Mechanochemical techniques for the activation and use of zero-valent metals in synthesis

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Abstract

Activating raw, zero-valent metals is an essential capability for chemical processes, including synthesis and catalysis. In recent years there has been the discovery and growing intensity in the use of mechanical action, through the utility of ball-mills, to facilitate the activation of zero-valent metals. The complexity of the synthetic reaction systems in which these processing techniques can be used has now reached a tipping-point, where, amongst others, cross-electrophile coupling, radical reactions and new modes of zero-valent reactivity have been demonstrated. In addition, the technique of ball-milling is synonymous with solvent minimisation for the reaction component of a synthetic process. In this review we demonstrate that together, these developments paint an intriguing picture where the combination of the technique of ball-milling and chemical synthesis mediated by zero-valent metals could deliver a sustainable platform for chemical synthesis, catalysis and new reaction discovery for the future.

1. Introduction

The formation of carbon-carbon bonds is paramount to the provision of synthetic organic molecules which serve all corners of society. Several key strategies exist for the forging of such C-C bonds, including the addition of a carbon-centred nucleophile to a carbon-centred electrophile and the metal catalysed cross-unison of two carbon containing starting materials. Typically, in the latter case, a wide-ranging selection of atoms or functional groups can be attached to the carbon of interest to facilitate selective coupling of the two materials at the desired position. Metalation is a common strategy for the generation of carbon nucleophiles, and can be achieved in a number of ways; 1.) direct insertion of a zero-valent metal into a C-X bond; 2.) metal/halogen exchange (distinct from 1 as it requires pre-formation of an organometallic species containing a carbon metal bond such as ^{n}BuLi or ^{i}PrMgX); 3.) deprotonation of a C-H bond with a metal containing base (such as 2,2,6,6-tetramethylpiperidinylmagnesium (MgTMP), lithium bis(trimethylsilyl)amide (LiHMDS,) ^{n}BuLi).[1-5]

Of these options the direct insertion approach (i.e. 1.) requires fewest chemical steps from raw materials and is the most tolerant to the broadest range of functional groups, however, it is perhaps the most capricious approach in solution phase. A large factor in the variation of outcomes arriving from a direct insertion approach is the activation of the zero-valent metal. Such metals come in a variety of forms and typically have an oxide coating on the outer layer which needs to be removed to expose the reactive metal surface beneath (Fig. 1a). Removal of the oxide surface or 'activation' of the metal is often achieved with the addition of chemical additives such as iodine crystals, dibromoethane, trimethylchlorosilane and a wealth of other alternatives, the choice of which is often user dependant or a preferred 'tried-and-tested' know-how.[6-9] Initiation of the activation process can be enabled thermally and most often coordinating solvents such as ethers (diethyl ether and tetrahydrofuran (THF)), or amides (*N*,*N*-dimethylformamide (DMF), *N*,*N*-dimethylacetamide (DMA), *N*-methyl-2-pyrrolidone (NMP), are typically required to help break up the freshly exposed metal (0) through chemical entrainment.[10,11] It is also documented that zero-valent metals can be activated by grinding with a mortar and pestle, where mechanical breakdown of the input form of the metal is achieved by particle size reduction or comminution. Such a manual approach can have variable outcomes owing to differences between operators, i.e. people will grind with different energies.[12,13] The mechanical activation of highly reactive zero-

valent metals is also familiar to all synthetic chemists that have drawn sodium wires for distilling solvents. For some time, there has existed electric powered milling and grinding devices used for (e.g.) grinding coffee beans, mixing dental amalgams, and analysing geological samples. More recently, such devices have been investigated for use in chemistry, with earlier applications being in the areas of formulation science, polymorphism, and crystal engineering, before moving into chemical synthesis applications such as the preparation of metal-organic frameworks (MOFs) and the construction of organic molecules.[14-29]

In recent years, research endeavours in these latter applications of ball mills have intensified, highlighting the minimisation of reaction solvent, and enabling alternative selectivity and reactivity to solvent-based approaches as significant drivers for continual development. A similar pattern can be found for the use of ball mills in the activation of zero-valent metals. Pioneering work from Komatsu and co-workers in 1996 highlighted that the functionalisation of [60]fullerene by a zinc (0) mediated Reformatsky reaction could be achieved in a 'vibrating mill', a challenge that at the time, had not been achieved by solution phase conditions (*vide infra,* Fig. 6b).[30] In 2003, Suzuki and co-workers highlighted that bismuth (0) would also afford the same Reformatsky type reactivity with non-fullerene substrates (Fig. 8c), and in 2016 Guan, Mack and co-workers demonstrated use of zero-valent nickel in a planetary mill to deliver tetracyclization of alkynes to afford non-aromatic cycloocatatetraenes (Fig. 5).[31,32] In 2018 the Browne group reported on the use of mixer mills to prepare organozinc reagents and engage them in milled Negishi cross-coupling reactions, showcasing the practical benefits of this technology (Fig. 6).[33] Activation of zero-valent metals using ball-milling does not require pre-dried and deoxygentated solvents, nor is a blanket of nitrogen or argon gas necessarily required, further, mills can be regularly/repeatedly operated for far longer than even the most optimistic/energetic mortar and pestle operator. As well as the preparation of organometallic reagents, zero-valent metals have recently found application as terminal reductants in reductive cross-coupling processes, where again the activation of the metal is critical to the success of these powerful transformations. Early efforts to improve the practicality and reliability of these reactions by mechanical activation have also started to appear in the literature. Thus far the combination of using the technique of ball milling to enable the insertion or catalyst turnover processes by zero-valent metals have been initially explored for Mg, Mn, Zn, Ag and Bi, this overview will highlight this

exciting emerging strategy. It is noteworthy that alongside the activation of zero-valent metals for their application as stochiometric reagents, there is also a related body of work where the milling balls or jars have been fabricated from catalytically active metals such as copper, palladium and even the iron and cobalt present in stainless steel materials have been implicated – these examples will not be covered here. [34-41]

2. Magnesium

Magnesium has a central role in organic synthesis due to the ubiquity and widespread utility of Grignard reagents. Treatment of an aryl/alkyl halide with Mg^0 affords the nucleophilic reagent which can participate in a wide range of reactivity including 1,2-addition to carbonyl species and Kumada-type cross-coupling. Due to the stalwart nature of Grignard reagents, they have become commonplace synthons in retrosynthetic analysis and feature heavily in synthetic routes to complex molecules such as natural products. Despite this, the activation of raw form zero-valent magnesium (typically supplied as magnesium turnings or powder), through removal of the outer MgO layer can be capricious. Various modes of activation have been reported, including chemical methods, such as the addition of an iodine crystal, 1,2-dibromoethane, hydride, or potassium metal (Riecke's method), or physical approaches, such as mechanical stirring under an inert atmosphere, activation using microwave irradiation or sonication.[42-46] The selection between these methods is often a personal choice by the user, and sometimes a combination of activation modes is used, especially for challenging substrates (Fig. 2a).

In the context of solid-state chemistry, initial environmental studies from Rowlands *et al.* in 1994, demonstrated that, among other additives, Mg^0 could be used in the ball-milling-enabled mechanochemical degradation of toxic chloroarenes to safer C–H analogues (e.g. conversion of chlorobenzene to benzene).[47] Whilst an intermediate organomagnesium or aryl radical species (formed through single electron reduction from magnesium(0)) was not initially postulated, later similar studies by Birke and co-workers exploring ball-milling-enabled activation and dehalogenation of chloroarenes propose the intermediacy of such magnesium(0)-derived intermediates (Fig. 2b).[48-49]

From a synthetic standpoint, the mechanochemical grinding of magnesium holds its own risks in the generation of highly pyrophoric finely ground magnesium particles. To this end, a majority of the reported reaction set-ups operate under strict inert atmospheres either through utility of a glovebox or gas-tight milling jars. For this reason, the authors of this review highly caution any user of this chemistry to take necessary anaerobic precautions. It should also be noted that solutions of Grignard reagents have been sparingly employed in mechanochemistry environments,[50] however the focus of this review is the mechanochemical generation of the active organomagnesium species.

In 2001, Harrowfield and co-workers reported that in a glovebox environment, milling of 1-halonapthalenes with magnesium powder (4 equiv.) for 1.5 h (X = Br) or 2.5 h (X = Cl) affords a fine black powder which can then be manipulated within the glovebox. This powder was then shown to quench with aqueous acid giving almost quantitative formation of naphthalene, or with acetophenone/benzophenone to give the addition adduct in good yields (74-80%).[51] A later report discussing these Grignard intermediates counter-hypothesises the intermediacy of the corresponding diarylmagnesium species in this process (Fig. 2c).[52] Furthermore, formation of reductive McMurry type coupling and subsequent elimination products were observed in the reaction mixture when the quenching step is conducted by milling for a further 20 minutes. Experiments without the halonaphthalene substrate reveal these dimerization structures as the major products in yields up to 40%. These observations highlight the two possible reactivity modes of Mg^0 in a ball mill, organomagnesium formation or as a single electron reductant.

The ability of Mg^0 to insert into C–F bonds has been demonstrated to be far more challenging than other halogenated counterparts. To explore the limitations of ball milling in organomagnesium formation, Hanusa and co-workers demonstrated that – setting up in a nitrogen-filled glovebox then sealing and removing to mill – using 8 equivalents of magnesium(0) and 2-fluoronaphthalene, the arylmagnesium fluoride (ArMgF) species could be formed.[53] This intermediate was then shown to be quenched with H_2O to form naphthalene in good yields (79%), and dimerised using $FeCl_3$, albeit in low yields (22%) (Fig. 2d). Notably, almost identical yields were achieved using the analogous aryl bromide (ArBr) as the starting material.

Recently, Bolm and co-workers reported a "one-jar" planetary mill-based multi-step protocol for the transformation of aryl and alkyl bromides to carboxylic acid derivatives using CO_2 gas.[54] Using a modified milling jar with gas in/outlets, the authors were able to add reagents to the jar, purge the reagents with the relevant gas, and then pressurise and seal the system before milling (Fig. 2e). Using this technique, they found that milling Mg^0 turnings in the presence of LiOH as an additive (contrary to well-established activation with LiCl for "Turbo" Grignard formation) under an argon atmosphere for one hour afforded the activated magnesium. Following this the relevant alkyl/aryl bromide was added along with 2-MeTHF (2 equiv.) as a liquid assisted grinding additive, and re-pressurised with argon and re-milled for a further hour to generate the corresponding organomagnesium species. Finally, the gases were smoothly exchanged from argon to CO_2 and the jar re-milled for 45 mins to give (after acidic work-up) the new carboxylic acid (Fig 2e). A small selection of acids was synthesised using this protocol (25-82% yield). Furthermore, the authors also demonstrated a more user-friendly alternative protocol using sodium methyl carbonate (SMC) as the CO_2 source, which in turn shortened the synthetic strategy to 2 steps, and importantly obviated the need for argon protection. Despite this, lower yields were observed compared to the gaseous CO_2 methodology.

In late 2021, Kubota and Ito disclosed a pioneering contribution to the field of the use of zero-valent metals in mechanochemistry. Here they report the generation of Grignard reagents under an air atmosphere, with no need for inert moisture-free reaction set-ups (Fig. 3A).[55] The simple mechanochemical mixing of magnesium turnings and an aryl/alkyl bromide with key addition of THF as a liquid assisting grinding agent delivers an orange paste containing the active Grignard reagent after just one hour of milling time. It could be seen that the paste-like morphology of this intermediate reduces any pyrophoricity of finely ground magnesium(0) or magnesium-derived intermediates. This lack of air sensitivity allows the user to open the jar and add a carbonyl derivative to the reaction mixture, where a further hour of milling under air affords the addition product. This robust strategy was then applied to a matrix system of aryl / alkyl bromides, and aldehyde / ketone acceptors, affording good yields. Increasing of the equivalents of magnesium(0) to 5 was shown to be beneficial for some substrates, especially secondary alkyl bromides. Whilst liquid halide feedstocks participated well in this methodology, solid at room temperature alternatives proved far less promising. To circumvent this issue, and

in line with their previous studies on the manipulation of insoluble materials,[56] the authors applied heat to the milling process via fastening a heat-gun over the milling jar. Setting the positioned heat-gun to 110 °C led to an internal jar temperature of 70 °C as measured by thermographic imaging. Pleasingly this re-activated these systems, leading to good yields of the direct addition products. Furthermore, substrates which show only trace reactivity in solution due to poor solubility in THF solvent, were highlighted to amenable to these heated mechanochemical conditions, including a phenyl-terphenyl derivative shown in Figure 3a. Following this, use of Grignard reagents as a synthetic linchpin was then showcased through addition to Weinreb amides (to afford ketone products), esters (to afford tertiary alcohols), as well as nitriles and chlorosilanes, and moreover regioselective addition to chalcone derivatives was reported, tuned by the addition (and lack of addition) of a copper(I) additive. Subsequently the authors applied this mechanochemical strategy to a nickel-catalysed Kumada-Tamao-Corriu coupling, fusing the organomagnesium species with an aryl tosylate to deliver the C–C coupled product. A small subset of these structures was synthesized in good to excellent yields for this two-stage protocol. Finally, deuteration studies and near-edge X-ray absorption fine structure (NEXAFS) spectroscopy were used to validate the proposed organomagnesium intermediate. This report could lead to a step-change understanding and application of zero-valent metals in mechanochemical synthesis.

Drawing inspiration from Hamdouchi and Garst's pioneering work that alkyl radicals could be generated as an intermediate towards Grignard reagent formation via single electron transfer between magnesium(0) surface and an organohalide species, in 2021, Yu and co-workers realised this concept in a mechanochemical setting (Fig. 3b).[57-60] Whereby under the correct circumstances this radical species could viably be intercepted by a suitable acceptor, such as a heteroarene species via a Minisci-type mechanism. Here they utilised a mixer mill to enable the coupling of alkyl bromides and chlorides and a variety of pyrimidine-based substrates (including 3 pyridine examples) using a magnesium chip in conjunction with TMEDA as the single electron reductant. Unlike in reports on ball-milling-enabled organozinc formation (*vide infra*) the nature of the source of magnesium was found to be important to reaction efficiency with alternatives such as Mg foil or Mg powder proving detrimental. Furthermore, and importantly, coupled with radical clock and racemisation studies, the authors demonstrated that the analogous Grignard reagent was ineffective in this reaction methodology,

supporting the single electron-based proposal. Notably this reaction methodology was conducted under an air atmosphere without the need for any precautionary set-up procedures. Whilst this is a practical benefit, as with above, caution is advised in post-reaction manipulation where finely ground magnesium may be present.

3. Manganese

Compared to organomagnesium and organozinc analogues, methods for the generation and manipulation of organomanganese species are much rarer, and they are often formed *via* transmetalation from other more accessible organometallic nucleophiles. Furthermore, commercial manganese(0) sources are often not active in the formation of such species, and accordingly activation methods – such as Rieke's protocol from manganese(II) chloride using lithium metal as a reductant – have been developed.[61-63] In addition to this, when manganese(0) pieces or powder are used as reductants in organic synthesis, again activation by heat or treatment with acid is often required, thus unlocking a reliable practical procedure for the activation of Mn[0] and its implementation in organic synthesis holds significant potential for the area of earth-abundant transition metal mediated chemistry.

Through studies exploring whether ball milling could be employed to form organomanganese species using mechanical activation, in 2021 Browne and co-workers discovered a method for the reductive dimerization of arylidene malonates using manganese metal.[64] Initially employing conditions previously used to form organozinc species in the ball mill (Fig. 4a), milling manganese(0) pieces with ethyl 4-bromobutyrate as a pronucleophile and benzylidenemalonate derivative as a viable electrophilic acceptor, none of the target conjugate addition product was formed. Instead, the product formed via the reductive dimerization of the arylidene malonate was isolated in 66% yield. In the absence of the alkyl bromide pronucleophile, optimization studies elucidated that the mechanochemical dimerization method found that manganese(0) metal (in the form of pieces), LiCl and a liquid assisted grinding (LAG) agent (especially THF) were essential for reactivity.

The same reaction was also demonstrated to be effective using zinc in place of Mn although with reduced yields. A modest selection of benzylidene malonate derivatives were submitted to the reaction conditions, showing variation on the aryl ring, as well as exploring different electron withdrawing groups. Notably when

the cyano-substituted substrate was employed in the reaction conditions, the dimer was formed with exquisite diastereoselectivity, where previously any induction was negligible to moderate. The authors suggest that the dimerization occurs through lithium-assisted activation of the benzylidene malonate and subsequent either single-electron or two-electron reduction from manganese metal to form either the intermediary radical or organomanganese species, which then can couple in a selection of mechanisms. This protocol was further explored through a set of control experiments using a mixture of solution- and solid-state studies with manganese(0) pieces and powder. Without any mechanical activation of the manganese(0) metal, the solution phase reaction in THF at room temperature over 24 hours resulted in complete recovery of the starting material. Upon heating to reflux Mn pieces gave trace amounts of product, whereas the powder led to an increase in the reductively dimerised product of 11% yield. In comparison, pre milling Mn pieces or the Mn powder for just 5 mins at 30 Hz before addition to the reaction at room temperature for 24 hours gave excellent yields of 86% and 78% for pieces and powder respectively. Notably these yields are comparative to those achieved in the mill for 3 hours. Comparing 2 minutes pre activation by hand grinding with a mortar and pestle and 2 minutes milling at 30 Hz before reaction in solution the hand ground reaction gave 2-3% yield while the pre milled version gave 65-69% highlighting the opportunities that mechanical pre-activation in a mill can offer in unlocking the reactivity of materials even in subsequent solution reactions (Fig 4a).

In 2021, Shi and Zou reported using manganese(0) metal, again as a reductant but this time in nickel catalysed cross-electrophile coupling between aryl and alkyl bromides under mechanochemical conditions (Fig. 4b).[65] Whilst solution-phase cross-electrophile coupling has been widely explored using manganese(0) reductants, manganese activation (either prior or *in situ*) is often required, along with the use of highly inert reaction set-ups.[66-68] To this end, ball milling could serve as a particularly attractive method for circumventing this, enabling the activation and use of manganese metal, without the need for chemical activation. The authors identified a model system using nickel catalysis to enable the coupling of 3-bromoanisole and ethyl 4-bromobutyrate using a planetary ball mill system, flushing the jars with a nitrogen atmosphere before sealing and milling. It was found that at a rotation speed of 525 rpm, using a polar solvent as a LAG agent was essential to the reaction success, with DMA proving most effective. Control experiments on the effect of water under LAG conditions

showed greater robustness compared to the solution-based reaction. This mechanochemical reaction still proceeded well when up to 8% water was added with respect to the DMA LAG agent, while just 0.5% of water in the solution reaction significantly reduced reaction efficiency (24 h, 57%). Using the optimized conditions, the scope of the reaction was studied using a range of aryl and alkyl bromide structures. Aryl bromide and iodide inputs performed similarly however the analogous aryl chloride, tosylate and triflate failed to produce C-C coupled products. A library of aryl bromides was effective in the reaction methodology including BPin-substituted arenes as well as a pyridine, albeit in slightly lower yields. Further to this, with respect to the alkyl fragment, primary alkyl bromides reacted readily giving good yields (69-81%), however coupling of both cyclic and acyclic secondary bromides gave significantly lower yields (17-32%). The applicability of this nickel catalysed cross coupling was demonstrated, gram-scale coupling of bromoanisole and ethyl 4-bromobutyrate under optimised conditions gave a yield of 81% delivering an impressive 5.39 g of product. Further manipulations afforded 6-methoxytetralone in an overall 61% yield over the 4 steps. Experiments with radical probes such as 2,2,6,6-tetramethylpiperidine 1-oxyl radical (TEMPO) and (bromomethyl)cyclopropane suggested that the cross coupling using mechanochemistry could follow a similar radical mechanism to the one established by Weix et al in solution.[66,69] However, the formation of a small amount of the C-C coupled structure with the cyclopropane ring in-tact highlights that there may also be a minor non-radical pathway.

4. Nickel

Interest in nickel catalysis has been steadily growing for the last 10 years, although often viewed as a cost effective replacement for palladium in cross-coupling methodology, a diverse range of nickel catalysed reactions have been reported.[62] Furthermore ready accessibility of Ni^I and Ni^{III} intermediary oxidation states allows nickel cycles to be used to facilitate reactivity through radical mechanisms, in addition to traditional two-electron pathways. Common sources of nickel(0) for catalysis such as $Ni(cod)_2$ are highly air sensitive and require handling in a glove box.[71-73] In some instances more stable higher oxidation state nickel precursors can be introduced as long as *in situ* reduction can be realised. To this end more-readily-activated nickel(II) complexes

as well as air-stable nickel(0) catalysts are an area of increasing interest. Despite this, the use of raw form nickel(0) in molecular organic synthesis remains largely unexplored (Fig. 5a).

To this end, in 2016 Guan, Mack and co-workers employed mechanochemistry in combination with unactivated raw-form nickel(0) to mediate a [2 + 2 + 2 + 2]-cyclotetramerization of alkynes to produce substituted non-aromatic cyclooctatetraene (COT) derivatives (Fig. 5b).[32] Previous investigations of nickel(0) catalysed oligomerisation of alkynes in solution found that electron deficient alkynes readily underwent [2+2+2]-cyclization to form a mixture of the aromatic 1,2,4- and 1,3,5 trisubstituted benzenes, with the 1,2,4 isomers generally being the major products, highlighting the divergent reactivity offered by mechanochemistry.[74-76] Initial experiments using both a vial and ball fabricated from nickel and milled at 18 Hz for 16 h found that there was around 10% conversion of starting material. Interestingly in contrast to the solution phase reaction the major products from milling were cyclooctatetraenes (COTs), formed in a ratio of 90:10 compared to aromatic products. Of the COT products the major isomers were the 1,2,4,6- and 1,2,4,7-substituted products in a ratio of 51:42. Further studies changing the hardness of the ball, the material of the vial, and the source of the nickel, elucidated that reusable nickel(0) pellets could be employed not only as the catalyst but also to create mechanical energy, where no ball was needed in the milling environment for optimal reactivity. Furthermore, using nickel pellets allowed them to be removed at the end of the reaction using a neodymium magnet. When exploring alternative terminal alkynes, further propiolate derivatives proceeded well (yields are combined yields for all tetramer products), however the selectivity for COTs over the trimer products was reduced for the tert-butyl propiolate (81: 19) compared to ethyl (93: 7) and methyl (98: 2) propiolate. This was suggested to be caused by the bulk of the *t*-butyl group promoting reductive elimination over the incorporation of a fourth alkyne. A range of substituted phenylacetylene derivatives were studied to determine electronic effects on the reaction. Whilst phenylacetylene gave a yield of 74% and an excellent ratio of COT to trimer products (94: 6), introducing other substituents reduced the tetra-trimer selectivity, whether electron-rich or electron-poor. This observation was most clear in the 4-methoxy example where interestingly a complete reversal in selectivity was noted.

5. Zinc

Organozinc reagents serve as an important nucleophilic component in many powerful C-C bond forming reactions, most notably the Nobel Prize winning Negishi cross coupling. Generally, these highly privileged organometallic reagents demonstrate excellent functional group compatibility. However, the commercial availability of organozinc reagents remains limited in comparison to other analogous organometallic reagents such as boronic acids/esters due to stability issues. Therefore, a majority of organozinc reagents are often synthesised just prior to use. This requirement results in their routine use often being overlooked, however recent work in the generation of stable zinc pivalate materials is going someway to address this shortfall.[77-79]

The formation of organozinc reagents can also be capricious and non-trivial. There are many different methods for the generation of organozinc materials. One method is the metalation of C-H bonds, either by transmetalation of organolithium/magnesium species,[80-82] or by direct zincation with zinc-amide bases.[83,84] Another popular method is via insertion of Zn^0 into C-X bonds. This was classically achieved by the formation of 'Rieke zinc' (Zn^0) from the reduction of $ZnCl_2$ and then subsequent oxidative addition to aryl/alkyl halides. More recently, different approaches have been taken whereby chemical additives such as TMSCl, iodine, bromine or 1,2-dibromoethane are used to remove the zinc oxide layer on the metal surface (Figure 6a).[5-8, 85-89]. This exposes the reactive Zn^0 which then undergoes oxidative addition to form the organozinc species. Whilst each of these methods carries its own merits, all are linked with the requirement for a strictly inert atmosphere and in cases where zinc metal is used, the physical form is of significance.

An early report by Toda and co-workers in 1991 disclosed the use of a pestle and mortar for the mechanochemical activation of zinc.[90] By manual grinding of a carbonyl derivative with an alkyl halide and zinc powder (5 equiv.), the authors demonstrated this concept to a set of Reformatsky additions and Barbier-type reaction systems. It was noted that the materials were *'thoroughly ground in an agate mortar and pestle, and the mixture kept at room temperature for 2-3 h'* implying that an initial input of mechanical energy was required to activate the zinc and provide mixing of the materials before allowing this mixture to 'age' and the reaction proceed over time without further mixing.

Following this initial report, and through translation to a ball-milling apparatus, the generation and use of organozinc intermediates by ball-milling was initially reported in 1996 by Komatsu and co-workers for a Reformatsky-type addition to [60] fullerene (Figure 6b).[30] In this protocol a vibrating ball-mill capable of operating at 2800 cycles per minute (46.7 Hz) was employed. For this protocol, ethyl bromoacetate, zinc dust and [60] fullerene were all loaded into a capsule along with a stainless-steel ball. This reaction set-up was all carried out in a nitrogen bag. Following 'agitation' using a vibrating mill for 20 minutes, the mixture was quenched with TFA and 1,2-dichlorobenzene to produce the alkylated adduct in 17% yield with various other products observed in <5% yield. This work represented the first addition of organozinc reagents to [60] fullerene, with no prior work being reported, even using analogous solution-based conditions. This Reformatsky-type reaction also demonstrated the first solid-state reactivity of fullerene, which has successfully circumvented the issue of poor-solubility in common solvents and led to extensive work exploring the reactivity of fullerenes by mechanochemical methods.[91]

Mechanochemical activation of zero-valent zinc(0) has continued to be explored by way of ball-milling as a method for the reliable and robust formation of organozinc intermediates. To this end, Browne and co-workers developed a simple procedure for the mechanical generation and subsequent use of organozinc reagents for a mechanochemical Pd-catalysed Negishi cross-coupling reaction (Fig. 6c).[33] Within this study is demonstrated the facile synthesis of both alkyl (sp^3) and aryl (sp^2) organozinc species by placing alkyl bromides or aryl iodides in a milling jar with zinc metal and N-N-dimethylacetamide as a LAG agent with no precaution taken to exclude air/moisture from the set-up. After 4 hours of milling time, the yield of organozinc formation was monitored through acidic quenching of the jar's contents and subsequent analytical determination of the hydrolysed / dehalogenated product. This organozinc formation from 4-ethyl bromobutyrate was seen to give high yields notably regardless of zinc(0) form used (12 commercial forms studied). To demonstrate the applicability of the simple organozinc formation, the mixture could then be subjected immediately to a (bulk) solvent-free Pd-catalysed Negishi cross-coupling simply by opening the jar and adding in the remaining reagents required for coupling and then milling for a further 4 hours. This ball-milling approach, utilising highly versatile Pd-PEPPSI type catalysts, allowed for the robust formation of a library of cross-coupled products, received in good to

excellent yields. To further explore the opportunities of this zinc activation and coupling manifold, a one-step, one-pot reaction was also demonstrated showing the successful organozinc generation / coupling simply by putting all reagents in the jar at the start of the process and milling for 8 hours without any manual interference.

Building upon this discovery, Browne and co-workers then turned attention to other useful C-C bond forming reactions that proceed *via* organozinc intermediates to showcase the versatility of mechanochemical activation of zinc. Suitable candidates for this were identified as the Reformatsky reaction (Fig. 6d) and a Barbier type allylation of carbonyl compounds (Fig. 6e).

As demonstrated above, the key step in the Reformatsky reaction is the formation of the organozinc which can also be represented as a zinc enolate. Under the mechanochemical manifold, Browne and co-workers found that the activation of zinc metal and insertion into the C-Br bond of α-halo esters proceeded efficiently without the need for any inert set-ups.[92] The initial organozinc / zinc enolate formation and following interception of a ketone derivative all happens within 2 hours by milling, a markedly shorter reaction time that previously observed with Negishi coupling. This is in part due to the higher susceptibility of α-halo esters to form organometallic reagents. The simplicity of this reaction was exemplified with the synthesis of a range of β-hydroxy esters / nitriles as well as the construction of a β-amino ester which, in-part, cyclised to form β-lactam structures. Notably, a single un-optimised example of this reactivity was previously reported in a planetary mill by König and co-workers in 2015.[93]

The Barbier reaction involves the nucleophilic attack of a carbonyl (or equivalent) using an organometallic intermediate, the most popular of which is use of organozinc reagents. These nucleophilic intermediates are derived from typically electrophilic alkyl halides *via* the insertion of activated zinc metal. Browne and co-workers again harnessed the efficient zinc activation technique previously observed for use in a Barbier type allylation of aldehydes, ketones, and imines.[94] After successful mechanical activation of zinc, the allyl organozinc reagent is formed and subsequently used for the synthesis of a library of homoallyl alcohols. In this case, DMSO is used as the LAG instead of DMA, which since the role of DMA has previously been discussed to stabilise organozinc materials, suggests that DMSO (a much less hazardous and environmentally benign alternative) can

also act in this way. Again, the reaction time is shortened in comparison to the Negishi reaction due to the ease of zinc insertion into allyl bromide. This process was also demonstrated at higher scales, where 1.5 grams of product could be isolated from a single run.

In addition to its use in organozinc generation, the use of zinc as a reductant in catalytic manifolds has become commonplace, particularly in cross-electrophile coupling reactions.[95,96] The limitations again presented in these reports can often be implementation of appropriate control measure to ensure the activation of zinc in solution phase as well as a general requirement for inert atmospheres. Browne and co-workers describe a zinc-mediated cross-electrophile coupling reaction between aryl and alkyl halides, analogous and contemporaneous to the Mn process reported by Shi and Zou (Fig. 7A).[65,97] This radical intermediate-based reaction requires activated Zn^0 to turn over the catalytic cycle and regenerate the active Ni^0 catalyst. Its utility allows the synthesis of a library of cross-coupled products in good to excellent yield in just 2 hours in air atmosphere Reductive coupling was shown to be applicable to substrates bearing electrophilic functionality (aldehydes) or base-sensitive sites (phenols). Pseudohalides were also shown to couple effectively as demonstrated by successful reaction from vinyl triflates or alkyl mesylates. The scale of the zinc-mediated process could also be increased with little degradation in yield for the reaction of iodobenzene and 1-iodooctanecante, achieving 1.48 g of octylbenzene.

Alternatively, it has been shown that mechanically activated zinc can act as a reductant whereby it is not directly involved in the catalytic cycle. In fact, it was shown that for many cases the addition of zinc was required for successful thiol arylation in a Pd-PEPPSI catalysed mechanochemical C-S coupling reaction (Fig. 7b).[98] In particular, in the absence of zinc, alkyl thiols did not undergo cross-coupling with aryl halides and instead formed the corresponding symmetrical disulfide. To combat this undesired disulfide formation, zinc was added and resulted in the remarkable switch in selectively to cross-coupled product. Further studies demonstrated that under a ball-milling manifold, thiols readily oxidise to their corresponding disulfide. It was found that the reduction of disulfides could be achieved mechanochemically by milling with zinc and base. The addition of activated zinc to C-S coupling has previously been explored in solution, however, the zinc must be activated by chemical treatment prior to use.[99] Furthermore, under these mechanochemical conditions, disulfides themselves serve as valid input to afford arylated-thiol products.

5. Silver

Inspired by previously reported cyclopropanation of sterically hindered alkenes using a AgSbF$_6$ catalyst in dichloromethane,[100] in 2015 Coleman, Mack, and co-workers reported a mechanochemical silver foil catalysed cyclopropanation of alkenes with diazoacetates (Fig. 8a).[101] Explorations using the model substrates styrene and methyl phenyl diazoacetate using silver shot as the diazoacetate activator in a stainless steel jar with a stainless steel ball afforded the cyclopropane product in 92% yield and 97:3 (E:Z) diastereomeric ratio. Replacing the silver shot with silver foil gave comparable yields (96%) and diastereoselectivity (98:2) and importantly allowed the catalyst to be recycled. Repeating the reaction 5 times using the same silver foil washing with ethyl acetate between runs also led to no appreciable reduction in yield or diastereoselectivity. The authors also explored systems using copper and nickel jars and balls, although with lower efficiency to the silver system. A range of electron rich and electron poor styrene derivatives were found to readily undergo cyclopropanation with excellent yields (85-96%) and diastereoselectivity (>92:8). Furthermore, both electron rich and electron poor donor-acceptor diazoacetates derived from methyl phenyl diazoacetate were effective in the cyclopropanation reaction giving yields of over 85% and good diastereoselectivity (>88:12).

Taking this further, Coleman, Mack, and co-workers subsequently built upon this work investigating the mechanochemical cyclopropenation of alkynes catalysed by silver or copper foil (Fig. 8b).[102] Interestingly, the authors found that silver foil selectively catalyses the cyclopropenation of internal alkynes while copper foil converts terminal alkynes to the cyclopropenation product. The chemoselectivity was investigated further by milling an equimolar mixture of olefins and acetylenes with methyl phenylacetate and either copper or silver foil. The silver foil was chemoselective for the olefins over the terminal acetylenes, while the copper was mildly selective for monosubstituted alkenes and terminal alkynes. Chemoselectively was most striking in submitting substrates bearing both an alkene and an alkyne moiety to the reaction conditions. Here silver foil was found to exclusively result in the cyclopropenation of terminal alkynes, while using copper foil resulted in only the cyclopropanation products. Finally, this reactivity was applied to a one pot Sonogashira coupling followed by

cyclopropenation of the newly formed internal alkynes. Silver foil was used as an additive for the Pd(II) catalysed Sonogashira and the catalyst for the cyclopropenation.

6. Bismuth

Interestingly an earlier mechanochemistry-enabled Barbier-type allylation of carbonyl derivatives was reported back in 2003 by Suzuki and co-workers (Figure 8c).[31] Employing bismuth shot in large excess (4-8 eq) as the zero-valent reductant, a small library of benzaldehyde derivatives was coupled with allyl bromide. and impressively one example of allyl chloride (which are usually unreactive in solution). Furthermore, more challenging acetophenone derivatives were coupled in moderate yields, and cyclohexanone (50% yield) and benzophenone (28%) substrates were also amenable. The authors demonstrated improved efficiency of bismuth metal vs. tin and indium-based protocols which led to increased by-product formation. A single electron transfer mechanism between an allyl-bismuth species and the carbonyl group – akin to those hypothesised in the magnesium-mediated 1,2-addition – was also postulated.

7. Outlook

Research in the emerging area of mechanical activation of zero-valent metals by ball-milling is diverse with early examples and applications in the generation of organometallic reagents, reductive turnover of important catalytic cross-coupling reactions, tetramerization of alkynes, reductive dimerization of alkylidene malonates and the generation of radical intermediates as early examples. Critical to the revitalisation of this important synthetic capability is the ability to mechanically activate the metal, in a manner that is essentially independent of the physical form of the input material and has initially been applied to a range of metals including magnesium, manganese, nickel, zinc, silver, and bismuth. This is further compounded by the observation that when reactions are conducted in this nature, they proceed without recourse to vigorously dried solvents or inert gas atmospheres and are consequently highly reproducible. Thus, the technique of ball-milling appears to provide a strong platform from which to further explore the chemistry of zero-valent metals. We anticipate

that this technology will enable the direct and reliable generation of hitherto difficult to obtain organometallic reagents whose reactivity could then be further explored and harnessed.

With that said there is still much to do in the area, including scaling up of such processes, whilst several of the examples highlighted here have been demonstrated on gram scale, scaling these processes to industrial manufacturing levels is not yet achieved and represents a significant target. Twin-screw extrusion holds promise in this area. In addition, there remains a comparatively small group of researchers that are currently active in the field of chemical synthesis by mechanical methods, primarily due to the non-typical equipment required, but also more will be encouraged with a comprehensive safety framework which is necessary to help facilitate adoption, especially for use in industrial settings. On this point, as a cautionary note, some finely divided metal particles can be pyrophoric in aerobic atmospheres, although none of the papers presented here report experiencing this – there are clear signs in the reported setups (especially in the case of magnesium) where precautions are built-in to the experimental design, and we direct the reader to a recent important commentary by Vilaivan.[103] As a practical note many milled reactions are reported using stainless steel jars, some trace metals present in stainless steel are not always innocent, [41] and careful control experiments or ICP-MS analysis could be used to support conclusions.

As well as building a stronger understanding of the capabilities and limitations of ball milling approaches to established zero-valent metals we anticipate a rich-seam of research using this technique to explore other metals such as chromium, iron, cobalt, copper, cerium, and indium for example; we hope this overview will inform and inspire future progress in this exciting field.

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Author Contributions

A.C.J., J.A.L., S.R.B. and D.L.B. created the initial outline for the review. All further drafts were written by contributions and discussion from all authors.

Competing Interests

The authors declare no competing interests.

References

1   Knochel, P. 1.7 - Organozinc, Organocadmium and Organomercury Reagents. in *Comprehensive Organic Synthesis* (eds. Trost, B. M. & Fleming, I.) 211–229 (Pergamon, 1991).

2   Knochel, Paul. & Singer, R. D. Preparation and reactions of polyfunctional organozinc reagents in organic synthesis. *Chem. Rev.* **93**, 2117–2188 (1993).

3   Berk, S. C., Yeh, M. C. P., Jeong, N. & Knochel, P. Preparation and reactions of functionalized benzylic organometallics of zinc and copper. *Organometallics* **9**, 3053–3064 (1990).

4   Langer, F., Schwink, L., Devasagayaraj, A., Chavant, P.-Y. & Knochel, P. Preparation of Functionalized Dialkylzincs via a Boron−Zinc Exchange. Reactivity and Catalytic Asymmetric Addition to Aldehydes. *J. Org. Chem.* **61**, 8229–8243 (1996).

5   Krasovskiy, A., Malakhov, V., Gavryushin, A. & Knochel, P. Efficient Synthesis of Functionalized Organozinc Compounds by the Direct Insertion of Zinc into Organic Iodides and Bromides. *Angew. Chem. Int. Ed.* **45**, 6040–6044 (2006).

6   Picotin, G. & Miginiac, P. Activation of zinc by trimethylchlorosilane. An improved procedure for the preparation of .beta.-hydroxy esters from ethyl bromoacetate and aldehydes or ketones (Reformatsky reaction). *J. Org. Chem.* **52**, 4796–4798 (1987).

7   Kimura, M. & Seki, M. A novel procedure for the preparation of zinc reagents: a practical synthesis of (+)-biotin. *Tetrahedron Lett.* **45**, 1635–1637 (2004).

8   Knochel, P. & Normant, J. F. Addition of functionalized allylic bromides to terminal alkynes. *Tetrahedron Lett.* **25**, 1475–1478 (1984).

9   Newman, M. S. Enolization in the Reformatsky Reaction. *J. Am. Chem. Soc.* **64**, 2131–2133

10   Ikegami, R., Koresawa, A., Shibata, T. & Takagi, K. Functionalized Arylzinc Compounds in Ethereal Solvent: Direct Synthesis from Aryl Iodides and Zinc Powder and Application to Pd-Catalyzed Reaction with Allylic Halides. *J. Org. Chem.* **68**, 2195–2199 (2003).

11   Huo, S. Highly Efficient, General Procedure for the Preparation of Alkylzinc Reagents from Unactivated Alkyl Bromides and Chlorides. *Org. Lett.* **5**, 423–425 (2003).

12   Baker, K. V., Brown, J. M., Hughes, N., Skarnulis, A. J. & Sexton, A. Mechanical activation of magnesium turnings for the preparation of reactive Grignard reagents. *J. Org. Chem.* **56**, 698–703 (1991).

13   Tanaka, K., Kishigami, S. & Toda, F. Reformatsky and Luche reaction in the absence of solvent. *J. Org. Chem.* **56**, 4333–4334 (1991).

14   Howard, J. L., Cao, Q. & Browne, D. L. Mechanochemistry as an emerging tool for molecular synthesis: what can it offer? *Chem. Sci.* **9**, 3080-3094 (2018).

15   Tan, D. & García, F. Main group mechanochemistry: from curiosity to established protocols. *Chem. Soc. Rev.* **48**, 2274-2292 (2019).

16   Kubota, K. & Ito, H. Mechanochemical Cross-Coupling Reactions. *Trends Chem.* **2**, 1066-1081 (2020).

17   Porcheddu, A., Colacino, E., De Luca, L. & Delogu, F. Metal-Mediated and Metal-Catalyzed Reactions Under Mechanochemical Conditions. *ACS Catal.* **10**, 8344-8394 (2020).

18   Friščić. T., Mottillo, C., & Titi, H. M. Mechanochemistry for Synthesis. *Angew. Chem. Int. Ed.* **59**, 1018-1029 (2020).

19   Ardila-Fierro, K. J. & Hernández, J. G. Sustainability Assessment of Mechanochemistry by Using the Twelve Principles of Green Chemistry. *ChemSusChem* **14**, 2145-2162 (2021).

20   Pérez-Venegas, M. & Juaristi, E. Mechanoenzymology: State of the Art and Challenges towards Highly Sustainable Biocatalysis. *ChemSusChem* **14**, 2682-2688 (2021).

21   Leitch, J. A. & Browne, D. L. Mechanoredox Chemistry as an Emerging Strategy in Synthesis. *Chem. Eur. J.* **27**, 9721-9726 (2021).

22   Michalchuk, A. A. L., Boldyreva, E. V., Belenguer, A. M., Emmerling, F. & Boldyrev, V. V. Tribochemistry, Mechanical Alloying, Mechanochemistry: What is in a Name? *Front. Chem.* **9**, 685789 (2021).

23   For a recent review on the synthesis of metal organic frameworks, see: Kim, S.-H., Hanson, M. V. & Rieke, R. D. Direct formation of organomanganese bromides using Rieke manganese. *Tetrahedron Lett.* **37**, 2197–2200 (1996).

24   Kubota, K., Pang, Y., Miura, A. & Ito, H. Redox reactions of small organic molecules using ball milling and piezoelectric materials. *Science* **366**, 1500-1504 (2019).

25   Schumacher, C., Hernández, J. G. & Bolm, C. Electro-Mechanochemical Atom Transfer Radical Cyclizations using Piezoelectric BaTiO₃. *Angew. Chem. Int. Ed.* **59**, 16357-16360 (2020).

26   Seo, T., Toyoshima, N., Kubota, K. & Ito, H. Tackling Solubility Issues in Organic Synthesis: Solid-State Cross-Coupling of Insoluble Aryl Halides. *J. Am. Chem. Soc.* **143**, 6165-6175 (2021).

27   Kralj, M., Lukin, S., Miletić, G. & Halasz, I. Using Desmotropes, Cocrystals, and Salts to Manipulate Reactivity in Mechanochemical Organic Reactions. *J. Org. Chem.* **86**, 14160-14168 (2021)

28   Ortiz-Trankina, L. N., Crain, J. Williams, C. & Mack, J. Developing benign syntheses using ion pairs via solvent-free mechanochemistry. *Green Chem.* **22**, 3638-3642 (2020).

29   Nicholson, W. I., Barreteau, F., Leitch J. A., Payne, R., Priestley, I., Godineau, E., Battilocchio, C. & Browne, D. L. Direct Amidation of Esters by Ball Milling. *Angew. Chem. Int. Ed.* **60**, 21868-21874 (2021).

30   Wang, G.-W., Murata, Y., Komatsu, K. & Wan, T. S. M. The solid-phase reaction [60]fullerene: novel addition of organozinc reagents. *Chem. Commun.* 2059–2060 (1996)

31   Wada, S., Hayashi, N. & Suzuki, H. Noticeable facilitation of the bismuth-mediated Barbier-type allylation of aromatic carbonyl compounds under solvent-free conditions. *Org. Biomol. Chem.* **1**, 2160–2163 (2003).

32   Haley, R. A., Zellner, A. R., Krause, J. A., Guan, H. & Mack, J. Nickel Catalysis in a High-Speed Ball Mill: A Recyclable Mechanochemical Method for Producing Substituted Cyclooctatetraene Compounds. *ACS Sustain. Chem. Eng.* **4**, 2464–2469 (2016).

33   Cao, Q., Howard, J. L., Wheatley, E. & Browne, D. L. Mechanochemical Activation of Zinc and Application to Negishi Cross-Coupling. *Angew. Chem. Int. Ed.* **57**, 11339–11343 (2018).

34   Su, W., Yu, J., Li, Z. & Jiang, Z. Solvent-free cross-dehydrogenative coupling reactions under high speed ball-milling conditions applied to the synthesis of functionalized tetrahydroisoquinolines. *J. Org. Chem.* **76**, 9144–9150 (2011).

35   Cook, T. L., Walker, J. A. & Mack, J. Scratching the catalytic surface of mechanochemistry: A multi-component CuAAC reaction using a copper reaction vial. *Green Chem.* **15**, 617–619 (2013).

36   Tan, D., Štrukil, V., Mottillo, C. & Friščić, T. Mechanosynthesis of pharmaceutically relevant sulfonyl-(thio)ureas. *Chem. Commun.* **50**, 5248–5250 (2014).

37   Fulmer, D. A., Shearouse, W. C., Medonza, S. T. & Mack, J. Solvent-free Sonogashira coupling reaction via high speed ball milling. *Green Chem.* **11**, 1821–1825 (2009).

38   Vogt, C. G., Oltermann, M., Pickhardt, W., Grätz, S. & Borchardt, L. Bronze Age of Direct Mechanocatalysis: How Alloyed Milling Materials Advance Coupling in Ball Mills. *Adv. Energy Sustain. Res.* **2**, 2100011 (2021).

39   Tireli, M., Maračić, S., Lukin, S., Kulcsár, M. J., Žilić, D., Cetina, M., Halasz, I., Raić-Malić, S. & Užarević, K. Solvent-free copper-catalyzed click chemistry for the synthesis of N-heterocyclic hybrids based on quinoline and 1, 2, 3-triazole. *Beilstein J. Org. Chem.* **13**, 2352–2363 (2017).

40   Vogt, C. G., Grätz, S., Lukin, S., Halasz, I., Etter, M., Evans, J. D. & Borchardt, L. Direct Mechanocatalysis: Palladium as Milling Media and Catalyst in the Mechanochemical Suzuki Polymerization. *Angew. Chemie - Int. Ed.* **58**, 18942–18947 (2019).

41   Sawama, Y.; Yasukawa, N.; Ban, K.; Goto, R.; Niikawa, M.; Monguchi, Y.; Itoh, M.; Sajiki, H. Stainless Steel-Mediated Hydrogen Generation from Alkanes and Diethyl Ether and Its Application for Arene Reduction. *Org. Lett.* **2018**, 20, 2892−2896.

42   Rieke, R. D., Li, P. T.-J., Burns, T. P. & Uhm, S. T. Preparation of highly reactive metal powders. New procedure for the preparation of highly reactive zinc and magnesium metal powders. *J. Org. Chem.* **46**, 4323–4324 (1981).

43   Tilstam, U. & Weinmann, H. Activation of Mg Metal for Safe Formation of Grignard Reagents on Plant Scale. *Org. Process Res. Dev.* **6**, 906–910 (2002).

44   Ley, S. V. & Low, C. M. R. Preparation of Activated Magnesium. in *Ultrasound in Synthesis* (eds. Ley, S. V. & Low, C. M. R.) 33–38 (Springer, 1989).

45   Baig, R. B. N. & Varma, R. S. Alternative energy input: mechanochemical, microwave and ultrasound-assisted organic synthesis. *Chem. Soc. Rev.* **41**, 1559–1584 (2012).

46   Rieke, R. D. & Hudnall, P. M. Activated metals. I. Preparation of highly reactive magnesium metal. *J. Am. Chem. Soc.* **94**, 7178–7179 (1972).

47   Rowlands, S. A., Hall, A. K., McCormick, P. G., Street, R., Hart, R. J., Ebell, G. F. & Donecker, P. Destruction of toxic materials. *Nature* **367**, 223–223 (1994).

48   Birke, V. Mattik, J. & Runne, D. Mechanochemical reductive dehalogenation of hazardous polyhalogenated contaminants. *J. Mater. Sci.* **39**, 5111-5116 (2004)

49   Birke, V., Schütt, C., Burmeier, H. & Ruck, W. K. L. Defined mechanochemical reductive dechlorination of 1,3,5-trichlorobenzene at room temperature in a ball mill. *Fresenius Environ. Bull.* **20**, 2794–2805 (2011).

50   Waddell, D. C., Clark, T. D. & Mack, J. Conducting moisture sensitive reactions under mechanochemical conditions. *Tetrahedron Lett.* **53**, 4510–4513 (2012).

51   Harrowfield, J. M., Hart, R. J. & Whitaker, C. R. Magnesium and Aromatics: Mechanically-Induced Grignard and McMurry Reactions. *Aust. J. Chem.* **54**, 423–425 (2001).

52   Kaupp, G. Mechanochemistry: the varied applications of mechanical bond-breaking. *CrystEngComm* **11**, 388–403 (2009).

53   Speight, I. R. & Hanusa, T. P. Exploration of Mechanochemical Activation in Solid-State Fluoro-Grignard Reactions. *Molecules* **25**, 570 (2020).

54   Pfennig, V., Villella, R., Nikodemus, J. & Bolm, C. Mechanochemical Grignard Reactions with Gaseous CO_2 and Sodium Methyl Carbonate. *Angew. Chem. Int. Ed.* doi.org/10.1002/anie.202116514. Initially reported on pre-print servers: Pfennig, V., Villella, R., Nikodemus, J. & Bolm, C. Mechanochemical Grignard Reactions with Gaseous CO2 and Sodium Methyl Carbonate. *Chemrxiv* **2021**, DOI: 10.33774/chemrxiv-2021-r0xdb

55   Takahashi, R. *et al.* Mechanochemical synthesis of magnesium-based carbon nucleophiles in air and their use in organic synthesis. *Nat. Commun.* **12**, 6691 (2021).

56   Seo, T., Toyoshima, N., Kubota, K., Ito, H. Tackling Solubility Issues in Organic Synthesis: Solid-State CrossCoupling of Insoluble Aryl Halides. *J. Am. Chem. Soc.* **143**, 6165-6175 (2021)

57   Hamdouchi, C. & Walborsky, H. M., Handbook of Grignard Reagents; (eds. Silverman, G. S., Rakita, P. E.) 145−218 (Dekker, 1996)

58   Garst, J. F. & Ungváry, F. Grignard Reagents: New Developments; (eds. Richey, H. G., Jr.) 185−275 (Wiley, 2000)

59   Garst, J. F. & Soriaga, M. P. Grignard reagent formation. *Coord. Chem. Rev.* **248**, 623–652 (2004).

60   Wu, C. *et al.* Mechanochemical Magnesium-Mediated Minisci C–H Alkylation of Pyrimidines with Alkyl Bromides and Chlorides. *Org. Lett.* **23**, 6423–6428 (2021).

61   Kim, S.-H., Hanson, M. V. & Rieke, R. D. Direct formation of organomanganese bromides using rieke manganese. *Tetrahedron Lett.* **37**, 2197–2200 (1996).

62   Cahiez, G., Duplais, C. & Buendia, J. Chemistry of Organomanganese(II) Compounds. *Chem. Rev.* **109**, 1434–1476 (2009).

63   Peng, Z. & Knochel, P. Preparation of Functionalized Organomanganese(II) Reagents by Direct Insertion of Manganese to Aromatic and Benzylic Halides. *Org. Lett.* **13**, 3198–3201 (2011).

64   Nicholson, W. I., Howard, J. L., Magri, G., Seastram, A. C., Khan, A., Bolt, R. R. A., Morrill, L. C., Richards, E. & Browne, D. L. Ball-Milling-Enabled Reactivity of Manganese Metal. *Angew. Chemie - Int. Ed.* **60**, 23128-23133 (2021)

65   Wu, S., Shi, W. & Zou, G. Mechanical metal activation for Ni-catalyzed, Mn-mediated cross-electrophile coupling between aryl and alkyl bromides. *New J. Chem.* **45**, 11269–11274 (2021).

66   Weix, D. J. Methods and Mechanisms for Cross-Electrophile Coupling of Csp2 Halides with Alkyl Electrophiles. *Acc. Chem. Res.* **48**, 1767–1775 (2015).

67   Durandetti, M., Nédélec, J. Y. & Périchon, J. Nickel-catalyzed direct electrochemical cross-coupling between aryl halides and activated alkyl halides. *J. Org. Chem.* **61**, 1748–1755 (1996).

68   Everson, D. A., Shrestha, R. & Weix, D. J. Nickel-catalyzed reductive cross-coupling of aryl halides with alkyl halides. *J. Am. Chem. Soc.* **132**, 920–921 (2010).

69   Biswas, S. & Weix, D. J. Mechanism and Selectivity in Nickel-Catalyzed Cross-Electrophile Coupling of Aryl Halides with Alkyl Halides. *J. Am. Chem. Soc.* **135**, 16192–16197 (2013).

70   Tasker, S. Z., Standley, E. A. & Jamison, T. F. Recent advances in homogeneous nickel catalysis. *Nature* **509**, 299–309 (2014).

71   Weber, J. M., Longstreet, A. R. & Jamison, T. F. Bench-Stable Nickel Precatalysts with Heck-type Activation. *Organometallics* **37**, 2716–2722 (2018).

72   Liu, C. & Szostak, M. Decarbonylative thioetherification by nickel catalysis using air- and moisture-stable nickel precatalysts. *Chem. Commun.* **54**, 2130–2133 (2018).

73   Guard, L. M., Beromi, M., M., Brudvig, G. W., Hazari, N. & Vinyard, D. J. Comparison of dppf-Supported Nickel Precatalysts for the Suzuki-Miyaura Reaction: The Observation and Activity of Nickel(I). *Angew. Chemie - Int. Ed.* **54**, 13352–13356 (2015).

74   Rodrigo, S. K., Powell, I. V., Coleman, M. G., Krause, J. A. & Guan, H. Efficient and regioselective nickel-catalyzed [2 + 2 + 2] cyclotrimerization of ynoates and related alkynes. *Org. Biomol. Chem.* **11**, 7653–7657 (2013).

75   Leto, J. R. & Leto, M. F. Tetrasubstituted Cycloöctatetraenes: Catalytic Cyclotetramerization of Propiolic Acid Esters With Tetrakis-(phosphorus trihalide)-Nickel(0) Complexes. *J. Am. Chem. Soc.* **83**, 2944–2951 (1961).

76   Meriwether, L. S., Colthup, E. C., Kennerly, G. W. & Reusch, R. N. The Polymerization of Acetylenes by Nickel-Carbonyl-Phosphine Complexes. I. Scope of the Reaction. *J. Org. Chem.* **26**, 5155–5163 (1961).

77   Stathakis, C. I., Manolikakes, S. M. & Knochel, P. TMPZnOPiv•LiCl: A New Base for the Preparation of Air-Stable Solid Zinc Pivalates of Sensitive Aromatics and Heteroaromatics. *Org. Lett.* **15**, 1302–1305 (2013).

78   Manolikakes, S. M., Ellwart, M., Stathakis, C. I. & Knochel, P. Air-Stable Solid Aryl and Heteroaryl Organozinc Pivalates: Syntheses and Applications in Organic Synthesis. *Chem. – Eur. J.* **20**, 12289–12297 (2014).

79   Chen, Y.-H., Tüllmann, C. P., Ellwart, M. & Knochel, P. Preparation of Solid Polyfunctional Alkynylzinc Pivalates with Enhanced Air and Moisture Stability for Organic Synthesis. *Angew. Chem. Int. Ed.* **56**, 9236–9239 (2017).

80   Campos, K. R., Klapars, A., Waldman, J. H., Dormer, P. G. & Chen, C.-Y. Enantioselective, Palladium-Catalyzed α-Arylation of N-Boc-pyrrolidine. *J. Am. Chem. Soc.* **128**, 3538–3539 (2006).

81   Hevia, E., Chua, J. Z., García-Álvarez, P., Kennedy, A. R. & McCall, M. D. Exposing the hidden complexity of stoichiometric and catalytic metathesis reactions by elucidation of Mg-Zn hybrids. *Proc. Natl. Acad. Sci.* **107**, 5294–5299 (2010).

82   Jin, L. et al. Revelation of the Difference between Arylzinc Reagents Prepared from Aryl Grignard and Aryllithium Reagents Respectively: Kinetic and Structural Features. *J. Am. Chem. Soc.* **131**, 16656–16657 (2009).

83   Wunderlich, S. H. & Knochel, P. (tmp)2Zn·2 MgCl2·2 LiCl: A Chemoselective Base for the Directed Zincation of Sensitive Arenes and Heteroarenes. *Angew. Chem. Int. Ed.* **46**, 7685–7688 (2007).

84   Haas, D., Sustac-Roman, D., Schwarz, S. & Knochel, P. Directed Zincation with TMPZnCl·LiCl and Further Functionalization of the Tropolone Scaffold. *Org. Lett.* **18**, 6380–6383 (2016).

85   Metzger, A., Schade, M. A. & Knochel, P. LiCl-Mediated Preparation of Highly Functionalized Benzylic Zinc Chlorides. *Org. Lett.* **10**, 1107–1110 (2008).

86   Ren, H., Dunet, G., Mayer, P. & Knochel, P. Highly Diastereoselective Synthesis of Homoallylic Alcohols Bearing Adjacent Quaternary Centers Using Substituted Allylic Zinc Reagents. *J. Am. Chem. Soc.* **129**, 5376–5377 (2007).

87   Jubert, C. & Knochel, P. Preparation of new classes of aliphatic, allylic, and benzylic zinc and copper reagents by the insertion of zinc dust into organic halides, phosphates, and sulfonates. *J. Org. Chem.* **57**, 5425–5431 (1992).

88   Bose, A. K., Gupta, K. & Manhas, M. S. β-Lactam formation by ultrasound-promoted reformatsky type reaction. *J. Chem. Soc. Chem. Commun.* 86–87 (1984)

89   Knochel, P., Yeh, M. C. P., Berk, S. C. & Talbert, J. Synthesis and reactivity toward acyl chlorides and enones of the new highly functionalized copper reagents RCu(CN)ZnI. *J. Org. Chem.* **53**, 2390–2392 (1988).

90   Tanaka, K., Kishigami, S. & Toda, F. Reformatsky and Luche reaction in the absence of solvent. *J. Org. Chem.* **56**, 4333–4334 (1991).

91   For a comprehensive review on the solid-state reactivity of fullerenes, see: Zhu, S.-E., Li, F. & Wang, G.-W. Mechanochemistry of fullerenes and related materials. *Chem. Soc. Rev.* **42**, 7535–7570 (2013).

92   Cao, Q., Stark, R. T., Fallis, I. A. & Browne, D. L. A Ball-Milling-Enabled Reformatsky Reaction. *ChemSusChem* **12**, 2554–2557 (2019).

93   Falenczyk, C., Pölloth, B., Hilgers, P. & König, B. Mechanochemically Initiated Achmatowicz Rearrangement. *Synth. Commun.* **45**, 348–354 (2015).

94   Yin, J., Stark, R. T., Fallis, I. A. & Browne, D. L. A Mechanochemical Zinc-Mediated Barbier-Type Allylation Reaction under Ball-Milling Conditions. *J. Org. Chem.* **85**, 2347–2354 (2020).

95   Everson, D. A., Jones, B. A. & Weix, D. J. Replacing Conventional Carbon Nucleophiles with Electrophiles: Nickel-Catalyzed Reductive Alkylation of Aryl Bromides and Chlorides. *J. Am. Chem. Soc.* **134**, 6146–6159 (2012).

96   Everson, D. A. & Weix, D. J. Cross-Electrophile Coupling: Principles of Reactivity and Selectivity. *J. Org. Chem.* **79**, 4793–4798 (2014).

97   Jones, A. C., Nicholson, W. I., Leitch, J. A. & Browne, D. L. A Ball-Milling-Enabled Cross-Electrophile Coupling. *Org. Lett.* **23**, 6337–6341 (2021).

98   Jones, A. C., Nicholson, W. I., Smallman, H. R. & Browne, D. L. A Robust Pd-Catalyzed C–S Cross-Coupling Process Enabled by Ball-Milling. *Org. Lett.* **22**, 7433–7438 (2020).

99   Jones, K. D., Power, D. J., Bierer, D., Gericke, K. M. & Stewart, S. G. Nickel Phosphite/Phosphine-Catalyzed C–S Cross-Coupling of Aryl Chlorides and Thiols. *Org. Lett.* **20**, 208–211 (2018).

100   Thompson, J. L. & Davies, H. M. L. Enhancement of cyclopropanation chemistry in the silver-catalyzed reactions of aryldiazoacetates. *J. Am. Chem. Soc.* **129**, 6090–6091 (2007).

101   Chen, L., Bovee, M. O., Lemma, B. E., Keithley, K. S. M., Pilson, S. L., Coleman, M. G. & Mack, J. An Inexpensive and Recyclable Silver-Foil Catalyst for the Cyclopropanation of Alkenes with Diazoacetates under Mechanochemical Conditions. *Angew. Chem. Int. Ed.*, **54**, 11084-11087 (2015).

102   Chen, L., Leslie, D., Coleman, M. G. & Mack, J. Recyclable heterogeneous metal foil-catalyzed cyclopropenation of alkynes and diazoacetates under solvent-free mechanochemical reaction conditions. *Chem. Sci.* **9**, 4650–4661 (2018).

103   Vilaivan, T. Crush It Safely: Safety Aspects of Mechanochemical Grignard Synthesis. *ACS Chem. Health Saf.* **29**, 132-34 (2022)

Fig. 1 | Use of zero-valent metals for chemical synthesis. **a**, Overview of zero-valent metals in solution-phase chemistry and mechanochemical activation. **b**, Key uses of zero-valent metals in synthesis in (i) in the preparation of organometallic species via insertion, and (ii) as terminal reductants in catalytic processes. **c**, Overview of ball milling equipment. Mixer mills show jar containing reagents and a ball, which vibrate in an oscillating shallow figure-of-eight at an inputted frequency. Planetary mills operate on a sun-wheel with jars, containing reagents and balls rotating counter-directionally to the sun wheel.

Fig. 2 | Use of magnesium(0) in mechanochemistry. **a**, Overview of chemical and physical activation methods for raw-form magnesium(0). **b**, Degradation of toxic chloroarene materials using magnesium(0) and ball milling.[47] Following reports suggest the pathway to dehalogenation proceeds via either intermediary aryl radical (via single electron reduction) or organomagnesium species (via insertion into the organohalide bond).[48-49] **c**, Formation of Grignard reagents using mechanochemistry.[51] By simple quenching of the organomagnesium species with the carbonyl derivative, leads to no formation of dimeric pinacol products formed via single electron reduction and coupling of carbonyl derivatives. Instead by conducting the 'quenching' step via milling with the carbonyl for a further 20 minutes, the by-products shown are formed in small quantities. Furthermore, in the absence of halonaphthalene starting material, these McMurry-type products are formed in substantial quantities (up to 40% of the alkene structure is formed). **d**, Formation of Grignard reagents from fluoroarenes and application to protonolysis and oxidative dimerization (using $FeCl_3$) protocols.[53] **e**, Mechanochemical synthesis of carboxylic acids from Grignard reagents and CO_2, via formation of the Grignard reagent under argon, followed by a gas exchange to CO_2 for the C-C formation step.[54] A specialised milling jar capable of being flushed with the appropriate gas and pressurised was used. SMC = sodium methyl carbonate

Fig. 3 | Use of magnesium(0) in mechanochemistry continued. **a**, Formation and utility of Grignard reagents under air using mechanochemistry.[55] For solid and poorly soluble aryl bromides, a heat-gun apparatus was used to heat the jars whilst milling. Using fine-tuned conditions, addition of butylmagnesium bromide to Weinreb amides afforded ketone products (53%), to esters formed the tertiary alcohol (61%), to nitriles formed ketone product (52%). Addition of phenylmagnesium bromide to chlorosilanes gave arylsilane products (46-62%), to chalcone substrates gave mixtures of 1,2- and 1,4-addition products biased based on additives, as well as a Kumada-Tamao-Corru coupling between aryl tosylate species and the alkyl Grignard reagent. CPME = cyclopentylmethyl ether. Ts = *para*-toluenesulfonyl. **b**, Use of magnesium(0) as a single electron reductant in mechanochemistry.[60] Mechanochemical impact of the alkyl halide on magnesium(0) surface suggested to form alkyl radical species which then add to the acceptor in Minisci-type reactivity whereby electron and proton loss reforms the heteroaromatic structure. TMEDA = *N,N,N',N'*-tetramethylethylenediamine. 1-ad = 1-adamantane.

Fig. 4 | Use of manganese(0) in mechanochemical synthesis. a, Use of manganese metal in reductive mechanochemistry, including representative scope and simplified mechanism.[64] Results from key control experiments shown, where (iii) refers to milling of just the manganese before addition to a solution-phase reaction (i). Proposed mechanism shows that the manganese(0) reduces via single electron reduction to form the intermediate radical species, or via a second single electron reduction to form the anionic carbon organomanganese intermediate. The former of these species can react with itself to form the dimerised product, and the latter can react with another molecule α,β-unsaturated ester starting material to form the dimerised product. Ar = 4-flourophenyl. **b**, Cross-electrophile coupling using manganese(0) as the stoichiometric reductant, including representative scope and plausible mechanism.[65] In this instance the nickel species is capable of inserting into the C(sp²) electrophile via oxidative addition, and then forming a radical intermediate from the C(sp³) alkyl electrophile and then fuse these two entities together via a Ni(0)/Ni(II)/Ni(III)/Ni(I)/Ni(II) cycle. XEC = cross-electrophile coupling. EWG = electron withdrawing group. Boc = *tert*-butoxycarbonyl. Bpy = 2,2'-dipyridine. TBS = *tert*-butyldimethylsilyl. DMA = N,N-dimethylacetamide. d.r. = diastereomeric ratio. E⁺ = electrophile

Fig. 5 | Use of nickel(0) in mechanochemical synthesis. **a**, Traditional reductive preparation of nickel(0) using solution based methods under inert atmospheres from Ni(II) precursors, and then mechanochemical activation under air atmospheres use ball milling. **b**, Mechanochemical alkyne tetramerization using raw form (0).[32] Using mechanochemical methods, tetramers predominate over trimers (favoured in solution), representative scope given with tetramer/trimer ratio.

Fig. 6 | Use of zinc(0) in mechanochemistry. **a**, Traditional methods for the synthesis of active zinc(0) for use in organic synthesis from raw form zinc(0) using chemical and mechanochemical techniques. TMSCl = trichloromethylsilane. **b**, Addition of Reformatsky-type reagents to fullerene (C_{60}) using mechanochemistry *via* mechanochemical formation of the organozinc species.[30] TFA = trifluoroacetic acid, *o*-DCB = *ortho*-dichlorobenzene. **c**, Mechanochemical generation of organozinc species via ball milling raw-form zinc in the presence of DMA as a liquid assisted grinding (LAG) agent, and further use in the mechanochemical Negishi coupling with aryl halide coupling partners.[33] The organozinc formation functions with alkyl bromides and also aryl iodides (although with higher zinc(0) equivalence), and a representative scope is shown. Pd-PEPPSI-IPent = [1,3-Bis(2,6-Di-3-pentylphenyl)imidazol-2-ylidene](3-chloropyridyl)dichloropalladium(II). TBAB = tetra *n*-butyl ammonium bromide. **d**, Zinc-mediated Reformatsky addition of organozinc species derived from α-halocarbonyl species to ketones, aldehydes, and imines using mechanochemistry.[92] **e**, Barbier reaction using mechanochemically activated zinc(0) to form allyl-Grignard species which then add to ketones, aldehydes, and imines.[93]

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Fig. 7 | Further examples of the use of zinc(0) in mechanochemistry. **a**, Cross electrophile coupling employing zinc(0) as a stoichiometric reductant.[97] Mechanochemical activation of the zinc(0) allows the turn-over of a nickel-based catalytic cycle similar to that shown in Figure 4b. Representative scope is shown including gram-scale example. Cross-coupling from activated alcohols such as alkyl mesylates and vinyl triflates as organo-pseudohalide species is also demonstrated. XEC = cross-electrophile coupling. 1,10-phen = 1,10-phenanthroline. **b**, Palladium-catalysed coupling of thiols and aryl halides using mechanochemistry, with representative scope shown.[98] Zinc in this case is used to reductively reform active thiol reagents, which under the standard reaction conditions form symmetrical disulfides *in situ*. Clean interconversion between thiol and disulfide was demonstrated by milling with and without zinc additive. Pd-PEPPSI-IPent = [1,3-Bis(2,6-Di-3-pentylphenyl)imidazol-2-ylidene](3-chloropyridyl)dichloropalladium(II).

Fig. 8 | Use of silver(0) and bismuth(0) in mechanochemistry. a, Silver foil-enabled cyclopropanation using mechanochemical reaction of alkenes and diazoacetate species.[101] A 1.5 inch^2 silver foil sheet was added to stainless steel jars containing stainless steel ball and reagents then milled for 16 hours. The foil sheet could then be recycled up to five times. **b**, Expansion of this chemistry to addition of diazoacetates to alkynes to form cyclopropenes.[102] In this case interesting and complementary reactivity was shown using silver and copper sheets. **c**, Sole example of the use of bismuth(0) in mechanochemistry, where addition of shot or powder of zero-valent bismuth enables Barbier type reactivity between allyl halides and carbonyl derivates.[31] The authors suggest the reaction proceeds via mechanochemical organobismuth formation followed by single electron transfer between the two reagents to form two open-shell reactive intermediates; these radical species can then couple together to form the C-C bond.