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Mechanochemistry in transition metal-catalyzed reactions

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Over the past 15 years, mechanochemistry has developed into a powerful tool for the synthesis of molecules and materials while avoiding the consumption of bulk solvents. With tailored instruments and well-understood milling/grinding techniques, experimentalists are now tackling synthetic problems of increasing complexity, such as implementing the use of a catalyst to enable specific chemical pathways and control reaction selectivity. This Opinion provides a snapshot of the current state of affairs in the field, highlighting recent examples that employ metal-based catalysts under mechanochemical conditions, as well as the context and specific features of the underlying methods.

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Introduction

Mechanochemistry, that is, enabling chemical transformations by mechanical force [1], has become the cornerstone of solvent-free synthesis, providing a general, readily optimized, scalable methodology to prepare molecules and materials without using bulk solvents. Reactions performed by grinding, milling, or other types of agitation (*e.g.* acoustic mixing [2], extrusion [3]) have been applied to a wide range of domains from molecular chemistry: organic [4–8], biomolecular [9–12] and organometallic [13,14]; to materials chemistry: inorganic materials [15,16], metal-organic frameworks [17,18], nanoparticles [19,20] and carbon-based materials [21,22]. Mechanochemical transformations by milling are often promoted by small quantities of liquids (liquid-assisted grinding, LAG), salts (ion- and liquid-assisted grinding, ILAG), and/or polymers (polymer-assisted grinding, POLAG), providing routes to optimize and/or direct reactivity [23].

Particularly exciting developments have emerged in catalysis. Mechanochemistry being perfectly adapted to poorly soluble substances, it opens previously unconceivable approaches to catalysis using either insoluble substrates (*e.g.* biomass or synthetic polymers, metal carbides [24,25]) or employing plain raw metals [26] or minerals [27] as catalysts. This Opinion article highlights the most recent and captivating advances and opportunities in mechanochemistry using metal catalysts [28,29], and discusses the similarities of metal catalysis to other areas of mechanochemistry.

Context: brief overview of transition metal-catalyzed mechanochemical transformations

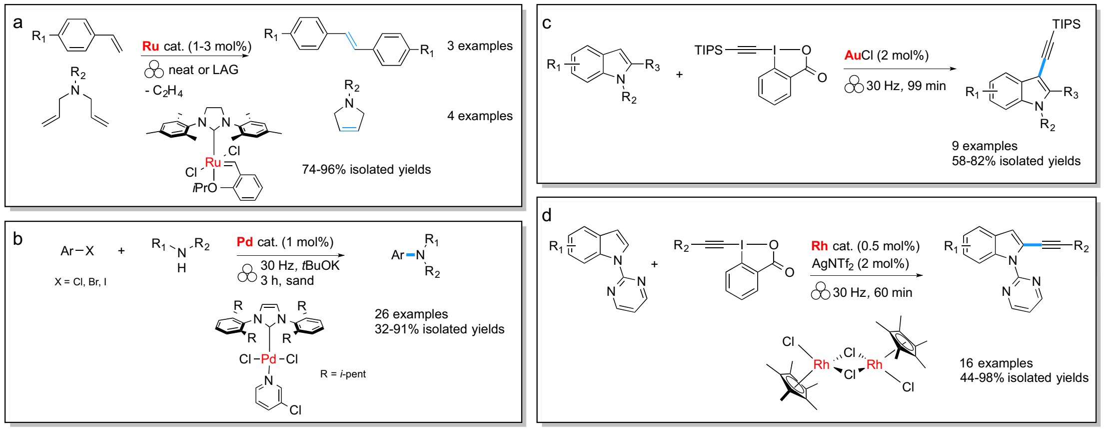
Metal-mediated transformations in a solvent-free environment have been known since at least the 1980s, when Toda *et al.* synthesized 2,2′-binaphthols (BINOLs, up to 95% yields) by gentle heating (50 °C) of preground mixtures of 2-naphthols with iron(III) salts [30]. An early example of a metal-catalyzed milling reaction was a palladium-catalyzed Heck-type coupling of aryl halides with protected aminoacrylates, with 13–88% yields within 60 min [31]. The ability to improve metal-catalyzed mechanochemical transformations by small amounts of a liquid was demonstrated by the Braga group who performed the Suzuki–Miyaura coupling of 1,10-ferrocenediboronic acid and 4-bromopyridine by kneading with a small amount of methanol, resulting in up to 57% isolated yield [32]. Today, metal-catalyzed mechanochemistry is a wide area, with many popular transformations adapted to the solvent-free environment, including ruthenium-catalyzed olefin metathesis [33], Suzuki–Miyaura [22], Heck [34], Buchwald–Hartwig [35], Sonogashira coupling [36] rhodium- and gold-catalyzed C–H activation [37], and many more [28,29] (Figure 1).

New opportunities for catalysis

Milling assembly as catalyst

One of the most captivating new opportunities that mechanochemistry offers to catalysis is the use of

Figure 1



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Selected examples of popular transition metal-catalyzed reactions adapted to mechanochemical reaction environment. **(a)** Ruthenium-catalyzed olefin metathesis [33]. **(b)** Palladium-catalyzed Buchwald–Hartwig coupling [35]. **(c & d)** Gold- and rhodium-catalyzed indole alkynylation [37].

elementary metals as catalysts, removing the need for specially designed, often costly and/or sensitive organometallic complexes employed in homogeneous catalysis [68]. This was demonstrated by the Mack group, who conducted a Sonogashira coupling using a copper-based milling assembly (copper jar and milling media) instead of the conventional copper(I) co-catalyst (Figure 2a) [36]. The concept of the milling assembly as catalyst was expanded to other processes, for example, ligand- and solvent-free Suzuki–Miyaura reactions developed by the Borchardt group using palladium balls (Figure 2b) [26].

Bulk metals as catalysts

A simple mechanochemical route to silver-catalyzed olefin cyclopropanation was described by the Mack group, by introducing a thin foil of silver metal into a stainless steel milling jar [38]. This strategy was expanded into a chemoselective strategy for alkyne cyclopropenation *versus* alkene cyclopropanation controlled by the nature of the metal foil (Figure 2e) [39]. Specifically, milling in the presence of a silver foil was selective for alkyne cyclopropenation while using a copper foil was selective for alkene cyclopropanation, even in mixtures or within the same substrate when the double and triple bonds are not conjugated. The reaction was also applicable to terminal acetylenes, which are otherwise known to deactivate silver catalysts in solution. The silver foil methodology was also combined with palladium-catalyzed Sonogashira coupling in a one-pot strategy to synthesize cyclopropenes from phenyl diazoacetate, 1-hexyne, iodobenzene, and palladium catalyst [39].

Base metal activation as substrate

Mechanochemical activation of a base metal was used by the Browne group [40] for *in situ* generation of organozinc reagents, by milling zinc with organohalides, in that way avoiding the need for inert atmosphere or dry solvents. The resulting organozinc derivatives were then used as effective substrates in palladium-catalyzed Negishi coupling in a two-step one-pot milling process using aryl chlorides (2 examples), bromides (32 examples) or iodides (4 examples), or in a one-pot telescoping milling reaction using aryl bromides (3 examples).

In situ formation of catalytically active metal complexes

Another route to simplify catalytic reactions is by *in situ* assembly of the catalyst from an inexpensive metal salt or a metal itself. An example of such a two-step process was demonstrated by Hernández *et al.* in a two-step procedure involving the mechanosynthesis of a Cp*-rhodium(III) catalyst (Cp* = pentamethylcyclopentadienyl ligand) directly from hydrated RhCl$_3$, followed by Rh-catalyzed C–H activation by ball milling [41]. Catalysts for Suzuki–Miyaura couplings were synthesized by Do *et al.* directly from palladium metal by combining mechanochemical oxidative halogenation with ligand exchange, providing a simple route for the direct recycling of laboratory waste palladium catalysts [42].

Minerals as precatalysts

Examples of nonconventional, inexpensive catalyst choices enabled by mechanochemistry are copper- and vanadium-containing minerals covellite and vanadinite, respectively, which were used by the Bolm group to catalyze intermolecular and intramolecular C–C bond formation through milling atom-transfer radical cyclization (ATRC) or oxidative coupling [27].

Figure 2

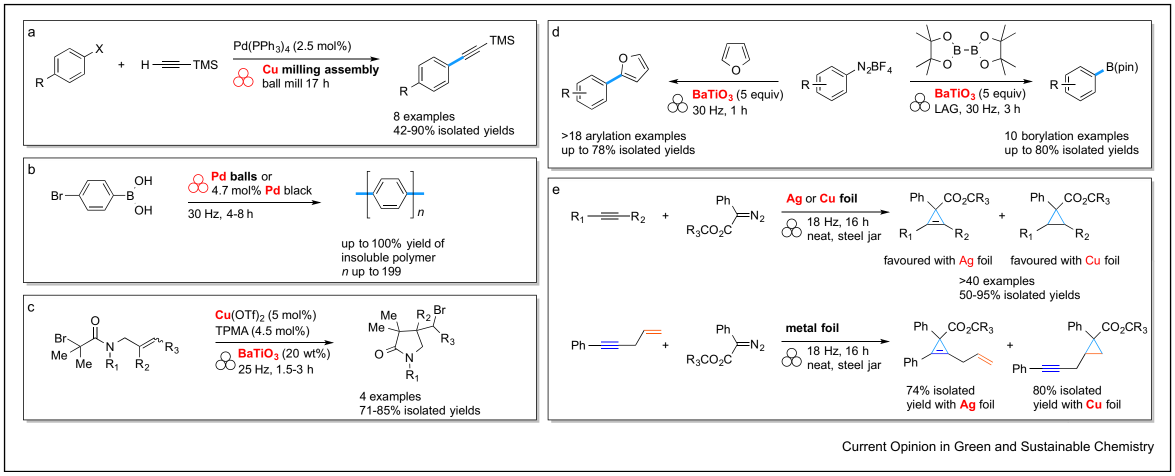

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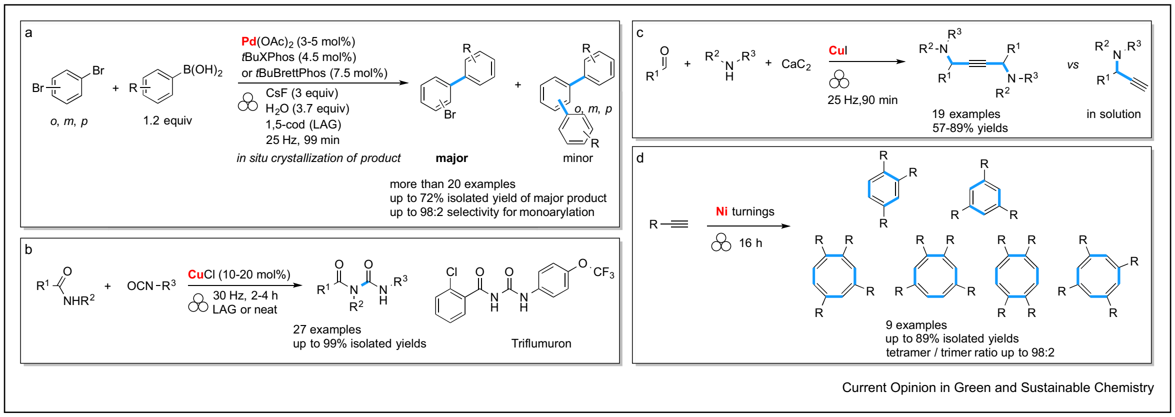
Illustration of new opportunities in mechanochemical metal-catalyzed reactions, including the use of milling media as catalysts, and catalysis activated by the piezoelectric effect. **(a)** Sonogashira coupling in a copper milling assembly [36]. **(b)** Suzuki–Miyaura coupling with palladium balls [26]. **(c)** Atom-transfer radical cyclization by mechanochemically enabled piezoelectric redox chemistry ($BaTiO_3$) [44]. **(d)** Arylation and borylation of diazonium salts by piezoelectric mechanoredox chemistry ($BaTiO_3$) [43]. **(e)** Selective alkyne cyclopropenation (silver foil) and alkene cyclopropenation (copper foil) [39].

Piezoelectric catalysis

A recent and exciting mechanochemical opportunity to develop novel catalytic systems is based on single-electron transfer processes activated by piezoelectric effect – charge separation in a material under mechanical impact [43]. Specifically, Kubota *et al.* have shown that ball milling in presence of piezoelectric ceramic $BaTiO_3$ enabled regioselective and gram-scale C–H arylation of furans, pyrroles, and thiophenes (Figure 2d). This mechanochemically enabled piezoelectric redox strategy was expanded by Bolm *et al.* to ATRC using $BaTiO_3$ along with a copper(II) co-catalyst (Figure 2c) [44], and by Kubota, Ito *et al.* for aromatic C–H trifluoromethylations [45]. Although not directly metal-catalyzed, piezoelectric catalysis with $BaTiO_3$ is an example of a mechanochemistry-specific catalytic

Figure 3



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New and modified reactivity made accessible by mechanochemistry. **(a)** Mechanochemically enabled selective Suzuki–Miyaura coupling monoarylation of dibromobenzenes [52]. **(b)** Mechanochemically enabled amide-isocyanate coupling to form urea-amides [56]. **(c)** Altered aldehyde-amine-alkyne (A^3) coupling using calcium carbide as the alkyne source [25]. **(d)** Mechanochemical nickel-catalyzed tetramerization of terminal alkynes, contrasting solution reactivity that yields trimers [57].

process, analogous to photoredox catalysis, but harnessing mechanical energy to accelerate chemical transformations.

Specific features of metal-catalyzed mechanosynthesis

Isolation of reaction intermediates

Mechanochemical methods are amenable to directly observe reactive intermediates, and sometimes even isolate them. Initially demonstrated in metal-free reactions, such as the Katritzky thiourea synthesis or the Knoevenagel condensation [46,47], this possibility was recently established in metal-catalyzed mechanochemistry by the Ito group, who reported simple synthesis and solid-state isolation of organopalladium halides, known as intermediates in Suzuki–Miyaura- or Heck-type coupling reactions [48].

Stoichiometric control

A hallmark of mechanochemical reactions of molecular solids is the highly improved control of reaction stoichiometry compared with analogous solution processes. The ability to selectively mono-functionalize bifunctional reactants by mechanochemistry was demonstrated in cocrystal synthesis by Karki *et al.* [49], and in organic synthesis by Štrukil *et al.* in click coupling of anilines and thiocyanates [50] and by Stolle *et al.* in oxidative bromination of mesitylene [51]. This improved stoichiometric control by mechanochemistry over solution conditions was recently extended to Suzuki–Miyaura coupling of symmetrical *o*-, *m*- or *p*-dibromobenzenes with a wide range or arylboronic acids [52]. Milling in approximate 1:1 stoichiometry provided a mono-arylated product reliably and selectively, enabling subsequent two-step synthesis of non-symmetrical diarylated products (Figure 3a). The selectivity for the monoarylated product, which exceeded that seen in solution, was explained by *in situ* crystallization: the conversion of the initially liquid dibromobenzenes into the solid monoarylated product, which reduces molecular mobility.

Liquid-assisted methods

Addition of small quantities of a liquid (LAG) is a well-established method to control and optimize milling reactions. The exact mechanism through which liquid addition controls mechanochemical reactivity remains unknown, with only a handful of mechanistic studies available [23]. A significant advance towards rational design of LAG reactions was made by Ito *et al.*, who discovered that catalytic amounts of olefins, such as 1,5-cyclooctadiene, were highly efficient in promoting Suzuki–Miyaura and Buchwald–Hartwig reactions by milling [53,54]. The olefin liquid additive was proposed to act *via* labile coordination to the palladium catalyst, which would prevent catalyst aggregation and maintain turnover efficiency.

New and modified metal-catalyzed transformations

Mechanochemistry provides an opportunity to achieve difficult catalytic reactivity, or reactivity that is strikingly different or even unobserved in solution. A new catalytic transformation, first discovered *via* mechanochemistry, was the copper-catalyzed C–N coupling of sulfonamides with carbodiimides [55]. This reaction worked with a range of arylsulfonamides and carbodiimides, achieving yields of 95% or more within hours. By contrast, the analogous solution transformations either did not take place or provided conversions below 10% after several days. The reactivity was adaptable to combinations of amides or imides with isocyanates, providing a simple, room-temperature route to urea-amides, including the insecticide Triflumuron (Figure 3b) [56]. This amide-isocyanate coupling was also difficult to reproduce in solution, even at temperatures >100 °C.

Modification of reaction selectivity by mechanochemistry was noted by Hernández *et al.*, for the copper(I)-catalyzed A^3 coupling of aldehydes, alkynes and amines. Specifically, the use of solvent-free procedures enabled the use of calcium carbide (CaC_2) as the alkyne source, selectively yielding 1,4-diamino-2-butynes, in contrast to solution-based approaches that mainly yielded propargylamines (Figure 3c) [25].

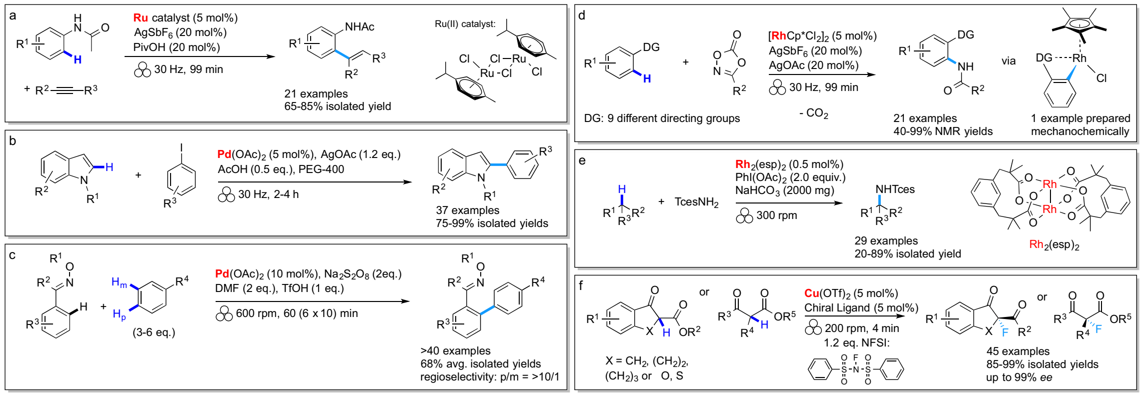
A striking example of a change in selectivity when switching from solution to a mechanochemical environment is the nickel-catalyzed oligomerization of terminal acetylenes. In solution, catalysis by nickel(0) species yielded benzene derivatives resulting from $[2+2+2]$ cyclotrimerization. Under mechanochemical conditions using nickel milling balls, the reaction led to efficient $[2+2+2+2]$ cyclotetramerization to produce mixtures of substituted cyclooctatetraenes, with the metal catalyst being easily removed and recyclable by a magnet (Figure 3d) [57].

Popular applications

Metal-catalyzed C–H functionalization using mechanochemistry

Mechanochemical functionalization of C–H bonds is a rapidly growing area. A number of mechanochemical C–H functionalization strategies have been recently described by Bolm *et al.*, using iridium-, ruthenium- and rhodium-based catalysts to modify sp^2 carbons, often quantitatively and chemoselectively (Figure 4a,d) [37,58,59]. An early report of a dehydrogenative cross-coupling by mechanochemistry appeared in 2016, using $Pd(OAc)_2$ catalyst to form biaryls by $C(sp^2)-H/C(sp^2)-H$ coupling of aromatic oximes or anilides with substituted benzenes (Figure 4c). Optimization of reactions by LAG led to improved yields and shorter reaction times compared

Figure 4



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Selected examples of metal-catalyzed mechanochemical C–H functionalization reactions. **(a)** Ruthenium-catalyzed hydroarylations of alkynes [59]. **(b)** Direct arylation of indoles, selective for the C-2 position. **(c)** Arylation of aromatic oximes or anilides by C–H/C–H (*sp*^{2}-*sp*^{2}) coupling [60]. **(d)** Rhodium-catalyzed C–H bond amidation with dioxazolones [57]. **(e)** Intermolecular C(sp^3)–H amination using Du Bois's Rh(II)-catalyst [62]. **(f)** Copper-catalyzed enantioselective C(sp^3)–H fluorination [63].

to solution approaches, with excellent chemoselectivity [60]. An approach for mechanochemical regioselective arylation of indoles using a palladium(II) catalyst was reported by Das *et al.*, with up to 99% isolated yields (37 examples, Figure 4b) [61]. Examples of reactions on *sp*^{3} centers are still rare, however. One recent example is an intermolecular C(sp^3)–H amination using Du Bois's Rh$^{II}{}_2$(esp)$_2$ catalyst in the presence of stoichiometric PhI(OAc)$_2$ oxidant (25 examples, 40–95% yields, Figure 4e) [62]. Mechanochemical activation of C(sp^3)–H center was also reported by Wang *et al.*, in copper-catalyzed fluorination of β-ketoesters which was not only solvent-free, but also highly enantioselective (Figure 4f) [63].

Medicinal mechanochemistry

An emergent mechanochemistry area of high academic and industrial interest is medicinal mechanochemistry [64], *i.e.* the use of mechanochemistry to reduce or eliminate the need for bulk solvents in the synthesis and discovery of pharmaceutical targets and materials molecules. The archetypal example of metal-catalyzed synthesis of an active pharmaceutical ingredient is the high-yield copper-catalyzed synthesis of antidiabetic drugs tolbutamide, chlorpropamide, and glibenclamide through copper-catalyzed coupling of sulfonamides and isocyanates [65]. The synthesis was recently adapted to an undergraduate teaching exercise, and scaled up using planetary milling techniques, demonstrating the simplicity and accessibility of mechanochemical catalysis [66]. A recent contribution in this area is the LAG Suzuki–Miyaura synthesis of Fenbufen ethyl ester, a nonsteroidal anti-inflammatory drug (NSAID, 91% yield) by Su *et al.* [67].

Conclusions and outlook

This brief Opinion articles provided a snapshot of transition-metal catalysis in organic synthesis by mechanochemistry, demonstrating that this area, which only emerged only three decades ago, has now taken the shape as a mainstream application. While a number of well-known catalytic reactions have been successfully transferred to the solvent-free ball milling environment, there is a number of new opportunities for reaction and catalyst design that are tailored for mechanochemical conditions. Some of these new opportunities, notably using raw metals and milling equipment itself as catalysts, are now attracting the attention of a growing number of research groups. With this in mind, it is easy to perceive this area developing into a standalone subdiscipline: metal-catalyzed mechanochemistry, with opportunities distinct and broader than those of solution-based catalysis.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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