

# ChemComm

Chemical Communications

rsc.li/chemcomm



ISSN 1359-7345

**FEATURE ARTICLE**

Lauren E. Wenger and Timothy P. Hanusa  
Synthesis without solvent: consequences for  
mechanochemical reactivity



Cite this: *Chem. Commun.*, 2023, 59, 14210

## Synthesis without solvent: consequences for mechanochemical reactivity

Lauren E. Wenger  and Timothy P. Hanusa \*

Solvents are so nearly omnipresent in synthetic chemistry that a classic question for their use has been: “What is the best solvent for this reaction?” The increasing use of mechanochemical approaches to synthesis—by grinding, milling, extrusion, or other means—and usually with no, or only limited, amounts of solvent, has raised an alternative question for the synthetic chemist: “What happens if there is no solvent?” This review focuses on a three-part answer to that question: when there is little change (“solvent-optional” reactions); when solvent needs to be present in some form, even if only in the amounts provided by liquid-assisted (LAG) or solvate-assisted grinding; and those cases in which mechanochemistry allows access to compounds that cannot be obtained from solution-based routes. The emphasis here is on inorganic and organometallic systems, including selected examples of mechanosynthesis and mechanocatalysis. Issues of mechanochemical depictions and the adequacy of LAG descriptions are also reviewed.

Received 6th October 2023,  
 Accepted 3rd November 2023

DOI: 10.1039/d3cc04929a

[rsc.li/chemcomm](http://rsc.li/chemcomm)

### Introduction

The “Fourth Way,” an approach to self-development proposed by the philosopher G. I. Gurdjieff in the early 20th century, was intended as a harmonization of the “ways”, or principles, of the body, emotions, and mind.<sup>1</sup> The “Fourth Way” was not meant to be a sophisticated combination of the other three, but a state of consciousness that existed apart from them. In a somewhat

parallel, although less esoteric manner, synthetic chemistry has three basic ways of conducting reactions—solvothermally, electrochemically, and photochemically—along with a “fourth way,” *i.e.*, mechanochemically. Like Gurdjieff’s Way, a mechanochemical reaction, defined by IUPAC as one “that is induced by the direct absorption of mechanical energy”,<sup>2</sup> is a distinct approach to conducting reactions. Mechanochemical processes have been known for far longer than the philosophical “Way”, however, with examples dating from antiquity and even pre-history (*e.g.*, the rubbing of wooden sticks to create fire), and their development has been detailed elsewhere in various

Department of Chemistry, Vanderbilt University, Nashville, Tennessee, 37235, USA.  
 E-mail: [t.hanusa@vanderbilt.edu](mailto:t.hanusa@vanderbilt.edu)

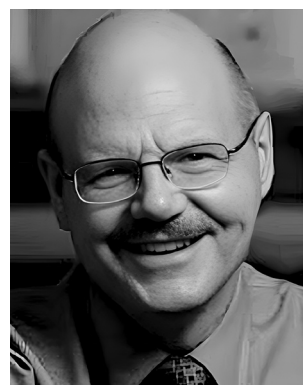


**Lauren E. Wenger**

Her graduate studies focus on the mechanochemical synthesis of main group organometallic complexes. Her research interests include the development of sustainable methodologies for organometallic and organic synthesis.

Lauren E. Wenger completed her Bachelor studies in Chemistry and Molecular Biology at Goshen College (Goshen, Indiana) in 2018. There, her research focused on organic synthesis in the lab of Prof. Douglas Schirch and on medicinal chemistry for neglected disease during an internship at AbbVie Pharmaceuticals. She joined the lab of Prof. Timothy Hanusa at Vanderbilt University (Nashville, Tennessee) in 2019.

Her graduate studies focus on the



**Timothy P. Hanusa**

His research has focused on organometallic complexes of the main group elements, and on mechanochemical approaches to organometallic synthesis across the periodic table.

Timothy P. Hanusa received his bachelor’s degree in chemistry from Cornell College (Mount Vernon, Iowa). He received his PhD in 1983 from Indiana University, Bloomington, working on heteroboranes under the direction of Lee J. Todd. After postdoctoral research on organolanthanides with William J. Evans at the University of California, Irvine, he joined the chemistry faculty at Vanderbilt University in Nashville, Tennessee in 1985, where he is now Professor













Fig. 5 Product selectivity for reactions of  $\text{K}[\text{O}^t\text{Bu}]$  and  $\text{Cp}_2\text{TiCl}_2$  (2:1 molar ratio) under solution and mechanochemical conditions.<sup>40</sup>

mechanochemically from  $\text{AsI}_3$  and  $\text{SbCl}_3$ , respectively, and 3 equiv.  $\text{K}[\text{A}']$ .<sup>59</sup> The  $[\text{MA}'_3]$  complexes are formed as two diastereomers, one of  $\text{C}_1$  ( $R,S,S$ ) symmetry and one of  $\text{C}_3$  ( $R,R,R$ ) symmetry, and the  $\text{C}_1$ : $\text{C}_3$  ratio varies with the preparation method (Fig. 6). The asymmetric  $\text{C}_1$  form is the major product from both solution and dry grinding methods for As and Sb, but compared to preparation in hexanes solution, the mechanochemical route increases the relative amount of  $\text{C}_1$  by a factor of 3.3 for As and 1.5 for Sb. The difference in selectivity has been attributed to the asymmetric environment around the As or Sb centers that is provided by the layered crystal lattice of each metal precursor, an asymmetry that disappears when the reagents are dissolved.

Sometimes reagent ratios can be adjusted to bring the results from mechanochemical reactions in line with expectations from stoichiometry. For example, depending on the R group, calcium amides  $[\text{Ca}(\text{NR}_2)_2]$  can serve as hydrocarbon-soluble sources of  $\text{Ca}^{2+}$  ions for organometallic synthesis,<sup>60</sup> as non-nucleophilic bases for enolizations,<sup>61</sup> and they have roles in catalysis.<sup>62</sup> The bis(trimethylsilyl)amido derivative,  $[\text{Ca}(\text{N}(\text{TMS})_2)_2]$ , is an exemplar of this class,<sup>63</sup> and multiple synthetic routes have been developed for it,<sup>64</sup> including metathetical preparations starting from various calcium salts.<sup>60a,61a,65</sup> These solvent-based syntheses are marked by relatively long reaction



Fig. 6 Diastereomeric forms of  $[\text{MA}'_3]$ . The  $\text{C}_1$  forms were crystallographically characterized for  $\text{M} = \text{As}, \text{Sb}$ ; the  $\text{C}_3$  forms were calculated.<sup>59</sup>

times (ranging from 3 hours to 5 days),<sup>64d</sup> the frequent formation of solvated species (with THF, DME, or  $\text{Et}_2\text{O}$ ), and most seriously with the salt metathesis methods, the simultaneous generation of calciate species,  $[\text{M}\text{Ca}(\text{NR})_3]$  ( $\text{M} = \text{Li}, \text{K}$ ;  $\text{R} = \text{N}(\text{TMS})_2$ ). A mechanochemical version of this system, which involves the milling of a 1:2 ratio of  $\text{CaI}_2$  and  $\text{K}[\text{NR}_2]$ , also produces a mixture of  $[\text{Ca}(\text{NR}_2)_2]$  and  $[\text{K}\text{Ca}(\text{NR}_2)_3]$ , but when the starting ratio of  $\text{CaI}_2$  and  $\text{K}[\text{NR}_2]$  is lowered to 1:1, a calciate-free product mixture forms during a 10 min grind. The use of the larger amounts of  $\text{CaI}_2$  evidently serve to suppress the formation of the calciate.

### Type 2 reactions: only a solvent-containing synthesis gives the desired product

Serious issues can arise when solvent is removed from a reaction environment. Some of these are matters of scale, as reactions that might be conducted successfully on a sub-gram laboratory scale can fail when they are attempted on multigram or larger amounts.<sup>66</sup> Some of these issues could potentially be addressed through different equipment choices, for example, specially designed mills or screw extrusion devices, or resonant acoustic mixers, which can be built to handle kilograms of reagents.<sup>14,67</sup> Apart from the basic issues of mixing, there are fundamental chemical issues that must be addressed, such as the dispersion of heat in highly exothermic reactions, which solvents can do efficiently. Critical reaction intermediates may be stabilized in the presence of solvents, and solvent removal may lead to deleterious changes in reaction mechanisms and outcomes.

Unless there are special considerations (*e.g.*, the final product must be a solvate or hydrate), the number of reagents that cannot form the desired product under mechanochemical activation and strictly require a solution environment may be relatively small. For example, the palladium  $\beta$ -diketonate  $\text{Pd}(\text{hfac})_2$  ( $\text{hfac} = \text{hexafluoroacetylacetonate}$ ) is readily formed between  $\text{Na}_2[\text{PdCl}_4]$  and  $\text{Na}[\text{hfac}]$  in solution.<sup>68</sup> Grinding the solids together at room temperature for 2 h, however, leaves only an intimate mixture of the reagents.<sup>69</sup> The reaction can be made to occur by heating the ground reagents and ultimately subliming the product, although such heating is not necessary in solution.

Liquid-assisted grinding and the related technique of solvate-assisted grinding (SAG)<sup>23</sup> have been used to extend the reach of mechanochemical reactions. The organic cocrystal formation experiments with hydrates that were used to establish the  $\eta$  scale have their counterparts in coordination chemistry. For example, experiments to form calcium urea sulfate ( $[\text{Ca}(\text{urea})_4]\text{SO}_4$ ) from anhydrous calcium sulfate and urea have found that essentially no reaction occurs between the reagents when they are ground at either room temperature or at 70 °C. Addition of LAG quantities of water to the reagents makes little difference. With the use of a hydrated sulfate  $\text{CaSO}_4 \cdot x\text{H}_2\text{O}$  ( $x = 0.5, 2$ ), however, the reaction is quantitative after an hour of milling in a mixer mill at both room temperature and 70 °C, demonstrating the importance of coordinated water to the reaction progress.<sup>31b</sup> A related result was observed in the formation of  $\text{Ca}[\text{urea}]_4(\text{H}_2\text{PO}_4)_2$  from the milling of urea, urea





Fig. 7 Reaction of  $\text{MX}_2$  ( $\text{M} = \text{Cr, Fe, Co}$ ) with  $\text{K}[\text{A}']$  in THF produces the intended  $[\text{MA}'_2]$  complexes via halide metathesis. Grinding the reagents together without solvent leads to a redox process with metal reduction and ligand coupling.

phosphate, and a calcium source ( $\text{CaCO}_3$  or  $\text{Ca}(\text{OH})_2$ ). Although the reaction will proceed with  $\text{CaCO}_3$ , and thus is not technically a type 2 reaction as defined here, the rate is much faster with  $\text{Ca}(\text{OH})_2$ . A neutralization reaction between  $\text{Ca}(\text{OH})_2$  and urea phosphate generates water, which then autocatalyzes the reaction even beyond the rate of externally added water.<sup>17c</sup>

The use of LAG or SAG to rescue reactions from undesirable outcomes is also known for organometallic systems. Previous work by our group and others has demonstrated that the preparation of substituted transition metal allyl complexes  $[\text{MA}'_2]$  of chromium,<sup>70</sup> iron,<sup>70a</sup> and cobalt<sup>71</sup> from the appropriate dichloride or acetylacetonate and  $\text{K}[\text{A}']$  proceeds in high yield ( $\geq 65\%$  with the dichlorides) in THF solution. When attempts are made to prepare these complexes in the solid state with the dichlorides, dry grinding gives very low yields of the desired metal complexes ( $\leq 12\%$ ), and instead promotes an undesired redox reaction to afford the substituted hexadiene  $\{\text{A}'\}_2$  and reduced metal (Fig. 7).<sup>23</sup> However, when small amounts of solvent are introduced to the mechanochemical reactions through LAG, the yield increases with the amount of solvent added, as shown in Fig. 8. This illustrates the need for at least small quantities of solvent in these reactions to obtain the allyl complexes in practical yields.

The effectiveness of LAG as a synthetic enhancement is clearly not uniform. An illustration of this is provided by the synthesis of  $[\text{NiA}'_2]$ , a bis(allyl) complex closely related to the just-described  $[\text{MA}'_2]$  compounds. In a detailed investigation of its synthesis, a wide variety of nickel halide precursors,



Fig. 8 Yields of  $[\text{MA}'_2]$  complexes ( $\text{M} = \text{Cr, Fe, Co}$ ) under conditions of neat milling, two regions of LAG, and in THF solution.<sup>23</sup>

including solvates of THF, pyridine (py), DME, and water, were used under neat milling, milling with LAG, and solution conditions. The identity of the nickel salt remains a key variable in the outcome of the reaction, regardless of whether or not LAG is used.  $[\text{NiA}'_2]$  can be prepared in modest to good yields by combining soluble  $\text{Ni}(\text{acac})_2$ <sup>71b</sup> or the modestly soluble  $[\text{Ni}(\text{dme})\text{Br}_2]$ <sup>72</sup> with  $\text{K}[\text{A}']$  in THF solution. In contrast, grinding  $[\text{Ni}(\text{dme})\text{Br}_2]$  and  $\text{K}[\text{A}']$  in the absence of solvent provides only a trace amount (3%) of  $[\text{NiA}'_2]$ ,<sup>23</sup> although adding THF in LAG quantities ( $\eta = 0.6$ ) boosts the yield to  $> 50\%$ , approaching solution-based outcomes. In contrast, the reaction of  $\text{NiCl}_2$  and  $\text{K}[\text{A}']$  under ball-milling conditions produces only a trace of the  $[\text{NiA}'_2]$  complex (the coupled allyl ligand  $\{\text{A}'\}_2$  and nickel black are the major products), and attempting LAG with 5 ( $\eta = 0.70$ ) or 10 ( $\eta = 1.40$ ) equiv. of THF yields only 1.5% and 2%, respectively, of  $[\text{NiA}'_2]$ .

More complex is the behavior of pyridine as a regular solvent, as a LAG additive, and as a solvated nickel precursor, *i.e.*,  $[\text{Ni}(\text{py})_4\text{Cl}_2]$ . In contrast to the behavior in THF, the reaction of anhydrous  $\text{NiCl}_2$  and  $\text{K}[\text{A}']$  in pyridine solution does give  $[\text{NiA}'_2]$  in low yield, but  $\{\text{A}'\}_2$  is formed as well, indicating that both metathetical and redox reaction pathways are involved. Interestingly, with the use of pyridine in LAG quantities (5 equiv. per metal center,  $\eta = 0.70$ ), the yield of  $[\text{NiA}'_2]$  from  $[\text{Ni}(\text{OH})_2\text{Cl}_2]$  increases to 46%, with no concomitant formation of  $\{\text{A}'\}_2$ . Finally, use of the pyridine solvate  $[\text{Ni}(\text{py})_4\text{Cl}_2]$  in a dry grinding reaction (with an effective  $\eta = 0.55$ ) proves the most successful of all, giving the nickel complex in 69% yield with no  $\{\text{A}'\}_2$  observed.

LAG is beneficial in the formation of Grignard reagents; although some investigators have worked under solvent-free conditions, as noted above, the addition of THF, 2-MeTHF or THP can greatly increase yields. For example, the Bolm group generated Grignard reagents in air (use of LiOH as an additive was beneficial), then combined them with gaseous  $\text{CO}_2$  or sodium methyl carbonate in the presence of LAG quantities of 2-MeTHF to produce carboxylic acids in a one-pot, three-step mechanochemical process.<sup>73</sup> Nickel-catalyzed Kumada-Tamao-Corriu coupling reactions between mechanochemically synthesized organomagnesium nucleophiles and aryl tosylates under ball-milling conditions will proceed with LAG amounts of THF.<sup>47</sup> Even more recently, the Ito group has been able to translate this chemistry to calcium-based heavy Grignard reagents; commercially-available calcium can be activated *in situ* by ball milling in air with an aryl halide, without the need for toxic and/or strong reducing agents (*e.g.* liquid  $\text{NH}_3$ , lithium biphenylide) or inert atmospheres,<sup>74</sup> conditions that are rigorously required for the solution-based counterparts.<sup>75</sup>

### Type 3 reactions: only the solid-state synthesis gives the desired product, or provides a new product not observed from solution synthesis

A compelling feature of mechanochemistry is the ability to prepare novel compounds that are not accessible from solution routes.<sup>76</sup> Apart from “green” benefits like reduced use of



solvent and energy, access to previously unobtainable compounds has become one of the most exciting frontiers of synthetic mechanochemistry.<sup>16,77</sup>

A straightforward example of this is the preparation of di(indenyl)beryllium, (C<sub>9</sub>H<sub>7</sub>)<sub>2</sub>Be.<sup>78</sup> Unlike the presumably similar beryllocene, Cp<sub>2</sub>Be, that readily forms in Et<sub>2</sub>O solution,<sup>79</sup> attempts to form the indenyl analogue in solution from BeBr<sub>2</sub> and K[Ind] were unsuccessful, yielding only various solvated beryllium bromides. In contrast, dry grinding of a 2 : 1 mixture of K[Ind] and BeBr<sub>2</sub> produced the desired (C<sub>9</sub>H<sub>7</sub>)<sub>2</sub>Be in high yield. It could be that the solvating power, driven by high Be...O interaction energy, that allows ethers to dissolve BeBr<sub>2</sub> also prevents further reaction with the potassium indenide. X-ray crystallography of (C<sub>9</sub>H<sub>7</sub>)<sub>2</sub>Be revealed a monomeric, mixed-hapticity (η<sup>5</sup>/η<sup>1</sup>) metallocene, very similar to the related beryllocene. Analogous mechanochemical means were used to prepare a bulky mono(indenyl) species [Be(1,3-TMS<sub>2</sub>Ind)Br], where the indenyl group binds in an η<sup>5</sup> manner. The same reaction again fails in solution.

An initially unanticipated development in mechanochemical synthesis is that it is possible to form solvate-free products from compounds originally made in solution, and these need not be the same as those produced mechanochemically from the same reagents. Examples are found in the chemistry of main-group allyl complexes. For instance, although π-bound, or η<sup>3</sup>, allyls are commonly found with the alkali metals and the heavier metals of group 2 (calcium, strontium, and barium), beryllium and magnesium complexes commonly display σ-bound, or η<sup>1</sup>, conformations, and the latter was thought at one point to be the preferred binding mode for magnesium.<sup>80</sup> In fact, halide metathesis of MgBr<sub>2</sub> with K[A'] in ethers produces the corresponding monomeric adducts [MgA'<sub>2</sub>(σ-L)<sub>2</sub>] (L = THF, Et<sub>2</sub>O).<sup>10</sup> With prolonged drying under vacuum, the Et<sub>2</sub>O adduct can be desolvated to yield the dimeric [(MgA'<sub>2</sub>)<sub>2</sub>] (Fig. 9(a)).<sup>10</sup>

Owing to the activity displayed by the dimer as a polymerization initiator (see Section 4), a solvent-free mechanochemical route was attempted in order to avoid the lengthy desolvation process. A 10 min milling of a 1 : 2 ratio of MgBr<sub>2</sub> and K[A'], followed by extraction of the ground mixture with hexanes did not lead to the formation of the neutral [(MgA'<sub>2</sub>)<sub>2</sub>], but rather to the magnesiate product [MgK<sub>2</sub>A'<sub>4</sub>]<sub>∞</sub>, which forms a coordination polymer in the solid state (Fig. 9(b)).<sup>81</sup> Intriguingly, one of the ligands is η<sup>3</sup>-bound to the magnesium, which is possible only because Mg is formally 4-coordinate (the allyl occupying 2 coordination sites) which is compatible with an sp<sup>3</sup> hybridized metal center in a way that higher-coordinate, usually solvated Mg centers are not. Two features of the synthetic outcomes are notable: (1) solvent-free versions of molecules obtained from solution-based reactions may not be the same as those generated mechanochemically; (2) although a 1 : 2 ratio of MgBr<sub>2</sub> and K[A'] was ground together, a balanced equation can be written if a 1 : 4 ratio were operational (Fig. 9(b)). Such nonstoichiometric outcomes are noted elsewhere in this review, and are perhaps a reflection



Fig. 9 Reaction between MgBr<sub>2</sub> and the potassium salt of the bulky ligand [A']: (a) in ethers, a monomer with η<sup>1</sup>-bonded allyl ligands is formed. The ethers can be removed from the diethyl etherate adduct to form a dimeric complex with bridging and terminal allyl ligands; (b) the mechanochemical outcome, leading to a coordination polymer that displays an η<sup>3</sup>-bound allyl ligand.

of the high-energy, far from equilibrium conditions that are often present in mechanochemical reactions.

An even more complex relationship between solution-based and mechanochemical reactions is found in a set of tin(II) allyl complexes. First prepared in THF solution from tin(II) chloride and 3 equiv. K[A'], the anionic tris(A')tin(II) species was isolated as a monomeric THF adduct, [K(SnA'<sub>3</sub>)(thf)].<sup>82</sup> Curiously, from milling a 1 : 2 ratio of SnCl<sub>2</sub> to K[A'], the same stannate can be obtained, but now in the form of a coordination polymer ([KSnA'<sub>3</sub>]<sub>∞</sub>), as the THF is missing that is evidently critical for the formation of the monomeric species (Fig. 10). The solvated and unsolvated forms contain three σ-bound allyls at tin, each of which are π-bound to the potassium cation; this μ:η<sup>2</sup>:η<sup>1</sup>-bonding arrangement of each allyl to the metals is isostructural with the related beryllium<sup>83</sup> and zinc<sup>84</sup> tris(A') complexes.

If the SnCl<sub>2</sub>:K[A'] ratio is adjusted to 1 : 3, to match that used in solution, a redox reaction occurs on 5 min of grinding, yielding a chiral Sn(IV) tetraallyl complex [SnA'<sub>4</sub>], in addition to [KSnA'<sub>3</sub>]. Extending the grinding to 15 min produces a stereochemical transition to a *meso* (R,S,R,S) version of the same tetraallyl complex, along with the chiral-[SnA'<sub>4</sub>] and [KSnA'<sub>3</sub>].<sup>85</sup> The disproportionation of Sn(II) into Sn(IV) and Sn(0) appears to be vital to the success of the synthesis, as attempts to prepare [SnA'<sub>4</sub>] directly from tin(IV) halides are unsuccessful. In such cases, reduction-oxidation occurs, resulting in {A'}<sub>2</sub> and tin metal as the major products.<sup>38b</sup>

Metal organic frameworks (MOFs) have emerged as versatile candidates in heterogeneous catalysis, and can be used to generate invaluable organic compounds.<sup>86</sup> In addition, MOFs





Fig. 10 Section of the coordination polymer of  $[KSnA_3]_\infty$ . The  $K \cdots C(H_3)$  contact (3.20 Å) does not exist in the solvated, solution-derived complex, although the coordination environment around the  $Sn(II)$  center is the same.

can be designed with specific structural motifs that deliver improved electrochemical and physical properties, and are tunable both in terms of porosity and chemical functionality.<sup>87</sup> Although mechanochemistry is often used to prepare MOFs that are already known in solution,<sup>67c</sup> this is not always the case, and there are topologically novel MOFs that are not available from solution-based reactions.<sup>88</sup> As an example, mercury(II) imidazolate MOF  $[Hg(Im)_2]$  was first isolated as a 3D structure with an interpenetrated diamondoid structure by Masciocchi and coworkers *via* a solution synthesis (Fig. 11(a)).<sup>89</sup> Later, the MOF was prepared with mechanochemical means, which afforded a novel, more stable polymorph, based on square-grid layers.<sup>90</sup> Attempts to reproduce the solution method afforded the same square-grid structure, with no evidence of the diamondoid structure, except as a short-lived intermediate in the mechanochemical synthesis (Fig. 11(b)). While the “disappearing polymorphs” phenomenon is a known problem for organic syntheses and pharmaceuticals, this was its first documented occurrence in metal-containing coordination compounds.<sup>90</sup>

## 4. Mechanochemistry and catalysis

Mechanochemistry is a promising means to prepare new organometallic complexes to be used as catalytic initiators. In principle, the absence of coordinated solvent leaves open coordination sites for substrates to bind more easily, without needing to displace a ligand first. This hypothesis was explored with various magnesium allyls, whose preparation is discussed above, and their initiation of polymerization of methyl



Fig. 11 (a) Portion of the crystal structure of  $dia-Hg(Im)_2$ , prepared in aqueous solution; (b) portion of the crystal structure of  $sql-Hg(Im)_2$ , prepared with mechanochemical means.

methacrylate (MMA). Room temperature polymerizations of MMA were performed using  $[K_2MgA'_4]$ ,  $[(MgA'_2)_2]$  and  $[MgA'_2(thf)_2]$ . At a monomer : initiator ratio of 100 : 1, the yield of PMMA for each initiator after 24 h was 72%, 19%, and 0%, respectively.<sup>81</sup> Interestingly,  $[K_2MgA'_4]$  was more active at lower temperature (0 °C) and at lower concentration (1000 : 1), giving PMMA in 89% yield after 1 h; in contrast,  $[(MgA'_2)_2]$  was less active, and did not initiate polymerization under these conditions. This system clearly demonstrates the enhanced ability of unsolvated magnesium allyls to polymerize MMA.

Even though  $[MgA'_2(thf)_2]$  is inactive for MMA polymerization, the calcium analogue  $[CaA'_2(thf)_2]$  is quite active, producing isotactic PMMA in 77% yield after 30 seconds at 0 °C in toluene.<sup>64,91</sup> Activity is reduced in THF solution to 18% conversion under the same conditions, probably due to ion solvation effects of polar solvents.<sup>92</sup> As net negative charges correlate with anionic polymerization activity,<sup>93</sup> an anionic calcite was sought by milling a mixture of  $CaI_2$  and  $K[A']$ . The crystal structure of  $[K(CaA'_3)]$  reveals it to be a coordination polymer, with  $\eta^3$ -bound allyl ligands around calcium; one allyl is terminally bound on calcium, and two bridge calcium and potassium in a  $\mu_2-\eta^3:\eta^3$  mode (Fig. 12).  $[K(CaA'_3)]$  was identified as a polymerization initiator for both MMA and isoprene and compared to  $[CaA'_2(thf)_2]$ .  $[CaA'_2(thf)_2]$  was more active for MMA polymerization, with a turnover frequency of  $317 \text{ min}^{-1}$  at 0 °C, while  $[K(CaA'_3)]$  was slower at  $61 \text{ min}^{-1}$  at 0 °C. Both produced isotactic-enriched PMMA. The results were the inverse for polymerization of isoprene. While  $[CaA'_2(thf)_2]$  was inactive,  $[K(CaA'_3)]$  produced high molecular weight, isotactic-enriched poly(isoprene) in 98% yield after 12 h at room temperature. The role of coordinating solvents is the likely cause of the inactivity of  $[CaA'_2(thf)_2]$ , as the addition of one equivalent of THF to  $[K(CaA'_3)]$  completely inhibits activity. The room temperature and atmospheric pressure used in these studies represent the mildest conditions yet reported for any calcium-based initiator for isoprene polymerization.<sup>93</sup>

Owing to the low cost and toxicity, and high natural abundance of aluminium,<sup>94</sup> the use of aluminium-based polymerization initiators is increasing in popularity. The desire to produce an unsolvated complex that could potentially serve



Fig. 12 Section of the coordination polymer of  $[K(CaA'_3)]$ . Mechanochemically generated, it is active as an isoprene polymerization initiator; addition of THF inhibits its reactivity.



as an initiator was a target in the preparation of a substituted tris(allyl)aluminium complex. The parent tri(allyl)aluminium is known only as a base adduct,  $[\text{Al}(\text{C}_3\text{H}_5)_3 \cdot \text{S}]$  (S = THF, pyridine,  $\text{OPPh}_3$ ).<sup>95</sup> Base-free  $[\text{AlA}'_3]$  can only be accessed through mechanochemical methods, and various attempts to prepare it in solution have been unsuccessful.<sup>96</sup> In stoichiometric reactions, e.g., an insertion reaction with benzophenone,  $[\text{AlA}'_3]$  was found to be more reactive than  $[\text{Al}(\text{C}_3\text{H}_5)_3 \cdot \text{THF}]$ , a difference ascribed to the lower coordination number of the Al center. On the possibility that the improved reactivity would be maintained in a catalytic context, both  $[\text{AlA}'_3]$  and related compounds of the form  $[(\text{NHC})\text{AlCl}_x\text{A}'_{3-x}]$  (NHC = IMes or IDipp and  $x = 1-3$ ) were studied as initiators of L-lactide polymerization.<sup>97</sup> Six NHC-containing complexes,  $[\text{AlA}'_3]$ , and  $[\text{Al}(\text{O}^i\text{Pr})_3]$  (as a reference), were tested, and all of them initiated polymerization to some degree. Activity of the NHC complexes increased with increased allyl incorporation, but  $[\text{AlA}'_3]$  was the most effective, displaying 81% conversion after 120 h. While initiation was slow compared to  $[\text{Al}(\text{O}^i\text{Pr})_3]$  (comparable conversion was seen in 27 h), the polylactide generated from  $[\text{AlA}'_3]$  had higher molecular weight ( $M_n$ ) and lower polydispersity than that produced from  $[\text{Al}(\text{O}^i\text{Pr})_3]$ .<sup>97</sup>

### Direct mechanosynthesis and mechanocatalysis

Numerous mechanochemical reactions involve direct mechanosynthesis or direct mechanocatalysis, in which elemental metal additives (in the form of turnings, powder, or foil) or components of the milling assembly (vials and balls) are incorporated into products or catalyse organic transformations.<sup>77a,98</sup> Direct mechanocatalysis is simpler than using catalyst initiators used in homogenous catalysis because many initiators have a limited shelf life, are available with erratic quality,<sup>99</sup> often require inert atmospheres, and are difficult to recover. In contrast, certain reactions that are air- and moisture-sensitive in homogenous catalysis can be conducted in ambient atmospheres with direct mechanocatalysis.<sup>47,100</sup> Thus, direct mechanosynthesis/catalysis is often a safer, cheaper, and easier alternative to solvothermal methods. Various transition metals including Pd and Ag have been used in these reactions.<sup>98b,101</sup> There is substantial interest in catalytic reactions based on earth-abundant metals,<sup>102</sup> although only a few of them have been studied *via* direct mechanochemistry.<sup>103</sup>

### Catalysis in the ball mill

Mechanochemistry invites creativity in reaction set-up. The Mack group has explored a variety of alternative methods of reaction environments to increase recyclability, decrease waste, and reduce the need for designer catalysts, by using simple metal foils as heterogeneous catalysts. This method was first introduced in the cyclopropanation of various alkenes with diazoacetate derivatives. Using silver foil and stainless-steel milling media, they were able to prepare cyclopropanation products with high diastereomeric selectivity (up to 98:2 d.r.) and high yield (up to 96%).<sup>104</sup> The yield and selectivity were in good agreement with the results of silver(I) homogeneous

catalysis, while avoiding the need for toxic solvents, refluxing conditions, and inert atmospheres.<sup>105</sup> Silver foil out-performed CuI and  $\text{Pd}(\text{OAc})_2$  catalysts, and stainless steel milling jars/balls were found to be important to maximize yield over copper, Teflon, or nickel jars. Silver foil was easily recycled, allowing for reproducible yields and diastereoselectivity over five catalytic runs. A broad substrate scope was achieved by modifying both the diazoacetate derivative and alkene.<sup>104</sup>

Cycloadditions of alkynes were also demonstrated using nickel pellets that serve as both the milling media and heterogeneous catalyst, without the need for additional ligands or inert atmospheres.<sup>103e</sup> Although nickel-catalysed cycloadditions of alkynes typically lead to substituted benzene rings *via* [2+2+2] cycloaddition, the mechanochemical route allows the inclusion of an additional equivalent into the ring to produce substituted cyclooctatetraene compounds *via* [2+2+2+2] addition. Nickel incorporation is vital to the reaction, whether in the form of the jar material, ball bearings, foil, powder, or pellets. The combination of nickel pellets and a stainless-steel jar was most successful, providing 94% yield after 16 hours. The use of many smaller (3 mm) nickel pellets was found to be more effective than a single large nickel ball. Using many balls simulated a planetary mill environment in the mixer mill by increasing the amount of shear friction from the balls.<sup>103e</sup>

This method was further extended to silver- and copper foil-catalysed cyclopropanation of internal and terminal alkynes with diazoacetate compounds, by lining stainless steel vials with silver or copper foil, respectively. This [2+1] cycloaddition was tested on a wide substrate scope. Building on this work and previous research on mechanochemical Sonogashira coupling,<sup>103d</sup> the Mack group attempted a one-pot, three-component coupling of a terminal alkyne, aryl halide, and a diazoacetate, catalysed by silver foil and palladium(II). Yields were excellent (80–95%) across a variety of substrates. This was expanded by using a one-pot domino Sonogashira coupling, followed by cyclopropanation to prepare a library of fully substituted cyclopropane compounds. Much better results were found by adding the diazoacetate after the initial Sonogashira reaction, but without isolation or purification of intermediates, resulting in good yields (60–75%) over two steps for the fully substituted cyclopropane products.<sup>106</sup>

Recent work from the Ito group involves the thorough exploration of mechanochemical Pd-catalysed cross couplings, including Suzuki–Miyaura, Sonogashira, and Buchwald–Hartwig reactions.<sup>20,107</sup> In many cases, their mechanochemical routes provide access to the same coupled products accessible *via* solution routes, but the mechanochemical routes provide distinct advantages, such as ease of reaction set-up, shorter reaction times, increased substrate scope, and tolerance towards air. The first step in the catalytic cycle of cross-couplings is the oxidative addition of the aryl halide to a Pd(0) species formed *in situ*. Pd(0) species are very sensitive to atmospheric oxygen, so reactions typically require an inert atmosphere. Kubota and Ito demonstrated that oxidative addition to Pd(0) can be done in air in the solid state, as gaseous oxygen diffuses inefficiently in solid-state reaction mixtures.<sup>100a</sup> Following this study, Pd-catalysed cross couplings were performed



between aryl halides and arylboronic acids, carbazoles, aryl amines, amides, and thiols.<sup>20,107</sup> Another exciting benefit of mechanochemical cross-couplings is an expanded substrate scope. Since solubility is no longer a factor to consider, solid-state cross-couplings are possible with insoluble polycyclic aryl halides, which are not amenable to solution methods.<sup>107e</sup> The use of LAG proved important in these systems through either a liquid reagent or a liquid additive for solid-state reactions. An olefin additive was used to act as a dispersant for the palladium catalyst, suppressing the aggregation of Pd nanoparticles and stabilizing the active Pd(0) species as a monomer, which promoted difficult solid-state C–C cross-couplings.<sup>20</sup>

## Conclusions

Although the term is often overused, a genuine “paradigm shift” in synthetic chemistry was marked by the change from using water as the sole solvent to employing organic liquids (ethers, arenes) in the mid-19th century.<sup>108</sup> The removal of all or most of the solvent from reactions in mechanochemically induced reactions has the potential to unleash a similar consequential shift, with far-reaching consequences for energy consumption, scaling, and most especially, new chemical species that have been inaccessible from traditional solvent-based approaches. The use of liquid-assisted and solvate-assisted grinding to modify the outcome of a reaction is certain to become even more widespread, and the changes in mechanism(s) of reaction will have to become an area of intensive study if the potential of mechanochemical synthesis is to be fully exploited. And although mechanochemistry may represent a “fourth way” of conducting reactions, it is also one that can be combined with others, as recent results blending mechanical approaches with photochemistry and electrochemistry have shown.<sup>109</sup> It is clear that tremendous advances can be anticipated for mechanochemically enhanced, (nearly) solvent-free organic, inorganic, and organometallic synthetic chemistry.

## Author contributions

L. E. W. and T. P. H. wrote the manuscript jointly.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

Financial support by the National Science Foundation (CHE-2155144) is gratefully acknowledged.

## Notes and references

- P. D. Ouspensky, in *The Fourth Way*, A. A. Knopf, New York, 1957.
- IUPAC Compendium of Chemical Technology (the Gold Book)*, ed. A. A. McNaught and A. Wilkinson, Blackwell Scientific, Oxford, 1997.
- (a) L. Takacs, *JOM*, 2000, **52**, 12–13; (b) L. Takacs, *Chem. Soc. Rev.*, 2013, **42**, 7649–7659.
- S. L. James, C. J. Adams, C. Bolm, D. Braga, P. Collier, T. Friščić, F. Grepioni, K. D. M. Harris, G. Hyett, W. Jones, A. Krebs, J. Mack, L. Maini, A. G. Orpen, I. P. Parkin, W. C. Shearouse, J. W. Steed and D. C. Waddell, *Chem. Soc. Rev.*, 2012, **41**, 413–447.
- D. Tan and F. García, *Chem. Soc. Rev.*, 2019, **48**, 2274–2292.
- J. Andersen and J. Mack, *Green Chem.*, 2018, **20**, 1435–1443.
- A. A. Gečauskaitė and F. García, *Beilstein J. Org. Chem.*, 2017, **13**, 2068–2077.
- A. Tuulmets and D. Panov, *J. Organomet. Chem.*, 1999, **575**, 182–186.
- J. G. Hernández and C. Bolm, *J. Org. Chem.*, 2017, **82**, 4007–4019.
- S. C. Chmely, C. N. Carlson, T. P. Hanusa and A. L. Rheingold, *J. Am. Chem. Soc.*, 2009, **131**, 6344–6345.
- J. M. Andersen and H. F. Starbuck, *J. Org. Chem.*, 2021, **86**, 13983–13989.
- D. Tan, L. Loots and T. Friščić, *Chem. Commun.*, 2016, **52**, 7760–7781.
- K. J. Ardila-Fierro and J. G. Hernández, *ChemSusChem*, 2021, **14**, 2145–2162.
- F. Effaty, L. Gonnet, S. G. Koenig, K. Nagapudi, X. Ottenwaelder and T. Friščić, *Chem. Commun.*, 2023, **59**, 1010–1013.
- E. J. Holmyard, *Alchemy*, Penguin Books, Harmondsworth, England, 1957.
- N. R. Rightmire and T. P. Hanusa, *Dalton Trans.*, 2016, **45**, 2352–2362.
- (a) S. Lukin, L. S. Germann, T. Friščić and I. Halasz, *Acc. Chem. Res.*, 2022, **55**, 1262–1277; (b) M. M. Mokhtar, J. M. Andersen, E. A. Kister, J. X. Hopkins, T. Estier, F. Hamilton, H. Guan, J. Mack and R. A. Haley, *Eur. J. Org. Chem.*, 2023, e202300492; (c) P. A. Julien, L. S. Germann, H. M. Titi, M. Etter, R. E. Dinnebier, L. Sharma, J. Baltrusaitis and T. Friščić, *Chem. Sci.*, 2020, **11**, 2350–2355; (d) B. G. Fiss, A. J. Richard, G. Douglas, M. Kojic, T. Friščić and A. Moores, *Chem. Soc. Rev.*, 2021, **50**, 8279–8318; (e) B. Karadeniz, D. Žilić, I. Huskić, L. S. Germann, A. M. Fidelli, S. Muratović, I. Lončarić, M. Etter, R. E. Dinnebier, D. Barišić, N. Cindro, T. Islamoglu, O. K. Farha, T. Friščić and K. Užarević, *J. Am. Chem. Soc.*, 2019, **141**, 19214–19220.
- A. A. L. Michalchuk, E. V. Boldyrev, A. M. Belenguer, F. Emmerling and V. V. Boldyrev, *Front. Chem.*, 2021, **9**, DOI: [10.3389/fchem.2021.685789](https://doi.org/10.3389/fchem.2021.685789).
- E. R. Caley and J. F. C. Richards, *Theophrastus on Stones*, Ohio State University Press, Columbus, OH, 1956, pp. 204–205.
- T. Seo, T. Ishiyama, K. Kubota and H. Ito, *Chem. Sci.*, 2019, **10**, 8202–8210.
- T. Friščić, C. Mottillo and H. M. Titi, *Angew. Chem., Int. Ed.*, 2020, **59**, 1018–1029.
- L. Chen, M. Regan and J. Mack, *ACS Catal.*, 2016, **6**, 868–872.
- H. P. DeGroot and T. P. Hanusa, *Organometallics*, 2021, **40**, 3516–3525.
- D. Hasa, G. Schneider Rauber, D. Voinovich and W. Jones, *Angew. Chem., Int. Ed.*, 2015, **54**, 7371–7375.
- (a) T. Friščić, I. Halasz, P. J. Beldon, A. M. Belenguer, F. Adams, S. A. J. Kimber, V. Honkimäki and R. E. Dinnebier, *Nat. Chem.*, 2013, **5**, 66–73; (b) P. J. Beldon, L. Fábian, R. S. Stein, A. Thirumurugan, A. K. Cheetham and T. Friščić, *Angew. Chem., Int. Ed.*, 2010, **49**, 9640–9643.
- Y. X. Shi, K. Xu, J. K. Clegg, R. Ganguly, H. Hirao, T. Friščić and F. García, *Angew. Chem., Int. Ed.*, 2016, **55**, 12736–12740.
- S. Karki, T. Friščić, W. Jones and W. D. S. Motherwell, *Mol. Pharmaceutics*, 2007, **4**, 347–354.
- T. Friščić, S. L. Childs, S. A. A. Rizvi and W. Jones, *CrystEngComm*, 2009, **11**, 418–426.
- M. Rodrigues, B. Baptista, J. A. Lopes and M. C. Sarraguça, *Int. J. Pharm.*, 2018, **547**, 404–420.
- (a) T. Friščić, *J. Mater. Chem.*, 2010, **20**, 7599–7605; (b) M. Tireli, M. Juribašić Kulsár, N. Cindro, D. Gracin, N. Biliškov, M. Borovina, M. Čurić, I. Halasz and K. Užarević, *Chem. Commun.*, 2015, **51**, 8058–8061.
- (a) M. Arhangelskis, D.-K. Bučar, S. Bordignon, M. R. Chierotti, S. A. Stratford, D. Voinovich, W. Jones and D. Hasa, *Chem. Sci.*, 2021, **12**, 3264–3269; (b) I. Brekalo, V. Martinez, B. Karadeniz, P. Orešković, D. Drapanauskaite, H. Vriesema, R. Stenekes, M. Etter, I. Dejanović,



- J. Baltrusaitis and K. Užarević, *ACS Sustainable Chem. Eng.*, 2022, **10**, 6743–6754.
- 32 J. A. Cabeza, J. Fernandez Reynes, F. García, P. García-Álvarez and R. García-Soriano, *Chem. Sci.*, 2023, DOI: [10.1039/D3SC02709K](https://doi.org/10.1039/D3SC02709K).
- 33 K. Budny-Godlewski, M. K. Leszczyński, A. Tulewicz, I. Justyniak, D. Pinkowicz, B. Sieklucka, K. Kruczała, Z. Sojka and J. Lewiński, *ChemSusChem*, 2021, **14**(18), 3887–3894.
- 34 D. H. Woen, C. M. Kotyk, T. J. Mueller, J. W. Ziller and W. J. Evans, *Organometallics*, 2017, **36**, 4558–4563.
- 35 V. D. Makhav, A. P. Borisov and L. A. Petrova, *J. Organomet. Chem.*, 1999, **590**, 222–226.
- 36 G. Wilkinson, *Org. Synth.*, 1956, **36**, 31–32.
- 37 (a) C. S. B. Gomes, P. T. Gomes and M. T. Duarte, *J. Organomet. Chem.*, 2014, **760**, 101–107; (b) H. P. Fritz, F. H. Köhler and K. E. Schwarzahns, *J. Organomet. Chem.*, 1969, **19**, 449–452.
- 38 (a) C. K. Gren, T. P. Hanusa and W. W. Brennessel, *Polyhedron*, 2006, **25**, 286–292; (b) N. R. Rightmire, PhD Thesis., Vanderbilt University, 2015.
- 39 A. P. Borisov, V. D. Makhav, A. Y. Usyatinskii and V. I. Bregadze, *Izv. Akad. Nauk, Ser. Khim.*, 1993, 1715–1717.
- 40 N. C. Boyde, N. R. Rightmire, E. J. Bierschenk, G. W. Steelman, T. P. Hanusa and W. W. Brennessel, *Dalton Trans.*, 2016, **45**, 18635–18642.
- 41 J. Lewiński, M. Dutkiewicz, M. Lesiuk, W. Śliwiński, K. Zelga, I. Justyniak and J. Lipkowski, *Angew. Chem., Int. Ed.*, 2010, **49**(44), 8266–8269.
- 42 M. C. Blanco, J. Cámara, M. C. Gimeno, A. Laguna, S. L. James, M. C. Lagunas and M. D. Villacampa, *Angew. Chem., Int. Ed.*, 2012, **51**, 9777–9779.
- 43 (a) V. Grignard, *C. R. Acad. Sci.*, 1900, **130**, 1322–1324; (b) T. Banno, Y. Hayakawa and M. Umeno, *J. Organomet. Chem.*, 2002, **653**, 288–291; (c) D. Seyferth, *Organometallics*, 2009, **28**, 1598–1605.
- 44 J. M. Harrowfield, R. J. Hart and C. R. Whitaker, *Aust. J. Chem.*, 2001, **54**, 423–425.
- 45 V. Birke, C. Schutt, H. Burmeier and W. Ruck, *Fresenius Environ. Bull.*, 2011, **20**, 2794–2805.
- 46 I. R. Speight and T. P. Hanusa, *Molecules*, 2020, **25**, 570.
- 47 R. Takahashi, A. Hu, P. Gao, Y. Gao, Y. Pang, T. Seo, J. Jiang, S. Maeda, H. Takaya, K. Kubota and H. Ito, *Nat. Commun.*, 2021, **12**, 6691.
- 48 Y. Gao, K. Kubota and H. Ito, *Angew. Chem., Int. Ed.*, 2023, **62**, e202217723.
- 49 R. Scholl and J. Mansfeld, *Ber. Dtsch. Chem. Ges.*, 1910, **43**, 1734–1746.
- 50 M. Rickhaus, A. P. Belanger, H. A. Wegner and L. T. Scott, *J. Org. Chem.*, 2010, **75**, 7358–7364.
- 51 K. Fujishiro, Y. Morinaka, Y. Ono, T. Tanaka, L. T. Scott, H. Ito and K. Itami, *J. Am. Chem. Soc.*, 2023, **145**, 8163–8175.
- 52 A. Sartori, N. El Habra, C. De Zorzi, S. Sitran, M. Casarin, G. Cavinato, C. Sada, R. Gerbasì and G. Rossetto, *Chem. Vap. Deposition*, 2012, **18**, 151–158.
- 53 J. Niinistö, M. Putkonen, L. Niinistö, F. Song, P. Williams, P. N. Heys and R. Odedra, *Chem. Mater.*, 2007, **19**, 3319–3324.
- 54 (a) T.-J. Hsiao and J.-C. Tsai, *J. Appl. Polym. Sci.*, 2010, **116**, 2040–2049; (b) A. V. Grafov, C. L. Firme, I. A. Grafova, F. Benetollo, M. L. Dias and M. J. M. Abadie, *Polymer*, 2005, **46**, 9626–9631.
- 55 (a) Z. R. Turner, J.-C. Buffet and D. O'Hare, *Organometallics*, 2014, **33**, 3891–3903; (b) J.-C. Buffet, G. R. Harris, J. J. Coward, T. A. Q. Arnold, Z. R. Turner and D. O'Hare, *J. Organomet. Chem.*, 2016, **801**, 87–95; (c) Y. Ning, Y. Zhang, A. Rodriguez-Delgado and E. Y. X. Chen, *Organometallics*, 2008, **27**, 5632–5640.
- 56 J.-C. Tsai, J. C. Kuo and Y.-C. Chen, *J. Polym. Sci., Part A: Polym. Chem.*, 2005, **43**, 2304–2315.
- 57 M. W. Carson, *e-EROS Encyclopedia of Reagents for Organic Synthesis*, 2003, pp.1–2.
- 58 K. C. Ott, E. J. M. De Boer and R. H. Grubbs, *Organometallics*, 1984, **3**, 223–230.
- 59 N. R. Rightmire, D. L. Bruns, T. P. Hanusa and W. W. Brennessel, *Organometallics*, 2016, **35**, 1698–1706.
- 60 (a) P. S. Tanner, D. J. Burkey and T. P. Hanusa, *Polyhedron*, 1995, **14**, 331–333; (b) E. D. Brady, S. C. Chmely, K. C. Jayaratne, T. P. Hanusa and V. G. Young, Jr., *Organometallics*, 2008, **27**, 1612–1616; (c) A. G. M. Barrett, M. R. Crimmin, M. S. Hill, G. Kociok-Kohn, D. J. MacDougall, M. F. Mahon and P. A. Procopiou, *Organometallics*, 2008, **27**, 3939–3946.
- 61 (a) X. He, B. C. Noll, A. Beatty, R. E. Mulvey and K. W. Henderson, *J. Am. Chem. Soc.*, 2004, **126**, 7444–7445; (b) X. He, E. Hurley, B. C. Noll and K. W. Henderson, *Organometallics*, 2008, **27**, 3094–3102.
- 62 (a) H. Bauer, M. Alonso, C. Färber, H. Elsen, J. Pahl, A. Causero, G. Ballmann, F. De Proft and S. Harder, *Nat. Catal.*, 2018, **1**, 40–47; (b) H. Bauer, M. Alonso, C. Fischer, B. Roesch, H. Elsen and S. Harder, *Angew. Chem., Int. Ed.*, 2018, **57**, 15177–15182; (c) J. P. Davin, J.-C. Buffet, T. P. Spaniol and J. Okuda, *Dalton Trans.*, 2012, **41**, 12612–12618.
- 63 (a) M. P. Coles, *Coord. Chem. Rev.*, 2015, **297–298**, 2–23; (b) M. Westerhausen and W. Schwarz, *Z. Anorg. Allg. Chem.*, 1991, **604**, 127–140.
- 64 (a) P. B. Hitchcock, M. F. Lappert, G. A. Lawless and B. Royo, *J. Chem. Soc., Chem. Commun.*, 1990, 1141–1142; (b) S. R. Drake, D. J. Otway and S. P. Perlepes, *Main Group Met. Chem.*, 1991, **14**, 243–256; (c) D. C. Bradley, M. B. Hursthouse, A. A. Ibrahim, K. M. Abdul Malik, M. Motavalli, R. Mösel, H. Powell, J. D. Runnacles and A. C. Sullivan, *Polyhedron*, 1990, **9**, 2959–2964; (d) M. M. Gillett-Kunnath, J. G. MacLellan, C. M. Forsyth, P. C. Andrews, G. B. Deacon and K. Ruhlandt-Senge, *Chem. Commun.*, 2008, 4490–4492; (e) M. Westerhausen, *Inorg. Chem.*, 1991, **30**, 96–101.
- 65 (a) S. Kriek, P. Schueler, H. Goerls and M. Westerhausen, *Inorg. Chem.*, 2018, **57**, 13937–13943; (b) E. D. Brady, T. P. Hanusa, M. Pink and V. G. Young, Jr., *Inorg. Chem.*, 2000, **39**, 6028–6037; (c) A. D. Frankland, P. B. Hitchcock, M. F. Lappert and G. A. Lawless, *J. Chem. Soc., Chem. Commun.*, 1994, 2435–2436; (d) A. D. Frankland and M. F. Lappert, *J. Chem. Soc., Dalton Trans.*, 1996, 4151–4152; (e) P. B. Hitchcock, M. F. Lappert, G. A. Lawless and B. Royo, *J. Chem. Soc., Chem. Commun.*, 1990, 1141–1142.
- 66 J. F. Reynes, V. Isoni and F. Garcia, *Angew. Chem., Int. Ed.*, 2023, **62**, e202300819.
- 67 (a) D. J. am Ende, S. R. Anderson and J. S. Salan, *Org. Process Res. Dev.*, 2014, **18**, 331–341; (b) A. A. L. Michalchuk, K. S. Hope, S. R. Kennedy, M. V. Blanco, E. V. Boldyreva and C. R. Pulham, *Chem. Commun.*, 2018, **54**, 4033–4036; (c) H. M. Titi, J.-L. Do, A. J. Howarth, K. Nagapudi and T. Frišćić, *Chem. Sci.*, 2020, **11**, 7578–7584.
- 68 S. Okeya, S. i Ooi, K. Matsumoto, Y. Nakamura and S. Kawaguchi, *Bull. Chem. Soc. Jpn.*, 1981, **54**, 1085–1095.
- 69 V. Makhav and L. Petrova, *Inorg. Chim. Acta*, 2021, **518**, 120231.
- 70 (a) J. D. Smith, T. P. Hanusa and V. G. Young, Jr., *J. Am. Chem. Soc.*, 2001, **123**, 6455–6456; (b) C. N. Carlson, J. D. Smith, T. P. Hanusa, W. W. Brennessel and V. G. Young, Jr., *J. Organomet. Chem.*, 2003, **683**, 191–199.
- 71 (a) J. D. Smith, K. T. Quisenberry, T. P. Hanusa and W. W. Brennessel, *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.*, 2004, **60**, m507–m508; (b) M. Schormann, S. Garratt and M. Bochmann, *Organometallics*, 2005, **24**, 1718–1724.
- 72 K. T. Quisenberry, J. D. Smith, M. Voehler, D. F. Stec, T. P. Hanusa and W. W. Brennessel, *J. Am. Chem. Soc.*, 2005, **127**, 4376–4387.
- 73 V. S. Pfennig, R. C. Vilella, J. Nikodemus and C. Bolm, *Angew. Chem., Int. Ed.*, 2022, **61**, e202116514.
- 74 P. Gao, J. Jiang, S. Maeda, K. Kubota and H. Ito, *Angew. Chem., Int. Ed.*, 2022, **61**, e202207118.
- 75 A. Koch, Q. Dufrois, M. Wirgenings, H. Görls, S. Kriek, M. Etienne, G. Pohnert and M. Westerhausen, *Chem. – Eur. J.*, 2018, **24**, 16840–16850.
- 76 F. Cuccu, L. De Luca, F. Delogu, E. Colacino, N. Solin, R. Mocchi and A. Porcheddu, *ChemSusChem*, 2022, **15**, e202200362.
- 77 (a) J.-L. Do and T. Frišćić, *ACS Cent. Sci.*, 2017, **3**, 13–19; (b) G.-W. Wang, *Chin. J. Chem.*, 2021, **39**, 1797–1803.
- 78 R. F. Koby, N. D. Schley and T. P. Hanusa, *Angew. Chem., Int. Ed.*, 2021, **60**, 21174–21178.
- 79 E. O. Fischer and H. P. Hofmann, *Chem. Ber.*, 1959, **92**, 482–486.
- 80 S. A. Solomon, C. A. Muryn and R. A. Layfield, *Chem. Commun.*, 2008, 3142–3144.
- 81 R. F. Koby, A. M. Doerr, N. R. Rightmire, N. D. Schley, B. K. Long and T. P. Hanusa, *Angew. Chem., Int. Ed.*, 2020, **59**, 9542–9548.
- 82 R. A. Layfield, F. Garcia, J. Hannauer and S. M. Humphrey, *Chem. Commun.*, 2007, 5081–5083.



- 83 N. Boyde, N. Rightmire, T. Hanusa and W. Brennessel, *Inorganics*, 2017, **5**, 36.
- 84 C. K. Gren, T. P. Hanusa and A. L. Rheingold, *Organometallics*, 2007, **26**, 1643–1649.
- 85 R. F. Koby, T. P. Hanusa and N. D. Schley, *J. Am. Chem. Soc.*, 2018, **140**, 15934–15942.
- 86 K. K. Gangu and S. B. Jonnalagadda, *Front. Chem.*, 2021, **9**, 747615.
- 87 I. Thomas-Hillman, A. Laybourn, C. Dodds and S. W. Kingman, *J. Mater. Chem. A*, 2018, **6**, 11564–11581.
- 88 (a) A. D. Katsenis, A. Puškarić, V. Štrukil, C. Mottillo, P. A. Julien, K. Užarević, M.-H. Pham, T.-O. Do, S. A. J. Kimber, P. Lazić, O. Magdysyuk, R. E. Dinnebier, I. Halasz and T. Friščić, *Nat. Commun.*, 2015, **6**, 6662; (b) T. Stolar, L. Batzdorf, S. Lukin, D. Žilić, C. Mottillo, T. Friščić, F. Emmerling, I. Halasz and K. Užarević, *Inorg. Chem.*, 2017, **56**, 6599–6608; (c) M. Arhangelskis, A. D. Katsenis, N. Novendra, Z. Akimbekov, D. Gandrath, J. M. Marrett, G. Ayoub, A. J. Morris, O. K. Farha, T. Friščić and A. Navrotsky, *Chem. Mater.*, 2019, **31**, 3777–3783.
- 89 N. Masciocchi, G. Attilio Ardizzoia, S. Brenna, F. Castelli, S. Galli, A. Maspero and A. Sironi, *Chem. Commun.*, 2003, 2018–2019.
- 90 I. R. Speight, I. Huskić, M. Arhangelskis, H. M. Titi, R. S. Stein, T. P. Hanusa and T. Friščić, *Chem. – Eur. J.*, 2020, **26**, 1811–1816.
- 91 K. T. Quisenberry, R. E. White, T. P. Hanusa and W. W. Brennessel, *New J. Chem.*, 2010, **34**, 1579–1584.
- 92 G. Odian, *Principles of Polymerization*, John Wiley, New York, 3rd edn, 1991.
- 93 R. F. Koby, A. M. Doerr, N. R. Rightmire, N. D. Schley, W. W. Brennessel, B. K. Long and T. P. Hanusa, *Chem. – Eur. J.*, 2021, **27**, 8195–8202.
- 94 J. Gao, D. Zhu, W. Zhang, G. A. Solan, Y. Ma and W.-H. Sun, *Inorg. Chem. Front.*, 2019, **6**, 2619–2652.
- 95 C. Lichtenberg, D. Robert, T. P. Spaniol and J. Okuda, *Organometallics*, 2010, **29**, 5714–5721.
- 96 N. R. Rightmire, T. P. Hanusa and A. L. Rheingold, *Organometallics*, 2014, **33**, 5952–5955.
- 97 (a) L. E. Wenger, N. M. Shawver, R. F. Koby, W. W. Brennessel, B. K. Long and T. P. Hanusa, *Organometallics*, 2023, **42**, 283; (b) L. E. Wenger, N. M. Shawver, W. W. Brennessel, B. K. Long and T. P. Hanusa, *Organometallics*, 2022, **41**, 3718–3723.
- 98 (a) A. Porcheddu, E. Colacino, L. De Luca and F. Delogu, *ACS Catal.*, 2020, **10**, 8344–8394; (b) S. Hwang, S. Grätz and L. Borchardt, *Chem. Commun.*, 2022, **58**, 1661–1671; (c) W. Pickhardt, S. Grätz and L. Borchardt, *Chem. – Eur. J.*, 2020, **26**, 12903–12911.
- 99 W. A. Carole and T. J. Colacot, *Chem. – Eur. J.*, 2016, **22**, 7686–7695.
- 100 (a) K. Kubota, R. Takahashi and H. Ito, *Chem. Sci.*, 2019, **10**, 5837–5842; (b) Y. Pang, T. Ishiyama, K. Kubota and H. Ito, *Chem. – Eur. J.*, 2019, **25**, 4654–4659; (c) D. C. Waddell, T. D. Clark and J. Mack, *Tetrahedron Lett.*, 2012, **53**, 4510–4513.
- 101 A. C. Jones, J. A. Leitch, S. E. Raby-Buck and D. L. Browne, *Nat. Synth.*, 2022, **1**, 763–775.
- 102 R. M. Bullock, J. G. Chen, L. Gagliardi, P. J. Chirik, O. K. Farha, C. H. Hendon, C. W. Jones, J. A. Keith, J. Klosin, S. D. Minteer, R. H. Morris, A. T. Radosevich, T. B. Rauchfuss, N. A. Strotman, A. Vojvodic, T. R. Ward, J. Y. Yang and Y. Surendranath, *Science*, 2020, **369**, eabc3183.
- 103 (a) Y. Sawama, M. Niikawa and H. Sajiki, *J. Synth. Org. Chem., Jpn.*, 2019, **77**, 1070–1077; (b) Y. Sawama, M. Niikawa, Y. Yabe, R. Goto, T. Kawajiri, T. Marumoto, T. Takahashi, M. Itoh, Y. Kimura, Y. Sasai, Y. Yamauchi, S.-I. Kondo, M. Kuzuya, Y. Monguchi and H. Sajiki, *ACS Sustainable Chem. Eng.*, 2015, **3**, 683–689; (c) T. L. Cook, J. A. Walker and J. Mack, *Green Chem.*, 2013, **15**, 617–619; (d) D. A. Fulmer, W. C. Shearouse, S. T. Medonza and J. Mack, *Green Chem.*, 2009, **11**, 1821–1825; (e) R. A. Haley, A. R. Zellner, J. A. Krause, H. Guan and J. Mack, *ACS Sustainable Chem. Eng.*, 2016, **4**, 2464–2469.
- 104 L. Chen, M. O. Bovee, B. E. Lemma, K. S. M. Keithley, S. L. Pilson, M. G. Coleman and J. Mack, *Angew. Chem., Int. Ed.*, 2015, **54**, 11084–11087.
- 105 J. L. Thompson and H. M. L. Davies, *J. Am. Chem. Soc.*, 2007, **129**, 6090–6091.
- 106 L. Chen, D. Leslie, M. G. Coleman and J. Mack, *Chem. Sci.*, 2018, **9**, 4650–4661.
- 107 (a) T. Seo, K. Kubota and H. Ito, *J. Am. Chem. Soc.*, 2023, **145**, 6823–6837; (b) K. Kubota, T. Seo and H. Ito, *Faraday Discuss.*, 2023, **241**, 104–113; (c) K. Kubota, K. Kondo, T. Seo and H. Ito, *Synlett*, 2022, 898–902; (d) K. Kubota, T. Endo, M. Uesugi, Y. Hayashi and H. Ito, *ChemSusChem*, 2022, **15**, e202102132; (e) T. Seo, N. Toyoshima, K. Kubota and H. Ito, *J. Am. Chem. Soc.*, 2021, **143**, 6165–6175; (f) K. Kubota, R. Takahashi, M. Uesugi and H. Ito, *ACS Sustainable Chem. Eng.*, 2020, **8**, 16577–16582; (g) T. Seo, K. Kubota and H. Ito, *J. Am. Chem. Soc.*, 2020, **142**, 9884–9889; (h) R. Takahashi, K. Kubota and H. Ito, *Chem. Commun.*, 2020, **56**, 407–410; (i) K. Kubota, T. Seo, K. Koide, Y. Hasegawa and H. Ito, *Nat. Commun.*, 2019, **10**, 111.
- 108 T. S. Kuhn, *The Structure of Scientific Revolutions*, University of Chicago Press, Chicago, IL, 2nd edn, 1970.
- 109 V. Martinez, T. Stolar, B. Karadeniz, I. Brekalo and K. Užarević, *Nat. Rev. Chem.*, 2023, **7**, 51–65.

