RSC
Mechanochemistry

ROYAL SOCIETY
OF CHEMISTRY

EDITORIAL

View Article Online
View Journal | View Issue

Check for updates

Cite this: *RSC Mechanochem.*, 2026, 3, 327

Moving mechanochemistry forward: mechanochemistry and organometallic synthesis

Dillon Button-Jennings and Timothy P. Hanusa *

DOI: 10.1039/d6mr90009g

rsc.li/RSCMechanochem

Although examples of mechanochemical processes appear in writings from antiquity,[1] the deliberate use of mechanical force to drive chemical reactions, once a relatively niche area of research with limited visibility, has undergone striking expansion over the past three decades.[2–4] In particular, ball-milling and grinding techniques have enabled synthetic transformations long associated with rigorously inert atmospheres or refluxing solvents to be carried out under near-solvent-free and, in some cases, ambient conditions.[5–7] Mechanochemical methods have transformed diverse classes of organometallic reactivity, including cross-coupling, C–H activation, small-molecule activation (*e.g.*, N_2,[8–10] CO_2 [6]), and the generation of nucleophilic reagents such as Grignard and organolithium compounds. An earlier Editorial in this series explored the impact of mechanochemistry on the broader field of inorganic chemistry.[11] This Editorial focuses specifically on organometallic chemistry and on how mechanochemical methods are clarifying the requirements for successful organometallic synthesis in two particular areas: (1) Grignard reagents and related compounds; and (2) solid-state catalysis (Fig. 1).

One of mechanochemistry's most notable contributions to organometallic chemistry is the production of classic organometallic reagents.[12] Although mechanochemical protocols are often celebrated for enabling the generation of organometallic reagents under ambient or non-anhydrous conditions, it is important to recognize that related behavior has precedent in solution-phase chemistry. For nearly a century after the discovery of Grignard chemistry, for example, it was often taken as axiomatic that successful reactions required rigorously dry ethers and inert-gas protection.[13,14] This assumption was disproved in the 1990s for the Barbier–Grignard allylation of aldehydes, where it was shown that the reaction of allyl bromide or iodide with benzaldehyde and Mg in aqueous HCl or NH_4Cl produces quantitative conversion of the aldehyde into allylation and pinacol coupling products.[15–17] Passivation of the Mg surface under aqueous or solid-state conditions was a chief difficulty to overcome, and efforts in the early 2000s to produce Grignard reagents through ball-milling magnesium with organohalides achieved only limited success.[18] In 2021, Takahashi, Kubota, Ito, and colleagues reported a mechanochemical synthesis of Grignard reagents in air by ball-milling Mg turnings with aryl halides and small amounts of ethereal solvents; the use of the latter was critical for obtaining high yields.[19] A crude mixture of organomagnesium nucleophiles was generated and used directly in one-pot additions to carbonyl compounds and in Ni-catalyzed cross-couplings, without requiring an inert atmosphere or flame-dried glassware. This solvent-minimized Grignard protocol delivered high yields and allowed reactions on substrates that usually fail under traditional conditions, such as aryl chlorides that are poorly soluble in solution. The stability of the reagents they generate appears to be due to their slow surface degradation under ambient conditions. The three equivalents of THF or CPME added during milling mean that the first coordination sphere of Mg was fully saturated (*i.e.*, the Grignard formula would be $RMgX(solv)_{3-4}$), perhaps providing some stability, but also confirming that the ten to hundreds of equivalents used in

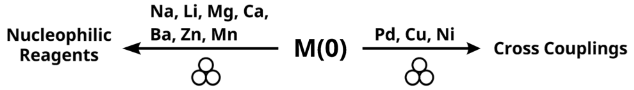

Fig. 1 Mechanochemistry has advanced organometallic synthesis in several ways, notably by forming classic reagents (organolithiums, Grignards, *etc.*) from elemental metals (M(0)) under ambient conditions and by enabling direct mechanocatalysis, in which grinding M(0) with substrates promotes cross-coupling reactions. See the text for details.

Department of Chemistry, Vanderbilt University, VU Station B #351822, Nashville, Tennessee 37235, USA. E-mail: t.hanusa@vanderbilt.edu

conventional solvent-based systems are not essential to reagent formation.

Mechanochemistry has similarly revolutionized the preparation of "heavy Grignard" reagents based on magnesium's congeners (Ca–Ba). Organocalcium reagents, for example, are potential alternatives to magnesium-based Grignards owing to the higher polarity of the C–Ca bond, but they have been notoriously difficult to prepare because bulk calcium metal is usually heavily passivated, often requiring pretreatment of the metal by dissolution in liquid ammonia or by preparing nanoparticulate metal powders *via* the Rieke method.[20,21] In 2022, Gao, Kubota, Ito, *et al.* demonstrated that ball-milling calcium metal with organohalides (and 4 equivalents of THF or THP) produces arylcalcium halides without a pre-activation step, as the mechanical impact itself is sufficient to initiate calcium insertion.[7] The generation and immediate *in situ* use of the organometallic intermediates bypasses the need to isolate or handle them in solution. Although this approach telescopes multistep sequences into a single jar, bypassing isolation also limits substrate scope; *e.g.*, residual calcium from direct mechanosynthesis can interfere with subsequent reactions involving compounds containing reducible functionalities.[7,22]

In addition to Grignard-type reagents, mechanochemical methods are proving general for generating organometallic reagents from other zero-valent metals, including zinc, manganese, sodium, and even lithium, which typically require specialized activation or ultradry conditions. These elements can be converted directly into organometallic nucleophiles by milling with organic halides. Browne and co-workers explored ball-milling strategies to activate zinc dust, forming organozinc intermediates that were immediately used in one-pot Barbier and Negishi-type C–C coupling sequences.[23] As with Grignard reagents, however, organozinc intermediates can be generated and consumed *in situ* in the presence of water or aqueous media for Zn-mediated Barbier-type reactions, enabling carbon–carbon bond formation without rigorous exclusion of moisture.[24–26] Even transformations analogous to Negishi couplings can proceed *via* micellar and aqueous cross-coupling methods under conditions traditionally considered incompatible with organozinc species.[27]

The apex of air- and moisture-sensitivity, as well as solubility problems, may be exemplified by organolithium and organosodium reagents, which, although historically challenging to prepare, can be synthesized under milling conditions. In 2025, Kondo, Kubota, and Ito reported the first direct mechanochemical generation of organolithium reagents.[28] A range of complexes was formed at room temperature without glovebox or Schlenk techniques, enabling one-pot carbon–carbon bond formations even for substrates that are sluggish in solution (*e.g.*, aryl fluorides).[28] In late 2025, Lu, Kubota, Ito, and colleagues reported the direct formation of organosodium compounds by milling Na metal lumps with aryl bromides, producing an array of reagents within minutes without strict exclusion of moisture or cooling.[29] These organosodium species facilitated one-pot nucleophilic additions and nickel-catalyzed cross-couplings, and notably enabled the efficient defunctionalization of inert aryl fluorides *via* C–F bond sodiation, a transformation that, under solvothermal conditions, produces only trace amounts of products.

The concept of direct mechanocatalysis[30] further blurs the line between reactor and catalyst: in some setups, the milling media serve as the catalysts.[31] Work by Hwang, Grätz, and Borchardt showed that catalytic metal balls (*e.g.*, of nickel or copper) can drive solvent-free reactions upon impact, effectively performing heterogeneous catalysis inside a mechanochemical reactor.[31] Such approaches have enabled solventless hydrogenations and C–C couplings, where each collision simultaneously provides mechanical energy and a catalytic surface. The synergy between organometallic catalysis and mechanochemical activation thus enables complex, multi-step transformations in a "one-pot" solid-state setting. Furthermore, the Mack group pioneered the use of copper reactor vessels to perform various catalytic transformations traditionally carried out under solvothermal conditions. Flagship examples include copper-mediated click reactions,[32] nickel-mediated cycloadditions,[33] and, more recently, the combined use of catalytically active milling media and vessels *via* palladium foil and copper vials for Sonogashira couplings of aryl halides and alkynyl substrates.[34]

To date, organometallic mechanochemistry has offered several compelling advantages over solution-based, processes–operational simplicity, solvent minimization, and sometimes different selectivity. These are not all *de novo* developments, however. For example, the tolerance of mechanochemically generated organometallic intermediates to air and moisture is part of a broader pattern in synthetic chemistry in which rapid *in situ* generation and consumption can mitigate the need for strictly anhydrous environments if a species is transient and consumed quickly. Nevertheless, the restriction of solvent use in mechanochemically based reactions opens avenues for novel chemical transformations by exploiting reactivity previously masked by solvent-mediated degradation. In fact, the most exciting developments to come will likely be found in the realm of "impossible" molecules—"impossible" only from a solution-based perspective.[2,35–39] Mechanochemistry, as a reaction-discovery tool, may thus take us far beyond the current limits of solution-oriented chemistry.

Acknowledgements

The authors would like to thank Prof. François Gabbaï (Texas A&M University, USA) for his insightful and constructive comments.

References

1 L. Takacs, *JOM*, 2000, **52**, 12–13.
2 J.-L. Do and T. Friščić, *ACS Cent. Sci.*, 2017, **3**, 13–19.
3 J. L. Howard, Q. Cao and D. L. Browne, *Chem. Sci.*, 2018, **9**, 3080–3094.
4 J. F. Reynes, F. Leon and F. García, *ACS Org. & Inorg. Au*, 2024, **4**, 432–470.
5 N. R. Rightmire and T. P. Hanusa, *Dalton Trans.*, 2016, **45**, 2352–2362.

6 V. S. Pfennig, R. C. Villella, J. Nikodemus and C. Bolm, *Angew. Chem., Int. Ed.*, 2022, **61**, e202116514.
7 P. Gao, J. Jiang, S. Maeda, K. Kubota and H. Ito, *Angew. Chem., Int. Ed.*, 2022, **61**, e202207118.
8 S. Reichle, M. Felderhoff and F. Schüth, *Angew. Chem., Int. Ed.*, 2021, **60**, 26385–26389.
9 S. Suginome, K. Murota, A. Yamamoto, H. Yoshida and Y. Nishibayashi, *Nat. Synth.*, 2025, **4**, 243–251.
10 J. S. Lee, G.-F. Han and J.-B. Baek, *ChemSusChem*, 2023, **16**, e202300459.
11 F. García, M. Senna and V. Šepelák, *RSC Mechanochem.*, 2025, **2**, 499–502.
12 J. V. Nallaparaju, R. Aav and D. Kananovich, *ChemPlusChem*, 2026, **91**, e202500445.
13 D. Seyferth, *Organometallics*, 2009, **28**, 1598–1605.
14 R. M. Peltzer, J. Gauss, O. Eisenstein and M. Cascella, *J. Am. Chem. Soc.*, 2020, **142**, 2984–2994.
15 C.-J. Li and W.-C. Zhang, *J. Am. Chem. Soc.*, 1998, **120**, 9102–9103.
16 U. M. Lindström, *Chem. Rev.*, 2002, **102**, 2751–2771.
17 C.-J. Li, *Tetrahedron*, 1996, **52**, 5643–5668.
18 J. M. Harrowfield, R. J. Hart and C. R. Whitaker, *Aust. J. Chem.*, 2001, **54**, 423–425.
19 R. Takahashi, A. Hu, P. Gao, Y. Gao, Y. Pang, T. Seo, J. Jiang, S. Maeda, H. Takaya, K. Kubota and H. Ito, *Nat. Commun.*, 2021, **12**, 6691.
20 S. Krieck and M. Westerhausen, in *Encyclopedia of Inorganic and Bioinorganic Chemistry*, ed. R. A. Scott, Wiley, 2015, pp. 1–17, DOI: 10.1002/9781119951438.eibc2297.
21 T. C. Wu, H. Xiong and R. D. Rieke, *J. Org. Chem.*, 1990, **55**, 5045–5051.
22 S. Harder and J. Langer, *Nat. Rev. Chem.*, 2023, **7**, 843–853.
23 A. A. Alharthi, B. M. Kariuki, L. C. Morrill and D. L. Browne, *Chem. Commun.*, 2026, **62**, 1864–1868.
24 L. W. Bieber, M. F. da Silva, R. C. da Costa and L. O. S. Silva, *Tetrahedron Lett.*, 1998, **39**, 3655–3658.
25 G. W. Breton, J. H. Shugart, C. A. Hughey, B. P. Conrad and S. M. Perala, *Molecules*, 2001, **6**, 655–662.
26 C. J. Li, *Chem. Rev.*, 1993, **93**, 2023–2035.
27 A. Krasovskiy, C. Duplais and B. H. Lipshutz, *J. Am. Chem. Soc.*, 2009, **131**, 15592–15593.
28 K. Kondo, K. Kubota and H. Ito, *Nat. Synth.*, 2025, **4**, 744–753.
29 K. Kondo, M. Lowe, N. Davison, P. G. Waddell, R. J. Armstrong, E. Lu, K. Kubota and H. Ito, *Nat. Synth.*, 2025, DOI: 10.1038/s44160-025-00949-7.
30 F. Schüth and C. Weidenthaler, *RSC Mechanochem.*, 2026, **3**, 141–143.
31 S. Hwang, S. Grätz and L. Borchardt, *Chem. Commun.*, 2022, **58**, 1661–1671.
32 T. L. Cook, J. A. Walker and J. Mack, *Green Chem.*, 2013, **15**, 617–619.
33 R. A. Haley, A. R. Zellner, J. A. Krause, H. Guan and J. Mack, *ACS Sustainable Chem. Eng.*, 2016, **4**, 2464–2469.
34 S. Shah, M. M. Mokhtar, T. Tran, K. Floyd, L. Mella, T. Dao, A. Garza, J. Batteas and J. Mack, *RSC Mechanochem.*, 2026, **3**, 46–55.
35 R. F. Koby, N. D. Schley and T. P. Hanusa, *Angew. Chem., Int. Ed.*, 2021, **60**, 21174–21178.
36 N. R. Rightmire, T. P. Hanusa and A. L. Rheingold, *Organometallics*, 2014, **33**, 5952–5955.
37 V. Štrukil, D. Gracin, O. V. Magdysyuk, R. E. Dinnebier and T. Friščić, *Angew. Chem., Int. Ed.*, 2015, **54**, 8440–8443.
38 Y. X. Shi, K. Xu, J. K. Clegg, R. Ganguly, H. Hirao, T. Friščić and F. García, *Angew. Chem., Int. Ed.*, 2016, **55**, 12736–12740.
39 J. D. Dunitz and J. Bernstein, *Acc. Chem. Res.*, 1995, **28**, 193–200.