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Direct mechanocatalysis by resonant acoustic mixing (RAM)†

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We demonstrate the use of a metal surface to directly catalyse copper-catalysed alkyne–azide click-coupling (CuAAC) reactions under the conditions of Resonant Acoustic Mixing (RAM) – a recently introduced and scalable mechanochemical methodology that uniquely eliminates the need for bulk solvent, as well as milling media. By using a simple copper coil as a catalyst, this work shows that direct mechanocatalysis can occur in an impact-free environment, relying solely on high-speed mixing of reagents against a metal surface, without the need for specially designed milling containers and media. By introducing an experimental setup that enables real-time Raman spectroscopy monitoring of RAM processes, we demonstrate 0th-order reaction kinetics for several selected CuAAC reactions, supporting surface-based catalysis. The herein presented RAM-based direct mechanocatalysis methodology is simple, enables the effective one-pot, two-step synthesis of triazoles *via* a combination of benzyl azide formation and CuAAC reactions on a wide scope of reagents, provides control over reaction stoichiometry that is herein shown to be superior to that seen in solution or by using more conventional CuCl catalyst, and is applied for simple gram-scale synthesis of the anticonvulsant drug Rufinamide.

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Mechanochemistry is a versatile synthetic approach which^{1–4} avoids the need for bulk solvents, making it intrinsically more green and environmentally-friendly,^{5,6} and can offer access to reactions and products otherwise difficult to achieve.^{7,8} While mechanochemistry traditionally relies on impact and mixing resulting from the use of balls or screws, Resonant Acoustic Mixing (RAM, Fig. 1a–c)^{9,10} has recently emerged as a strategy to conduct mechanochemical reactions without such milling or crushing media. Instead, RAM achieves reactivity by shaking materials at a low acoustic frequency (*e.g.*, 60 Hz), with energy input modulated through changes in the vertical acceleration of the reaction vessel (0–100 g, where $g = 9.81 \text{ m s}^{-2}$). By avoiding the need for milling media, RAM enables simplification of reaction design, avoids product contamination resulting from chipping and abrasion, and facilitates scale-up. So far, RAM has been shown to enable a simple, efficient, and rapid approach to metal–organic frameworks, cocrystals, mechano-redox catalysis, as well as several metal-catalyzed transformations.¹¹

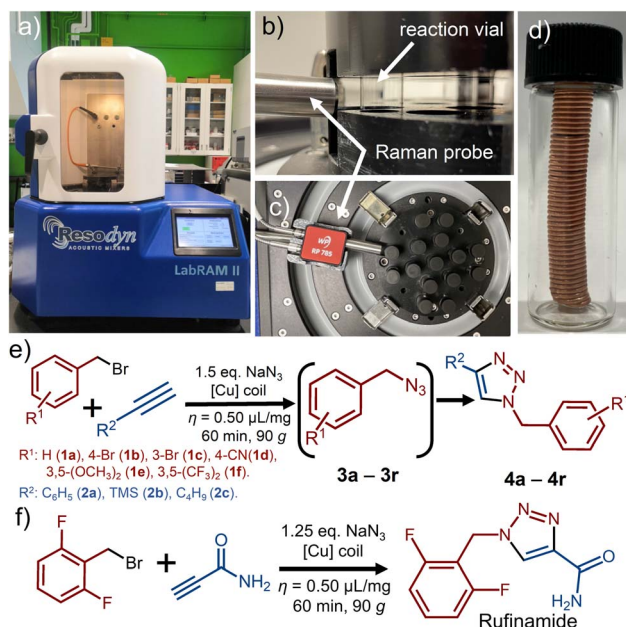


Fig. 1 (a) The LabRAM II instrument used in this work; (b) side-view of the custom-made LabRAM II sample holder with a cut-out to accommodate the Raman probe spectroscopy and (c) top-view of the holder enabling the use of commercial sample vials as reaction vessels, and (d) a typical copper coil used for direct mechanocatalysis by RAM. Reaction scheme for herein developed: (e) model RAM direct mechanocatalysis reactions and (f) RAM direct mechanocatalysis reaction leading to the API Rufinamide. The η -value is the ratio of liquid additive volume (μL) and weight of reagents (mg).

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An exciting emergent opportunity in ball-milling mechanochemistry is direct mechanocatalysis, where components of the milling assembly itself (*e.g.*, balls and/or vessel walls) acts as the metal catalyst.^{12–17} This methodology, pioneered by the Mack and Borchardt groups, has so far been applied to several copper-, palladium-, silver- or nickel-based transformations.^{8b,12,15,18–20} The key advantages of direct mechanocatalysis are straightforward introduction, removal, and reusability of metal catalyst, as well as simplicity of product recovery, but the methodology is challenged by the need to manufacture specialised ball-milling equipment.

As direct mechanocatalysis involves dynamic contact between the reaction mixture and a metal, we speculated it should be compatible with RAM, potentially offering an even simpler, more efficient synthesis by bringing into contact the reaction mixture and a metal surface, without the need to design specialised equipment or generate impact by using milling media.

Here, we provide a proof-of-principle demonstration of direct mechanocatalysis by RAM, focusing on the copper-catalyzed alkyne–azide click-coupling (CuAAC) as a model reaction. RAM enabled a surprisingly uncomplicated approach to direct mechanocatalysis, replacing custom-made milling equipment with simple copper wire. This straightforward reaction platform allowed fast (≤ 60 minutes) direct mechanocatalysis, without copper-based milling media or vessels ubiquitous in previous examples of copper-based direct mechanocatalysis. While the herein developed process is applicable to a range of solid or liquid benzyl bromide and alkyne reactants, we also show that it permits selective mono- or bis-derivatization, as well as desymmetrization of a symmetrical dialkyne reactant, and is readily scalable to at least one gram, as demonstrated in the RAM synthesis of the anticonvulsant API Rufinamide.

As the model reaction we used the one-pot, two-step reaction of benzyl bromide (**1a**) and phenylacetylene (**2a**) in the presence of 1.5 equivalents (50% excess) of NaN_3 . The reaction is expected to proceed *via* the intermediate benzyl azide (**3a**) to form the click coupling product **4a** (Fig. 1e). As the catalyst, we used a piece of copper wire of 0.9 mm diameter (#20-gauge), wound into a coil of 45 mm \times 10 mm dimensions. The coil was wedged between the vial cap and the bottom of the vial, preventing it from moving during mixing. The reaction was conducted by RAM in the presence of a liquid additive, with the ratio of the volume of liquid additive to the weight of reaction mixture $\eta = 0.50 \mu\text{L mg}^{-1}$. As the liquid additive, we explored dimethylsulfoxide (DMSO), water, methanol (MeOH), and a 1 : 1 by volume mixture of water and DMSO, among which DMSO alone was found to be the most effective. While the initial attempt of reaction gave **4a** in conversion below $4 \pm 3\%$ after 60 minutes (Table 1, Entry 2), subsequent attempts using the same copper coil gave **4a** quantitatively within 60 minutes (Fig. 2a, Table 1, Entry 3, also ESI†).

Similar behaviour was observed when the reaction was conducted using 20 minute cycles: improvement in reactivity was seen only after the third cycle (Fig. 2a, also ESI†). Overall, these observations indicate an induction period of *ca.*

60 minutes, after which the copper coil becomes a highly effective catalyst.¹² For comparison, the analogous one-pot reaction using either CuCl or copper(II) acetate monohydrate as the catalyst (3 mol% relative to **1a**) gave no more than 30% conversion after 60 minutes of RAM (Table 1, Entries 4 and 5, and ESI†). Using either MeOH or water as a liquid additive led to maximum conversions of *ca.* 80% and 30% at η -value of $0.50 \mu\text{L mg}^{-1}$, respectively, while the mixture of water and DMSO led to conversions below 10% in all cases (see ESI†).

Using a piece of uncoiled copper wire (45 mm length, diameter 0.9 mm, #20-gauge) gave significantly lower conversion to **4a** ($24 \pm 4\%$), indicating the importance of metal surface. We also explored the potential effect of atmosphere on this direct RAM mechanocatalysis procedure, revealing only $13 \pm 4\%$ conversion under an argon atmosphere after 60 minutes, while conducting the same reaction in an O_2 atmosphere led to complete conversion to **4a**. No product arising from a Glaser-type homocoupling was ever observed. X-ray photoelectron spectroscopy (XPS) on a copper coil before and immediately after a 60 minute RAM reaction revealed the appearance Cu(I) after RAM, which upon exposure to air further oxidized to Cu(II). We conclude that the process of activating the copper coil is related to the formation of Cu(I) species on the surface, which requires the presence of oxygen (see ESI†).

Next, we investigated the possibility to deliberately activate the copper coil through different treatments (Table 1, Entries 6–12). Considering that cleaning the metal surface might play a role, we investigated RAM in the presence of abrasive Celite, which did not improve reactivity in the first cycle. Using SiO_2 as the additive, however, led to $36 \pm 2\%$ conversion. We also explored the effect of soaking a fresh copper coil in **2a** for 24 h before use, with little improvement on reactivity. However, soaking in **2a** in a coil that had previously been treated with SiO_2 led to quantitative conversion. Indeed, quantitative conversion to **4a** was achieved by RAM within 60 minutes, by using a coil that has been primed by RAM in the presence of SiO_2 and **2a** for 60 minutes at 90 g. This priming procedure resulted in a Cu(I)-containing surface, as observed by XPS, suggesting that the induction period involves a surface-cleaning process and oxidation to an activated, likely copper(I)-acetylide, layer. Importantly, if the copper coil is stored in an inert Ar atmosphere immediately after activation, it remains catalytically active for at least two weeks. However, if stored in air, the coil loses catalytic activity within 24 hours and needs to be re-activated. This also indicates that coil activation involves the formation of surface Cu(I) species.

To investigate whether coil activation and reaction conversion might be related to leaching of copper from the coil, the conversion to **4a** and any changes to the weight of the coil were measured over a set of 10 sequential 60 minutes reaction cycles. The analysis was performed for four separate copper coils, amounting to a total of 40 experiments, which revealed an average copper loss of $0.9 \text{ mol} \pm 0.3\%$ (relative to **2a**) in each reaction cycle (Fig. 2a, also ESI†). For each of the four coils, we also verified the amount of copper leached in the third cycle by inductively coupled plasma mass spectrometry (ICP-MS), revealing a loss of 0.81 mol%, consistent with the value



Table 1 Conversions for the RAM reaction between **1a**, **2a** and NaN_3^a

Entry	Copper source	Copper treatment	Conversion ^b (%)
1	—	n/a	0
2	Cu coil	n/a	4 ± 3
3	Cu coil	1a , 2a , NaN_3^a	>95
4	CuCl^c	n/a	31 ± 4
5	$\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}^c$	n/a	26 ± 6
6	Cu coil	Celite	6 ± 1
7	Cu coil	SiO_2^d	36 ± 2
8	Cu coil	2a ^e	14 ± 6
9	Cu coil	SiO_2^d followed by 2a ^e	>95
10	Cu coil	2a and SiO_2^f	>95
11	Cu coil	125 °C for 24 h	34 ± 2
12	Cu coil	CH_3COOH^e followed by 125 °C for 24 h	68 ± 1
13	Cu coil	1a , 2a , $\text{NaN}_3^{a,g}$	>95 ^g

^a Reactions conducted by RAM of equimolar (2 mmol) amounts of **1a** and **2a** with 1.5 equivalents of NaN_3 , and DMSO ($\eta = 0.50 \mu\text{L mg}^{-1}$) at 90 g for 60 minutes. ^b Based on triplicate experiments and ¹H NMR analysis following dissolution of the entire reaction mixture in CDCl_3 . ^c RAM of equimolar amounts of **1a** and **2a** with 1.5 equivalents of NaN_3 , 3 mol% (relative to **1a**) copper salt, with DMSO ($\eta = 0.50 \mu\text{L mg}^{-1}$) at 90 g for 60 minutes. ^d 300 mg of solid with DMSO ($\eta = 0.50 \mu\text{L mg}^{-1}$). ^e Coil soaked for 24 h in 2 mL alkyne **2a** in a sealed vial at room temperature. ^f RAM of 300 mg SiO_2 , 256 μL **2a**, and DMSO ($\eta = 0.50 \mu\text{L mg}^{-1}$) at 90 g for 60 minutes, followed by washing with EtOAc. ^g Reaction performed at a three times larger scale: 6 mmol of **1a** and **2a** each and 9 mmol of NaN_3 , with DMSO ($\eta = 0.50 \mu\text{L mg}^{-1}$) at 90 g for 60 minutes.

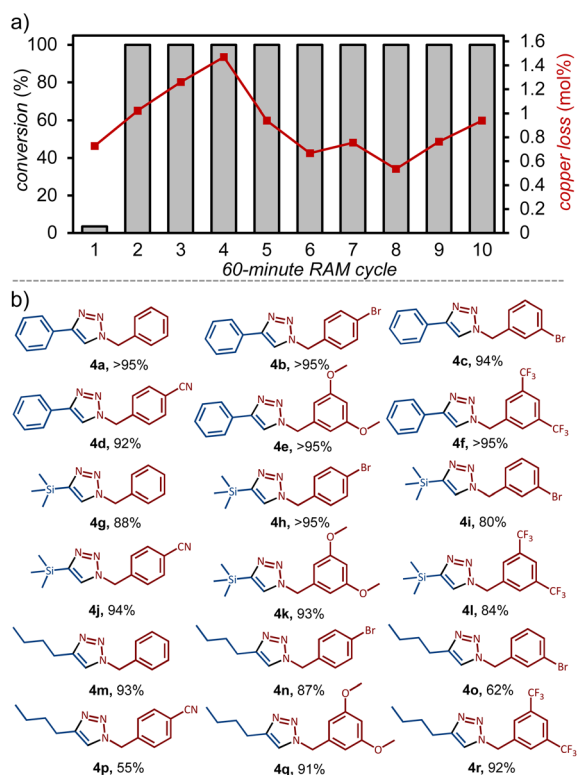


Fig. 2 (a) Conversion to **4a** compared to copper loss from the coil (in mol% with respect to **2a**) for 10 consecutive 60 minutes RAM cycles conducted using the same copper coil, based on quadruplicate measurements. (b) Substrate scope for herein developed RAM click-coupling reaction, with isolated yields indicated.

obtained by weighing. No correlation was observed between the amount of copper leached and reaction conversion after each reaction cycle – after the first cycle, all reactions exhibited quantitative conversion (Fig. 2a). As using 3 mol% of CuCl as

the catalyst led to only *ca.* 30% conversion to **4a**, we conclude that a significant amount of catalysis must be occurring on the metal coil surface (Table 1, Entries 3–5, also ESI†).²¹

Moreover, we have conducted the catalytic synthesis of **4a** using a three-fold increase of starting materials (Table 1, Entry 13). Under these conditions, the amount of copper lost from the coil averaged to 0.95 ± 0.3 mg across four experiments, *i.e.* the amount of copper lost from the coil was now only 0.25 ± 0.08 mol% with respect to the alkyne reactant, while the conversion remained at quantitative level. These observations are consistent with the entire copper coil being exposed to the sample throughout the RAM process, and also support the view that the majority, if not all, of catalysis is taking place on the metal surface and not *via* copper lost by abrasion.

With reaction conditions for direct mechanocatalysis by RAM in hand, we extended the method to a range of liquid and solid alkyl bromides **1a–1f** and alkynes: phenylacetylene (**2a**), trimethylsilylacetylene (**2b**), and 1-hexyne (**2c**). With few exceptions, the expected cycloaddition products **4a–4r** (Fig. 2b) were obtained after workup in near-quantitative conversions and >90% isolated yields, following RAM of an equimolar (2 mmol) amount of alkyl bromide and alkyne, with 1.5 equivalents NaN_3 in the presence of a copper coil and DMSO liquid additive ($\eta = 0.50 \mu\text{L mg}^{-1}$). The workup consisted of adding 2 mL of ethyl acetate (EtOAc) to the reaction vial, followed by RAM for an additional 5 minutes, and filtration to remove excess NaN_3 and the byproduct NaBr . The cycloaddition product was then precipitated by adding 3 mL of a water:MeOH mixture (1 : 2 v/v), followed by another 5 minutes of RAM and filtration to yield white or yellow solids. For **4g–4l**, work-up involved washing with a mixture of concentrated aqueous solution of NH_4Cl and EtOAc (1 : 2 v/v), before evaporation *in vacuo* to yield a yellow solid or oil.[‡]

To verify that the reaction was indeed taking place by RAM rather than during subsequent analysis, the synthesis of **4a** was



interrupted after 20 minutes, and immediately accessed by ^1H -NMR in CDCl_3 which revealed *ca.* 25% conversion, and then again 24 hours later, revealing no change in conversion. The products were characterised by ^1H -, ^{13}C -NMR, FTIR spectroscopy, and HR-MS, and **4e** was additionally characterized by single crystal X-ray diffraction, confirming that [2 + 3] cycloaddition took place (see ESI†). Investigation of selected samples by scanning electron microscopy (SEM) revealed that crude materials from RAM synthesis were composed of well-developed micrometre-sized crystals (see ESI†).

Noting that the RAM platform should be highly amenable to *in situ* monitoring,²² we devised a setup for real-time reaction monitoring using Raman spectroscopy, previously not described in the context of RAM mechanochemistry (see ESI†). Specifically, real-time reaction monitoring was done using a RamanRxn1™ analyser by Kaiser Optical Systems Inc., equipped with a power tuneable 1–400 mW 785 nm Raman probe. Spectra were recorded with an integration time of 5–10 seconds and 3–5 accumulations to optimise the signal-to-noise ratio. All spectra were dark and intensity corrected using the Holograms® software package before being processed with MATLAB. In a typical monitoring experiment, a 1-dram volume glass vial was placed in the custom-made sample holder containing an entrance slit (Fig. 1b, also ESI†). The 785 nm Raman probe was then placed approximately 10 mm from the vial, with the focus on the vial centre (see ESI†). Using this monitoring setup enabled us to observe linear kinetics for the formation of **4a** (Fig. 3a–c).

Accuracy of the method was validated by *ex situ* monitoring of the reaction progress by ^1H NMR in separate experiments, which also showed a linear profile (Fig. 3d). A linear kinetic profile was also observed for the coupling of **2a** with the solid reactant 3,5-dimethoxybenzyl bromide (**1e**) to give the triazole **4e** (see ESI†). Overall, the experimentally observed linear kinetic

profiles indicate 0th-order reaction kinetics, consistent with surface catalysis.

Mechanochemical reactions by ball milling have previously been shown to permit excellent control of reaction stoichiometry, enabling selective functionalization of substrates bearing multiple reaction sites.²³ In order to investigate if such selectivity is accessible in RAM, we explored the reactivity of the symmetrical dialkyne *p*-diethynylbenzene (**2d**) (Fig. 4a). Real-time Raman spectroscopy monitoring revealed that the reaction selectivity is strongly affected by η , even independent of reaction stoichiometry. Specifically, following the reaction of **2d** and **1a** in a 1 : 2 respective stoichiometric ratio in the presence of DMSO ($\eta = 0.50 \mu\text{L mg}^{-1}$) revealed almost complete conversion into the non-symmetrical **4s** within 60 minutes. After 4 hours, only a small amount of the symmetrical **4t** was observed. At $\eta = 1.0 \mu\text{L mg}^{-1}$, however, the reaction rapidly proceeds further and **4s** only appears as a reaction intermediate, quantitatively yielding **4t** after 2 hours (Fig. 4b and c).¹⁴ The ability to selectively obtain either **4s** or **4t** by RAM contrasts with reactivity observed in solution: performing the same reaction under dilute conditions (10 mol% CuCl , 25 mL DMSO) produced after 24 hours only **4t**, in 28% conversion.

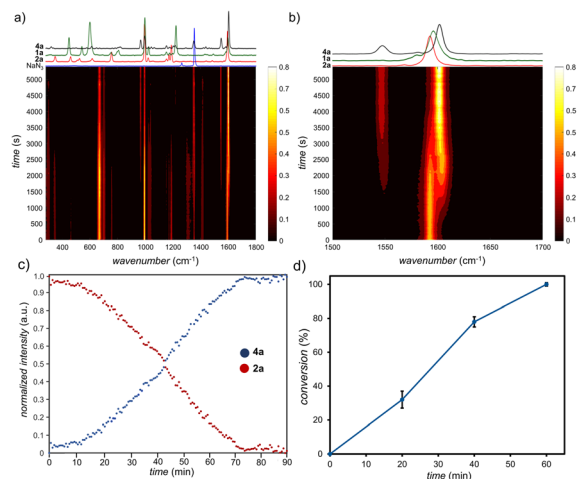


Fig. 3 Time-resolved Raman spectra for *in situ* monitoring of the formation of **4a** by RAM direct mechanocatalysis: (a) the entire spectral range and (b) close-up of the 1500–1700 cm^{-1} range, demonstrating the disappearance of **1a** and **2a**, and the formation of **4a**. (c) Time-resolved changes in intensity of Raman bands corresponding to a decrease of **2a** (red) and formation of **4a** (blue); (d) *ex situ* reaction profile measured by ^1H -NMR analysis upon dissolution of the entire reaction mixture in CDCl_3 .

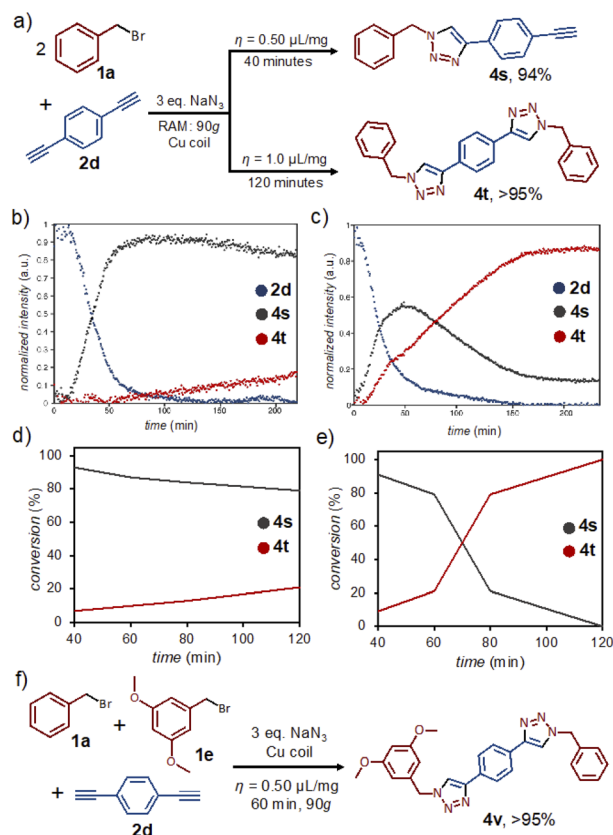


Fig. 4 (a) Reaction of **1a** and **2d** to form non-symmetrical (**4s**) and symmetrical (**4t**) products. *In situ* Raman data for reactions with: (b) $\eta = 0.50 \mu\text{L mg}^{-1}$, and (c) $\eta = 1.0 \mu\text{L mg}^{-1}$, showing conversion to **4s** (black line) or **4t** (red line). NMR monitored conversion accessed over time for reactions with: (d) $\eta = 0.50 \mu\text{L mg}^{-1}$, (e) $\eta = 1.0 \mu\text{L mg}^{-1}$. (f) Desymmetrization reaction with **1a**, **1e** and **2d**, revealing quantitative conversion to **4v** within 60 minutes with DMSO liquid additive ($\eta = 0.50 \mu\text{L mg}^{-1}$).



The observations made by *in situ* Raman monitoring were also confirmed by ^1H NMR analysis of the entire reaction mixture, which revealed selective formation of **4s** at $\eta = 0.50 \mu\text{L mg}^{-1}$ within 40 minutes, and switching of the selectivity to **4t** at $\eta = 1.0 \mu\text{L mg}^{-1}$ within 2 hours (Fig. 4d, e). The formation of **4s** and **4t** was verified by ^1H - and ^{13}C -NMR, FTIR spectroscopy and HR-MS (see ESI†). The reaction kinetics based on ^1H -NMR analysis of reaction mixtures in separate experiments was similar, but not identical to that based on Raman monitoring, most likely because the latter is limited to only a small fraction of the sample surface. The selectivity for the non-symmetrical **4s** at lower η -values might be related to poorer mixing in the presence of NaBr byproduct. This view was supported by two separate experiments. First, the introduction of one equivalent of NaBr to a mixture of **1a** and **2a** was found to prevent the normally high-yielding formation of **4a** within 60 minutes. Second, complete conversion to the di-substituted **4t** is readily achieved within 60 minutes of RAM if previously isolated **4s** is used as the reactant in combination with one equivalent of **1a**.

A similar stepwise process was also observed for the solid reactant **1e**, as established by ^1H -NMR analysis. The reaction of the dialkyne **2d** with **1e** was much faster, however, leading to complete conversion to the disubstituted product **4u** at $\eta = 0.50 \mu\text{L mg}^{-1}$ in 60 minutes (see ESI†).

The ability to achieve desymmetrisation of the dialkyne **2d**, and the notably higher reactivity observed for **1e** compared to **1a** under RAM conditions, led us to explore the one-pot synthesis of a non-symmetrical target bis(triazole) **4v** (Fig. 4f) directly from equimolar amounts of **1a**, **1e**, and the dialkyne **2d**. After 60 minutes of RAM with a copper coil, 3 equivalents of NaN_3 and DMSO liquid additive ($\eta = 0.50 \mu\text{L mg}^{-1}$), the reaction selectively and quantitatively gave targeted **4v**, as confirmed by ^1H - and ^{13}C -NMR, ^1H - ^1H COSY-NMR, FTIR spectroscopy and HR-MS (see ESI†). The selectivity of this process is remarkable, as the analogous solution reaction using CuCl as catalyst (10 mol%, 25 mL DMSO) gave a mixture of **4s** (25%), **4t** (18%), **4u** (21%), **4v** (19%), along with the mono-triazole product (16%) arising from a 1 : 1 reaction of **1a** and **1e** after 24 hours. Moreover, the high selectivity appears to be associated to using the copper coil as the catalyst, as the RAM reaction using CuCl catalyst (10 mol%) also led to a mixture of products **4s** (62%), **4t** (2%), **4u** (23%) and **4v** (5%) after 60 minutes. We speculate that selectivity of direct mechanocatalysis for **4v** might be related to adsorption of the reactant **2d** on the coil surface, and continue to investigate this effect.

Finally, to evaluate the applicability of RAM direct mechanocatalysis for the synthesis of a functional molecule, we targeted Rufinamide, an anti-epileptic triazole-containing API. The RAM reaction of equimolar amounts of 2,5-difluorobenzyl bromide and propiolamide with DMSO ($\eta = 0.50 \mu\text{L mg}^{-1}$), 1.5 equivalents of NaN_3 and a copper coil, gave Rufinamide in 88% isolated yield after 60 minutes at 90 g, as confirmed by ^1H - and ^{13}C -NMR, FTIR spectroscopy and HR-MS (see ESI†). The reaction was readily scalable at least 5-fold, to provide 1.2 grams of Rufinamide within 1 hour. This creates an alternative synthetic route to the high temperatures, long reaction times, and multi-step processes currently used in solution.²⁴

Conclusions

In summary, we have provided the first proof-of-principle for direct mechanocatalysis by resonant acoustic mixing. This work shows that RAM enables using a simple copper coil as the catalyst for rapid, simple, and high-yielding direct-mechanocatalytic copper-catalyzed alkyne-azide coupling on a wide range of substrates, enabling also the simple and gram-scale synthesis of the API Rufinamide. Direct mechanocatalysis by RAM also enabled stoichiometric selectivity greatly superior to that seen when using a more conventional CuCl catalyst, either in solution or under ball-milling conditions, enabling the high-yielding, rapid and one-pot synthesis of non-symmetrical products from an initially symmetrical dialkyne reactant. Herein introduced technique for real-time Raman spectroscopy monitoring, validated by stepwise ^1H NMR spectroscopy analysis, reveals that reactions follow a 0th-order kinetic profile consistent with surface catalysis. Overall, this work shows that direct mechanocatalysis can occur in a mild, impact-free environment, relying solely on high-speed mixing of reagents against a copper surface. This offers a basis for the further simplification and development of highly selective mechanochemical surface-catalysed synthesis using the so far poorly explored but readily scalable RAM platform. More broadly, reactions involving raw metals either as catalysts or reactants are emerging as a particularly interesting area of mechanochemistry, and the herein presented work opens an exciting new entry to such developments, based on the RAM technology.²⁵

Data availability

Details of experimental procedures, and selected NMR, FTIR spectroscopy, HR-MS, ICP-MS, SEM, XPS, and single crystal X-ray diffraction data are provided in the ESI.†

Author contributions

All authors have contributed to the writing of this manuscript. Development of mechanochemical synthesis procedure and characterization was performed by CBL and LG, *in situ* Raman spectroscopy monitoring was done by CBL and THB. The research was organized and coordinated by SGK, KN, and TF.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

‡ Workup was developed to minimise overall solvent consumption, with aqueous MeOH serving to hydrolyze any remaining benzyl bromide or benzyl azide reactant.

- (a) J. Andersen and J. Mack, *Green Chem.*, 2018, **20**, 1435–1443; (b) J. L. Howard, Q. Cao and D. L. Browne, *Chem. Sci.*, 2018, **9**, 3080–3094; (c) W. Pickhardt, S. Grätz and L. Borchardt, *Chem.–Eur. J.*, 2020, **26**, 12903–12911; (d) O. Maurin, P. Verdié, G. Subra, F. Lamaty, J. Martinez and T.-X. Métro, *Beilstein J. Org. Chem.*, 2017, **13**, 2087–2093; (e) T. Friščić, C. Mottillo and H. M. Titi, *Angew. Chem., Int. Ed.*, 2020, **59**, 1018–1029.
- (a) D. Tan and F. García, *Chem. Soc. Rev.*, 2019, **48**, 2274–2292; (b) N. R. Rightmire and T. P. Hanusa, *Dalton Trans.*, 2016, **45**, 2352–2362.
- (a) C. Bolm and J. G. Hernández, *Angew. Chem., Int. Ed.*, 2019, **58**, 3285–3299; (b) P. A. Julien, C. Mottillo and T. Friščić, *Green Chem.*, 2017, **19**, 2729–2747.
- (a) P. Baláž, M. Achamovičová, M. Baláž, P. Billik, Z. Cherkezova-Zheleva, J. M. Criado, F. Delogu, E. Dutková, E. Gaffet, F. J. Gotor, R. Kumar, I. Mitov, T. Rojac, M. Senna, A. Streletskii and K. Wiczorek-Ciurawa, *Chem. Soc. Rev.*, 2013, **42**, 7571–7637; (b) A. A. L. Michalchuk, E. V. Boldyreva, A. M. Belenguer, F. Emmerling and V. V. Boldyrev, *Front. Chem.*, 2021, **9**, 685789.
- (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**, 413–447; (b) E. Boldyreva, *Chem. Soc. Rev.*, 2013, **42**, 7719–7738; (c) A. Bose and P. Mal, *Beilstein J. Org. Chem.*, 2019, **15**, 881–900; (d) R. T. O'Neill and R. Boulatov, *Nat. Rev. Chem.*, 2021, **5**, 148–167; (e) D. E. Crawford, C. K. G. Miskimmin, A. B. Albadarin, G. Walker and S. L. James, *Green Chem.*, 2017, **19**, 1507–1518.
- (a) D. Tan, L. Loots and T. Friščić, *Chem. Commun.*, 2016, **52**, 7760–7781; (b) E. Colacino, A. Porcheddu, C. Charnay and F. Delogu, *React. Chem. Eng.*, 2019, **4**, 1179.
- (a) J. G. Hernández and C. Bolm, *J. Org. Chem.*, 2017, **82**, 4007–4019; (b) K. Kubota, R. Takahashi and H. Ito, *Chem. Sci.*, 2019, **10**, 5837–5842.
- (a) R. F. Koby, T. P. Hanusa and N. D. Schley, *J. Am. Chem. Soc.*, 2018, **140**, 15934–15942; (b) R. A. Haley, A. R. Zellner, J. A. Krause, H. Guan and J. Mack, *ACS Sustainable Chem. Eng.*, 2016, **4**, 2464–2469; (c) F. Cuccu, L. DeLuca, F. Delogu, E. Colacino, N. Solin, R. Mocchi and A. Porcheddu, *ChemSusChem*, 2022, **15**, e202200362.
- (a) J. G. Osorio, E. Hernández, R. J. Romañach and F. J. Muzzio, *Powder Technol.*, 2016, **297**, 349–356; (b) A. Vandenberg and K. Wille, *Constr. Build. Mater.*, 2018, **164**, 716–730; (c) D. H. Leung, D. J. Lamberto, L. Liu, E. Kwong, T. Nelson, T. Rhodes and A. Bak, *Int. J. Pharm.*, 2014, **473**, 10–19.
- (a) C. J. Wright, P. J. Wilkinson, S. E. Gaultier, D. Fossey, A. O. Burn and P. P. Gill, *Propellants, Explos., Pyrotech.*, 2021, **46**, 1–15; (b) M. Solares-Briones, G. Coyote-Dotor, J. C. Páez-Franco, M. R. Zermeño-Ortega, C. M. de le O Contreras, D. Canseco-González, A. Avila-Sorrosa, D. Morales-Morales and J. M. Germán-Acacio, *Pharmaceutics*, 2021, **13**, 790.
- (a) 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; (b) 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.*, 2023, **241**, 128–149; (c) H. M. Titi, J.-L. Do, A. J. Howarth, K. Nagapudi and T. Friščić, *Chem. Sci.*, 2020, **11**, 7578–7584; (d) K. Nagapudi, E. Y. Umazor and C. Masui, *Int. J. Pharm.*, 2017, **521**, 337–345; (e) F. Effaty, L. Gonnet, S. G. Koenig, K. Nagapudi, X. Ottenwaelder and T. Friščić, *Chem. Commun.*, 2023, **59**, 1010–1013.
- A similar induction period was seen for direct mechanocatalysis by ball-milling: (a) W. Su, J. Yu, Z. Li and Z. Jiang, *J. Org. Chem.*, 2011, **76**, 9144–9150; (b) L. Chen, D. Leslie, M. G. Coleman and J. Mack, *Chem. Sci.*, 2018, **9**, 4650–4661; (c) T. L. Cook, J. A. Walker and J. Mack, *Green Chem.*, 2013, **15**, 617; (d) C. G. Vogt, S. Grätz, S. Lukin, I. Halasz, M. Etter, J. D. Evans and L. Borchardt, *Angew. Chem., Int. Ed.*, 2019, **58**, 18942–18947.
- Y. Zhao, S. V. Rocha and T. M. Swager, *J. Am. Chem. Soc.*, 2016, **138**, 13834–13837.
- Appearance of a mono-substituted intermediate in the mechanochemical click reaction of a di-alkyne was previously observed for the ball-milling reaction of 2d with decyl azide, see: R. Thorwirth, A. Stolle, B. Ondruschka, A. Wild and U. S. Schubert, *Chem. Commun.*, 2011, **47**, 4370–4372.
- (a) D. A. Fulmer, W. C. Shearouse, S. T. Medonza and J. Mack, *Green Chem.*, 2009, **11**, 1821–1825; (b) S. Hwang, S. Grätz and L. Borchardt, *Chem. Commun.*, 2022, **58**, 1661–1671; (c) R. A. Haley, J. Mack and H. Guan, *Inorg. Chem. Front.*, 2017, **4**, 52–55; (d) M. Wolgemuth, M. Mayer, M. Rappen, F. Schmidt, R. Saure, S. Grätz and L. Borchardt, *Angew. Chem., Int. Ed.*, 2022, **61**, e202212694.
- S. Jung and H. J. Yoon, *Angew. Chem., Int. Ed.*, 2021, **59**, 4883–4887.
- (a) W. Pickhardt, S. Grätz and L. Borchardt, *Chem.–Eur. J.*, 2020, **26**, 12903–12911; (b) L. Chen, M. O. Bovee, B. E. Lemma, K. S. M. Keithley, S. L. Pilsen, M. G. Coleman and J. Mack, *Angew. Chem., Int. Ed.*, 2015, **54**, 11084–11087.
- (a) W. Su, J. Yu, Z. Li and Z. Jiang, *J. Org. Chem.*, 2011, **76**, 9144–9150; (b) C. G. Vogt, S. Grätz, S. Lukin, I. Halasz, M. Etter, J. D. Evans and L. Borchardt, *Angew. Chem., Int. Ed.*, 2019, **58**, 18942–18947.
- (a) Y. Sawama, N. Yasukawa, K. Ban, R. Goto, M. Niikawa, Y. Monguchi, M. Itoh and H. Sakiji, *Org. Lett.*, 2018, **20**, 2892–2896; (b) Y. Sawama, M. Niikawa and H. Sajiki, *J. Synth. Org. Chem., Jpn.*, 2019, **77**, 1070–1077.
- C. G. Vogt, M. Oltermann, W. Pickhardt and S. Grätz, *Adv. Energy Sustainability Res.*, 2021, **2**, 2100011.



- 21 The Borchardt group has recently shown that catalysis in the Suzuki-Miyaura reactions conducted using a palladium-based milling assembly occurs exclusively on the ball, rather than abraded material, see: W. Pickhardt, C. Beaković, M. Mayer, M. Wohlgemuth, F. J. L. Kraus, M. Etter, S. Grätz and L. Borchardt, *Angew. Chem., Int. Ed.*, 2022, **61**, e202205003.
- 22 (a) A. A. L. Michalchuk, K. S. Hope, S. R. Kennedy, M. V. Blanco, E. V. Boldyreva and C. R. Pulham, *Chem. Commun.*, 2018, **54**, 4033–4036; (b) A. G. Buzanich, C. T. Cakir, M. Radtke, M. B. Haider, F. Emmerling, P. F. M. de Oliveira and A. A. L. Michalchuk, *J. Chem. Phys.*, 2022, **157**, 214202; (c) G. I. Lampronti, A. A. L. Michalchuk, P. P. Mazzeo, A. M. Belenguer, J. K. M. Sanders, A. Bacchi and F. Emmerling, *Nat. Commun.*, 2021, **12**, 6134.
- 23 (a) V. Štrukil, D. Margetić, M. D. Igrc, M. Eckert-Maksić and T. Friščić, *Chem. Commun.*, 2012, **48**, 9705–9707; (b) M. Ferguson, N. Giri, X. Huang, D. Apperley and S. L. James, *Green Chem.*, 2014, **16**, 1374–1382; (c) J. L. Howard, Y. Sagatov, L. Repousseau, C. Schotten and D. L. Browne, *Green Chem.*, 2017, **19**, 2798–2802; (d) T. Seo, K. Kubota and H. Ito, *J. Am. Chem. Soc.*, 2020, **142**, 9884–9889; (e) R. Schmidt, A. Stolle and B. Ondruschka, *Green Chem.*, 2012, **14**, 1673.
- 24 (a) R. Portmann and A. G. Novartis, Basel, Switzerland. U.S. Patent 6,156,907, 2000; (b) P. Bodhuri, S. P. Green, A. Karadeolian, and E. G. Cammisa, Apotex Technologies Inc., WO2014121383A1, 2014.
- 25 For recent ball-milling examples, see: (a) A. C. Jones, M. T. J. Williams, L. C. Morrill and D. L. Browne, *ACS Catal.*, 2022, **12**, 13681–13689; (b) Q. Cao, J. L. Howard, E. Wheatley and D. L. Browne, *Angew. Chem., Int. Ed.*, 2018, **130**, 11509–11513; (c) R. R. A. Bolt, L. C. Morrill, E. Richards and D. L. Browne, *Angew. Chem., Int. Ed.*, 2021, **60**, 23128–23133; (d) W. I. Nicholson, J. L. Howard, G. Magri, A. C. Serastram, A. Khan, R. R. A. Bolt, L. C. Morrill, E. Richards and D. L. Browne, *Angew. Chem., Int. Ed.*, 2021, **60**, 23128–23133; (e) P. Gao, J. Jiang, S. Maeda, K. Kubota and H. Ito, *Angew. Chem., Int. Ed.*, 2022, **41**, e202207118; (f) R. Takahashi, A. Hu, P. Gao, Y. Pang, T. Seo, J. Jiang, S. Maeda, H. Takaya, K. Kubota and H. Ito, *Nat. Commun.*, 2021, **12**, 6691; (g) V. S. Pfennig, R. C. Viellella, J. Nikodemus and C. Bolm, *Angew. Chem., Int. Ed.*, 2022, **61**, e202116514; (h) I. R. Speight and T. P. Hanusa, *Molecules*, 2020, **25**, 570.

