Mechanochemistry-Amended Barbier Reaction as an Expedient Alternative to Grignard Synthesis

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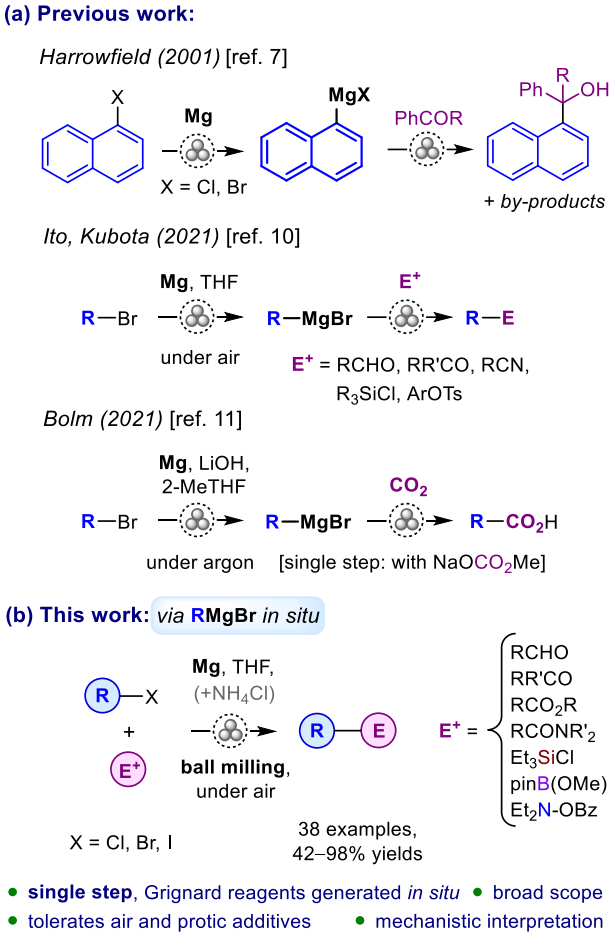
Abstract: Organomagnesium halides (Grignard reagents) are essential carbanionic building blocks widely used in carbon-carbon and carbon-heteroatom bond-forming reactions with various electrophiles. In the Barbier variant of the Grignard synthesis, the generation of air- and moisture-sensitive Grignard reagents occurs concurrently with their reaction with an electrophile. Although operationally simpler, the classic Barbier approach suffers from low yields due to multiple side reactions, thereby limiting the scope of its application. Here, we report a mechanochemical adaptation of the Mg-mediated Barbier reaction, which overcomes these limitations and facilitates the coupling of versatile organic halides (*e.g.*, allylic, vinylic, aromatic, aliphatic) with a diverse range of electrophilic substrates (*e.g.*, aldehydes, ketones, esters, amides, *O*-benzoyl hydroxylamine, chlorosilane, borate ester) to assemble C–C, C–N, C–Si, and C–B bonds. In contrast to the classic two-step Grignard synthesis, the mechanochemical approach has the advantage of being essentially solvent-free, single step, operationally simple, immune to air, and surprisingly tolerant to water and other proton donors. Mechanistic studies have clarified the role of mechanochemistry in the process, indicating that the reaction predominantly proceeds *via* the generation of transient organometallics, which occurs rapidly due to improved mass transfer and activation of the surface of magnesium metal.

Introduction

In recent years, mechanochemistry has become increasingly popular as an essentially solvent-free methodology for organic synthesis.[1a-e] Facilitated by various instrumental techniques,[1f-h] mechanochemical synthesis enables a range of transformations without the use of solvents or with solvents in catalytic amounts only (*e.g.*, liquid-assisted grinding technique; LAG).[1e,2] This approach offers several advantages over traditional solution-based methods, including fast reaction rates, and a reduction in safety hazards and environmental impacts.[3] In addition, mechanochemical activation significantly increases

the reactivity and catalytic properties of solids, including metals.[4] This advantage improves the performance of metal-catalyzed transformations and enables the preparation of organometallic reagents with an efficiency that is frequently unattainable with conventional solution-based chemistry.[5]



Scheme 1. Key previous work on mechanochemical Grignard syntheses and outline of this work.

Many classic organic reactions have been adapted for the mechanochemical approach, including the venerable Grignard reaction. In the latter, avoiding or minimizing the use of flammable and peroxide-forming ethereal solvents (Et_2O, THF) leads to substantially attenuated safety hazards.[6] The mechanochemical Grignard reaction was pioneered by Harrowfield and co-workers in 2001,[7] who reported the first successful solvent-free preparation of a naphthyl Grignard reagent followed by its reaction with ketones (Scheme 1, a). The reaction delivered a mixture of products in addition to the anticipated tertiary alcohol, *e.g.*, McMurry coupling and other side processes were observed. Despite a few

sporadic examples of the synthetic use in the context of C–C bond formation reported by Hanusa, Yang and Dai,[8,9] the synthetic utility of the mechanochemistry-driven Grignard reaction has not been appreciably expanded and systematically explored until very recently. In 2021, the research groups of Ito, Kubota,[10] and Bolm[11] independently reported the facile generation of versatile Grignard reagents using THF or 2-MeTHF as liquid additives to ball milling, followed by subsequent reaction with various electrophiles. However, the prior preparation of air- and moisture-sensitive Grignard reagents was necessary in this approach, which could result in partial oxidation[10] of the organometallic intermediate or required protection with an inert atmosphere.[11] A more convenient one-step reaction with sodium methyl carbonate was used by Bolm and co-workers[11] as an alternative to the two-step synthesis with CO_2 but the methodology has not been expanded to other electrophiles.

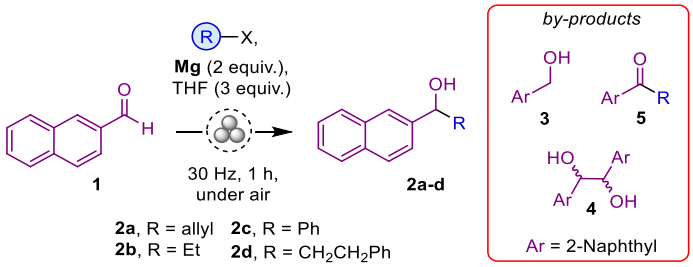
Here, we report that many of synthetically useful transformations of organomagnesium nucleophiles can be efficiently performed under mechanochemical conditions by generating Grignard reagents *in situ* from Mg and the respective organic halide (*i.e.*, with the Barbier variant). A variety of electrophilic reaction partners are compatible with this single-step reaction design (Scheme 1, b). The proposed alternative is operationally simpler, inherently immune to air exposure, and remarkably tolerant to moisture and some other proton sources. Furthermore, the mechanochemical approach retains the high efficiency of the generic Grignard synthesis, delivering similar yields and exhibiting a broad range of amenable organic halides and electrophilic substrates. This approach outperforms the traditional solution-based, Mg-mediated Barbier reaction, which typically delivers low and irregular yields,[12] with the exception of the reaction of allylic halides.[13,14] The previously reported mechanochemical Barbier reactions with zinc[15] and bismuth[16] demonstrate similar limitations when compared with the newly developed method.

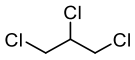
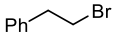
Results and Discussion

During the development of new routes for the remediation of persistent organic pollutants, we noted that the reaction of 1,2,3-trichloropropane (TCP) with Mg powder and 2-napthaldehyde (**1**) produced homoallylic alcohol **2a** (R = allyl) in much better yield under mechanochemical conditions (1 h of ball milling in a shaker mill at 30 Hz) than in THF solution (Table 1, Entry 1). Importantly, Mg was essential for the reaction, while other

metals tested (*i.e.*, Zn, Al, Mn, In; Scheme S1 in the Electronic Supplementary Information [ESI]) were ineffective. Similarly, much better yields of alcohols **2a**-**d** were obtained under mechanochemical conditions (conditions A, Table 1) than in solution (conditions B) in the Barbier reactions of allyl chloride (Entry 2), bromoethane (Entry 3), bromobenzene (Entry 4), and 2-phenylethyl bromide (Entry 5). The lower yields in the solution-based Barbier syntheses were due to enhanced side reactions, which produced 2-naphthalenemethanol **3**, pinacols **4**, and 2-naphthyl ketones **5** (*e.g.*, **5b** for R = Et) as the most abundant by-products. Remarkably, the classic Grignard synthesis in THF solution (conditions C) afforded alcohols **2a**-**d** in nearly the same yields as that those from the mechanochemical Barbier-Grignard reaction. Notably, the latter was performed under air, rather than inert atmosphere protection, which is essential for the Grignard synthesis.

Table 1. Synthesis of alcohols **2a-d** *via* Barbier reaction under mechanochemical conditions (**A**), in THF solution (**B**), and *via* the addition of Grignard reagents in THF solution (**C**).

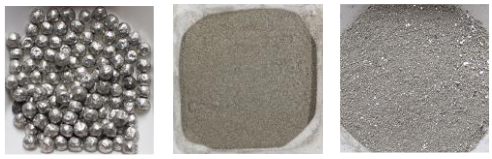


entry	organic halide	product	conditions,[a] yield (%)[b] A	B	C
1		**2a**	72[c]	38	–[d]
2		**2a**	98	73	98
3	EtBr	**2b**	94[e]	57	96
4	PhBr	**2c**	92	57	–[d]
5		**2d**	88	52	90

[a] **A**: ball milling, **1** (200 mg, 1.28 mmol), RX (1–1.2 equiv.), activated Mg powder (2 equiv.), THF (3 equiv.), 30 Hz, 60 min, under air. **B**: in THF solution at stirring, same reactants as in A, under argon. **C**: in THF solution with RMgX (1 equiv.), under argon. [b] Yields are determined by ^{1}H NMR with internal standard after the hydrolytic workup (aq. NH_4Cl). Yields of isolated products are similar, see ESI. [c] Performed with non-activated Mg powder. [d] Not performed. [e] 72% yield with non-activated Mg powder.

Table 2. Selected optimization experiments for the mechanochemical synthesis of homoallylic alcohol **2a**.

entry	conditions	yield (%)[a]
1	optimal conditions: allyl chloride (1.1 equiv.), activated[b] Mg powder (2 equiv.), THF (3 equiv.), 60 min, 30 Hz, under air	98
	variation from the optimal conditions:	
2	no THF:	14
3	1.5 equiv. THF:	64
4	0 Hz (in a slurry):	66
5	7 Hz milling frequency:	78
6	Mg beads, 3 mm (2 equiv.):	63
7	Mg beads, 3 mm (30 equiv.):	86
8	non-activated Mg powder (2 equiv.):	96

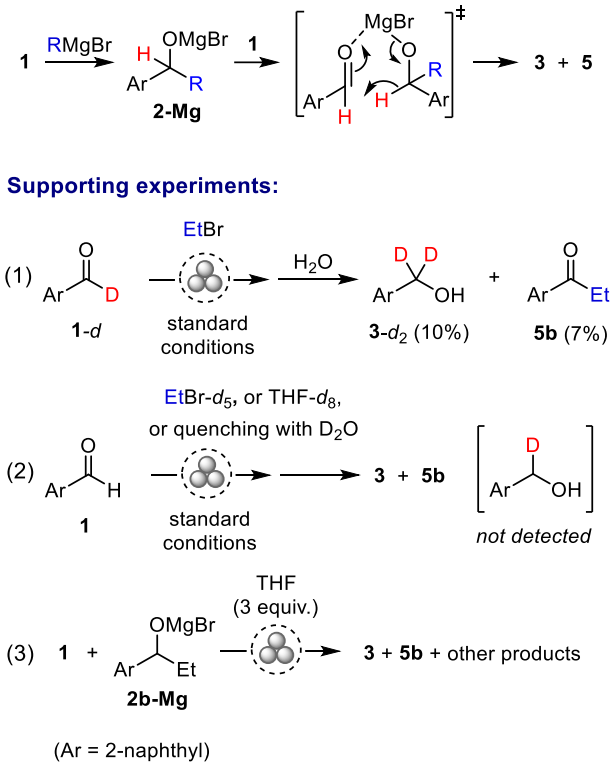


beads, 3 mm powder, <75 μm activated powder

[a] Yields were determined by ^{1}H NMR with an internal standard after the hydrolytic workup (aq. NH_4Cl). For more details, see the ESI. [b] Obtained by ball milling (3 h, 30 Hz) of commercial Mg powder.

The three most important factors that enabled high yields of alcohols **2a**-**d** were revealed during the optimization studies for the synthesis of **2a** (Table 2): (i) the presence of THF (at least 3 equiv.), which acts as a Lewis base ligand to stabilize the organomagnesium intermediate (Entry 1 vs. 2 and 3), (ii) milling frequency, with yields of **2a** remarkably improved at high frequencies (Entry 1 vs. 4 and 5, Table S2 in ESI), and (iii) the surface area of the Mg metal, *i.e.*, smaller particles (Entry 6 vs. 8) or higher loading (Entry 6 vs. 7) resulted in better yields (Entries 6–8). The latter factor indicated the on-surface nature of the reaction, while the dependence on milling frequency was clearly manifested in the mechanochemical origin of the observed yield enhancement. In line with these results, the best outcome (98% yield of **2a**, Entry 1) was obtained with Mg powder activated by prior ball milling (3 h at 30 Hz). Following activation, the powder acquired a distinct metallic luster due to the removal of the passivating "oxide" layer.[17] The beneficial effect of the activated powder was particularly clear in the Barbier reactions of other halides, *e.g.*, the yield of **2b** was noticeably improved from 72% to 94% (Table S4). The mechanochemical

synthesis of **2a** was fast and afforded 93% yield after just 10 min of milling at 30 Hz (Table S3). Importantly, no induction delay was observed. This delay is common in the solution-based Grignard and Barbier reactions and may lead to sudden exothermic initiation and the risk of thermal runaway.[6] Inspection with a thermal camera (Fig. S4, ESI) revealed only insignificant temperature increases outside and inside the milling jars, which did not exceed 29°C. Despite the exothermic nature of the reaction, the rather low temperature increase was an indication of efficient heat dissipation and suggests that thermal activation is an unlikely cause of the short induction period and fast reaction rate.

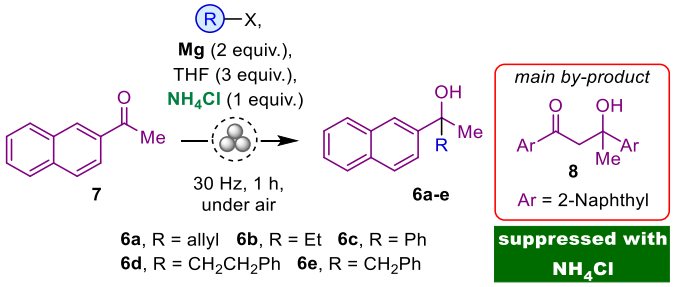


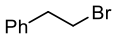
Scheme 2. Dominant side process: Meerwein-Ponndorf-Verley (MPV) reaction of aldehyde **1** with magnesium alkoxides **2-Mg**. Standard conditions: EtBr (1.1 equiv.), non-activated Mg powder (2 equiv.), THF (3 equiv.), 60 min, 30 Hz, under air.

The dominant side process that resulted in the generation of alcohol **3** and ketone **5** was attributed to the Meerwein-Ponndorf-Verley (MPV) reaction of aldehyde **1** with magnesium alkoxide products **2-Mg** (Scheme 2). This assumption was confirmed by performing the mechanochemical and solution-state Barbier reactions with deuterium-labeled aldehyde **1**-*d*, which featured a double deuterated alcohol **3**-d_2 and ketone **5b** as side products (Scheme 2, eq. 1). In contrast, no deuterium incorporation by **3** was observed when the

same reaction of **1** was carried out with THF-d_8, EtBr-d_6, or by quenching with D_2O (eq. 2), which made it possible to rule out hydrogen atom abstraction from the solvent, β-hydride transfer from the ethyl Grignard reagent, or Bouveault-Blanc-type reduction as alternative possibilities (see section 4.2 in ESI for more details). As additional evidence, the MPV reaction of alkoxide **2a**-**Mg** and aldehyde **1** was attempted and occurred both under mechanochemical conditions and in THF solution (eq. 3). Notably, the pinacol coupling of **1** was suppressed in the mechanochemical experiments, while the parasitic MPV reaction was significantly inhibited.

Table 3. Synthesis of tertiary alcohols **6a-e** *via* mechanochemical Barbier-Grignard reaction of ketone **7**.

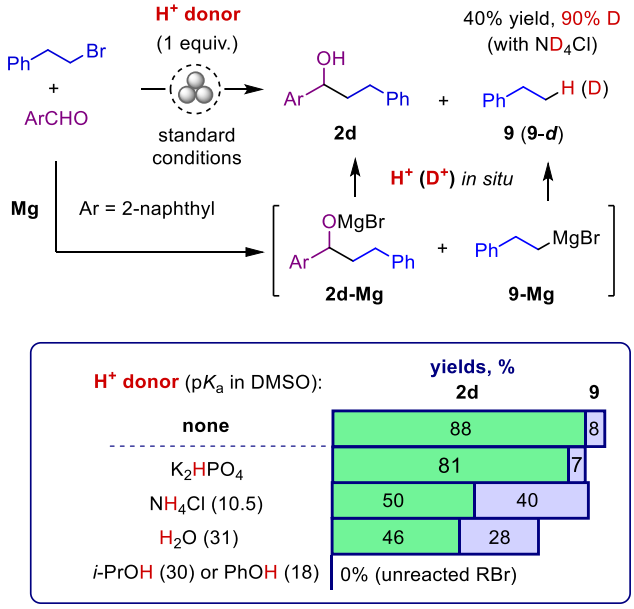


entry	R—X	product	conditions,[a] yield (%)[b] **A**, no additive	**D**, with NH_4Cl
1		**6a**	78[c]	92[d]
2	EtBr	**6b**	57	78
3	PhBr	**6c**	33	68
4		**6d**	53	49
5	$PhCH_2Br$	**6e**	67	82

[a] **A**: ball milling, **7** (200 mg, 1.2 mmol), RX (1.5 equiv.), activated Mg powder (2 equiv.), THF (3 equiv.), 30 Hz, 60 min, under air, followed by hydrolysis (aq. NH_4Cl). **D**: same as **A**, but with NH_4Cl (1 equiv.), followed by treatment with EtOAc, filtration and solvent evaporation. [b] Yields are determined by ^1H NMR with internal standard Yields of isolated products are similar, see ESI. [c] **8** (7%) formed as main by-product. [d] **8** (<1%) formed as the only by-product.

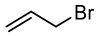
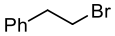
For the mechanochemical synthesis of tertiary alcohol **6a** from ketone **7**, enolization was promoted with basic magnesium alkoxide of **6a** and was the main side process that led to aldol **8** (Table 3, Entry 1, conditions A). To our delight, the side process was suppressed by performing the reaction with solid ammonium chloride (1 equiv., conditions D) which acted as an efficient proton quencher for the alkoxide and delivered alcohol **6a** in 92%

yield. Moreover, the *in situ* release of alcohol **6a** from the respective alkoxide allowed us to bypass the conventional hydrolytic work-up and streamline the preparative protocol (see also the discussion on the gram-scale preparation of **6a** below). Likewise, notably better yields of alcohols **6b**-**e** were obtained with NH_4Cl compared to other organic halides, with the exception of **6d** (Table 3, Entries 2–5). However, the yields were lower compared to that of similar reactions with the more reactive aldehyde **1** (Table 1), and the use of activated Mg powder did not lead to any improvement in this case (Table S8).



Scheme 3. Tolerance of the mechanochemical Barbier-Grignard reaction of aldehyde **1** to proton sources. Proton quenching of alkoxide **2d-Mg** and a transient Grignard intermediate **9-Mg**.

Table 4. Tolerance of the mechanochemical Barbier-Grignard reactions of aldehyde **1** to water and solid ammonium chloride.

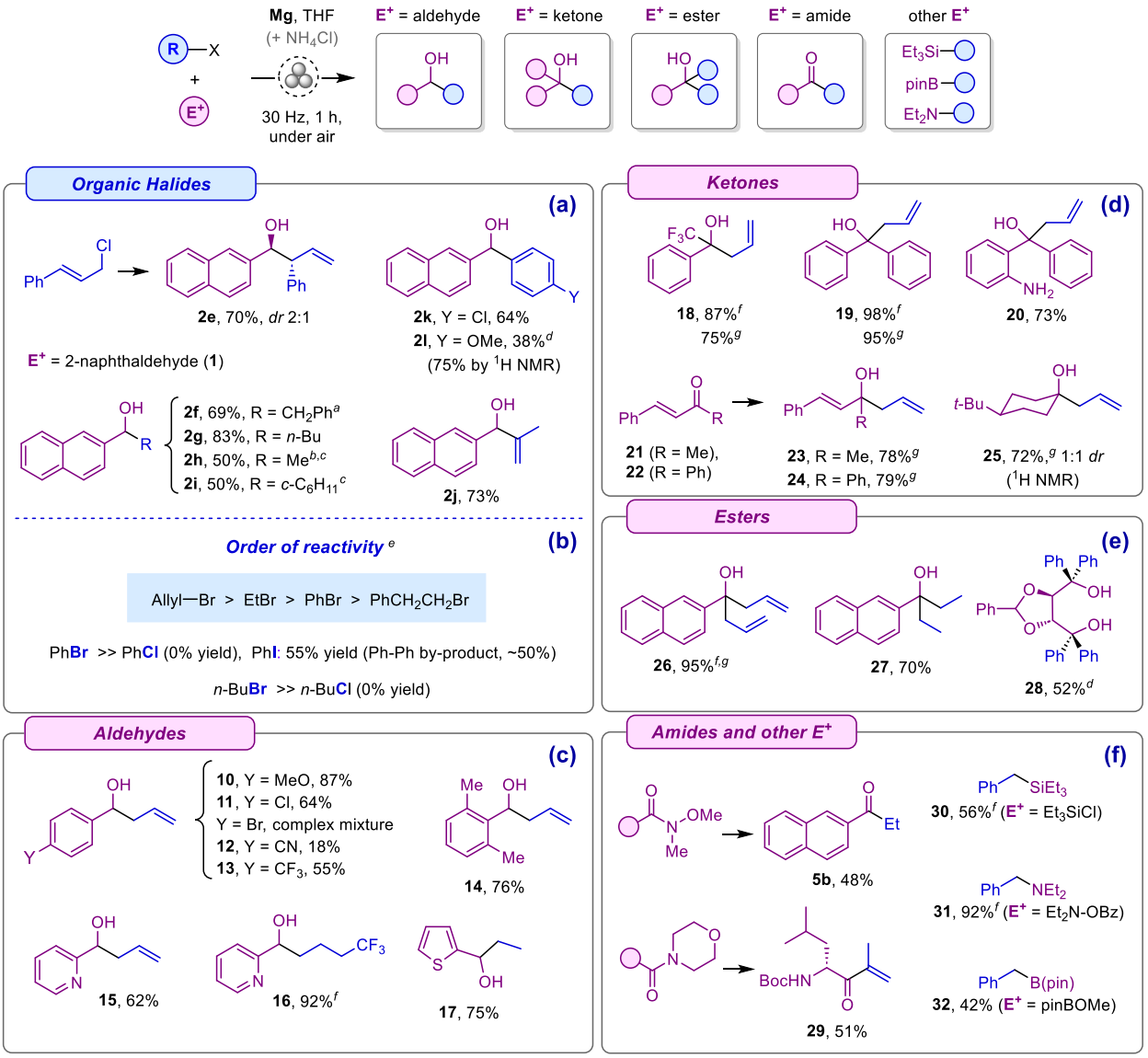
entry	R—Br	product	yield (%)[a,b]		
			no additive	NH_4Cl	H_2O
1		**2a**	98	62	65
2	EtBr	**2b**	94	57	61
3	PhBr	**2c**	92	53	46
4		**2d**	88	50[c]	46[d]

[a] Conditions: **1** (200 mg, 1.28 mmol), RBr (1.1 equiv.), activated Mg powder (2 equiv.), an additive (1 equiv.), THF (3 equiv.), 60 min, 30 Hz, under air. [b] Yields are determined by ^1H NMR with internal standard. [c] 40% of **9** formed. [d] 28% of **9** formed.

Tolerance of a presumably organomagnesium-mediated process to a Brønsted acid (NH_4Cl) was extraordinary, since Grignard reagents are known to be ready proton acceptors. This intriguing outcome led us to investigate in more detail the limits of such tolerance in the reactions of aldehyde **1**, given the high practical significance and mechanistic relevance of these results. We found that Barbier reactions of aldehyde **1** (Table 4, Scheme 3) occurred not only with NH_4Cl but also in the presence of water, although the yields of alcohols **2a**-**d** were 30–40% lower than those obtained in the additive-free process. Remarkably, water (1 equiv.) completely inhibited the same reactions in THF solution, which did not start even after prolonged (24 h) stirring at room temperature or heating. This failure could be attributed to passivation of the magnesium surface with $Mg(OH)_2$,[14] whereas in the ball milling process the passive layer is readily removed. The mechanochemistry-initiated reactions of **1** with 2-phenylethyl bromide (Scheme 3) showed that yields of **2d** were reduced due to competitive protonation of organomagnesium intermediate **9-Mg**, a process that produced ethyl benzene **9**. The generation of transient Grignard reagent **9-Mg** and proton transfer from the ammonium salt have been confirmed in the experiment with ND_4Cl, which afforded the corresponding deuterium-labelled hydrocarbon **9**-*d* in 40% yield. In the reaction with water (1 equiv.), **9** was formed in 28% yield, indicating a plausible intermediate of **9-Mg** and its fast addition to a carbonyl group of **1** concurrently with hydrolysis.[18] The similar behavior of liquid water and solid NH_4Cl under mechanochemical conditions was also notable (Table 4) and could be explained by coordination of water to Mg^{2+} in the solid phase, a process which may also account for the attenuated reactivity of water.[18] The extent of protonation for **9-Mg** did not correlate with the pK_a values of the selected proton donors, indicating that Brønsted acidity is not a relevant factor (Table S9). In addition to ammonium chloride, K_2HPO_4 was identified as a promising Mg alkoxide quencher, which afforded **2d** in 81% yield (Scheme 3). In contrast to the effect of water, the Barbier reaction did not occur in the presence of PhOH or *i*-PrOH.

After establishing the optimal conditions for the synthesis of alcohols from aldehydes and ketones, a broader range of organic halides and a more diverse set of electrophilic reaction partners were evaluated. In addition to other examples of functionalized

aldehydes and ketones, we tested the reactions of esters, amides, and several non-carbonyl electrophiles that furnish C–Si, C–B and C–N bonds (Scheme 4).



Scheme 4. Synthetic applications of *in situ* generated organomagnesium nucleophiles. General conditions: E^+ (0.6–3 mmol), RX (1.1–1.5 equiv.), activated Mg powder (2 equiv.), THF (3 equiv.), ball milling at 30 Hz, 1 h, under air, followed by hydrolytic work-up (aq. NH_4Cl). The reactions were performed with bromides (X = Br) except for R = allyl and benzyl (X = Cl). Yields of isolated products are shown (column chromatography on silica gel). [a] X = Br. [b] X = I. [c] With 12 equiv. of activated Mg powder. The same yield of **2i** was obtained in reaction with *c*-$C_6H_{11}MgBr$ in THF solution. [d] Yield after purification by crystallization. [e] Based on competition experiments. See section 2.7 in the ESI for details. [f] No column chromatography was carried out. [g] With NH_4Cl (1 equiv.) as an additive.

In its reaction with aldehyde **1**, cinnamyl chloride reacted almost exclusively *via* allylic rearrangement, affording alcohol **2e** in a 70% yield of the isolated product and as a 2:1 mixture of *anti*- and *syn*-diastereomers (Scheme 4, a). Benzyl bromide readily afforded

the corresponding alcohol **2f** (in 69% yield). Among other examples of aliphatic halides, *n*-butyl bromide showed high efficacy and afforded **2g** in 83% yield, while the methyl carbinol **2h** was obtained in a modest 50% yield in the reaction with methyl iodide. Nevertheless, the reaction with CH_3I occurred, even though the iodide passivates Mg in THF, rendering it unsuitable for preparing the respective Grignard reagent.[19] The reaction of **1** with bromocyclohexane required an excess of activated Mg (12 equiv.) to obtain **2i** in 50% yield. Notably, the reaction of **1** with *c*-$C_6H_{11}MgBr$ in THF solution afforded the same outcome. 2-Bromopropene produced the corresponding addition product **2j** in 73% yield, suggesting that vinylic bromides are also amenable substrates. Among the functionalized aromatic bromides, *p*-OMe and *p*-Cl-substituted bromobenzenes have been successfully employed, producing alcohols **2k** and **2l**. In these two cases, additional activation of Mg with a crystal of iodine was required to trigger the reactions. Synthesis of **2l** also featured a chemoselective transformation in which the C–Cl bond remained intact due to its much lower reactivity in comparison to the arylic C–Br bond. The higher reactivity of bromides compared to chlorides is common for the preparation of the respective Grignard reagents in solution, in which the reaction rate decreases in the order C–I > C–Br > C–Cl > C–F.[12b] For the mechanochemical Barbier reaction, we found that aliphatic and aromatic chlorides were unreactive in comparison to the respective bromides (Scheme 4, b), while allylic and benzylic chlorides demonstrated high reactivity comparable to their corresponding bromides. The yield of **2c** was lower for iodobenzene (55%) compared to that of bromobenzene (92%) due to an intensified Wurtz coupling reaction that resulted in biphenyl formation (ca. 50% yield). The relative reactivity of organic bromides was investigated in a series of competition experiments (see section 2.7 in ESI) and revealed the following order: $CH_2{=}CHCH_2Br$ > EtBr > PhBr > $PhCH_2CH_2Br$. This order is also similar to that observed in the reaction with Mg in Et_2O solution, leading to the formation of the corresponding Grignard reagents.[20] Notably, the more reactive halides usually delivered better yields of alcohols in their reactions with carbonyl substrates (Tables 1, 3) and demonstrated an increased tolerance to water and NH_4Cl (Table 4). Due to the accompanying protonation of the organometallic intermediate (Scheme 3), the use of NH_4Cl for *in situ* release of the alcoholic product from the respective Mg alkoxide is justified only when (i) the organic halide delivers a highly reactive Grignard reagent, (ii) to

suppress undesired enolization, or (iii) when a streamlined work-up protocol is advantageous for technical reasons.

In a series of *p*-substituted benzaldehydes (Scheme 4, c), the electron-donating methoxy substituent on *p*-anisaldehyde favored a smooth reaction that afforded the corresponding alcohol **10** in 87% yield. In contrast, benzaldehydes with electron-withdrawing substituents (Cl, CF_3) were less efficient and delivered lower yields, while *p*-CN and *p*-Br-substituents were intolerant and resulted in complex mixtures of products. The lower yields obtained with electron-deficient aldehydes were due to intensified reductive side processes, resulting in the formation of corresponding arylmethanol or pinacol by-products. Successful preparation of alcohol **14** (76% yield) demonstrated that steric hindrances caused by the two *o*-Me substituents did not significantly impede the allylation reaction. Heterocyclic aldehydes with thiophene and pyridine moieties were both amenable substrates in their reactions with ethyl bromide, 4-bromo-1,1,1-trifluorobutane, and allyl chloride, repectively, producing the corresponding alcohols **17**, **16** and **15** in 62–92% yields. The successful preparation of **15** is notable, since 2-pyridinecarboxaldehyde was reported to be unreactive in the mechanochemical Barbier reaction with zinc.[15]

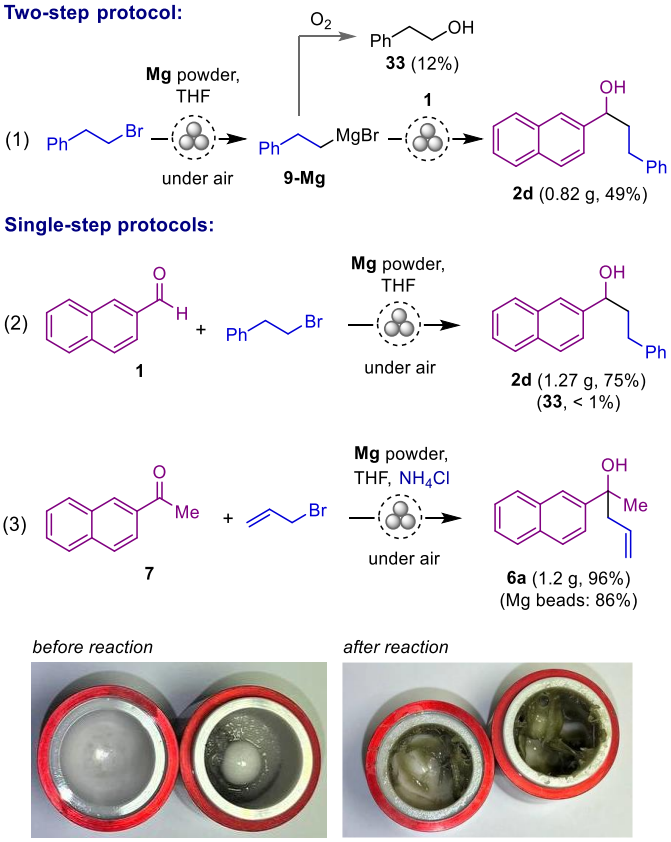
Non-enolizable ketones, such as 2,2,2-trifluoroacetophenone and benzophenone, did not require NH_4Cl as an essential additive and furnished the respective carbonyl adducts with allyl chloride **18** and **19** in a high yield of 87% and 98%, respectively (Scheme 4, d). Same alcohols were obtained in 75% and 95% yields in the presence of NH_4Cl (1 equiv.), showing a good tolerance to this protic source. Accordingly, the unprotected NH_2-moiety was a compatible functional group, as exemplified by the synthesis of aminoalcohol **20**. The reactions of benzylideneacetone (**21**) and chalcone (**22**) occurred exclusively as a 1,2-addition, affording alcohols **23** and **24**. No accompanying 1,4-addition process was observed. Diastereoselectivity of the allylation reaction was tested by the synthesis of alcohol **25**, which was obtained in 75% yield and in a non-stereoselective fashion (1:1 *dr*), similar to the analogous reaction with allylmagnesium chloride in solution.[21]

Next, we examined the behavior of less reactive carboxylic esters, which are rarely used in the Barbier-type processes (Scheme 4, e). To our delight, ethyl 2-naphthoate produced the corresponding tertiary alcohols **26** and **27** in 95% and 70% yields, respectively, in the reactions with allyl chloride and ethyl bromide. The reaction with allyl chloride perfectly

tolerated NH_4Cl as an additive. α,α,α´,α´-Tetraphenyl-1,3-dioxolan-4,5-dimethanol (TADDOL) ligand **28** was prepared from the corresponding methyl ester in 52% yield by the reaction with phenyl bromide. Furthermore, we prepared ketones **5b** and **29** from the respective Weinreb and morpholine amides (Scheme 4, f). Ketone **29** is a building block in the synthesis of the anti-cancer drug Carfilzomib and has been previously prepared by the Barbier reaction in THF solution.[22] In addition to the carbonyl-centered electrophiles, reactions with triethylchlorosilane and *O*-benzoyl-*N*,*N*-diethylhydroxylamine enabled the synthesis of the respective products **30** and **31** with newly formed C–Si and C–N bonds. The synthesis of benzylic amine **31** represents an umpolung alternative to the conventional synthesis of valuable amines *via* nucleophilic substitution.[23] The reaction with pinB(OMe) furnished boronic ester **32** but occurred with ca. 50% conversion and therefore delivered only a modest 42% yield. Although no additional optimization studies have been performed for these cases, the successful use of esters, amides, and heteroatom-centered electrophiles implies that further expansion of amenable electrophilic substrates is possible.

In a gram-scale preparation of alcohol **2d** (Scheme 5), a comparison was made between the developed one-step approach and the two-step mechanochemical Grignard synthesis. The results revealed the superiority of the single-step Barbier protocol, which produced **2d** in a noticeably better yield (75% vs. 49%) from stoichiometric amounts of **1** and 2-phenylethyl bromide. The two-step method was found to be susceptible to oxidation of the Grignard intermediate **9-Mg** in the presence of air, which resulted in the formation of alcohol **33** (12% yield). These conditions led to intensification of the MPV reaction as an accompanying side process (Table S11). In sharp contrast, the one-step protocol was immune to the oxidation process, yielding only a trace of **33**. In addition, we successfully performed a gram-scale allylation of 2-acetylnaphthalene **7** using NH_4Cl as an additive. Alcohol **6a** was isolated in 96% yield after treating obtained paste-like reaction mixture with ethyl acetate followed by filtration and evaporation of the solvent. Although no significant safety hazards were encountered in our work with Mg powder, less reactive Mg beads appeared preferable from a safety standpoint, particularly in the development of upscaled preparations. Keeping in mind that the high surface area of Mg is crucial for attaining high yields, a gram-scale synthesis of **6a** was repeated with an excess

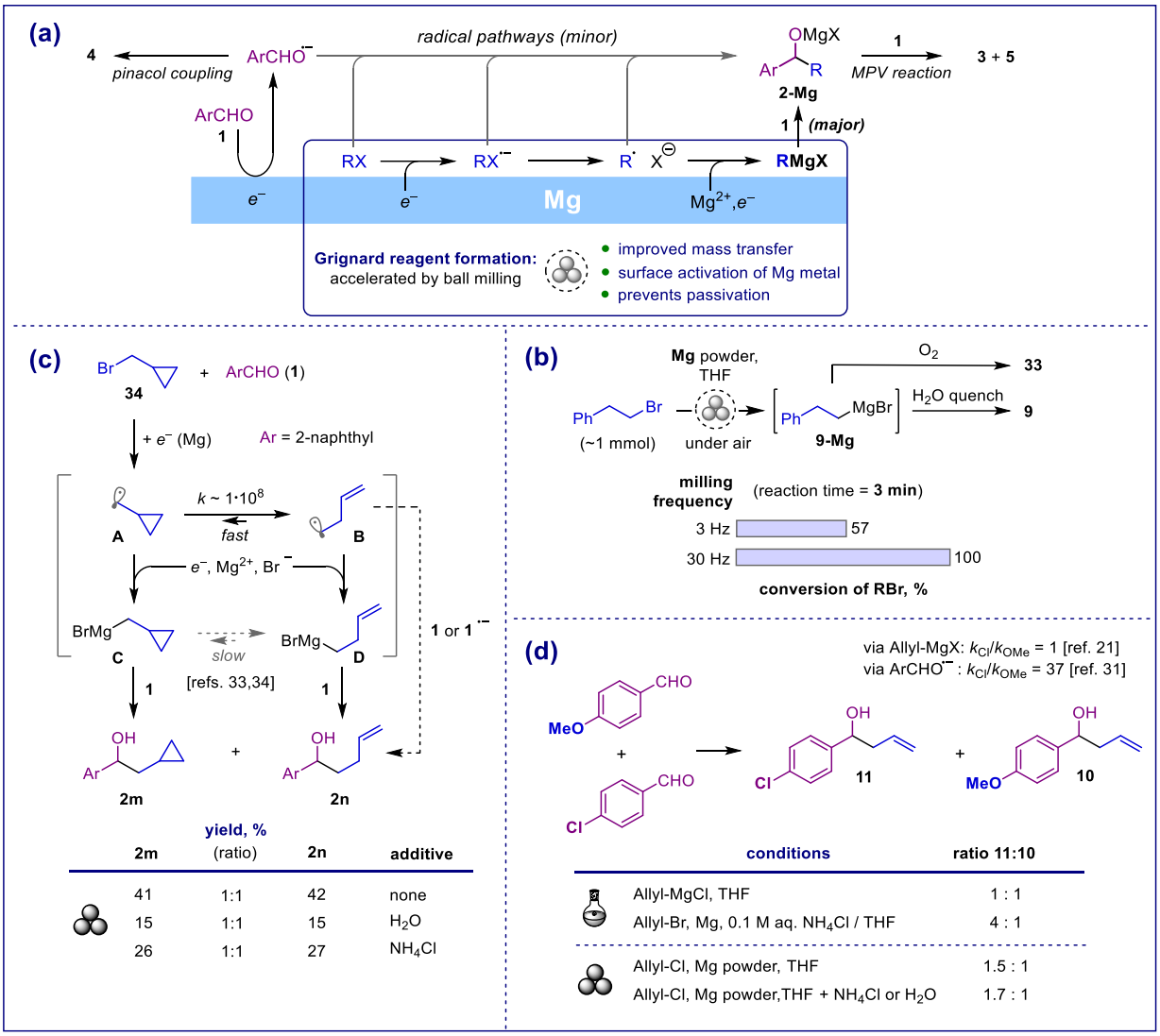
(10 equiv.) of the less reactive Mg beads and afforded **6a** in 86% yield. The beads were not fragmented during milling and eroded from the surface, which enabled ready recovery of the excess Mg (Fig. S9, ESI). Nevertheless, organic halides that could react violently or even explosively with Mg (*e.g.*, CF_3-containing aromatic bromides)[24] must be avoided in mechanochemical preparations. For substrates with unknown reactivity with Mg metal, it is advisable to carry out safety investigations[25] prior to small-scale test experiments.



Scheme 5. Gram-scale preparations and a comparison of two-step and single-step protocols.

The deuterium quenching experiment with ND_4Cl (Scheme 3) provided conclusive evidence for a Grignard reagent as an intermediate, which adds to the carbonyl group of **1** to form the magnesium alkoxide product **2-Mg** (Scheme 6, a). A competing MPV reaction of **2-Mg** with the remaining aldehyde may lead to the formation of side products **3** and **5**, particularly if the consumption of **1** during its reaction with the Grignard reagent is relatively slow. Since the addition of Grignard reagents to carbonyl compounds is typically very fast,[21,26] we concluded that Grignard reagent formation (GRF) is the rate-limiting step in the entire process. To minimize competitive reactions, GRF must be greatly

intensified under the mechanochemical conditions to ensure fast consumption of the aldehyde. This conclusion is supported by previous kinetic studies of GRF in solution, which have shown that the rate of GRF depends on the area and physical characteristics of the magnesium surface (also clearly observed in our experiments), the viscosity of the medium, and the stirring rate.[20,27,28] The latter two factors are important because organic bromides often react with magnesium at a transport-controlled rate,[20,27] meaning that the delivery of bromide to the surface of magnesium is the rate-limiting step of GRF.



Scheme 6. (a) Mechanistic interpretation and supporting experiments: (b) dependence of rate on milling frequency for generation of Grignard reagent **9-Mg**; (c) radical clock experiment; (d) competitive allylation of *p*-OMe and *p*-Cl benzaldehydes.

Therefore, rapid agitation in a ball mill, which results in improved mass transfer,[2] should enhance the rate of GRF and consequently improve yields at higher milling frequencies.

As other supporting evidence, we observed a clear increase in the generation rate of Grignard reagent **9-Mg** at higher milling frequencies (3 Hz vs 30 Hz, Scheme 6, b). The reaction was rapid at 30 Hz, with full conversion of the starting bromide achieved after just 3 minutes, whereas the process was noticeably slower at 3 Hz. The second important factor that contributes to the accelerating effect is activation of the magnesium surface[17,29] by generating active sites in the ball milling process. In this way, passivation is also prevented,[2] and the reactive surface of the metal is continuously renewed, enabling the start the reaction even in the presence of water. In addition to increasing the rate of GRF, this factor also reduces the induction delay.

Although the formation of organometallic intermediates was apparent, the possibility of additional radical-mediated pathways could not be entirely overlooked.[30,31] These pathways have been suggested as an alternative mechanism for the Barbier reaction,[12c] in which radical and radical-anion species that mediate GRF[17,32] may be intercepted by carbonyl substrate **1** or by anion-radical $\mathbf{1}^{\cdot-}$, which were generated from it (Scheme 6, a). The latter can also produce pinacols **4**, which were formed in significant amounts only in the reactions with electron-deficient aldehydes. The organometallic-free mechanism could also account for the formation of alcohol products in the presence of water.[14,31] Therefore, additional mechanistic experiments have been carried out with the aim of detecting whether the contribution of the radical intermediates is significant, especially in the presence of proton sources and in the reactions of electron-deficient carbonyl substrates. First, cyclopropylmethyl bromide (**35**) was utilized as a radical clock probe (Scheme 6, c).[33] The reaction yielded a mixture of alcohols **2m** and **2n** in an almost equal ratio of 1:1, regardless of the presence or absence of proton sources (H_2O or NH_4Cl). The observation of an equal ratio of **2m** and **2n** is consistent with the rapid formation[17] of Grignard reagent **C** from the cyclopropylmethyl radical **A**, which occurs at the same high rate as its intramolecular rearrangement into **B** ($k \sim 10^8\ s^{-1}$).[34] The short-lived alkyl radicals are unlikely to be intercepted by either **1** or its anion-radical $\mathbf{1}^{\cdot-}$, as these second-order processes either have much lower rate constants (such as the radical addition to **1**)[35] or require high concentrations of radical species (such as $\mathbf{1}^{\cdot-}$)[36] to proceed at a competitive rate. Moreover, if the organometallic-mediated pathway does not operate in the presence of proton donors, the radical mechanism should predominantly deliver the rearranged

alcohol **2n**. However, both NH_4Cl and H_2O reduced yields of the alcohols without altering their ratio. This outcome is consistent with the competitive protonation and carbonyl addition of the organometallic intermediates **C** and **D**.[18] Based on these findings, we anticipated that substrates that generate more stable and long-lived radical or radical anion species, such as aromatic aldehydes (particularly those with electron-withdrawing substituents) and allyl halides, may be more prone to react *via* the radical mechanism. To test this hypothesis, we selected the allylation reactions of *p*-methoxy- and *p*-chlorobenzaldehydes (Scheme 6, d) as an appropriate mechanistic probe based on the distinct electronic properties of these substrates (Hammett constants of *p*-substituents, σ_p = −0.27 and +0.23, respectively). It has been previously shown that the rate of the anion-radical-mediated Barbier reaction of benzaldehydes is highly sensitive to the nature of *p*-substituents (k_{Cl}/k_{OMe} = 37, based on the Hammett equation).[31] In contrast, the addition of allyl Grignard reagents to carbonyl compounds is extremely fast and therefore non-selective.[21] In the competition experiments we performed, the Barbier reaction in aqueous THF produced *p*-Cl-substituted alcohol **11** as the kinetic product, while the addition of allylmagnesium chloride in THF solution was non-selective. The mechanochemical Barbier reaction (with and without NH_4Cl and H_2O additives) delivered product ratios close to 1:1.5, and slightly in favour of *p*-Cl-substituted product **11**. Notably, *p*-chlorobenzaldehyde was also involved in the accompanying pinacol coupling. These results indicate an operation of the anion-radical-mediated pathway, although as a minor contributor that becomes apparent in electron-deficient aldehydes. A greater contribution of the radical mechanism could be expected for carbonyl substrates, which are more prone to single electron reduction and produce long-lived ketyl radicals, such as benzophenones. However, this hypothesis has not been verified in our study.

Conclusions

In conclusion, we have demonstrated that Grignard syntheses can be expediently performed in a single step under mechanochemical conditions *via* organomagnesium intermediates generated *in situ* in the presence of several electrophilic reaction counterparts (*i.e.*, Barbier conditions). Essentially, high reactivity of organomagnesium compounds and reduced side processes enabled by mechanochemistry facilitated the expansion of the scope of the Barbier reaction beyond the conventional allylation of

aldehydes. A broad range of suitable electrophiles (*e.g.*, aldehydes, ketones, esters, amides, chlorosilane, borate ester, hydroxylamine) and organic halides (*e.g*., allylic, aromatic, vinylic, aliphatic) are compatible with the single-step reaction design, which is essentially solvent-free, features short reaction times, and employs an operationally simple protocol. The yields of products obtained from 2-naphthaldehyde were considerably better than that in the analogous solution-based Barbier reaction and attained high efficiency in the classic Grignard synthesis. In contrast to the latter approach, the one-step process we developed is resistant to oxidation when exposed to air, can be performed without a protective inert atmosphere, and shows unusually high tolerance to water and some other proton donors. Solid proton-donating salts (*e.g.*, NH_4Cl) can be used to release the alcoholic products from the respective alkoxides *in situ*, thereby streamlining the work-up protocol and suppressing the enolization side process. Mechanistic studies have indicated that the organomagnesium-mediated pathway is the dominant mechanism, at least in the reactions of aldehydes, with the ball milling process resulting in the accelerated generation of transient Grignard reagents by improving mass transfer and activating the surface of magnesium metal. The contribution of alternative radical-mediated mechanistic scenarios has been evaluated and their minor input in the reactions of aromatic aldehydes has been demonstrated. The developed approach described here provides a convenient alternative to traditional Grignard synthesis, while the established reactivity trends and mechanistic insights offer a starting point for further innovations toward greener and safer implementation of industrial organometallic processes.

Experimental Section

Detailed information about optimization of the studies, experimental methods, and the corresponding structure characterization data is provided in the ESI.

Data availability

Data for all compounds described in this manuscript are available in the ESI, which includes experimental details, characterisation, copies of ^{1}H and ^{13}C NMR spectra.

Author contributions

J.V., T.N., D.M. carried out the investigation and formal analysis of the data. T.J. carried out HRMS analyses and assisted with analytical chemistry measurements and data analysis. D.K. conceptualized the project and prepared the original draft of the manuscript. D.K. and R.A. were involved with supervision and funding acquisition. All authors were involved in reviewing and editing the manuscript.

Conflict of interest

There are no conflicts of interest to declare.

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Keywords: mechanochemistry • Grignard reagent • Barbier reaction • magnesium • mechanism

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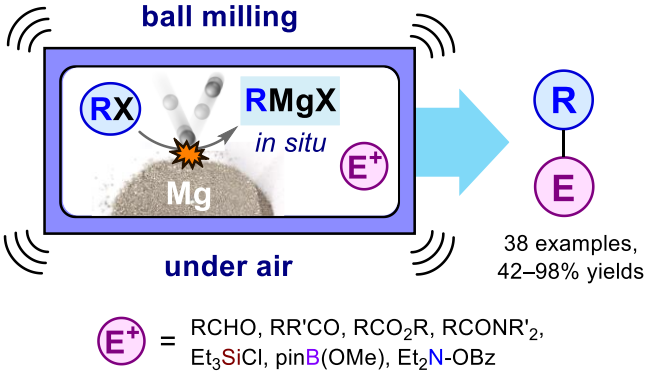
Graphical Abstract



single step, broad scope, immune to air

Shaken, not stirred: mechanochemistry enables the rapid *in situ* generation of Grignard reagents, thereby overcoming the longstanding limitations of the Mg-mediated Barbier reaction.