarafdar, H. C. Bajaj and A. B. Panda, *ChemCatChem*, 2013, **5**, 331.