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Advances in Organometallic Synthesis with Mechanochemical Methods

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Solvent-based syntheses have long been normative in all areas of chemistry, although mechanochemical methods (specifically grinding and milling) have been used to good effect for decades in organic, and to a lesser but growing extent, inorganic coordination chemistry. Organometallic synthesis, in contrast, represents a relatively underdeveloped area for mechanochemical research, and the potential benefits are considerable. From access to new classes of unsolvated complexes, to control over stoichiometries that have not been observed in solution routes, mechanochemical (or ‘M-chem’) approaches have much to offer the synthetic chemist. It has already become clear that removing the solvent from an organometallic reaction can change reaction pathways considerably, so that prediction of the outcome is not always straightforward. This *Perspective* reviews recent developments in the field, and describes equipment that can be used in organometallic synthesis. Synthetic chemists are encouraged to add mechanochemical methods to their repertoire in the search for new and highly reactive metal complexes and novel types of organometallic transformations.

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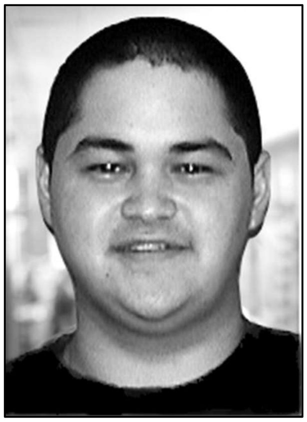

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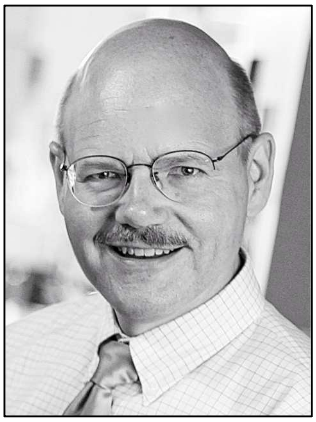

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1. Introduction

All of us involved with chemistry are reminded—perhaps not often enough—to "question our assumptions" about concepts and conventions that seem too well-established or reasonable to doubt.[1] It is prudent advice, as the failure to reconsider long-held beliefs has repeatedly stalled advances in multiple areas of the science, including synthetic studies. Entire chemical families, such as molecular complexes containing 'inaccessible' divalent lanthanides (e.g., those with Pr^{II}, Gd^{II}, Ho^{II}, and others[2, 3]), or compounds of the 'unreactive' noble gases,[4, 5] were at one time thought to be unisolable, for seemingly impeccable scientific reasons. Yet an assumption far older and more pervasive than those associated with these examples is still too rarely questioned: namely, that a solvent is indispensable for conducting reactions. The roots of this supposition go back centuries, if not millennia; the obvious dependence of biological processes on liquid water perhaps helped ingrain the idea that solvents are required for essentially all chemical transformations. In recognition of the solvent/reaction relationship, the alchemists even had a Latin phrase for it: "*corpora non agunt nisi soluta*" (bodies do not react unless dissolved).[6, 7]

It would be wrong to characterize the use of solvents as purely reflexive, however; solvent-based reactions remain the overwhelming norm in synthetic chemistry, and for empirically sound reasons. Solvents promote the interaction of reagents, affect the rates of reactions, often change the distribution of products, and disperse heat in exothermic reactions. There are significant issues to contend with when solvents are *not* used: many reactions are simply not compatible with a solvent-free approach, particularly on a large scale, where efficient mixing can be problematic. Solvents are frequently required for the extraction, separation and purification of products.[8] Thus 'solvent-free' (or often more accurately, 'reduced solvent') chemistry is not necessarily a completely green approach to synthesis.[9, 10]

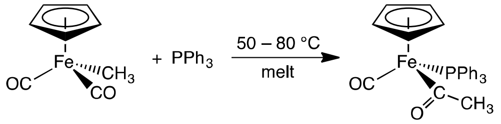
Despite such limitations, reactions conducted through grinding or milling, rather than solvent mediation, hold great promise for synthetic chemists.[11] This has already been extensively demonstrated in organic chemistry[12-15] and, to a lesser but growing extent, in inorganic and coordination chemistry,[16-19] especially in the area of metal organic frameworks (MOFs).[10, 20, 21] In addition, the formation of ionic co-crystals has been investigated through grinding methods, and supramolecular species have been constructed from metallocenes and carboxylic acids.[22-24] In contrast, what could be thought of as specifically mechanochemical *organometallic* synthesis is a comparatively underdeveloped area of research. As noted below, the first papers on the subject appeared scarcely a quarter-century ago, and only in the present decade have such solid-state syntheses become more widely appreciated, even if not broadly practiced. A goal of this *Perspective* is to call attention to recent developments in the area, and to highlight some possibilities for future exploration. This is a rapidly evolving field, and the various consequences—some advantageous, others perhaps less so—that can arise when solvents are removed from an organometallic system are not fully known. There are, however, multiple entry points into the field, several quite inexpensive and well worth exploiting. We would encourage more chemists to consider mechanochemical approaches when designing strategies for preparing new organometallic molecules and studying their reactions.[15]

1.1 A brief history of mechanochemical synthesis

It should be stressed that, despite the alchemical adage mentioned above, the grinding or milling of chemical compounds to initiate reactions is not a recently invented practice. Recognition of the distinctive activation processes involved in grinding was slow in coming, however. A detailed history of this area can be found elsewhere;[25] we summarize only a few points here. Among the earliest recorded reactions that could be considered mechanochemical is one mentioned by Theophastus of Eresos (4th century BC), who noted that the grinding of cinnabar (HgS) with vinegar in a copper vessel results in the formation of elemental mercury (i.e., $HgS + Cu \rightarrow Hg + CuS$).[26] (This process would today be considered a type 'liquid assisted grinding' (LAG), in which a very small amount of a solvent is added to assist molecular diffusion; it is sometimes considered a type of 'solvent catalysis'.[27-29]) Grinding has also long been known to facilitate displacement reactions between a metal oxide and a more reactive metal (e.g., $4\ CuO + 3\ Fe \rightarrow 4\ Cu + Fe_3O_4$). In 1820, Michael Faraday published his research on the reduction of AgCl with various active metals (Zn, Sn, Fe, Cu) by grinding in a mortar, in a procedure he called 'the dry way'.[30] Even though not all his results can be cleanly replicated today,[31] his work represented one of the first systematic studies of mechanochemical processes. The problem with interpreting the nature of these reactions is that they can be initiated with either grinding or heat (note that the HgS/Cu, CuO/Fe, and AgCl/Zn reactions above are also thermodynamically spontaneous, $\Delta G^{\circ}_{rxn} < 0$). A reasonable assumption (that word again!) made when discussing these systems was that the only direct result of grinding was the generation of heat through friction, and that any chemical changes were due to subsequent thermochemical processes. Not surprisingly, in a discussion of this topic in a well-regarded chemistry textbook from the 1880s, it was categorically stated: "One cannot assume that chemical changes come about through mechanical action itself".[32]

Within a decade, this viewpoint began to change, as at the end of the 19th century the American chemist M. Carey Lea (1823–1897) began to distinguish systematically the results of grinding and pressure from thermochemical effects. He identified chemical systems that behaved differently depending on how they were activated. Among these were the silver halides, which form elemental silver on grinding, but melt without decomposition when simply heated.[33, 34] Lea's work was important in the recognition of *mechanochemistry* (as it was termed by Wilhelm Ostwald in 1919[35]) as a distinct subdiscipline of chemistry.[36]

The extent to which transformative results can be achieved in organometallic chemistry through mechanochemical means is currently unknown, although the potential would seem to be be considerable. In fact, reactions of organometallic compounds in the solid state have been known for at least half a century.[37, 38] In this context, Coville and his collaborators must be recognized for their pioneering studies in solvent-free synthesis,[39-41] including migratory insertion and ligand substitution reactions induced by melting (e.g., the reaction depicted in eq 1, which generates 90% of the insertion product after 4 hr at 80 °C).[42]



(1)

Many of these tranformations, however, including thermally induced ligand isomerizations and reactions at surfaces, do not involve the application of mechanical energy, and are not, strictly speaking, mechanochemical in nature. The range of organometallic complexes synthesized through truly mechanochemical methods is relatively small, but growing; some examples are provided in Fig. 1.[43-50] Indicative of the relative infancy of the field is that many reaction types that have long been known in solution-based chemistry, such as C-H bond activation through cyclopalladation (Fig. 1c)[45] and cyclorhodation,[50] have been demonstrated mechanochemically only in the past few years. Combined thermal and mechanochemical synthesis is also known, such as with the solid-state thermal desolvation of the dimeric alkoxide $[\{t\text{BuZn}(\mu\text{-O}(t\text{-Bu}))(\text{thf})\}_2]$ to produce the trimeric $[\{(t\text{-Bu})\text{ZnO}(t\text{-Bu})\}_3]$; grinding of the latter generates the tetrameric cubane $[\{(t\text{-Bu})\text{ZnO}(t\text{-Bu})\}_4]$.[51]

The first reports of these organometallic reactions appeared in the early 1990s, and included the preparation of various cyclopentadienyl, indenyl, and metallocarborane complexes.[46, 52, 53] Despite the novelty of the solvent-free approach and a steady accumulation of synthesis reports on various metal complexes over the next decade,[54-57] interest in the technique remained low, at least if judged by paper citation counts. Part of the reason for this may have been that many of the compounds made in the initial years were already known from conventional solution routes, so any special advantages (apart from reduced solvent use) of the mechanochemical alternatives were not apparent. In addition, it was not always clear what role grinding or milling actually played in the processes. The products were typically removed from reaction mixtures by sublimation (with heating) or solvent extraction, and the possibility that most or all of a reaction occurred during workup could not be excluded. This was explicitly shown to be true in the formation of $Cr(acac)_3$ from the reaction of $CrCl_3$ and Na[acac]; grinding was said to have 'activated' the mixture, but no product was actually detected until external heat was subsequently applied.[58] This was also demonstrated during the formation of various monocyclopentadienyl complexes, whose reagents, although ground, had to be heated to form products.[39, 40]

One of the first reports to clarify this issue involved a detailed investigation with IR and powder X-ray diffraction of ground reaction mixtures of $FeCl_2$ and TlCp; ferrocene formation was shown to increase as a function of milling time.[43] Later, solid state NMR was added to the list of techniques used for characterizing reaction mixtures, confirming that reactions to form *cis*-$(Ph_3P)_2PtCl_2$ and *cis*-$(Ph_3P)_2PtCO_3$ from $PtCl_2$ and the other ligands occurred before any workup procedures.[59] It is now well established that organometallic syntheses can occur in a truly mechanochemical fashion, without the assistance of auxiliary heating or solvents, thus vindicating (with a nod to the informally used abbreviations of physical chemistry as 'P-chem' and electrochemistry as 'E-chem') truly 'M-chem' methods.

1.2 The Mechanochemical Regime

IUPAC has formalized the definition of a mechanochemical process as: "a chemical reaction that is induced by the direct absorption of mechanical energy".[60] Although this leaves many specifics undefined, it does help distinguish mechanochemical reactions from purely thermal ones. Heat may be involved, but it should not be the major driving force of a mechanochemical transformation. Several processes are understood to be active during grinding and milling, including mass transfer and the generation and relaxation of mechanical stress; the latter is associated with the disruption of crystalline lattices.[9] The cracking of crystals, for example, has been estimated to involve the energy equivalent of 1000–5000 K, crack propagation near velocity of sound (10^5 cm s^{-1}), and bond excitation lifetimes of ~100 fsec.[9] In this regard, there are parallels to the processes associated with ultrasonic cavitation in solution, where during bubble collapse temperatures over 1000 K for a time period of 10^{-4}–10^{-3} sec

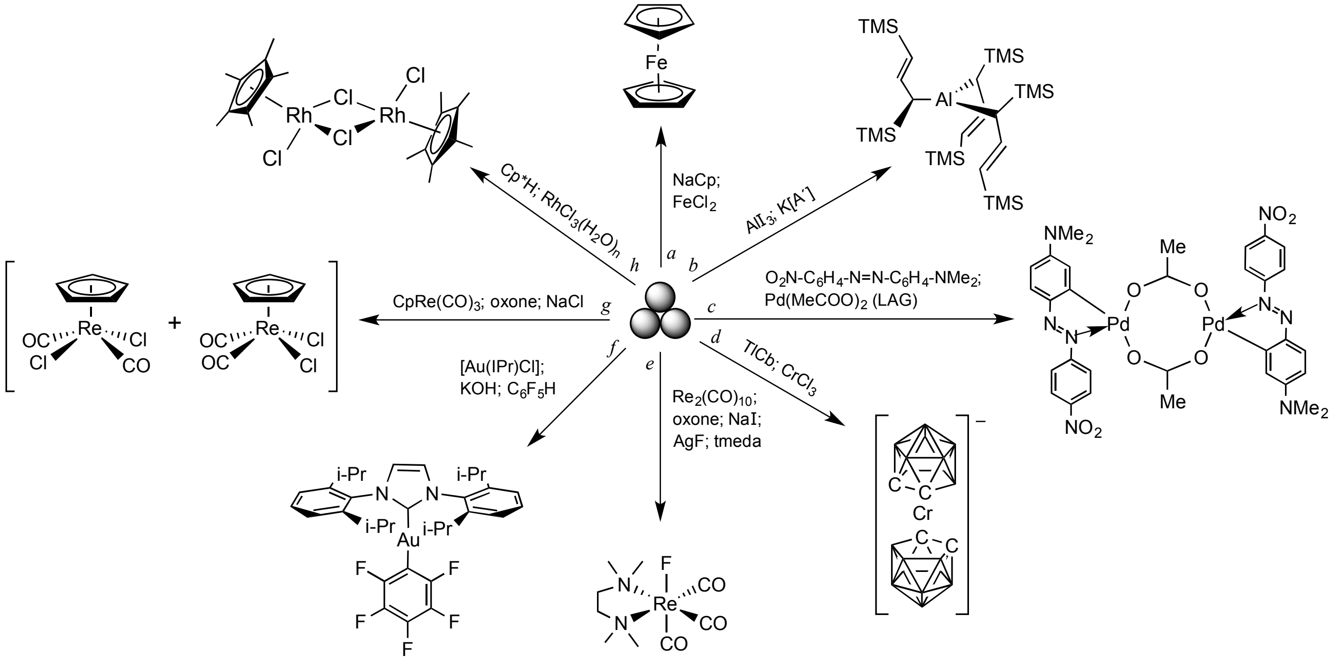


Fig. 1 A sampling of organometallic species produced through mechanochemical methods: a) ferrocene;[43] b) $Al[1,3\text{-}(SiMe_3)_2C_3H_3]_3$;[44] c) a dimeric monopallated complex from an azobenzene;[45] d) the metallocarborane $[Me_4N][Cr(C_2B_9H_{11})_2]$;[46] e) *fac*-$(TMEDA)ReCO)_3F$;[47] f) $[Au(IPr)(C_6H_5)]$ (IPr = 1,3-bis(2,6-di-isopropylphenyl)imidazol-2-ylidene);[48] g) *diag*-$CpRe(CO)_2Cl_2$ and *lat*-$CpRe(CO)_2Cl_2$;[49] h) $[(C_5Me_5)RhCl_2]_2$.[50]

and pressures of several tens of kilobars may be involved.[61] A considerable amount of energy can be added to the system with a negligible increase in macroscopic temperature. Furthermore, the magnitude of the electric field near the tip of a mobile crack has been estimated at ~10^8 V m^{-1},[62] and the high defect density introduced in crystals by grinding may also contribute as a driving force.[63] Such energies can fracture bonds and create radicals in ways that do not occur in solution. Not surprisingly, the outcome of mechanochemical reactions need not be the same as in solution, or when externally heated.

A fundamental difficulty in studying the mechanism of mechanochemical reactions is monitoring their progress; developments in this area have been reviewed.[64] In some cases, grinding can be stopped after different intervals of time and the reaction mixture analyzed; this of course disrupts the reaction environment and is unsatisfactory if volatile species are present or transiently stable intermediates are involved. In other cases, mechanochemical activation is required only to initiate a reaction, which will proceed without continuous grinding. In these instances, powder X-ray diffraction[65] or solid-state NMR[59] have been used to monitor the appearance of products and disappearance of reagents. More recently an *in situ* Raman spectroscopic technique has been developed that employs a translucent milling chamber;[66] it can be used with either crystalline or amorphous (including liquid) reaction constituents. During the synthesis of a coordination polymer and organic cocrystals, the high sensitivity of the mechanochemical outcome to reaction conditions (e.g., the mass of the grinding balls) and the effect of LAG conditions on the reaction speed could be monitored. The same technique was used to monitor the relative rates of formation of cyclopalladated reaction products and their luminescence properties.[45] A particularly elegant demonstration of real-time monitoring of reaction progress during grinding has been provided with diffraction of high-energy synchrotron X-rays though the work of Friščić and coworkers.[67] Such instrumental investigation, as valuable as it is, is not widely available, and some mechanochemical reactions can be completed on relatively short time scales (30-60 sec), providing little time for conventional data acquisition. Most reactions mechanisms are still generally inferred from an *ex situ* analysis of the product mixtures, although real-time monitoring of mechanochemical reactions is an area that will likely see considerable development in the coming years.

2. Equipment for Mechanochemical Synthesis

Mechanochemical reactions can be conducted under a range of conditions with equipment ranging from nearly free to tens of thousands of dollars. More expensive equipment can conveniently and consistently process larger amounts of reagents and decrease reaction time, but is certainly not required for exploratory work or proof-of-concept investigations. Several mechanochemical techniques ranging from low to high cost are described here. The inventory is not exhaustive: motorized mortar and pestles are commercially available, for example, but these have not found extensive use in small-scale organometallic synthesis.

2.1 Mortar and Pestle

As the most time-honoured and one of the least expensive tools for mechanochemistry, mortar and pestles are routinely employed for size reduction. Depending on the system of interest, these may also be used to promote mechanochemical reactivity. Many chemists have inadvertently done so when preparing pellets for IR spectra by grinding KBr with an organic compound, and discovering bromine incorporation into the sample. This has been done with coordination polymers to deliberately promote anion exchange.[68] Although widely available, mortar and pestle grinding can complicate establishing precise reaction conditions.[14] Factors ranging from atmospheric conditions (if performed on a benchtop), grinding frequency, strength of the (human) grinder, and mixing of reagents can all play an important role during milling reactions.[69] Despite these challenges, the venerable mortar/pestle combination offers an inexpensive entry point for examining organometallic mechanochemistry, and has been used, e.g., to produce disubstituted pyridine/pyrimidine ferrocenyl complexes through Sukuzi coupling reactions[70] and various salts or molecular complexes of $[Fe(\eta^5\text{-}C_5H_4\text{-}C_5H_4NH)_2]$ through grinding with solid carboxylic acids.[71, 72]

2.2 Glass vessel milling

In a round bottom flask partially filled with ball bearings, reagents can be gently milled when the flask is swirled by hand[73] or attached to a rotary evaporator; the latter allows for greater control of reaction conditions. An advantage of this method is the ability to visually monitor reactions; furthermore, reaction size in principle is limited only by flask volume. In practice, however, small ball bearings (ca. ≤ 6 mm dia) and slow rotational speeds must be used in order to avoid glass breakage. This consequently limits the mechanical energy that can be transferred to the reagents, which has the effect of reducing yields and extending reaction times. Nevertheless, we have found this method useful for initial studies and screenings. The tri(allyl) complexes MA'_3 ($A' = 1,3\text{-}(SiMe_3)_2C_3H_3$); M = Al, Sc) were first produced by glass flask milling; the aluminium compound was isolated in ca. 30% yield after 2 hr.[44] A more energetic, yet still inexpensive version of this milling equipment can be had with the combination of a glass vial, several ball bearings and a vortex mixer/shaker. This setup permits simultaneous grinding and UV-irradiation, and as with the flasks, *in situ* monitoring of solid-state reactions.[74]

2.3 Wig-L-Bug™ and Tube Disperser Milling

Several 'mid-level' milling techniques are available that use commercially available, easily portable equipment, such as the Wig-L-Bug™ (Dentsply Rinn.), tube dispersers (e.g., the Ultra-Turrax® Tube Drive, IKA) and lapidary grinders. These provide higher energy, greater adaptability, and increased control for moderate cost (< USD 1000). It should be noted that although such equipment is designed for grinding and mixing samples, their use in mechanochemical synthesis can tax their efficiency. The Wig-L-Bug™, tube dispersers and similar homogenizers employ different motions for the grinding of samples, so it is possible that one may be better suited to a given application than another. Typically, such units require little space and can easily be used in glove boxes. However, as these are not designed for bulk grinding, reaction scale-up is limited.

A tube disperser, which uses a spinning agitator to move ball bearings, is easily adaptable to air-sensitive chemistry. Reactions can be taken to completion in as little as 10-15 min, visually monitored (the tubes are translucent), and the products easily extracted. There are limits to the system; in particular, a practical maximum of ca. 0.5 g total reagents can be used at one time.

2.4 Mixer and Planetary Mills

Specialized ball mills such as mixer (shaker) mills and planetary mills occupy the high end of the ball-milling spectrum, and serve as gold standards for mechanochemical synthesis. Both mill types are designed for high-energy milling and size reduction of a wide range of materials over long periods, and are ideally suited for controlled, consistent mechanochemical synthesis. As with the mid-level techniques, mixer and planetary mills differ in how grinding is accomplished. Planetary mills use a spinning jar on an oppositely spinning sunwheel to impart high centrifugal and frictional forces on materials through the motion of ball bearings.[75-77] In contrast, mixer mills use cylindrical jars oscillating horizontally to impart high impact forces between the ball bearing and the curved ends of the jar. Mixer mills in general provide overall higher energy impacts than planetary mills. Planetary mills tend to have a wider distribution of mechanical energy and generally offer larger reaction volumes. Despite these differences, both mixer and planetary mills have been used to synthesize a variety of inorganic complexes.[19] As a measure of the relative amounts of energy imparted by these mills, the preparation of AlA'_3 that required 2 hr of glass flask milling (see above) was completed in 20 min in a tube disperser (80% yield) and in 88% yield after 5 min grinding at 600 rpm in a planetary ball mill.[44]

The energy input into a mechanochemical reaction can be varied not only by the design of the mill itself but also by the use of ball bearings of different materials or size, and by the frequency of grinding. Balls for grinding are available in a variety of materials, including Teflon® (2.3 g cm^{-3}), alumina (Al_2O_3, 4.0 g cm^{-3}), zirconia (ZrO_2, 5.7 g cm^{-3}), stainless steel (ca. 8.0 g cm^{-3}) and tungsten carbide (WC, 15.6 g cm^{-3}), with the denser materials providing more kinetic energy during impact. Grinding chambers themselves can be made of sundry materials, and their combination with various ball bearings can change the mechanochemical outcome, such as initiating redox chemistry.[78]

3. Removing solvent from organometallic synthesis

Just as "solventless" and "mechanochemical" are not interchangeable terms when describing reactions, the absence of a solvent during a mechanochemical synthesis can have varied consequences. For simplicity, one can anticipate three different outcomes: 1) solid-state and solution syntheses give the same or closely related products, in roughly the same yields or time (i.e., "solvent optional" reactions); 2) solution synthesis gives the desired product, whereas solid state does not; and 3) solid-state synthesis gives the desired product, but solution does not. Which of these is the most likely is not yet readily predictable. Whether the first case is obtained certainly depends on the stability of the product and how saturated the metal coordination sphere is. If the compound is commonly isolated with coordinated solvent, then its absence leaves open the possibility that other reactions may occur.

3.1 Solvent removal is optional not change the product

Coordinatively saturated metal complexes may be among the most predictably synthesized with mechanochemical methods. This is typified by ferrocene, prepared from $FeCl_2$ and TlCp,[43] or bis(indenyl)nickel, from $NiBr_2$(dme) and Na[Ind].[79] We have found the same to be true with sterically congested homoleptic allyl complexes. [ScA'_3] can be made from $ScCl_3$ and K[A′] in THF in approximately 60% yield, and mechanochemically in 15, 25, and 42% yield by glass flask, disperser, and planetary ball milling, respectively.[44] The same is true of HoA'_3 and ErA'_3, which can be made equally well in solution[80, 81] or by ball milling.[82] Some multimetallic clusters are also in this category; the 1:2 reactions of Au(C≡CPh)PPh_3 with Ag(OTf) or Ag(OTf)(tht) (tht = tetrahydrothiophene) lead to the high nuclearity species $Ag_{12}Au_{10}(C{\equiv}CPh)_{17}(OTf)_5(PPh_3)_3$ and $Ag_{26}Au_{20}(C{\equiv}CPh)_{34}(OTf)_{12}(PPh_3)_6(tht)_{12}$, respectively. The same products are produced whether the reactions are conducted in acetone or with ball milling.[83]

3.2 Solvent removal is detrimental

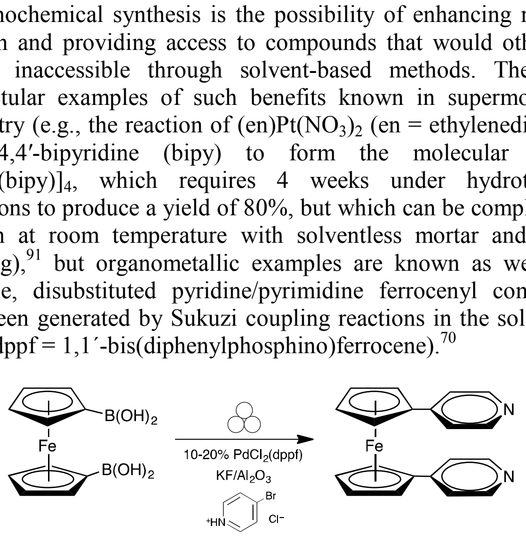
Solvent removal may not always be benign in an organometallic reaction. Some of these cases have been discussed already; e.g., when heat must be added to ground reaction mixtures to initiate a reaction that would have occurred without heating in a solvent (sec. 1.1). In other cases, limited product stability or the subsequent interaction with a byproduct (see section 4.1) can reduce the attractiveness of a mechanochemical approach. In still other cases, the effect of lack of solvent during a reaction may be more subtle. This situation was encountered during attempts to synthesize the trimethylsilylated bis(allyl)metal nickel complex NiA'_2 from the combination of the substituted THF-soluble potassium allyl K[A′] with various nickel salts.[84] Use of any of the anhydrous nickel halides NiX_2 (X = Cl, Br, I) yields the dimerized (1,3,4,6-tetrakis(trimethylsilyl)-1,5-hexadiene) ($\{A'\}_2$) as the major product. Based on the known ability of nickel centers to couple allyl ligands,[85] it was proposed that oxidative coupling of the allyl anions occurred at the surface of the insoluble NiX_2 in THF. Switching to the more soluble $NiBr_2$(dme) as the nickel allows the reaction to proceed smoothly in THF in 72% yield. Interestingly, under solvent-free ball milling conditions, the reaction, even with $NiBr_2$(dme), yields the dimerized $\{A'\}_2$ (eq 2).[82, 86]

$$NiBr_2(dme) + 2K[A'] \xrightarrow{\overset{\circ}{\circ\circ}} \{A'\}_2 + 2\,KBr + Ni\ byproducts \quad (2)$$

Clearly, dissolution of the metal reagent is critical to avoid unwanted coupling reactions. It is the absence of solubilized metal ions, rather than specifically the grinding, that promotes the coupling. Allyl coupling reactions also occur during the preparation of other first-row allyl complexes MA'_2 (M = Cr–Co)[87-90] from the metal halides MX_2 and K[A′] under solvent-free milling conditions, even though all the reactions are successful in THF.[82]

3.3 Solvent removal is advantageous

Apart from reduced solvent use, a great attraction of mechanochemical synthesis is the possibility of enhancing rates of reaction and providing access to compounds that would otherwise remain inaccessible through solvent-based methods. There are spectactular examples of such benefits known in supermolecular chemistry (e.g., the reaction of (en)Pt$(NO_3)_2$ (en = ethylenediamine) with 4,4′-bipyridine (bipy) to form the molecular square $[(en)Pt(bipy)]_4$, which requires 4 weeks under hydrothermal conditions to produce a yield of 80%, but which can be completed in 10 min at room temperature with solventless mortar and pestle grinding),[91] but organometallic examples are known as well. For example, disubstituted pyridine/pyrimidine ferrocenyl complexes have been generated by Sukuzi coupling reactions in the solid state (eq 3; dppf = 1,1′-bis(diphenylphosphino)ferrocene).[70]

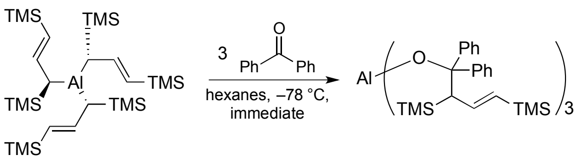


(3)

Grinding for less than an hour at room temperature was sufficient to produce the pyridine-substituted product; in contrast, a solution-based route required 2 days at reflux conditions (dioxane/H_2O/DME).[92]

The synthesis of AlA'_3 provides an instructive example of the power of organometallic mechanochemistry to circumvent otherwise intractable synthetic difficulties. Although several complexed versions of tri(allyl)aluminium are known (L:Al(C_3H_5)$_3$; L = THF, OPPh$_3$, pyridine),[93] no base-free version has been prepared in solution, even though attempts to do so date from the 1920s.[94] The use of substituted allyls has faired no better; salt metathesis between AlX_3 and K[A´] in ethereal solvents (Et_2O, THF) gives complex, unidentifiable mixtures, and in a hydrocarbon solvent (hexanes) no reactivity is observed. Attempted deprotonation of HA′ with $AlEt_3$, or $AlMe_3$ is similarly unsuccessful.

By grinding K[A′] and AlX_3 (X = Cl, Br, I), however, AlA′$_3$ can be isolated as large yellow crystals in near 90% yield on a multigram scale.[44] Despite the bulk of the A′ ligands, they do not appear to interfere with the reactivity of the metal center. In a test with benzophenone, AlA′$_3$ reacted immediately at -78 °C to yield the insertion product Al(COPh$_2$A′)$_3$ in quantitative yield (eq 4).[44]



(4)

Interestingly, treatment of the Al(C_3H_5)$_3$(thf) complex with benzophenone forms the equivalent Al(COPh$_2C_3H_5$)$_3$(THF) compound in approximately 10 min at room temperature on an NMR reaction scale.[95] The speed of reaction of AlA´$_3$ is likely a result of the unsaturation of the three-coordinate Al center, and is an illustration of the sort of enhanced reactivity that mechanochemical methods of synthesis are able to provide.

Solvent removal or reduction can be beneficial to synthesis even when the product obtained is ultimately the same. This was demonstrated in the synthesis of the CVD precursor [SrCp´$_2$(OEt$_2$)] (Cp´ = C_5Me_4(*n*-Pr)) on a 0.5 kg scale.[96] Although the compound can be produced in small amounts through conventional metathesis in diethyl ether (i.e., SrI_2 + 2 K[Cp´]), the reaction does not scale, as the reagents are poorly soluble in OEt_2, and the magnetic or mechanical stirring that is sufficient for gram-scale reactions is inadequate with larger amounts of reagents, owing partially to the density of SrI_2 (5.46 g mol^{-1}). With the aid of ball milling and the use of a small amount of OEt_2 to create a LAG environment, however, the solvated metallocene is produced in 88% yield. The ether can be subsequently removed through distillation.

4. Challenges and Opportunities

4.1 Degradation of products

A particular issue that must be addressed during mechanochemical synthesis is that, even if macroscopic temperatures do not rise significantly during grinding, a continual input of energy is involved. At the minimum, this can cause degradation of the product and place a cap on product yield. The production of ferrocene from $FeCl_2$ and TlCp was found to reach a maximum after 60 min of milling; decomposition of ferrocene was responsible for the subsequent decrease in yield as milling continued.[43] This was established in two ways; one was by grinding ferrocene itself in a ball mill; the compound degraded detectably after 75 min, with release of cyclopentadiene. A second, more interesting test was the grinding of ferrocene with TlCl; in addition to the decomposition of ferrocene, some TlCp could be detected in the mixture (eq 5).

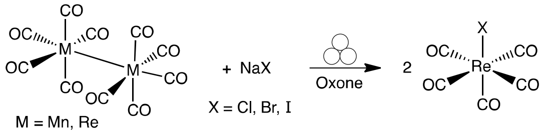
$$Cp_2Fe + 2\,TlCl \rightleftarrows FeCl_2 + 2\,TlCp \quad (5)$$

This reaction is of course the reverse of the one that formed ferrocene, and touches on the question of the extent to which equilibrium is established in mechanochemical reactions.[97] The reaction in eq. 5 also hints at another potential problem with a mechanochemical reaction; namely, that by-products of a reaction are usually in the same phase as the reactants and products, and can react with them. This may require a redesign of the reaction to avoid the formation of such species; this of course is beneficial when pursuing ‘green’ synthesis.

4.2 Multistep Synthesis

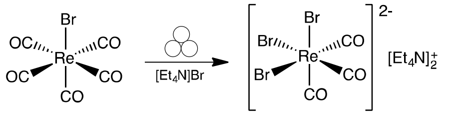
The concentrations of reagents in a solid-state reaction are high, if measured on a purely reagent/volume ratio. Yet this does not necessarily translate into the speed of mass transport of reagents, which is dependent on the grinding environment (e.g., milling balls). Although mechanochemical synthesis can increase control over reaction stoichiometries,[98-100] there can also be shifts in steroisomer ratios.[101, 102]

Despite the uncertainties in mechanism that can accompany mechanochemical reactions, advances have been made in multistep organometallic synthesis. Multistep mechanochemical coordination chemistry has been demonstrated before,[103] but even more complex transformations, involving both redox chemistry and covalent bond transformations, have been demonstrated with metal carbonyls. For example, the reaction of the decacarbonyls of manganese and rhenium with sodium halides in the presence of an oxidant (Oxone®, K[HSO$_5$]) can be carried out in a single pot reaction with yields up to 91% depending on the metal and halide.[47]

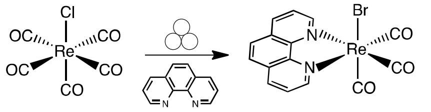


(6)

Displacement of carbonyl groups can be achieved both with (eq 7) and without (eq 8) change of metal oxidation state. Both of the final products can be obtained in one-pot reactions starting from the decacarbonyl.



(7)



(8)

Perhaps the most elaborate example known to date is illustrated in Fig. 2, in which Re$_2$(CO)$_{10}$ is converted to *fac*-(TMEDA)Re(CO)$_3$F through the agency of NaI, Oxone®, AgF and *N*,*N*,*N*´,*N*´-tetramethylethylenediamine (TMEDA).[47] The individual steps of the reaction, which can be conducted separately, comprise oxidative addition of a zero-valent metal carbonyl, halogen exchange, and addition of a chelating ligand. Most impressively, however, they can be conducted in a one-pot five-reagent process, generating the final rhenium tricarbonyl complex in 45% yield, an elegant example of *orthogonal synthesis*.[104] The potential for expanding such multicomponent reactions to other systems could be large.

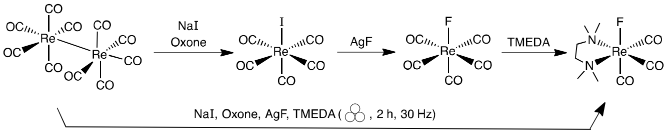
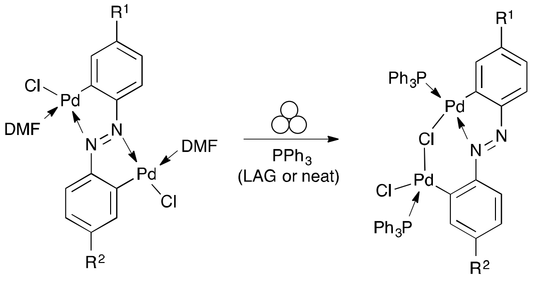


Fig. 2 Mechanochemical synthesis of *fac*-(TMEDA)ReCO)$_3$F from $Re_2(CO)_{10}$. The steps can be performed separately, but a one-pot multicomponent synthesis works also.

A different sort of multistep reaction has also been demonstrated in the reaction of dicyclopalladated azobenzenes and PPh_3 (eq. 9).[65] Although only a single reagent is added to the starting material, substantial changes were required to form the observed *cis*-alpha isomers. These included: 1) substitution of DMF with PPh_3; 2) *cis–trans* isomerization; 3) breaking of one Pd–N bond; 4) rotation of the phenyl ring with a bulky substituent and positioning of both palladium atoms on the same side of azobenzene and 5) the formation of the monochloride bridge. Although the complexity of the rearrangements did not allow complete confirmation of all the mechanistic steps, the general progress of the reaction could be followed with IR and powder X-ray diffraction.

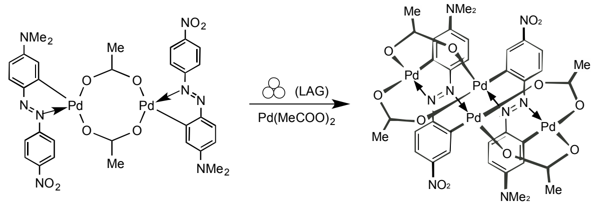


(9)

4.3 Catalyzed reactivity

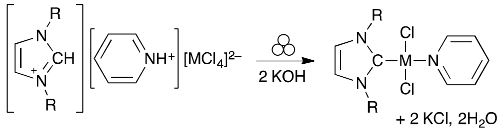
Heterogeneous catalysis is another frontier in organometallic mechanochemistry that has much room for growth. Both condensation[105, 106] and coupling reactions have been examined;[107-111] developments in this area have been reviewed.[14]

Compounds that could be used in catalytic processes have been generated through mechanochemical means. Already noted above is the production of a dimeric monopalladated complex from mechanochemical cyclometalation and C–H bond activation with an azobenzene (Fig. 1c).[45] Treatment of the complex with extra $Pd(OAc)_2$ under LAG conditions yields a dicyclopalladated compound that is not available from solution routes (eq. 10).



(10)

A few minutes grinding in an agate mortar is sufficient to initiate the reaction between K_2MCl_4 (M = Pd, Pt), pyridinium hydrochloride (py•HCl) and imidazolium hydrochloride salts in a 1:1:1 ratio to produce salts of general formula $[HL]^+[Hpy]^+[MCl_4]_2$.[112] Subsequent grinding of these salts with KOH generates the compounds *trans*-MCl_2(py)(NHC) (eq 11). The latter are catalysts of a type that find use in coupling reactions.[113, 114]



(11)

Recently Ru-catalyzed olefin metathesis, including cross-metathesis and ring-closing metathesis, has been demonstrated with commercially available catalysts, including first and second-generation Grubbs catalysts, and the second-generation Hoveyda–Grubbs catalyst (Fig. 3).[115]

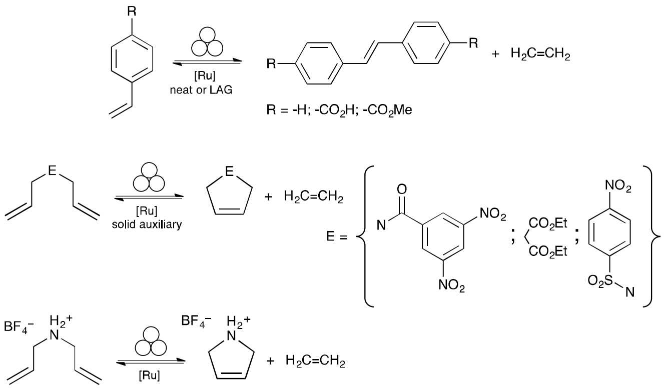
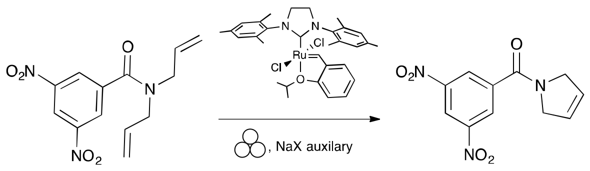


Fig. 3 Mechanochemically induced Ru-catalyzed olefin metathesis reactions, including cross-metathesis and ring-closing metathesis.

Steel-based equipment had to be avoided with neat liquids, owing to irreproducible behavior, and in some cases an inert abrasive auxiliary (e.g., NaCl, K_2SO_4) had to be added to prevent the balls from being coated with reaction mixtures, limiting the product yields. In many cases high yields were obtained, with minimal solvent use required in workup. Especially notable was the higher conversion (90+ %) observed with ball milling compared to reactions conducted under other conditions, such as with the ring-closing metathesis of *N*,*N*-diallyl-3,5-dinitrobenzamide to 1-(3,5-dinitrobenzoyl)-2,5-dihydro-1H-pyrrole (eq 12); a static solid state reaction (reagents ground, but subsequently left undisturbed) produced the pyrrole in only ca. 3% yield after one day.[116] The scalability and solvent efficiency of mechanochemically driven catalysis promises broad avenues for future exploration.



(12)

5. Conclusions

In this *Perspective*, we have shown that mechanochemistry, and specifically ball milling, offers the organometallic community a powerful synthetic tool that complements standard solution-based methodologies. 'M-chem' brings its own challenges and sets of rules to synthesis, and many of the latter are not yet fully understood. Mechanism(s) of reactions in the solid state are by no means required to follow those of their solution-based counterparts. Manipulating solid materials introduces different issues of mass transport, and can reduce the effects of steric hindrance to reactivity.[99] These changes can contribute to (as yet) unpredictable patterns of reactivity, whether they involve the promotion of undesired decomposition routes or the generation of products previously believed to be unattainable. The latter is of course a part of the great allure of mechanochemistry, especially if solvent-free species have considerably higher reactivity than do comparable solvated complexes. This has implications for the design of more active reagents and catalytic initiators.

What can be said with certainty even at this point, however, is that mechanochemistry offers a route to circumvent solvent effects in organometallic chemistry, and can be practiced with readily available or inexpensively sourced equipment. As more data are gathered that compare the outcomes of mechanochemical and solution-based reactions, the potential of solid-state synthesis to challenge prevailing assumptions about the role of solvents should become increasingly apparent. It may even help to identify those situations in which "the best solvent is no solvent at all."[117]

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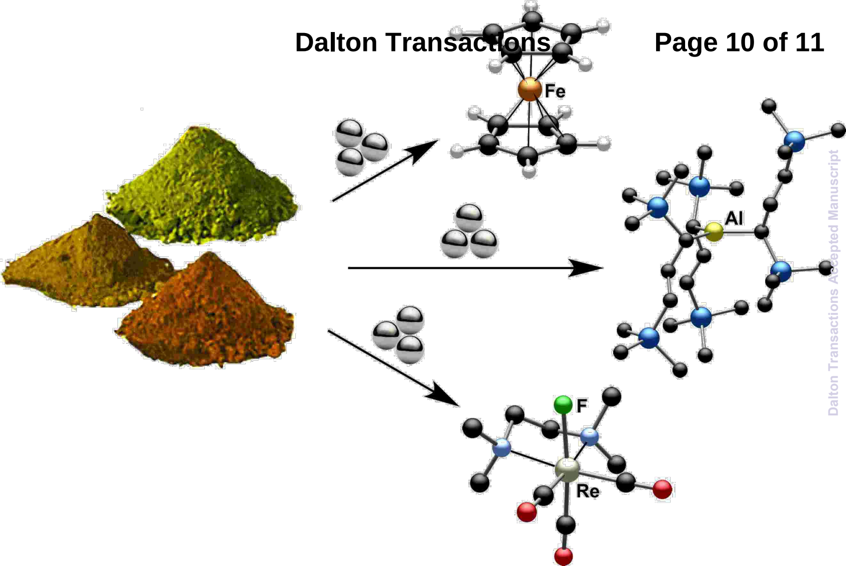
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Mechanochemical methods of synthesis (specifically grinding and milling) have not yet been widely used by organometallic chemists, but there is growing interest in their potential. This *Perspective* surveys recent developments in the field, describing the outcomes of organometallic reactions conducted in the absence of solvents.