

TALLINN UNIVERSITY OF TECHNOLOGY
DOCTORAL THESIS
54/2025

Mechanochemical Activation of Alkaline Earth Metals and Its Applications in Organic Synthesis

JAGADEESH VARMA NALLAPARAJU



TALLINN UNIVERSITY OF TECHNOLOGY
School of Science
Department of Chemistry and Biotechnology
The dissertation was accepted for the defence of the degree of Doctor of Philosophy
in Chemistry on 26/06/2025

Supervisor: Dr. Dzmitry Kananovich
School of Science, Department of Chemistry and Biotechnology
Tallinn University of Technology
Tallinn, Estonia

Co-supervisor: Prof. Riina Aav
School of Science, Department of Chemistry and Biotechnology
Tallinn University of Technology
Tallinn, Estonia

Opponents: Assoc. Prof. Erli Lu
School of Chemistry
University of Birmingham
Birmingham, United Kingdom

Prof. Lauri Vares
Institute of Technology
University of Tartu
Estonia

Defence of the thesis: 22/08/2025, Tallinn

Declaration:

Hereby I declare that this doctoral thesis, my original investigation and achievement, submitted for the doctoral degree at Tallinn University of Technology has not been submitted for doctoral or equivalent academic degree.

Jagadeesh Varma Nallaparaju

signature



Copyright: Jagadeesh Varma Nallaparaju, 2025

ISSN 2585-6898 (publication)

ISBN 978-9916-80-343-1 (publication)

ISSN 2585-6901 (PDF)

ISBN978-9916-80-344-8 (PDF)

DOI

TALLINNA TEHNIKAÜLIKOOL
DOKTORITÖÖ
54/2025

Mehhanokeemiline leelismuldmetallide aktiveerimine ja selle rakendused orgaanilises sünteesis

JAGADEESH VARMA NALLAPARAJU



Contents

List of Publications	7
Author's Contribution to the Publications	8
Author's Other Publications and Conference Presentations	9
Introduction	11
Abbreviations and Pictograms	12
1. Literature Overview	13
1.1 Mechanochemistry	13
1.1.1 Mechanochemical equipment and scalability.....	13
1.1.2 Key variables affecting chemical reactions in a ball mill	15
1.1.3 Operational parameters under direct control	16
1.1.4 Liquid-assisted grinding.....	17
1.1.5 Grinding auxiliaries.....	18
1.1.6 Established benefits of mechanochemistry in organic synthesis.....	19
1.2 Mechanochemical Generation of Polar Organometallic Reagents	20
1.2.1 Factors influencing the preparation of polar organometallics.....	21
1.2.2 Mechanochemistry addresses challenges of organometallic chemistry	22
1.2.3 Generation of organozinc reagents	23
1.2.4 Generation of organomagnesium reagents	25
1.2.5 Generation of organocalcium reagents	28
1.2.6 Generation of organobarium reagents	31
1.2.7 Generation of organolithium reagents	32
1.3 The Birch Reduction: Classical Approach and Recent Innovations	33
1.3.1 Mechanism and regioselectivity	33
1.3.2 History and recent advances	34
1.3.3 Alkaline earth metal-mediated Birch reductions	37
1.4 Process Safety Considerations and Technological Challenges for Scaling Up Metal-Mediated Mechanochemical Reactions.....	39
1.5 Summary of the Literature Overview.....	40
2. Motivation and Aims of the Present Work	41
3. Results and Discussion	42
3.1 Mechanochemistry-Amended Barbier Reaction as an Expedient Alternative to Grignard Synthesis (Publication I)	42
3.1.1 Optimization studies with 2-naphthaldehyde.....	43
3.1.2 Mechanistic study to elucidate the nature of the major side process.....	47
3.1.3 Optimization studies with 2-acetylnaphthalene	48
3.1.4 Tolerance to protic additives	50
3.1.5 Substrate scope of organic halides and electrophiles.....	52
3.1.6 Mechanistic experiments and the role of mechanical energy	56
3.2 Mechanochemical Birch Reduction with Low Reactive Alkaline Earth Metals (Publication II)	58
3.2.1 Optimization studies with calcium.....	59
3.2.2 Reaction kinetics and comparison with the solvent-based method.....	60
3.2.3 The role of protic source and reduction of electron-rich arenes.....	61
3.2.4 Deuterium labelling experiments.....	63

3.2.5 Substrate scope and limitations.....	63
3.2.6 The Birch reduction with magnesium	65
3.2.7 Other dissolved metal-type reductive transformations.....	67
4. Conclusions	70
References	71
Acknowledgements.....	78
Abstract.....	79
Lühikokkuvõte.....	80
Appendix 1	81
Appendix 2	95
<i>Curriculum vitae</i>	107
Elulookirjeldus.....	108

List of Publications

The list of author's publications, based on which the thesis has been prepared:

- I **J. V. Nallaparaju**, T. Nikonovich, T. Jarg, D. Merzhyevskiy, R. Aav, D. G. Kananovich. Mechanochemistry-Amended Barbier Reaction as an Expedient Alternative to Grignard Synthesis. *Angewandte Chemie International Edition*, **2023**, *62*, e202305775.
- II **J. V. Nallaparaju**, R. Satsi, D. Merzhyevskiy, T. Jarg, R. Aav, D. G. Kananovich. Mechanochemical Birch Reduction with Low Reactive Alkaline Earth Metals *Angewandte Chemie International Edition*, **2024**, *63*, e202319449.

Author's Contribution to the Publications

Contribution to the papers in this thesis are:

- I The author had a major role in the method development, synthesis and characterisation of compounds used in the study. The author had a significant role in the preparation of the manuscript and a major role in the compilation of the supporting information.
- II The author had a major role in the method development, synthesis and characterisation of compounds used in the study. The author had a significant role in the preparation of the manuscript and a major role in the compilation of the supporting information.

Author's Other Publications and Conference Presentations

Other publications:

1. E. Suut-Tuule, T. Jarg, P. Tikker, K.-M. Lootus, J. Martõnova, R. Reitalu, L. Ustrnul, J. S. Ward, V. Rjabovs, K. Shubin, **J. V. Nallaparaju**, M. Vendelin, S. Preis, M. Öeren, K. Rissanen, D. Kananovich, R. Aav. Mechanochemically Driven Covalent Self-Assembly of a Chiral Mono-Biotinylated Hemicucurbit[8]uril. *Cell Reports Physical Science* **2024**, *5*, 102161.
2. Dalidovich, T., **Nallaparaju, J. V.**, Shalima, T., Aav, R., Kananovich, D. G. Mechanochemical Nucleophilic Substitution of Alcohols via Isouronium Intermediates. *ChemSusChem* **2022**, *15*, e202102286.
3. Šakarašvili, M., Ustrnul, L., Suut, E., **Nallaparaju, J. V.**, Mishra, K. A., Konrad, N., Adamson, J., Borovkov, V., Aav, R. Self-Assembly of Chiral Cyclohexanohemicucurbit[n]urils with Bis(Zn Porphyrin): Size, Shape, and Time-Dependent Binding. *Molecules* **2022**, *27*, 937.
4. Ponugoti, M., Panda, SP., Kulandaivelu, U., Koteswara Rao, GSN., Alavala, RR., **Nallaparaju, J. V.** Isolation and Evaluation of Anti-inflammatory activity of Epigallocatechin from *Senegalia rugata* along with PUFAs. *Research Journal of Pharmacy and Technology* **2021**, *14*, 5739.

Patent application:

1. Method for reduction of organic compounds with mechanochemical treatment; Tallinn University of Technology, School of Science, Department of Chemistry and Biotechnology; Jagadeesh Varma Nallaparaju, Riina Aav, Dzmitry Kananovich; Priority number: EP24157530.7; Priority date: 14.02.2024.

Conference presentations:

1. Nallaparaju, J.V.; Nikonovich, T.; Satsi, R; Aav, R; Kananovich, D. G. Shaking-Up Metal-Mediated Organic Reactions Using Ball Mill. National Organic Chemistry Symposium (NOS 2025), 22-26 June **2025**, in Troy, Newyork, USA. (Poster)
2. Nallaparaju, J.V.; Nikonovich, T.; Satsi, R; Aav, R; Kananovich, D. G. Shaking-Up Metal-Mediated Organic Reactions Using Ball Mill. 9th EuChemS Chemistry Congress (ECC 9), 7-11 July **2024**, in Dublin, Ireland. (Poster)
3. Nallaparaju, J.V.; Nikonovich, T.; Satsi, R; Aav, R; Kananovich, D. G. Shaking-Up Metal-Mediated Organic Reactions Using Ball Mill. 18th Belgian Organic Synthesis Symposium (BOSS), **2024**, 30th June - 5th July, in Liège, Belgium. (Poster)
4. Nallaparaju, J.V.; Dalidovich, T.; Aav, R; Kananovich, D. G. Mechanochemical Barbier-Type Grignard Reactions of Organic Halides. Balticum Organicum Syntheticum (BOS), **2022**, 3-6 July, Vilnius, Lithuania, 157. (Poster)
5. Nallaparaju, J.V.; Dalidovich, T.; Aav, R; Kananovich, D. G. Mechanochemical Barbier-Type Grignard Reactions of Organic Halides. 10th International Conference on Mechanochemistry and Mechanical Alloying (INCOME), **2022**, 6-10 June, University of Cagliari, Italy. (Poster)

6. Nallaparaju, J. V.; Shalima, T.; Kananovich, D. G.; Aav, R. Mechanochemical Conversion of 1,2,3-Trichloropropane into Homoallylic Alcohols. International Symposium on Synthesis and Catalysis (ISySyCat), **2021**, 31st August – 3rd September, University of Évora, Portugal. (Poster)
7. Nallaparaju, JV; Kananovich, DG; Aav, R. Mechanochemical Conversion of 1,2,3-Trichloropropane into Homoallylic Alcohols. GSFMT Scientific Conference, 14-15 June, **2021**, Tartu, Estonia. (Oral & Poster)

Introduction

The pursuit of safer, efficient and more sustainable synthetic methodologies has led to a growing interest in solvent-free chemical transformations. Mechanochemistry is one of the leading technologies addressing these demands, that utilizes mechanical forces to initiate and accelerate chemical transformations.^[1] Unlike conventional solution-phase methods, mechanochemical processes avoid the use of bulk solvents, unlock new reactivity pathways and offer operational simplicity.^[2-4] Moreover, mechanochemistry is well-aligned with the 12 principles of green chemistry, often showing significant improvements in green chemistry metrics compared to benchmarking solution methods.^[5,6]


One of the notable advantages of mechanochemistry is its ability to activate insoluble materials including zero-valent metals, inorganic salts etc., under ambient temperature conditions.^[7] The mechanical energy applied to metals during ball milling enhances metal reactivity through removal of surface passivation layers, pulverization of bulk metals into smaller particles, increasing the reactive surface area, and generates active sites necessary for initiating chemical reactions. This approach opens new possibilities for generating reactive polar organometallic species and carrying out reductive transformations without the need for toxic chemicals, cryogenic temperatures, and inert atmosphere.

This doctoral thesis opens with an overview of mechanochemistry, highlighting its significant potential and unique advantages. The subsequent sections of the literature review focus on demonstrating the activation of zero-valent metals via ball milling and its applications in the generation of polar organometallic reagents and dissolving-metal reductions.

The primary objective of this doctoral work was to investigate the mechanochemical activation of the two most abundant alkaline earth metals (Mg and Ca) which are low-cost and non-toxic in their compounds, and hold high practical significance in organic synthesis. First, we developed a mechanochemical equivalent of the Barbier-Grignard reaction, in which organomagnesium reagents (R-MgX) are generated *in situ* by using magnesium metal and various organic halides. This method offers a practical and efficient alternative to the classical Grignard reaction, which typically requires anhydrous solvents and an inert atmosphere. Subsequently, we developed a mechanochemical method for the Birch reduction of aromatic systems by using calcium and magnesium metals as reductants. These metals serve as safer and more sustainable alternative to the traditional alkali metal reductants (Li, Na, K).

Through these studies, this thesis highlights the synthetic potential and practical advantages of mechanochemical strategies, especially in the activation of zero-valent metals (Ca, Mg) and inorganic salts (NH₄Cl, K₂HPO₄) for performing arduous chemical transformations.

Abbreviations and Pictograms

Ac	Acetyl
ACS	American Chemical Society
API	Active pharmaceutical ingredient
Ar	Aryl
Cy	Cyclohexyl
DFT	Density functional theory
DMA	<i>N,N</i> -dimethylacetamide
DMI	dimethyl isosorbide
DDT	dichlorodiphenyltrichloroethane
E ⁺	Electrophile
EDA	ethylenediamine
EDG	electron-donating group
Et	ethyl
EtOAc	ethyl acetate
EWG	electron-withdrawing group
GRF	Grignard reagent formation
IUPAC	International Union of Pure and Applied Chemistry
LAG	liquid-assisted grinding
LiHMDS	lithium bis(trimethylsilyl)amide
Me	methyl
2-MeTHF	2-methyltetrahydrofuran
MOF	Metal–organic framework
MPV	Meerwein–Ponndorf–Verley
NEXAFS	Near-edge X-ray absorption fine structure
NIR	Near Infrared spectroscopy
NMR	Nuclear Magnetic Resonance
PCBS	Polychlorinated biphenyls
Ph	Phenyl
PMI	Process Mass Intensity
ppm	Parts Per Million
RAM	Resonance Acoustic Mixer
TCP	1,2,3-trichloropropane
THF	Tetrahydrofuran
THP	Tetrahydropyran
TMEDA	Tetramethylethylenediamine
TMSCl	Trimethylsilyl chloride
TSE	Twin-screw extrusion
±	with or without
	Ball milling

1 Literature Overview

1.1 Mechanochemistry

For a chemical reaction to take place, the energy input must be sufficient to overcome the activation barrier for chemical transformation. Traditionally, this energy is delivered by heating the reaction mixture. Besides heating, the advancement of enabling technologies has led to the development of alternative energy input methods, such as photochemical and electrochemical techniques, which are widely adopted as greener methodologies in organic synthesis.^[8,9] In contrast, historically well-known mechanochemical techniques^[10] have been less explored until recently and were primarily limited to fields such as crystallography and the manual grinding of materials.^[11,12]

Mechanochemical reactions are defined as “chemical reactions that are induced by the direct absorption of mechanical energy” in the IUPAC Gold Book.^[13] This includes techniques such as sonication, grinding, hammering, extrusion, and ball-milling. Over the last two decades, interest in mechanochemistry for the synthesis of organic compounds has grown substantially.^[1,2,4,14] Because the required energy is provided through mechanical forces rather than stirring in solution, it means the usage of bulk solvents can be excluded. This directly resolves a major challenge in implementing green chemistry practices within the chemical industry by solvent reduction, as highlighted by the ACS Green Chemistry Pharmaceutical Roundtable in 2007.^[15,16] In addition, mechanochemistry also offers an opportunity to explore chemical reactions in highly-concentrated environment, which led to discovery of new reaction pathways.

1.1.1 Mechanochemical equipment and scalability

Early approaches to mechanochemical synthesis involved manual grinding with a mortar and pestle.^[17] However, this method was prone to variability caused by human error, especially during longer grinding periods.^[18] The introduction of automated equipment, capable of delivering uniform and regulated energy input, effectively addressed these inconsistencies. Mixer mills and planetary mills are very common ball mills in academic laboratories, and there are now many different brands and models available. As a concept, these two ball mills work in a similar way, through providing kinetic energy to one or more milling balls (most commonly made of ZrO₂ or stainless steel), which can then transfer the energy to initiate the chemical reaction via strong collisions with the reactant material.^[19]

In the case of a **mixer mill** (also known as a shaker mill or a vibratory ball mill), the reaction jars (typically, 10–30 mL volume) are placed horizontally and vibrate rapidly in a horizontal back-and-forth motion at the desired frequency (typically, maximum 30–50 Hz) (Figure 1). The main mechanical energy applied to the reaction mixture is impact and compressive forces. Studies suggest that the majority of the energy is transferred through the ball's direct impact with the chemical substance at the jar's end/walls^[20]. However, the balls do not move only a perfectly straight path and instead move in a more variable manner. This results in additional energy transfer possibilities, such as shearing or occasional glancing collisions along the jar's sides. In a typical mixer mill reaction, one or two 10-mm milling balls are used, although sometimes several smaller 5-mm balls can be added to improve mixing. Various jar sizes and materials are available, with different levels of compatibility between jars and mixer mills.^[4]

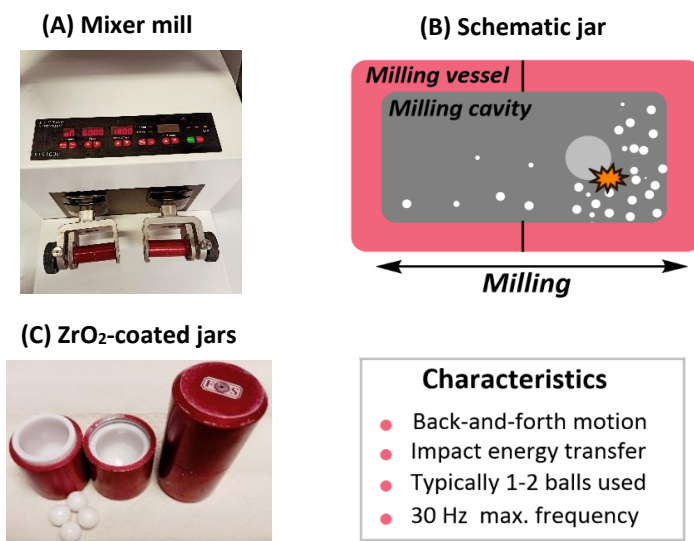


Figure 1. Mixer-mill equipment used in this work. **(A)** Form-Tech scientific (FTS-1000) mixer mill (<https://formtechscientific.com/fts-1000-shaker-mill/products.html>). **(B)** Schematic representation of mixer mill. **(C)** 14 mL ZrO₂-coated milling jars, 10 mm ZrO₂ milling balls.

In **planetary mills**, the milling jars are positioned vertically on a rotating platform, and the operational principle differs from that of mixer mill (Figure 2, A). In this setup, the platform rotates in clockwise direction, while the jars simultaneously rotate around their own axes in the counterclockwise direction. The primary mode of mechanical energy transfer in planetary mills is shear force.^[21] Multi-gram syntheses can be performed by using larger jars and milling balls.^[22] However, both the mixer mill and planetary mill have limited capacities on the reaction scale, which is approximately under 10 g for mixer mills and under 100 g for planetary mills, when using most commonly available jars. Reactions at these scales require careful attention to safety, as controlling thermal dissipation becomes difficult due to the absence of a solvent to serve as a heat sink. To address the limitations of ball milling technology, alternative methods such as continuous synthesis via **twin-screw extrusion** (TSE) have been developed.^[23] In this method, material is continuously processed between two parallel, counter-rotating screws driven by motors. Throughout the system, the screws can be fitted with several parts, including “conveying”, “reverse”, and “kneading” sections (Figure 2, B). TSE has proven effective for large-scale organic reactions and has also shown advantages in the synthesis of active pharmaceutical ingredients (APIs)^[24,25] and metal-organic frameworks (MOFs).^[26] The extruder’s design often allows to perform the reactions with precise control of the reaction temperature, which can blur the distinction between mechanochemistry and thermochemistry. Additionally, the screw design can be modified to enhance the applied mechanical forces, using kneading and reverse screw configurations to introduce extra shearing and compressive forces. Alternative mechanochemical instruments are available, for example, **resonance acoustic mixers** (RAM) facilitate reactions without milling media, relying instead on high-frequency acoustic vibrations to promote mixing (Figure 2, C).^[27] Hybrid batch/continuous devices such as the Dyno[®]-mill further expand the mechanochemical toolbox, allowing for scalable synthesis under controlled conditions.^[28]

(A) Planetary mill**(B) Twin-screw extruder****(C) Resonance acoustic mixer**

Figure 2. (A) Planetary mill, Fritsch (B) Twin-Screw Extruder (TSE), Thermo Fisher Scientific. (C) Resonance acoustic mixer. (images reproduced from the <https://www.fritschinternational.com>, www.thermofisher.com, <https://resodyn.com/>).

1.1.2 Key variables affecting chemical reactions in a ball mill

To maximize efficiency, it is important to understand and control the variables involved in any chemical process. There are three key factors which influence on how mechanical energy is transferred to the reactants: (i) the kinetic energy of the ball(s) before impact, (ii) the efficiency of energy transfer to the reagents during collisions and (iii) the frequency of the collisions.^[20,29] When using ball mills, it is challenging to control or even evaluate these variables independently.

The maximum energy that can be transferred to the reagents during each collision is determined by the kinetic energy of the ball(s) prior to impact. This energy depends on both the mass and speed of the ball(s). While the mass of the ball(s) can be controlled, their speed depends on conditions inside the milling jar, which are influenced by jar's dimensions and filling degree, the weight and number of milling balls, and the milling speed (Hz).^[30,31]

In a collision, the way energy is transferred can influence significantly on the reaction outcome. Energy can be delivered either through direct impact, which locally compresses the material, or via shear forces. Studies have shown that different modes of energy transfer can lead to different reaction outcomes.^[32] The ratio between impact and shear forces varies across different types of ball mills. The amount of energy absorbed during a collision also depends on how much of energy is lost due to the physical deformation of the material. Therefore, it depends on the rheology of the reaction mixture, particularly its Young's modulus.^[33,34]

Another crucial factor is the frequency of collisions per second. Higher collision rate allows more energy to be transferred, thus it enhances the rate of the reaction. Similarly to kinetic energy mentioned above, the collision rate is also by milling speed, the size and number of balls, and the filling degree of the jar.

Differences in mass transfer or mixing can also strongly affect the result of the reaction. In solution-based reactions, mass transfer is usually not a concern, as all reactants are dissolved and well mixed. However, in the solid-state reactions, mass transfer can greatly impact the results and is harder to measure or control. Mass transfer could be directly influenced by all the mechanochemical parameters which includes type of mill, weight and number of balls, material of the jar, filling degree, volume of the jar, reactants

volume, milling frequency, and the physical properties of the reactants. Fortunately, most of these variables can be experimentally adjusted and controlled.

Finally, standard reaction variables such as temperature, milling time, and stoichiometry of the reactants also play important role. Although cryo-mills offer external cooling,^[35] the temperature control is not so easy as the reaction jar heats up during the repeated collisions. This heat dissipation makes difficult to understand whether the reaction is driven by heat or by mechanochemical forces. Among the several factors that influence reaction outcomes, very few can be altered or controlled independently. However, several variables can be managed, and they often work together to affect the overall reactivity and efficiency of the process.

1.1.3 Operational parameters under direct control

One of the initial considerations in a mechanochemical reaction is selecting the appropriate **type of ball mill**. As previously discussed, there are two main common options: either a mixer mill or a planetary mill. While the choice of mill may depend on the reaction scale – since planetary mills can accommodate larger-scale reactions than mixer mills – the key differences between the two primarily relate to the motion of the grinding media within the milling jar. This motion directly affects the ratio of impact to shear forces, the amount of kinetic energy transferred, and the overall mixing efficiency. Although there have been relatively few comparative studies and reported different outcomes while using different mills.^[36,37] When multiple type of mills are available, it is often difficult to predict which will lead to the best results. Therefore, early stages of process optimization may benefit from testing several types of mills in parallel.

The next important parameter to consider is the **filling degree**, which refers to how much volume of the milling jar is occupied by both the reactants and milling balls, relative to the total jar's volume. This factor significantly effects the trajectories of the balls, thereby affecting energy transfer and mixing efficiency. For example, the impact of filling degree has been studied in the Knoevenagel condensation of vanillin with barbituric acid using a planetary mill, by varying the number of grinding balls in the jar.^[38] At low filling degrees, the limited number of balls resulted in poor mixing and reduced kinetic energy. Conversely, when a greater number of balls is used, they restrict each other's motion and cannot move freely, which limits their velocities and, consequently, their kinetic energy. Therefore, an optimal filling degree of both reactants and number of balls should be maintained to ensure maximal mixing efficiency.

The **size of the milling ball** can be controlled and is typically choose based on the volume of the milling jar to ensure optimal performance. Generally, larger balls may not lead to good mixing and smaller balls can improve the mixing. This is because when the ball diameter is large and approaches that of the jar, there is limited space for reagents to circulate around the ball, which hinders effective mixing. In addition to size, the **mass of the milling ball** is another crucial factor. The larger the mass, the more kinetic energy can the ball possess before collision, resulting in higher energy transfer during collisions. As larger balls tends to be greater mass, choosing the ball size involves a trade-off between maximizing mixing efficiency and highest energy input. However, this compromise can be addressed by varying the material of the balls. By selecting materials with different densities, it is possible to adjust the mass of the ball without altering the size, allowing for more precise control over the milling conditions.

Another important parameter in mechanochemical reactions is the **material** of the grinding jars and balls. Physical properties such as density, hardness, abrasion resistance,

and chemical stability can significantly influence the reaction outcome. Common materials used for milling accessories include tungsten carbide, stainless steel, zirconium oxide, sintered corundum, agate, and Teflon. Because of its high density and hardness, tungsten carbide delivers the greatest energy input to the system (density 14.8 g/cm³, Vickers hardness 1500–2600), followed by stainless steel (density 7.8–7.9 g/cm³, Vickers hardness 825). Zirconium oxide jars and balls, with moderate density and hardness (density 5.9 g/cm³, Vickers hardness 1500), provides moderate energy input. Although sintered corundum is very hard, but its relatively low density (3.9 g/cm³) results in lower energy transfer. Finally, agate (density 2.7 g/cm³, Vickers hardness ~200) and Teflon (density 2.1 g/cm³) are materials associated with minimal energy input during milling.^[39] After choosing the right material according to its physical properties, chemical resistance is yet another crucial factor to consider.

Stainless steel is not an ideal choice when aiming to avoid cross-contamination from abraded iron or iron compounds leaching, especially when working with corrosive media. Materials such as tungsten carbide and zirconium oxide are better choices due to their lower abrasion. Additionally, their chemical resistance makes them well-suited for milling corrosive substances frequently encountered in organic synthesis.^[40]

However, in some cases, the milling material is specifically selected to participate in the reaction. Mechanochemistry offers a particularly unique approach to running catalytic reactions by utilizing catalytically active sites on the surface of milling media, a method known as direct mechanocatalysis. This methodology was pioneered by Mack et al.^[41,42] and further developed by Borchardt group.^[43]

Milling speed is the parameter that is the most straightforward to understand and the simplest to control, as it is selected directly through the mill's control interface. Increasing the milling frequency causes the grinding balls to move faster, thereby increasing their kinetic energy.^[44] This offers an easy and effective method to adjust the amount of mechanical energy introduced into the chemical system. Additionally, general reaction conditions like the proportions of reactants (stoichiometry) and the duration of milling are also easily managed, just as in traditional chemical reactions.^[45]

1.1.4 Liquid-assisted grinding

Liquid-assisted grinding (LAG), also known as solvent-drop grinding, is an extension of traditional solvent-free mechanochemical techniques (neat grinding) in which a small amount of liquid (referred as LAG additive or agent) is used as an additive to enhance or control the reactivity.^[46–48] It is empirically characterized by the parameter (η), which reflects how mechanochemical reactivity is influenced by the ratio of the volume of liquid additive (μL) to the total weight of the solid reactants (mg). A value of $\eta = 0$ corresponds to neat grinding without any liquid additive, and a value in the range of $0 < \eta \leq 1$ corresponds to LAG. Reaction mixtures with higher η values typically would form a slurry ($1 < \eta$) or homogenous solutions ($10 \leq \eta$). These do not fall under the category of LAG regime (Figure 3).

$\text{LAG} (\eta) = \frac{\text{Volume of liquid additive} (\mu\text{L})}{\text{Weight of solid reactants} (\text{mg})}$	$\eta = 0$ neat grinding
	$0 < \eta \leq 1$ liquid assisted grinding (LAG)
	$1 < \eta < 10$ slurry
	$\eta \geq 10$ homogenous dissolved solution

Figure 3. The definition of Liquid-Assisted Grinding (LAG).

LAG was initially applied in mechanochemical co-crystallization, where it was observed to accelerate the co-crystallization process.^[11] It has also been demonstrated that LAG can yield different outcomes compared to slurry reactions, and that the results are not necessarily dependent on the solubility of the starting materials in the liquid additive.^[49] The Browne group reported a LAG-controlled selective fluorination of β -diketones, in which chemoselectivity could be switched by altering the LAGs or neat grinding conditions.^[47] Although the mechanism of LAG remains not fully understood, recent studies suggest that its effectiveness may be attributed to some physical factors such as dissolution,^[50] molecular mobility,^[51] and liquid polarity.^[52] Despite these uncertainties, LAG is widely considered as a key contributor to the success of mechanochemistry.

1.1.5 Grinding auxiliaries

The rheology of the reaction mixture plays an important role in determining how a mechanochemical reaction proceeds.^[36] This is largely influenced by the physical state of both the starting materials and products. For example, liquids are generally poor at absorbing mechanical energy, as they tend to freely move away from the position of impact, thereby reducing the efficiency of energy transfer. To overcome these challenges, the reaction mixture can be supplemented with a grinding aid – usually an inert solid such as silica, sand, alumina, or an inorganic salt like sodium chloride.^[53–55] Then, the liquid reactants can then be adsorbed onto the solids, which can restrict the motion of the liquid and reduces its ability to move away from the position of an impact. The addition of a grinding additive can enhance the transfer of mechanical energy to the liquid reagents. Reaction mixtures that consists both solids and liquid components can also form sticky solids or paste-like textures, which hinders effective mixing. In such cases, grinding additives can improve not only energy transfer but also the homogeneity of the reaction mixture. This strategy is widely used in pharmaceutical processing to facilitate the flow of materials through an extruder, where these additives are referred to as glidants or lubricants.^[56] In practice, selecting a suitable grinding additive in order to improve energy transfer and for effective mixing is not straightforward and typically requires a trial-and-error approach. Importantly, not all the grinding additives have to be innocent and sometimes those directly participate in the reaction.^[18,57]

In addition, the most common important factors are to investigate the choice of reagents, their stoichiometries, and the reaction times.^[14] However, once a reaction is found to be proceeded via mechanochemistry, then further investigate the influence of each variable separately and look for observable trends (Figure 4), which can guide the identification of improved conditions through trial and error method. A more advanced alternative way is to use the statistical tools, such as Design of Experiments (DoE), to systematically explore variable effects and predict optimal conditions. These methods are widely and successfully applied in industrial settings.^[58]

Factors affecting reactions	Optimization Parameters
<ul style="list-style-type: none"> ■ Kinetic energy of the ball(s) prior to collision 	<ul style="list-style-type: none"> ● number of balls ● size of balls ● ball material ● type of mill ● size of jar ● filling degree ● milling frequency
<ul style="list-style-type: none"> ■ Efficient mixing 	<ul style="list-style-type: none"> ● number of balls ● size of balls ● size of jar ● filling degree ● LAG ● grinding additive ● milling frequency ● type of mill
<ul style="list-style-type: none"> ■ How energy is transferred to the reagents 	<ul style="list-style-type: none"> ● number of balls ● size of balls ● size of jar ● filling degree ● LAG ● grinding additive ● type of mill
<ul style="list-style-type: none"> ■ Frequency of collisions 	<ul style="list-style-type: none"> ● milling frequency ● number of balls
<ul style="list-style-type: none"> ■ Reaction time 	<ul style="list-style-type: none"> ● milling time
<ul style="list-style-type: none"> ■ stoichiometry, temperature 	<ul style="list-style-type: none"> ● stoichiometry, reaction temperature

Figure 4. Summary of the key factors affecting chemical reactions in a ball mill and the respective optimization parameters.

1.1.6 Established benefits of mechanochemistry in organic synthesis

One of the most immediate and obvious benefits of mechanochemical techniques is the absence of bulk organic solvents. Usually, solvents contribute to 80–90% of PMI, and they are major source of toxicity along with safety concerns.^[59] Mechanochemical approach offers a more sustainable route for organic synthesis by significant reduction of PMI and this leads to lower waste generation and overall environmental impact.^[60,61] In addition, solvent-free or solvent-minimized environment eliminates solubility limitations and boosts reaction rates through high concentration of reactants.

Beyond their green advantages, mechanochemical methods have several other unique benefits. The energy input associated with mechanical force, combined with a solvent-free or solvent-minimized environment, has enabled the discovery of various advantages not typically observed in solution-based methods,^[2,4,14,62] as detailed below.

Enhanced reactivity: The reaction rates are increased, what reduces greatly reaction times, improves yields, lowers catalyst loading and enables reactivity not possible in solution. These advantages span across multiple areas of organic synthesis, including complex formation,^[63] cross-couplings,^[64] C–H functionalisation,^[65] and organocatalysis.^[43,66]

Alternate reactivity/selectivity: Mechanochemistry has a potential to offer unique reactivity and provides selective products that are not achievable by conventional methods.^[37,67] In addition, there have been many examples reported where selectivity can be controlled, often by selecting proper additives.^[68,69]

Robust protocols/no need for air-sensitive techniques: Ball-milling is an accessible enabling technology that requires little training and simple reaction setup. While some protocols involve inert conditions using a glovebox or a nitrogen bag, most of the ball-milling reactions are well tolerant to air, with reactants loaded directly into the jar under ambient conditions.^[2,64] This has been shown to be particularly advantageous for sensitive metal-mediated organic reactions.^[63]

Activation of zero-valent metals (Topic of this work): Mechanochemistry offers a distinct advantage in activating zero-valent metals by promoting direct and efficient metal–substrate interactions through mechanical force.^[7] These intense grinding conditions can effectively remove the oxide layers and expose fresh reactive metal surfaces, enhancing reactivity without the need for harsh conditions. This makes mechanochemistry particularly valuable for metal-mediated transformations where conventional activation methods are limited or inefficient.

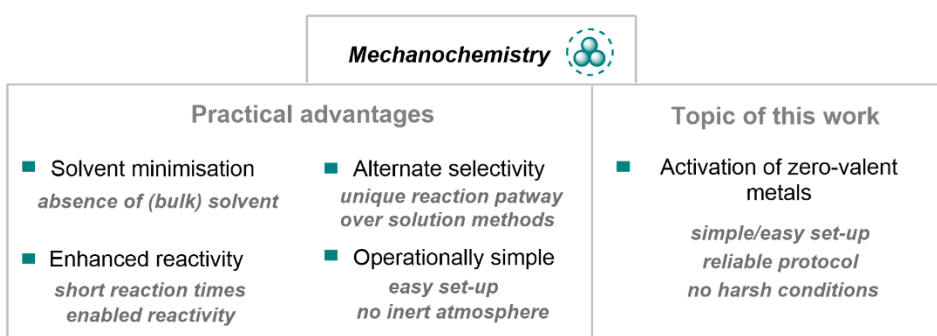


Figure 5. Overview of advantages of mechanochemistry.

1.2 Mechanochemical Generation of Polar Organometallic Reagents

Organic derivatives of alkali and alkaline earth metals, along with similarly reactive organozinc and organoaluminium compounds, constitute an important class of polar organometallic reagents. Characterized by a strongly polarized carbon–metal bond these compounds function as powerful nucleophiles, enabling the formation of carbon–carbon and carbon–heteroatom bonds through reactions with a wide range of electrophilic partners. Since the discovery of dialkylzinc compounds by Frankland in 1849,^[70] the reactions of alkyl halides with metals have played a central role in the generation of polar organometallics, including the development of organomagnesium and organolithium reagents.^[71–73] The industrial significance of polar organometallics is also profound. Grignard reagents, organozinc and organolithium compounds have become the most widely used reagents to access important pharmaceuticals, fine chemicals, polymers, and advanced materials.^[74–76] These reagents serve as key intermediates in the synthesis of alcohols, ketones, acids, heterocycles, and other complex scaffolds. Reactions involving Li and Mg organometallics rank among the top 20 most widely used transformations in medicinal chemistry, with the Grignard reaction listed among the top three C–C bond-forming methods in natural product synthesis.^[77,78] Despite the long history, the synthesis of polar organometallic reagents continues to pose significant practical challenges.

1.2.1 Factors influencing the preparation of polar organometallics

The preparation of polar organometallics is governed by several factors that influence reaction efficiency, stability of the product, and applicability in synthetic chemistry. First, the reaction efficiency is governed by properties of a metal. Its reactivity is determined by reductive properties (reduction potential), surface area (which increases as particle size decreases) and surface characteristics, such as surface cleanliness (i.e., the absence of a passive oxide layer) and physical defects important for initiation of a reaction (so-called “active sites”).^[79] Metal powders^[80] (especially finely dispersed Rieke metals), with their correspondingly large surface areas,^[81,82] exhibit significantly higher reactivity than other metal forms such as granules, wires, or turnings. However, unless prepared under inert atmospheric conditions, these powders are often coated with a passive oxide layer that must be removed to expose the highly reactive active sites.^[83] Activation is traditionally achieved by the addition of chemical additives such as iodine, 1,2-dibromoethane, trimethylchlorosilane (TMSCl) and similar metal etching agents.^[84–86] In addition, heating, sonochemical treatment^[87] or dry stirring^[88] are also known to disrupt the passive layer and increase the surface reactivity.

Second, the nature of the organic halide plays a crucial role. The two important properties to be considered are carbon-halogen dipole moment and the respective bond dissociation energies, that follow the order $I < Br < Cl \ll F$. So, metal insertion in the C–F bond is particularly challenging due to its exceptional bond strength.^[89] Additionally, the highest reactivity of C–I often leads to the formation of homocoupling (Wurtz coupling) side products. Moreover, presence of electron-withdrawing groups or sterically hindered groups adjacent to the halogens can be greatly influence the metal insertion. The rate of Grignard reagent formation is influenced by the viscosity of the reaction medium^[82,90] and the mixing efficiency,^[82] as organic halides typically react with metals at a transport-controlled rate,^[90,91] where the diffusion of the organic halide to the metal surface becomes the rate-limiting step.

Third, the choice of the solvent is another important factor. For Grignard reagents, coordinating solvents such as ethers (diethyl ether, THF) are crucial, acting as ligands to stabilize the generated organometallics and enhance its solubility.^[73] However, these solvents present serious safety concerns, as they are volatile, flammable, and subject to peroxide formation,^[92] posing significant hazards during scale-up, particularly under thermal activation.^[93] The exothermic nature of the reaction may result in thermal runaway, posing a serious safety challenge.^[94] Careful control of dosing rates, reaction temperature and importantly minimizing solvent usage can be highly beneficial to avoid accidents. Moreover, preparation of such highly reactive organometallic reagents is incompatible with oxygen and moisture. It requires inert atmosphere (N_2 , argon)^[95] and strictly dry and degassed solvent. Thus, the development of safer, operationally simpler and more sustainable methods for the generation of polar organometallics attracts considerable interest.^[96]

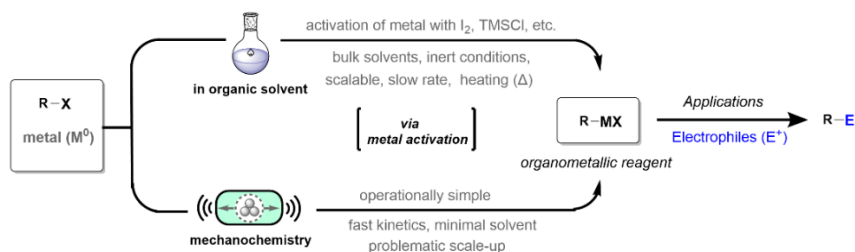


Figure 6. Preparation of organometallic reagents through the reaction of organic halides with metals.

1.2.2 Mechanochemistry addresses challenges of organometallic chemistry

In recent years, there has been growing interest in harnessing mechanical forces, particularly through ball milling and other mechanochemical techniques, to enhance the reactivity of metals in organic reactions, including the generation of polar organometallic reagents^[7] and dissolved-metal-type reductive transformations.^[97] However, the origins of this approach date back to earlier works, already hinting at the potential of mechanical activation to influence the chemical reactivity of metals.

In 1962, Wittenberg and co-workers^[98] reported the activation of aluminium in the presence of aluminium chloride using mixer mill under inert conditions, which was required to synthesize organoaluminium compounds. Zinc^[99] and magnesium^[88] metals were activated for the synthesis of organometallics by mortar and pestle grinding in 1991, but this method has found a limited use because of its difficulty with handling and poor reproducibility. Later, Komatsu^[100] and Harrowfield^[101] pioneered the use of vibratory mill for the activation of Zn and Mg, respectively. In 2003, Suzuki and co-workers^[102] reported the bismuth-mediated Barbier-type allylation of aromatic aldehydes under solvent-free conditions using ball mill. In 2016, Mack and co-workers^[103] demonstrated the activation of nickel in a mixer mill to achieve the tetracyclization of alkynes, yielding non-aromatic cyclooctatetraenes.

Since 2018, the field has been expanding rapidly with numerous reports on the mechanical activation of various metals like Zn,^[104] Li,^[105] Mg,^[106] Ca,^[107] Ba,^[108] Mn,^[109] etc., to generate organometallic reagents. A key driving force behind this progress is the unique advantages offered by high-speed ball milling. Performing reactions in a ball mill significantly enhances metal activation by mechanically pulverizing bulk metals into micro- or even nanoscale particles,^[110,111] greatly increasing the available reactive surface area and continuously removing passivating product layers. Mechanochemical activation in the solvent-free or solvent-minimized environment eliminates solubility limitations and boosts reaction rates through high concentration of reactants, besides significant reduction of PMI. Mixing also facilitates the delivery of organic halides to the metal surface, thereby intensifying the diffusion-limited synthesis of organometallics. In addition, the absence of bulk solvents circumvents their incompatibility with reactive organometallic intermediates, enabling the isolation of previously inaccessible species, what is important for progress in coordination chemistry.^[112] As was already mentioned, mechanochemical methods also exhibit reduced sensitivity to moisture and oxygen, allowing the generation of organometallic reagents in air without the need for rigorous inert atmosphere techniques. This robustness was attributed to the low levels of oxygen and water present in the sealed reaction vessels, along with the decreased reactivity of gaseous components under mechanochemical conditions.^[113] The latter may result from the slow diffusion of gases in the highly concentrated solid-state mixtures, which leads to slower reactions at the solid-gas interface (Figure 7).^[114]

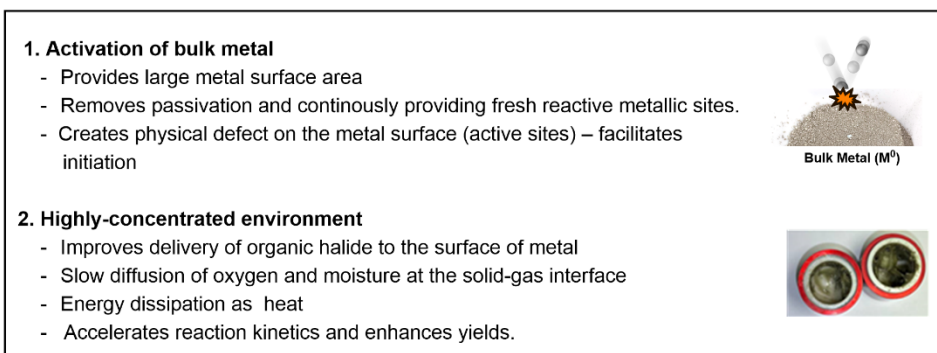


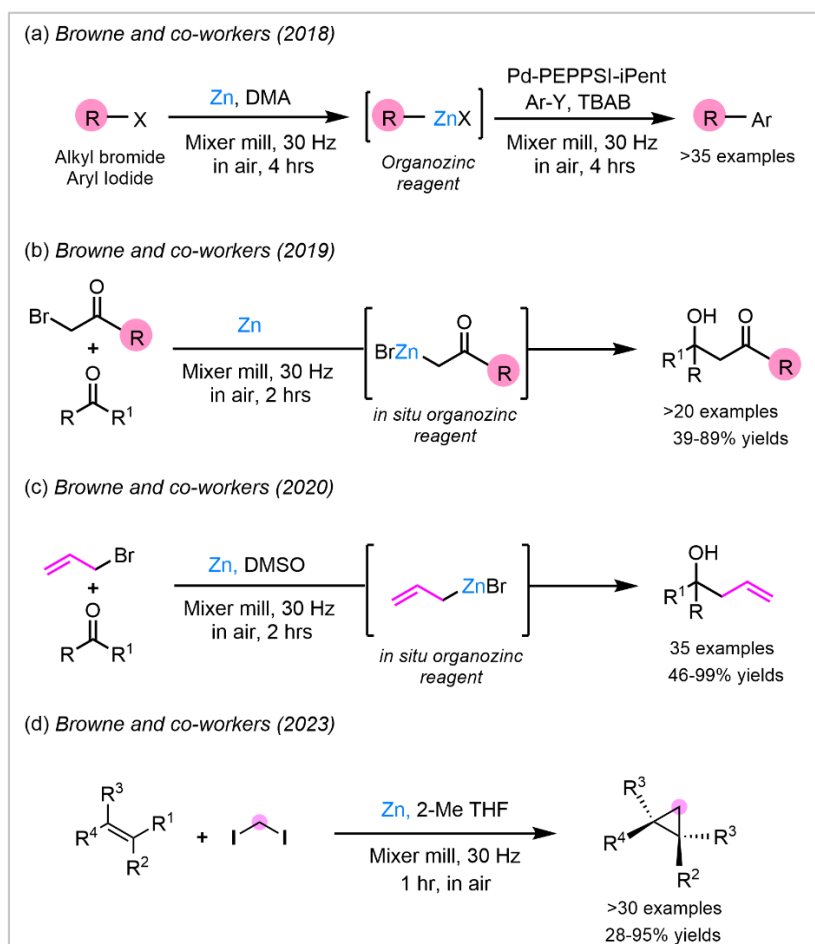
Figure 7. Key factors that facilitate organometallic synthesis under ball milling conditions.

Some selected case studies on the mechanochemical generation of polar organometallic reagents are highlighted below, underscoring the significant progress in this field and its expanding role in sustainable synthetic methodologies.

1.2.3 Generation of organozinc reagents

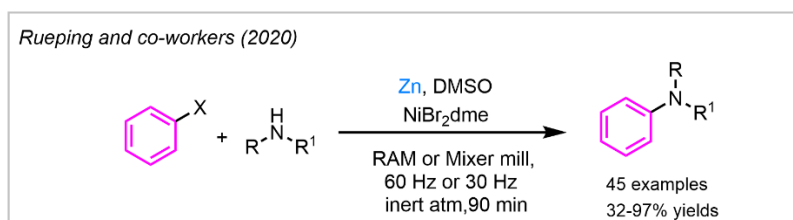
As one of the earliest and most significant organometallic reagents in traditional organic synthesis,^[70] organozinc compounds have also emerged at the forefront of mechanochemical methodologies. In an early study by Toda and co-workers (1991), solvent-free Reformatsky additions and Barbier-type allylations were achieved by manually grinding a carbonyl compound (aldehyde or ketone) with an excess of organic bromide (α -bromo ester or allylic bromide), zinc powder, and NH_4Cl in an agate mortar and pestle.^[99] Much later, in 2015, Köning and co-workers applied a similar protocol in a planetary ball mill to perform the Reformatsky reaction of furfural with ethyl bromoacetate.^[115] In 1996, Komatsu and co-workers reported the functionalization of [60]fullerene by a zinc-mediated Reformatsky reaction in a vibrating mill.^[100]

Since 2018, the Browne group has made significant contributions to the mechanochemical generation and application of organozinc compounds. In 2018, they developed a mechanochemical protocol for the generation of organozinc reagents and their direct use in palladium-catalysed Negishi cross-coupling reactions.^[104] Using ball milling under ambient conditions with zinc metal and DMA as a liquid additive, both alkyl and aryl organozinc species were efficiently formed within 4 hours, regardless of the zinc form. These reagents were then directly subjected to Pd-catalysed cross-coupling, producing a variety of products in good to excellent yields (Scheme 1, a). Additionally, a one-pot, one-step protocol was demonstrated, in which all components were milled together for 8 hours, eliminating the need to isolate or handle organozinc intermediates. The group further expanded their work by developing robust protocols for other key organic transformations involving organozinc compounds, including the Reformatsky reaction (2019) (Scheme 1, b),^[116] Barbier-type allylation (2020) (Scheme 1, c),^[117] and the Simmons–Smith reaction (2023) (Scheme 1, d).^[118] Nickel-catalysed cross-electrophile coupling mediated by $\text{Zn}(0)$ has also been demonstrated,^[119] where the *in situ* generation of organozinc intermediates may also play a role.



Scheme 1. Mechanochemical generation of organozinc reagents and their applications.^[104,116–118]

Very recently, Šebesta, Čarný, and co-workers reported mechanochemical generation of air-stable organozinc pivalates through transmetalation of organomagnesium reagents, and their application in Pd-catalysed cross-coupling with thianthrenium salts.^[120] Same group also reported Pd-catalysed α -arylations of carbonyl compounds under mechanochemical conditions through *in situ* generated Reformatsky Zn-enolates.^[121] Rueping and co-workers reported a method for Ni-catalysed C–N cross-coupling reactions in a RAM and a mixer mill, in which Zn(0) serves as a reductant (Scheme 2).^[122]

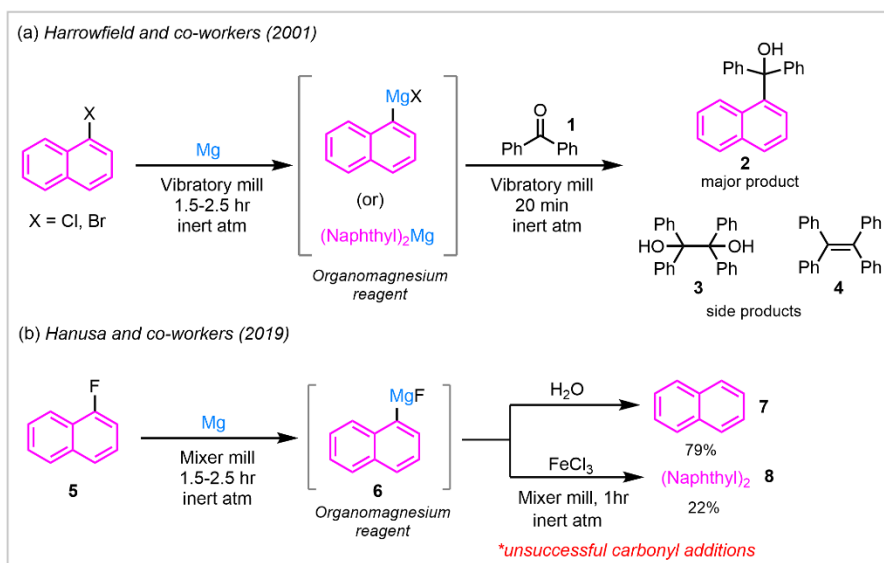


Scheme 2. Mechanochemical zinc-mediated cross-coupling amination.^[122]

1.2.4 Generation of organomagnesium reagents

Early work in the field was driven by the need to develop an efficient method for the destruction of toxic halogenated organic pollutants. In 1994, Rowland and co-workers reported a method for reductive dehalogenation of pollutants like DDT and PCBs through milling with magnesium and calcium metals in a vibratory mill.^[123] In subsequent studies by Birke in the 2000s, a similar method using magnesium and an organic amine as a proton donor was investigated, providing evidence for the *in situ* generation of Grignard intermediates from chlorinated benzenes.^[124,125] Ten years later, Dan, Yang, and co-workers employed the reaction of polyhalogenated benzenes with magnesium powder in a high-speed vibrating ball mill to achieve aromatic ring knitting, resulting in the formation of polyaromatic conjugated porous networks.^[126] The transformation was proposed to proceed either via Grignard reagent intermediates or through homocoupling of aryl radicals.

The first preparation of an organomagnesium reagent under mechanochemical conditions was reported in 2001 by Harrowfield and co-workers.^[101] A mixture of 1-naphthyl bromide or chloride and an excess of magnesium powder (4 equiv.) was milled in a mixer mill under an argon atmosphere for 1.5 or 2.5 hours, for the bromide and chloride, respectively (Scheme 3). The resulting black powder, presumably containing the 1-naphthyl Grignard reagent, was shown to react with dilute aqueous acid to produce predominantly naphthalene. It also reacted with acetophenone or benzophenone **1**, affording the corresponding addition products in 74–80% yields after aqueous work-up. Due to the excess magnesium present in the reaction mixture, side products from pinacol and McMurry couplings of the ketones were also observed (Scheme 3, a). The solid reagent remained stable for at least 10 weeks when stored under an inert atmosphere, retaining its Grignard reactivity. Later in 2019, Hanusa and co-workers^[127] demonstrated that, in addition to bromonaphthalenes, magnesium could also be inserted into the C–F bonds of fluoro-naphthalenes. This transformation is particularly challenging due to the lowest reactivity of fluorides among the organic halides. Using ball milling under inert conditions with an excess of magnesium (8 equiv.), bromo- and fluoronaphthalenes produced the respective organomagnesium halides, which yielded naphthalene **7** in 78–95% yield upon quenching with water, while milling with FeCl₃ afforded binaphthyl **8** in 20–22% yield. Interestingly, the fluoro-Grignard reagents were found unreactive toward aldehydes and ketones (Scheme 3, b).

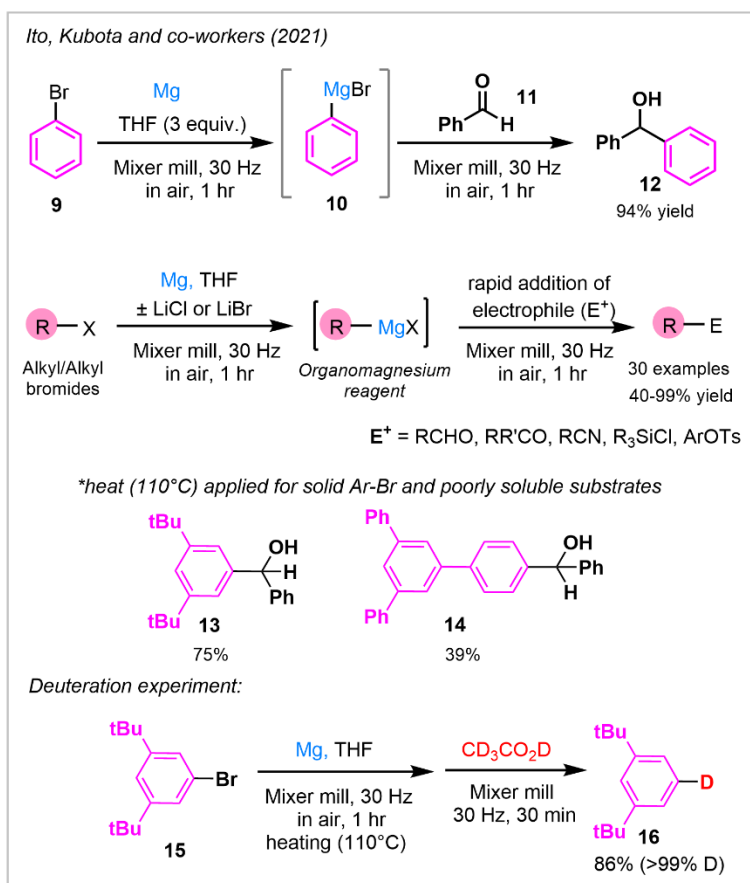


Scheme 3. The first examples of mechanochemical generation of organomagnesium reagents.^[101,127]

In 2021, Ito, Kubota and co-workers^[128] reported the generation of various Grignard reagents in a mixer mill under air, demonstrating their utility as versatile carbon nucleophiles in reactions with diverse electrophilic partners. The method was broadly applicable across various aryl and alkyl bromides, as well as a range of electrophiles, including aldehydes, ketones, esters, nitriles, and Weinreb amides. Initially, the reaction of magnesium turnings with bromobenzene **9**, followed by nucleophilic addition to benzaldehyde **11**, yielded diphenylmethanol **12** in only 6%. The key to success was the addition of ethereal solvents as additives, particularly THF (2 equiv.), which increased the yield to 94% and highlighted the crucial role of ethereal solvents in promoting Grignard reagent formation. Rapid addition of the electrophile, within 10 seconds after opening the jar to air, was essential for achieving high yields (Scheme 4). Gram-scale preparation of diphenylmethanol **12** was also demonstrated. Notably, performing the reaction under a nitrogen atmosphere did not improve the outcome, suggesting that organomagnesium compounds degrade relatively slowly upon short exposure to air, primarily due to protonation by moisture. For example, the yield of diphenylmethanol **12** dropped from 75% to 41% after 10 minutes of air exposure.

Secondary alkyl bromides required higher magnesium loading (5 equiv.) to achieve moderate to good yields. For solid halide substrates with limited solubility, which typically fail under conventional solution-phase conditions, the researchers employed heating during the milling process. By positioning a heat gun over the milling jar (set to 110 °C), internal temperatures of ~70 °C were achieved, enabling efficient Grignard reactions even with poorly soluble substrates such as 4-bromobiphenyl or phenyl-terphenyl derivatives. The synthetic utility was further demonstrated in regioselective additions of Grignard reagents to enones, favouring 1,2-addition, and highly selective 1,4-addition in the presence of copper(I) catalyst. Furthermore, the method was applied to cross-coupling chemistry, successfully demonstrating Ni-catalysed Kumada-Tamao-Corriu coupling between aryl Grignard reagents and aryl tosylates, achieving yields of up to 88%. Generation of organomagnesium compounds was supported by a deuterium labelling experiment showing > 99% deuterium incorporation

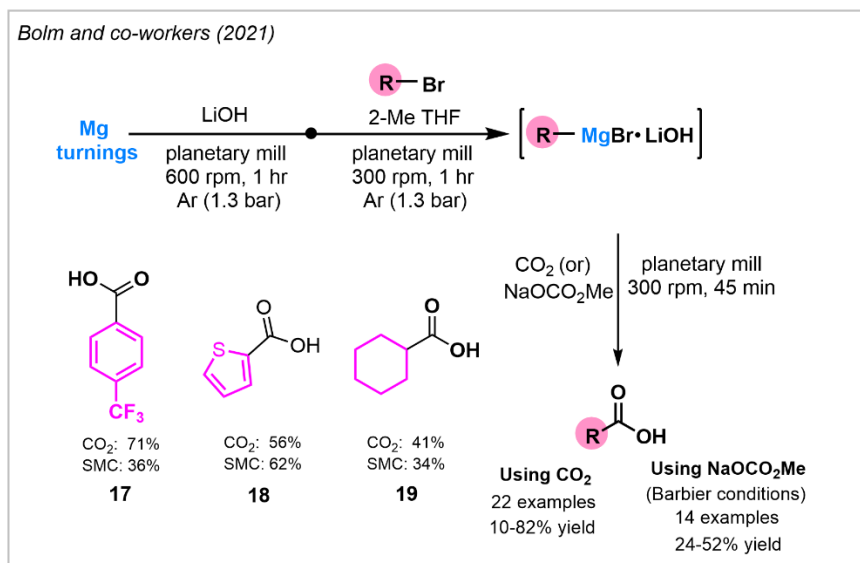
in 1,3-di-*tert*-butylbenzene **16** (86%), and near-edge X-ray absorption fine structure (NEXAFS) spectroscopy, which confirmed the presence of C–Mg bonds and Mg²⁺ species analogous to a Grignard reagent generated in solution.



Scheme 4. One-pot two-step protocol for the mechanochemical generation of organomagnesium reagents and their applications towards various electrophiles.^[128]

Nearly the same time, Bolm and co-workers^[106] reported carboxylation of mechanochemically-generated Grignard reagents with gaseous CO₂ or solid sodium methyl carbonate (SMC). The reactions were carried out in a planetary mill as a three-step process. In the first step, magnesium turnings were activated by ball milling with lithium hydroxide (LiOH) under argon atmosphere. Under mechanochemical conditions, LiOH outperformed the traditionally used LiCl in the generation of Turbo-Grignard reagents. In the second step, an aryl or alkyl bromide was added along with 2-MeTHF as an additive under an argon atmosphere. The choice of 2-MeTHF as a LAG additive played a crucial role. As a bio-derived ether, 2-MeTHF matched the performance of THF while offering better safety, reduced volatility, and greater resistance to thermal runaway. Finally, the reaction vessel was filled with CO₂ (4 bar) and the content was milled for additional 45 minutes (Scheme 5). The developed protocol was applied to the scope of various aryl and alkyl bromides, that delivered the corresponding carboxylic acids in 25–82% yields. Furthermore, solid sodium methyl

carbonate (SMC) was investigated as a convenient CO₂ substitute, with Grignard reagents generated *in situ* under Barbier conditions and without inert gas protection. Although these reactions generally provided lower yields than gaseous CO₂ (e.g., 40% vs. 63% for 4-tolyl bromide), the need for the specialized equipment typically required for handling gases was avoided (Scheme 5).



Scheme 5. Mechanochemical generation of Turbo-Grignard reagents and their reactions with CO₂ (or) NaOCO₂Me.^[106]

Mechanochemical activation of magnesium metal has also been applied in the synthesis of low-valent Mg complexes,^[129] to perform Minisci-type alkylation of pyridines and pyrimidines,^[130,131] Barbier-type synthesis of organosilicon^[132] and organochalcogen compounds,^[133] as well as iron- and cobalt-catalysed C–H arylation of indoles.^[134] Ni-catalysed reductive cross-coupling of aryl ethers and aryl fluorides was achieved in a mixer mill with Mg(0) as reductant.^[135]

1.2.5 Generation of organocalcium reagents

Calcium is the third most abundant metal in the Earth's crust, after iron and aluminium. Organocalcium reagents are strong carbon nucleophiles and are therefore attractive as more reactive analogues of Grignard reagents, owing to the greater electronegativity difference between calcium and carbon compared to magnesium.^[136–138] The major difference in reactivity can be attributed to the larger ionic radius of Ca²⁺ (100 pm) compared to Mg²⁺ (72 pm).^[139] This lower charge-to-size ratio in calcium results in a more ionic character of the bonding, which in turn increases the kinetic lability of the ligands.^[140,141] However, despite their promising reactivity, the generation of heavier analogues of Grignard reagents are challenging and have been underexplored.^[142]

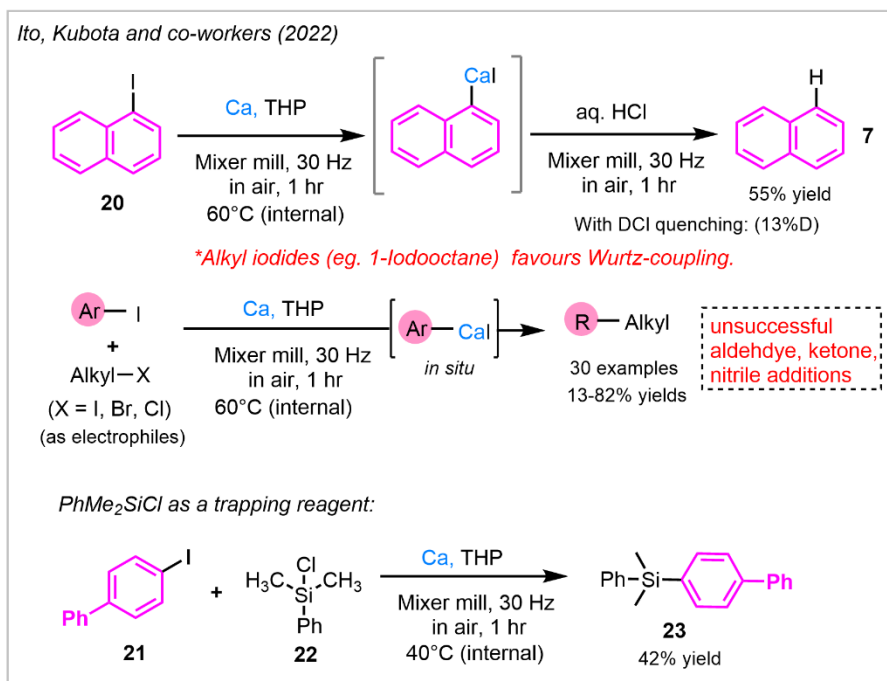
Dialkylcalcium and alkylcalcium halides were first described by Beckman in 1905^[141] and were subsequently studied by Gilman and co-workers from the mid-1920s through the mid-1940s, with the aim of developing more reactive analogues of Grignard reagents.^[143] These investigations were generally disappointing, as many of the compounds

prepared were thermally unstable and either insoluble or only slightly soluble in organic solvents. Moreover, their synthesis from organic halides was often accompanied by significant Wurtz coupling.

Until 2022, the known applications of organocalcium nucleophiles in mechanochemistry were limited to reactions involving calcium carbide (CaC_2), a source of acetylide anions (a C_2 -synthon).^[144] However, in 2022, Ito, Kubota, and co-workers reported a breakthrough mechanochemical method that overcame long-standing limitations of solution-phase organocalcium chemistry. They demonstrated that aryl calcium compounds could be generated directly by milling commercially available calcium granules with aryl iodides (Scheme 6)^[107]. This approach eliminated the need for previously arduous activation methods, such as generating highly reactive calcium in liquid ammonia or preparing Rieke calcium.

Similar to Grignard reagent chemistry, the use of ether additives (THF or THP) proved crucial. Without these additives, the reactions proceeded with very low efficiency. The generation of 1-naphthyl calcium reagent from 1-naphthyl iodide **20** was achieved in up to 55% yield after ball milling at 30Hz for 1 hour at 60°C in the presence of THP (4 equiv.), as confirmed by quenching with dilute aqueous HCl, which produced naphthalene **7**. However, deuterium quenching experiments of the same reaction with DCl, performed in the presence of THF or THF- d_8 , resulted in only 13–18% deuterium incorporation to naphthalene, suggesting protonation of the organocalcium species by an unidentified protic source. Despite this, *in situ* trapping of the organocalcium intermediate derived from 4-iodo-1,1'-biphenyl **21** with PhMe_2SiCl **22** was successful, affording the corresponding [1,1'-biphenyl]-4-yl dimethyl(phenyl)silane **23** in 42% yield. Attempts to use *in situ* generated organocalcium reagents in addition reactions with aldehydes, ketones, or nitriles were unsuccessful due to predominant side reactions of these electrophiles. Moreover, the generation of organocalcium compounds from aliphatic iodides proved less efficient. For instance, milling 1-iodooctane afforded only 15% of *n*-octane upon quenching, with 64–72% of the corresponding Wurtz coupling by-product.

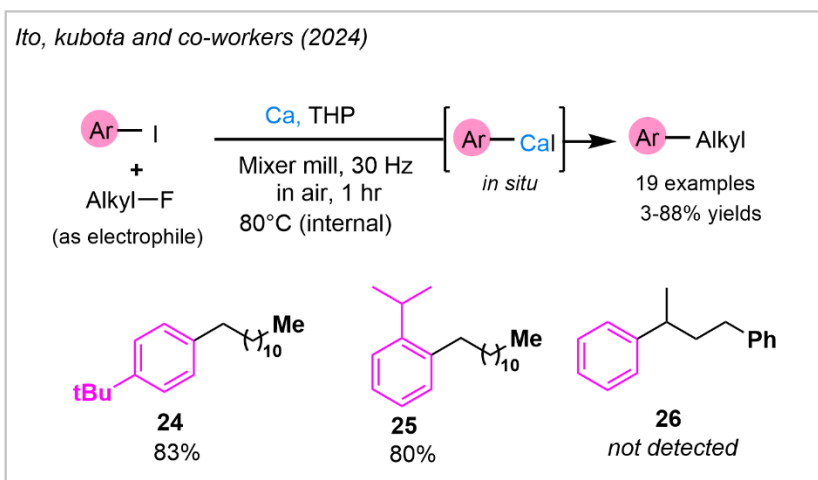
Nevertheless, the distinct reactivity profiles of aryl and alkyl iodides enabled the development of a calcium-mediated cross-electrophile coupling between them. This reaction was proposed to proceed *via* formation of arylcalcium nucleophiles, followed by nucleophilic substitution in the alkyl iodides. This mechanism was supported by a radical clock experiment and DFT calculations. Control experiments using ZrO_2 jars gave comparable results to those with stainless steel, ruling out transition metal contamination as a catalytic factor. Using this method, a variety of aryl iodides were successfully coupled with primary alkyl iodides, achieving yields of up to 60–80%. The reaction showed good tolerance toward functional groups such as alkynes, thioethers, amines, fluorides, and bromides.



Scheme 6. Mechanochemical generation of the aryl calcium reagents and their applications under Barbier conditions.^[107]

Building on the success of their initial work, in 2024 Ito, Kubota, and co-workers reported a transition-metal-free nucleophilic substitution of otherwise inert C(sp³)-F bonds in fluoroalkanes using organocalcium species generated *in situ* from aryl iodides.^[145] Under optimized conditions (80°C, 30Hz, 1 hour), ball milling calcium metal with aryl iodides and alkyl fluorides in the presence of tetrahydropyran (THP) yielded the corresponding cross-electrophile coupling products in up to 86% yield, significantly outperforming conventional Grignard reagents (Scheme 7). The method demonstrated broad substrate scope, effectively transforming electron-rich and sterically hindered aryl iodides, as well as primary alkyl fluorides bearing various functional groups. However, reduced reactivity was observed with substrates containing methoxy or carbonyl groups on the aryl ring, secondary fluorides, and benzyloxy- or thiophene-substituted compounds. Mechanistic studies, supported by DFT calculations, suggested that tetrameric arylcalcium species promote substitution by weakening the C-F bond via Lewis acid activation. Control experiments confirmed the essential role of mechanochemical activation, as comparable solution-phase reactions were unsuccessful. Additionally, the use of ZrO₂ jars ruled out transition-metal catalysis as a contributing factor.

These pioneering studies highlight the significance of mechanochemically generated organocalcium reagents as a sustainable and efficient approach to C-C bond formation.

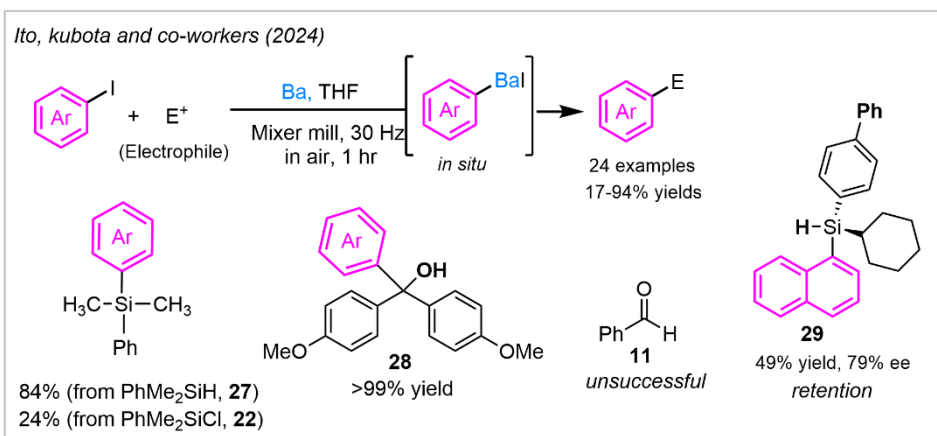


Scheme 7. Mechanochemical nucleophilic substitution of $\text{C}(\text{sp}^3)\text{-F}$ bond by using *in situ* generated arylcalcium nucleophiles.^[145]

1.2.6 Generation of organobarium reagents

In 2024, Ito, Kubota and co-workers^[108] reported a mechanochemical method for generating aryl barium reagents directly from unactivated barium metal and aryl iodides, eliminating the need for highly reactive Rieke barium. By ball milling the reactants with tetrahydrofuran (THF) as an additive at room temperature, they achieved efficient formation of aryl barium species within just 30 minutes. These *in situ* generated arylbarium reagents underwent successful reactions with hydrosilanes, affording organosilicon products up to 91% yields (Scheme 8). Compared to their magnesium and calcium analogues, organobarium compounds exhibited superior reactivity in this transformation, which was attributed to lower electronegativity of barium and more favourable redox properties. Notably, the reaction with an enantiomerically pure (>99% *ee*) hydrosilane proceeded with retention of configuration at the silicon stereocenter and only a slight loss of enantiomeric purity in **29** (79% *ee*). However, chlorosilane **22** was less efficient in this transformation (only 24% yield), and (pin)B(OMe) failed to generate the desired borylation product. Benzaldehyde **11** and an aliphatic aldehyde yielded complex mixtures of carbonyl reduction products.

Nevertheless, the study reported the first example of successful nucleophilic additions of organobarium reagents to carbonyl compounds. Several diaryl ketones reacted smoothly with *in situ* generated aryl barium species, producing tertiary alcohols (e.g., **28**) in up to quantitative yields and without the reductive side products commonly observed in analogous reactions with magnesium.



Scheme 8. Mechanochemical generation of aryl barium reagents and their applications under Barbier conditions.^[108]

1.2.7 Generation of organolithium reagents

Since their discovery in 1917 by Schlenk and Holtz, organolithium reagents have become one of the most fundamental and valuable organometallic compounds in organic synthesis.^[72,146] Traditionally, the reaction of lithium metal with organic halides (typically bromides or chlorides) requires the use of hazardous or environmentally harmful solvents such as diethyl ether or hexane, along with strictly anhydrous, oxygen-free conditions and low temperatures. These demands necessitate complex reaction setups and careful handling due to the pyrophoric nature of organolithium compounds.^[147]

Very recently, Ito, Kubota, and co-workers^[105] reported the first mechanochemical method for synthesizing organolithium compounds by ball milling organic halides with lithium wire at room temperature. The addition of diethyl ether significantly improved yields, achieving up to 81% within just five minutes. This approach enabled the efficient generation of aryllithium species from a variety of aryl halides, including those with poor solubility. The method demonstrated broad applicability, supporting reactions with a wide range of electrophiles such as ketones, aldehydes, and Weinreb amides, and enabling transformations such as C–F bond activation and silylation. Notably, gram-scale reactions were successfully performed under ambient air, eliminating the need for strict inert conditions. A custom-designed milling vessel with a sealable port improved operational safety by minimizing air exposure during the addition of electrophiles. Overall, this protocol offers a practical and efficient alternative to conventional solvent-based organolithium synthesis (Scheme 9).

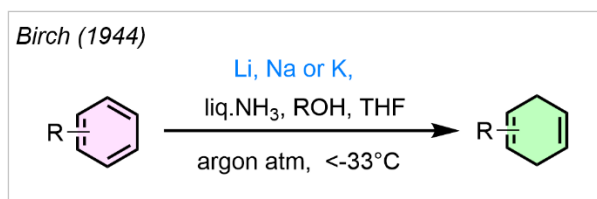
Additionally, mechanochemically-activated lithium metal has found applications as a powerful reductant,^[148] as detailed in the next section.



Scheme 9. Mechanochemical generation of organolithium reagents and their applications.
*This picture is directly adapted from the original source. ^[105]

1.3 The Birch Reduction: Classical Approach and Recent Innovations

Discovered by Arthur J. Birch in 1944^[149], the Birch Reduction remains one of the most iconic transformations in organic chemistry. The classic approach transforms benzene derivatives into unconjugated cyclohexadienes by reduction with alkali metals (Li, Na or K) dissolved in liquid ammonia with alcohol as a protic source at low temperatures (below $-33\text{ }^{\circ}\text{C}$, the boiling point of ammonia) (Scheme 10). As a powerful dearomatization approach, the reaction has found multiple applications in the synthesis of natural products, pharmaceuticals, and fine industrial chemicals from readily available aromatic feedstock.^[150–152]



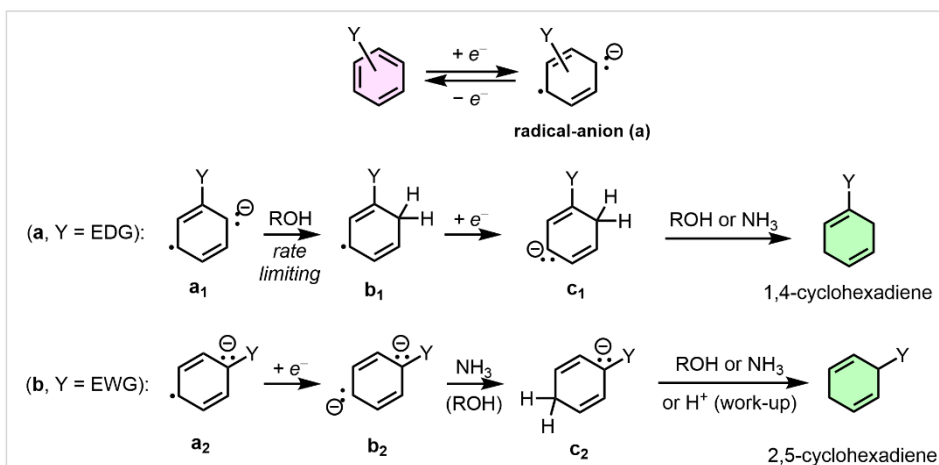
Scheme 10. The classic-Birch reduction.^[149]

1.3.1 Mechanism and regioselectivity

A thorough understanding of the mechanism and the factors controlling product selectivity is essential for synthetic applications. Alkali metals are soluble in liquid ammonia and amine solvents, producing deep blue solutions that contain solvated electrons, alkali metal anions (alkalides, e.g., $\text{Na}^{\bullet-}$), and electrides – complexes of alkali metal cations with trapped electrons (e.g., $[\text{Na}(\text{NH}_3)_6]^+e^-$). All these species serve as the key reducing agents in the reaction.^[153] The core mechanistic pathway of the Birch reduction involves a sequence of events of single-electron transfer (SET) and protonation steps: an initial electron transfer to the aromatic system is reversible and generates a radical anion intermediate **a**, which is subsequently protonated (Scheme 11). This is followed by a second electron transfer and a final protonation step, resulting in the formation of the unconjugated diene product.

The regioselectivity of the reaction is mostly influenced by the nature of substituents attached to the aromatic ring. When electron-donating groups (EDGs), such as methoxy or methyl, are attached to the benzene ring (pathway a), the initially formed radical anion intermediate abstracts a proton from the alcoholic proton source in the reaction medium, yielding a cyclohexadienyl radical **b**₁. Mechanistic studies indicate that the stabilization of the radical anion is a key factor, strongly influenced by electron density distribution.^[153] This makes protonation at the ortho position more favourable than at the meta or para positions. Importantly, no second electron transfer occurs until after the initial protonation step, which is considered rate-limiting. Following this, a second electron is transferred to the cyclohexadienyl radical **b**₁, generating a cyclohexadienyl anion **c**₁. Final protonation of this carbanion leads predominantly to the formation of the 1,4-diene product, the kinetically favoured isomer, rather than the thermodynamically more stable conjugated 1,3-diene, which appears only as a minor by-product. The presence of an alcohol is crucial, as it ensures rapid protonation of anionic intermediates, thereby suppressing isomerization of the initially formed 1,4-diene into the more stable but undesired 1,3-diene.

Conversely, with the electron-withdrawing groups (EWGs), such as carboxyl, ester, amide, the regioselectivity of the Birch reduction is altered. In these cases, protonation typically occurs after the addition of two electrons (pathway b), generating the dianion **b**₂. The carbanionic centres are located at the para and ipso positions relative to the EWG. The dianion is basic enough to abstract the protons from ammonia or amine in the reaction medium. This results in the formation of 2,5-cyclohexadiene product (Scheme 11).



Scheme 11. Commonly accepted mechanism of the classic Birch reduction for electron-poor (pathway a) and electron-rich (pathway b) arenes and the role of the protic additive.

1.3.2 History and recent advances

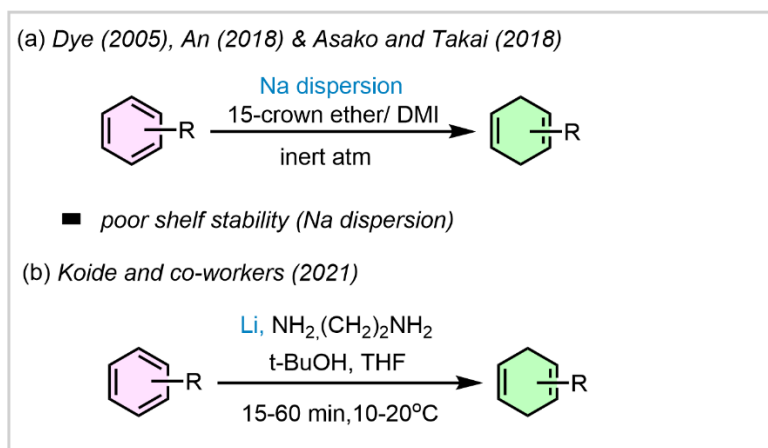
The use of pyrophoric alkali metals and hazardous liquid ammonia at cryogenic temperatures makes the classical Birch method both dangerous and technically challenging. In 1950–70s, Benkeser and co-workers made a seminal attempt to improve the practicality of the Birch reduction by replacing liquid ammonia with low-molecular-weight amines^[154,155] (e.g., MeNH₂ or EtNH₂) and substituting alkali metals with less reactive calcium. Around the same time, Wender and co-workers^[156] reported the use of

a lithium/ethylenediamine system. However, both approaches tended to cause over-reduction to alkanes and alkenes, and presenting several practical limitations. In 2000, the Dolby group introduced a modified method employing a mixed solvent system consisting of *n*-propylamine/ethylenediamine, and *tert*-butanol as the proton source. This approach improved selectivity in the formation of Birch-type products.^[157]

Over the past decade, a range of alternative strategies have been extensively developed. For example, Baran and co-workers reported a practical electrochemical reduction method inspired by lithium-ion batteries technology.^[158] In addition, photochemical and enzymatic pathways have also been studied as innovative alternatives.^[159,160] Furthermore, several ammonia-free modifications of alkali-metal-mediated Birch reductions under ambient temperature conditions have been reported.

For example, several methods utilize sodium dispersions in anhydrous solvents (typically, THF) with alcohols such as *tert*-butanol or 2-propanol serving as proton sources at below 0 °C under inert atmosphere. These sodium dispersions possess a high surface area, enabling efficient Birch reductions even in the absence of liquid ammonia. In 2005, Dye and co-workers reported an ammonia-free method using sodium absorbed on silica gel as the reductant in THF.^[161] The same group later introduced a modification incorporating 15-crown ether as an additive.^[162] More recently, Takai, Asako, and co-workers disclosed that 1,3-dimethyl-2-imidazolidinone (DMI) can act as a ligand to facilitate Birch reductions using sodium dispersion (Scheme 12, a).^[163] Although these advances are significant, the requirement to prepare sodium dispersions, combined with their relatively short shelf life, remains a practical limitation.^[164]

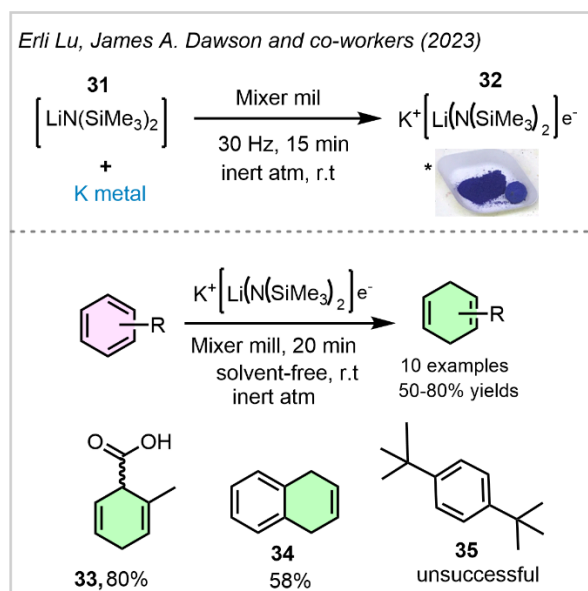
In 2021, Koide and co-workers^[165] reported a convenient protocol for Birch reduction with lithium/ethylenediamine system in THF with *tert*-butanol as a proton source, enabling highly efficient Birch reductions of both electron-rich and electron-deficient substrates within just one hour at ambient temperatures (Scheme 12, b).



Scheme 12. Recent advances in solvent-based ammonia-free Birch reduction with sodium and lithium.^[161–163,165]

Considering mechanochemistry as an efficient tool for activating bulk metals and enabling solvent-free reactions, mechanochemically-based Birch reductions have recently emerged. In 2023, the Erli Lu group^[166] reported the first variant of the mechanochemical Birch reduction using the room-temperature-stable electride

$\text{K}^+(\text{LiHMDS})\text{e}^-$ **32**. This compound was prepared by ball milling potassium metal with LiHMDS **31**. Following its synthesis, the group demonstrated its reductive properties in Birch reduction (Scheme 13). In this procedure, aryl substrates (10 examples) were milled with the electride in a stainless-steel jar for 20–25 minutes at room temperature under inert atmosphere, achieving 50–80% yields of the respective reduction products. Notably, this electride-mediated Birch reduction did not require a protic source until the quenching stage, a marked contrast to the classical Birch method.



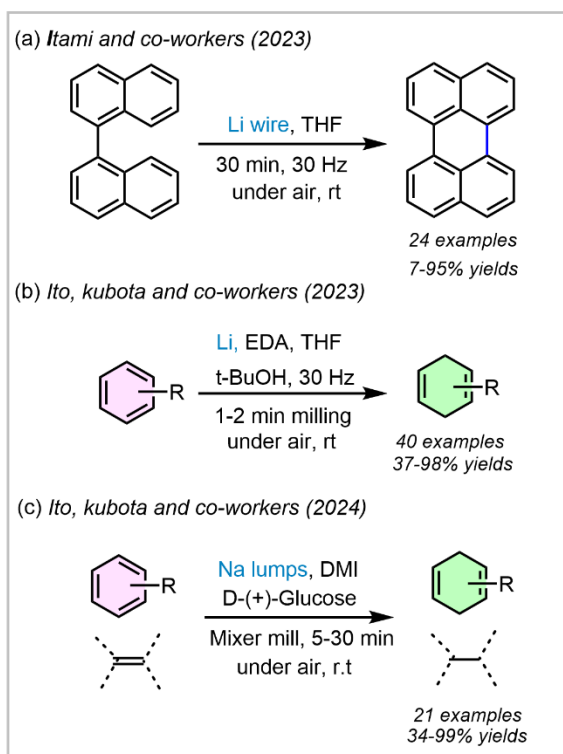
Scheme 13. Mechanochemical synthesis of potassium electride and its application in Birch reduction. *This picture is directly adapted from the original source.^[166]

Nearly same time, Itami and co-workers^[167] reported the lithium-mediated mechanochemical cyclodehydrogenation reaction, in which lithium wire was milled with various binaphthyls using THF as an additive in a stainless-steel jar at room temperature. The reaction afforded polycyclic aromatic hydrocarbons in high yields and proceeds through radical-anion intermediates (Scheme 14, a).

Again in 2023, Ito, Kubota and co-workers^[97] reported the mechanochemical lithium-based Birch reduction. The reaction was carried out by milling an aromatic substrate with ethylenediamine (EDA), *tert*-butanol as a proton source, and THF as an additive at room temperature without inert atmospheric conditions in a stainless-steel milling jar (Scheme 14, b). Notably, the reaction was extremely fast (< 1 min) and applied to a broad range of aromatic substrates including carboxylic acids, ethers, alcohols, polycyclic hydrocarbons, nitrogen heterocycles, natural and bioactive compounds. A gram-scale reaction was also successfully performed, highlighting the method's synthetic utility.

Building on the success of their initial work, in 2024 the same group reported mechanochemical sodium-mediated Birch reduction by using D-(+)-glucose as solid protic source and 1,3-dimethyl-2-imidazolidinone (DMI) as an additive (Scheme 14, c).^[168] The reaction was performed at room temperature in a 10 mL stainless-steel milling jar without inert atmosphere and completed in 5–30 minutes. A broad range of aromatic

and alkene substrates was successfully reduced, delivering the respective products in 34–99% yield. Interestingly, classic protic sources such as *tert*-butanol and 2-propanol were less effective than glucose. The solid protic source produces solid reaction mixture after milling, facilitating transfer of mechanical energy in contrast to the reactions with liquid additives. Control experiments showed that mechanical activation was crucial, as the same reaction in solution gave <9% conversion, underscoring the role of mechanochemistry in this transformation.



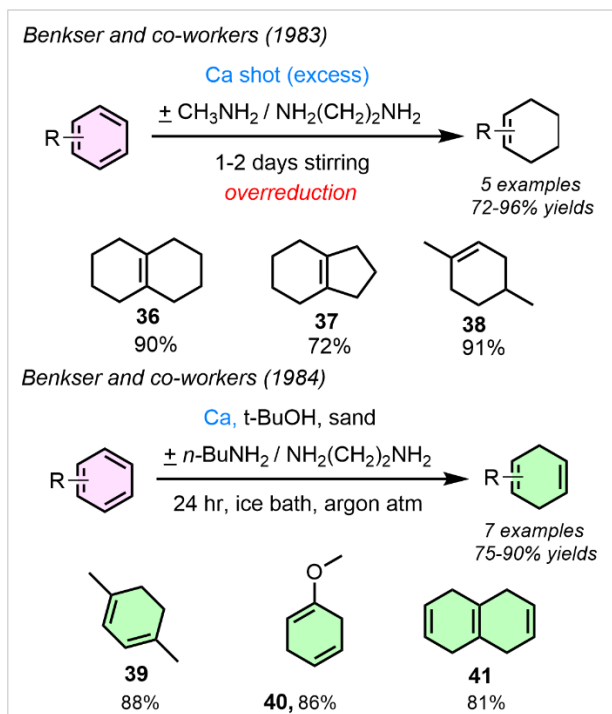
Scheme 14. Recent advances in mechanochemical Birch reductions and related transformations with Li^[97] and Na.^[168]

1.3.3 Alkaline earth metal-mediated Birch reductions

Birch reductions using alkaline earth metals such as calcium or magnesium offer a potentially safer alternative to the classical method, which relies on pyrophoric and hazardous alkali metals like sodium or potassium. Although lithium is the least reactive among the alkali metals, its limited availability (crustal abundance of 0.0016%) raises concerns about resource depletion in the coming decades. In comparison, calcium and magnesium are significantly more abundant, with crustal abundances of 2.8% and 4.2%, respectively.^[169]

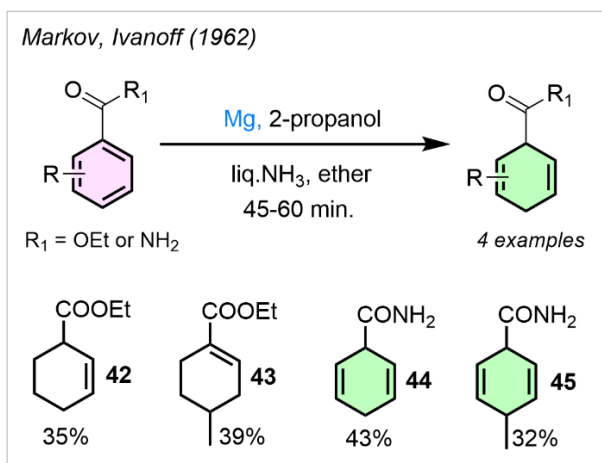
However, major limitation is the lower reactivity of calcium and magnesium compared to alkali metals. While solutions of these metals in liquid ammonia or low-molecular-weight amines can act as strong reductants,^[170,171] their robust crystalline lattices hinder reactivity. For example, calcium's high atomization energy (178 kJ mol⁻¹)^[142] significantly limits its solubility and requires pre-activation for effective electron transfer.

As a result, the use of alkaline earth metals in Birch reductions and other reductive transformations has been largely overlooked, and only a few examples have been reported.^[172–176] Calcium-mediated Birch reductions in amine solvents have required either large excess of metal,^[175] vigorous mechanical stirring with sand to remove passivation layers (Scheme 15),^[176] or sonochemical activation^[177] to initiate efficient electron transfer. These solution-phase methods often lead to complex product mixtures and have been applied mainly to simple aromatic hydrocarbons.^[172,178]



Scheme 15. Calcium-based Birch reduction in solution.^[175,176]

The first reported use of magnesium in a Birch reduction dates back to 1962,^[179] when Markov and Ivanoff used 2-propanol as a proton source to reduce four aromatic derivatives **42–45** of esters and amides in liquid ammonia, achieving modest yields of 32% and 44% (Scheme 16). Despite this early contribution, there have been no significant developments in improving or expanding this strategy.



Scheme 16. Magnesium-based Birch reduction in solution.^[179]

1.4 Process Safety Considerations and Technological Challenges for Scaling Up Metal-Mediated Mechanochemical Reactions

Scaling up chemical synthesis from the laboratory scale to industrial production is a cornerstone of manufacturing pharmaceuticals, advanced materials, and fine chemicals. The reduced reliance on solvents and the significantly lower PMI make mechanochemistry highly appealing as method for industrial-scale production. However, scaling up mechanochemical reactions remains a challenge, often requiring dedicated studies independent of initial method development. So far, only a few examples of large-scale synthesis of organic compounds (in the range of 50–100 mmol) have been reported,^[22,180–183] with most relying on continuous synthesis using TSE.

However, the challenge becomes even greater when it comes to the generation of polar organometallic reagents and their reactions with electrophiles. The main concern arises from the highly exothermic nature of these reactions, which, when combined with high reaction rates and the pyrophoric properties of both the dispersed metals and the organometallic intermediates, poses a significant safety risk. Unfortunately, these safety issues are rarely addressed in studies focused on method development. The works of Browne and co-workers^[184] and Vilaivan^[114] represent two rare exceptions that analyse the hazards.

At the laboratory scale, the heat release may not be a major issue for gram-scale preparations, as it can dissipate efficiently. However, this becomes a critical factor when scaling up to kilogram-scale processes, where proper heat management is essential for both safety and efficiency. Without adequate thermal control and regulation of reaction rates, scale-up efforts risk thermal runaway, pressure buildup, or uncontrolled side reactions, all of which can compromise yield and safety. Therefore, scaling up is not simply a matter of increasing batch size. It requires dedicated milling equipment and process engineering, appropriate safety infrastructure, and real-time process monitoring.

Another major challenge is the air- and moisture-sensitivity of organometallic compounds, which, although reduced under mechanochemical conditions, still persists upon exposure to air. This sensitivity necessitates the rapid addition of the electrophilic reactant immediately after opening the milling vessel. Combined with the exothermic and potentially violent nature of these reactions, this significantly increases safety risks.

One effective strategy to mitigate this issue is the *in situ* generation of organometallic reagents, using them as short-lived intermediates. However, this approach is not compatible with many electrophilic substrates. As alternatives, stabilizing additives^[185] can be introduced to limit exposure to moisture and oxygen, or the milling equipment must be adapted to maintain an inert atmosphere throughout the process.

One of the most pressing technological needs in the field is the development of mechanochemical equipment suitable for scaling up exothermic processes involving air-sensitive organometallic reagents. Whether in closed-batch or continuous-flow configurations, such systems must support kilogram-scale synthesis while ensuring uniform energy transfer and precise control over the reaction environment. First and foremost, effective heat management (both heating and cooling) is essential. This not only prevents thermal runaway but can also be used to drive selective transformations and improve reaction efficiency. Equally important is the integration of pressure monitoring to detect and manage pressure build-up within the reaction vessel. This is particularly critical for reactions involving volatile intermediates or gas evolution, especially at larger scales. To further enhance process control and safety, the incorporation of real-time, *in situ* spectroscopic techniques such as near-infrared (NIR) spectroscopy would be highly beneficial. These tools allow for monitoring the formation of reactive organometallic intermediates, correlating this information with reaction kinetics and thermal behaviour. They also provide insights into reaction mechanisms and the structure of transient species, offering valuable data for process optimization and safe operation under solid-state conditions. Additionally, the milling system should be equipped with gas inlet and outlet ports to maintain an inert atmosphere. The inclusion of multiple feed ports would allow precise control over the dosing rate of reactants or quenching agents during or after milling. This not only improves safety but also enables better control of stoichiometry, facilitates safer work-up, and may enhance yields while reducing waste.

With the right technological advancements, mechanochemical organometallic reactions can evolve from laboratory-scale procedures into a robust, scalable platform suitable for industrial applications, offering advantages in sustainability, efficiency, and operational simplicity. This transformation would represent a significant milestone in modern chemical process development by uniting green chemistry principles with efficient large-scale synthesis.

1.5 Summary of the Literature Overview

Mechanochemistry has emerged in organic synthesis as a greener and more efficient alternative to traditional solution-based methods. By using mechanical energy to induce and drive chemical reactions in readily available equipment like ball mills, this technique eliminates or significantly reduces the need for bulk solvents, enhances reaction rates, and enables access to unique reactivity and simple operational conditions. Mechanochemistry has shown great promise in organometallic chemistry by enabling the activation of zero-valent metals for the generation of polar organometallic reagents and enhancing the efficiency of reductive transformations. It is especially notable that most developments in mechanochemical organometallic chemistry have appeared only recently, primarily after 2022, when the present doctoral research was already in progress. This recent surge in activity underscores the growing interest of the research community and highlights the significant potential of mechanochemistry to overcome limitations associated with conventional solvent-based organometallic methods, improving both safety and practicality in organic synthesis.

2 Motivation and Aims of the Present Work

The drive towards more sustainable, safer, and simpler synthetic methods has spurred growing interest in solvent-free and energy-efficient transformations, positioning mechanochemistry as a powerful tool to meet these demands and offering unique advantage of activating insoluble materials, such as metals and inorganic salts, which are difficult to achieve under conventional conditions.

Within this context, the motivation for this work lies in the development of mechanochemical protocols that utilize calcium and magnesium metals for synthetically valuable chemical transformations, both through the generation of polar organometallic reagents and in reductive processes. When this research began, calcium and magnesium had been applied in only a few seminal studies,^[101,123,125,127] leaving much of their potential in organometallic mechanochemistry untapped. We envisioned that these earth-abundant, low-cost and non-toxic metals can be employed in effective reductive transformations, as well as in carbon–carbon and carbon–heteroatom bond-forming reactions under mechanochemical conditions, offering appealing synthetic methodologies for both academic research and industrial applications.

The specific aims of the study were:

- To develop the Mg-mediated mechanochemical Barbier reaction, featuring the generation of organomagnesium halides *in situ*, as a practical and efficient alternative to the traditional Grignard synthesis.
- To develop a mechanochemical method for Birch reduction using calcium and magnesium metals, enabling the reduction of aromatic compounds in a mixer mill under ambient conditions.

3 Results and Discussion

All the experimental protocols and specific additional information have been described in the supporting information of publications I & II.

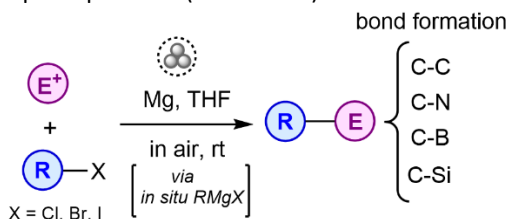
3.1 Mechanochemistry-Amended Barbier Reaction as an Expedient Alternative to Grignard Synthesis (Publication I)

As outlined in the literature overview (section 1.2), mechanochemical activation of zero-valent metals enables efficient generation of polar organometallic reagents under essentially solvent-free conditions, with ethereal solvents as stoichiometric additives. Concerning organomagnesium chemistry, while this work was in progress, significant contributions by the Bolm^[106] and Ito/Kubota^[128] groups were published, demonstrating the generation of Grignard reagents and their use in two-step mechanochemical processes. In Bolm's study, reactions were conducted under an inert atmosphere, whereas the Ito/Kubota group successfully generated organometallics in air, followed by rapid addition of the electrophilic partner immediately after opening the milling jar.

Our approach, however, was initially inspired by the Barbier variant of Grignard chemistry, in which the formation of RMgX and its reaction with an electrophile occur concurrently in a single step. This strategy reduces the likelihood of RMgX degradation upon air exposure and improves operational simplicity. The Bolm group demonstrated a Barbier-type reaction using sodium methyl carbonate, but the method was not extended to other electrophiles.

In solution-phase chemistry, the Barbier approach, despite its conceptual appeal, has not gained widespread use as a replacement for the traditional Grignard reaction due to limited robustness and versatility.^[186] Except for highly reactive substrates such as allylic and benzylic halides, magnesium-mediated Barbier reactions often give low and inconsistent yields due to multiple parasitic side reactions. Prior mechanochemical Barbier methods have reflected similar substrate scope limitations and employed less reactive metals such as zinc^[117] or bismuth.^[102] An example of the solvent-free magnesium-mediated protocol was reported by Wang et al.,^[187] which suffers from the same shortcomings as the conventional Barbier approach.

In our work, we successfully addressed these long-standing challenges by developing a mechanochemical variant of the Mg-mediated Barbier reaction that operates under ambient conditions without the need for an inert atmosphere. The method proved applicable to a wide range of organic halides (including alkyl, aryl, benzyl, and allyl) as well as diverse electrophilic partners (Scheme 17).

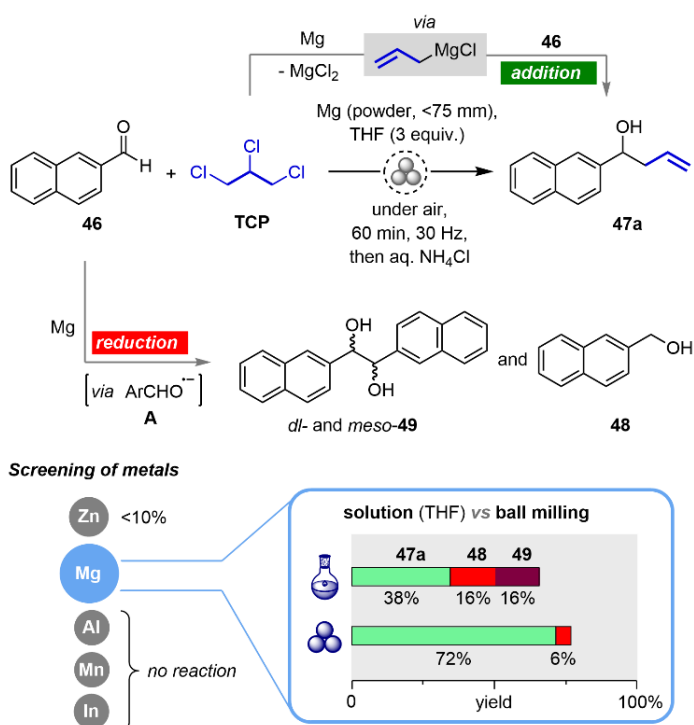


Scheme 17. Mechanochemical Barbier-Grignard reaction using magnesium metal.

3.1.1 Optimization studies with 2-naphthaldehyde

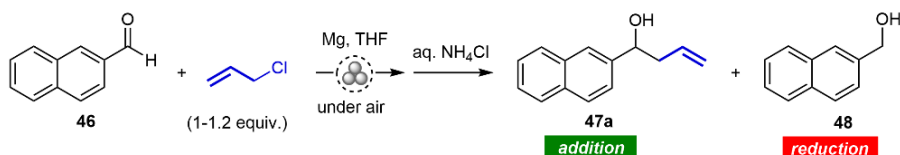
As a part of our research project focused on removing organic pollutants from aqueous media using macrocyclic hosts, this study was initiated with the goal of developing new remediation methods for the captured halogenated pollutants. Drawing inspiration from the early works of Rowland^[123] and Birke,^[124,125] we aimed to innovate this approach and employ Grignard chemistry for C–C bond construction and synthesis of value-added chemicals from the pollutants. In this regard, the groundwater pollutant 1,2,3-trichloropropane (TCP)^[188] was used as a precursor of allylmagnesium chloride in the synthesis of homoallylic alcohols under Barbier conditions.

The experiments were performed using a Form-Tech Scientific FTS-1000 shaker mill, operating at 30 Hz maximal milling frequency in 15 mL ZrO₂ jars containing a single 10-mm ZrO₂ milling ball. We observed that the reaction of 1,2,3-trichloropropane with magnesium powder and 2-naphthaldehyde **46** yielded the homoallylic alcohol **47a** (R = allyl) nearly twice as efficiently under mechanochemical conditions (1 hr milling at 30 Hz in a mixer mill) compared to conventional THF solution-based method. Notably, side-reactions leading to the formation of 2-naphthalenemethanol **48** and pinacols **49**, which were prominent in solution-state conditions (16% combined yield), were significantly suppressed in the mechanochemical protocol, results only 6% of **48** and almost < 0.5% of **49**. The magnesium was essential for the reaction, as alternative metals such as Zn, Al, Mn, and In were ineffective (Scheme 18).

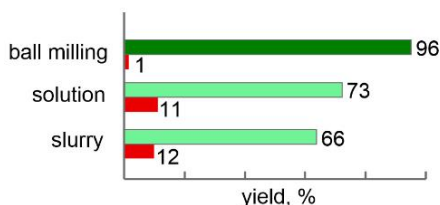


Scheme 18. Remediation of 1,2,3-trichloropropane (TCP) via the Barbier-Grignard reaction in solution and under ball milling conditions.

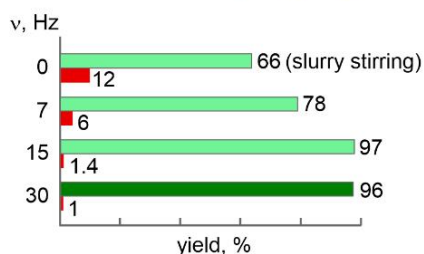
Encouraged by the initial results, we extended our investigation to other organic halides, starting from allyl chloride as a direct precursor of the transient allylmagnesium intermediate (Scheme 19). Its model reaction with 2-naphthaldehyde **46**, under standard mechanochemical conditions (Mg (2 equiv.), THF (3 equiv.), 30 Hz, 1 hr milling), after hydrolysis, yields alcohol **47a** in an excellent 96% yield and only trace amount alcohol **48** (~1% yield) was observed. In contrast, solution and slurry-stirred reactions results significantly lower yields of **47a** due to favourable formation of side product alcohol **48** (Scheme 19, A). It is worth noting that the slurry stirring experiment was conducted with the same quantity of chemicals as in the mechanochemical process, and the result highlights that the superior performance under ball milling is due to mechanical agitation rather than concentration effects.



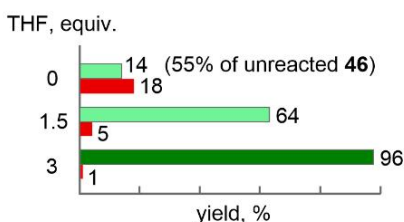
A. Ball milling vs solution



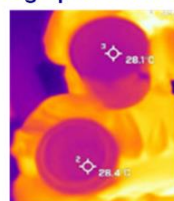
B. Effect of milling frequency



C. Effect of THF loadings



D. Thermographic measurement

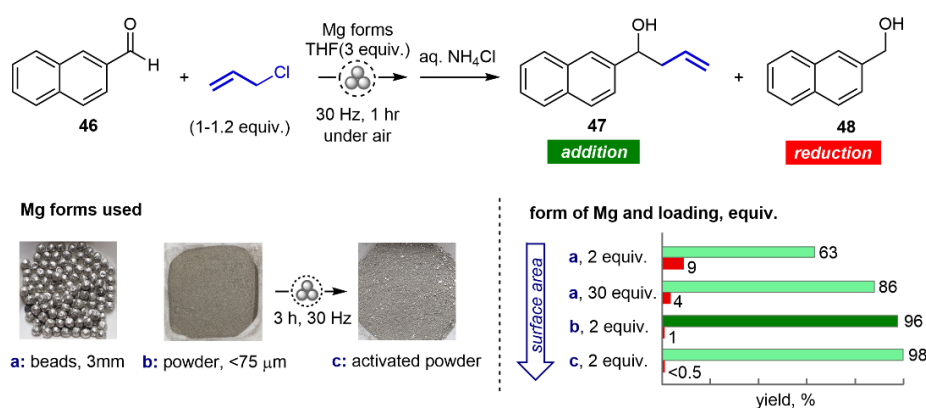


After 10 min, 30 Hz (<29°C)

Scheme 19. Optimization studies for the model reaction of allyl chloride and 2-naphthaldehyde. Standard reaction conditions: 2-naphthaldehyde **46**, allyl chloride (1–1.2 equiv.), Mg powder (<75 μm, 2 equiv.), THF (3 equiv.), 60 min, milling frequency 30 Hz, under air, hydrolysis with aq. NH₄Cl. All other experiments display variations from the standard conditions as indicated. Yields are determined by ¹H NMR with internal standard after the hydrolytic workup (aq. NH₄Cl).

In support, the yield of **47a** and the by-product **48** were markedly dependent on milling speed, i.e., high milling frequency significantly improving yields of alcohol **47a** while minimizing the formation of side-product alcohol **48** (0 Hz vs 30 Hz, Scheme 19, B). Consistent with previous studies,^[106,128] the presence of THF or 2-MeTHF was essential for achieving high yields of **47a**. A minimum of 3 equiv. of THF was required, as lower amounts led to diminished performance (Scheme 19, C). Given that Grignard reagents

typically coordinate with two or three THF molecules,^[189] and ionic magnesium species with up to four or even six,^[190] we propose that THF primarily acts as a Lewis base ligand stabilizing the organomagnesium intermediate, and to a lesser extent, serves as a liquid-assisted grinding medium. Moreover, the mechanochemical Barbier synthesis of **47a** proceeded rapidly and delivered 93% yield just after 10 minutes of milling at 30 Hz frequency. Nevertheless, all the subsequent optimization experiments were carried out for 1 hour for the sake of consistency. Unlike conventional solution-state Grignard and Barbier reactions, which often exhibits prolonged induction periods that can trigger sudden exothermic reactions and pose a risk of thermal runaway,^[191] no such delay was observed for the ball milling experiments. An inspection using a thermal camera revealed only a small temperature increase (which did not exceed 29 °C within the milling jar, Scheme 19, D), indicating effective heat dissipation and implying that thermal activation is an unlikely cause for the short induction period and fast reaction rate.



Scheme 20. Studying the effect of surface area and pre-activation of magnesium.

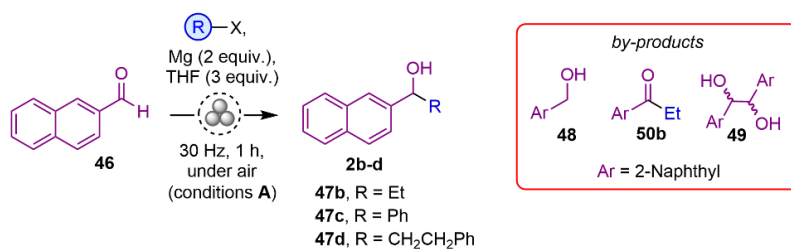
Next, the reaction was found to be dependent on the surface area of magnesium, with larger surfaces resulting in a cleaner conversion to the main product **47a** (Scheme 20). The surface area was altered by changing the form of magnesium using different particle sizes and metal loadings. Thus, when equal amount (2 equiv.) of spherical beads (diameter ~3 mm, “form a”) and fine powder (particle size < 75 μm, “form b”) were used, the beads gave a lower yield of **47a** (63%). However, the yield was improved to 86% when excess (30 equiv.) of the beads was loaded, which corresponds to a 15-fold increase of the surface area. Importantly, the metal beads were not fragmented during milling and their erosion occurred from the surface. This surface area-based dependence encouraged us to activate the initially used magnesium powder (“form b”, < 75 μm) by dry ball milling to enhance its reactivity. After 3 hours of ball milling at 30 Hz, shiny metal powder (“form c”) was obtained, in contrast to the original grey appearance. The activated magnesium (“form c”) showed better performance, producing alcohol **47a** in 98% yield (Scheme 20). This is likely due to the removal of the passive oxide layer from the surface of the metal and likely generation of finer, particles with more reactive metallic sites. Such activation is often critical in traditional solution-phase Grignard reagent synthesis. Notably, the activated metal (“form c”) also proved more effective in Barbier reactions involving 2-naphthaldehyde with other and less reactive organic halides (see below).

To test the generality of the approach, the representative examples of less reactive organic bromides have been tested (Table 1). The activated Mg powder (conditions A*

vs A, with non-activated Mg) notably enhanced the Barbier reactions involving EtBr (entry 1), increasing the yield of **47b** from 72% to 94% and significantly lowering the formation of by-products **48** and **50b**. Similar improvements were also observed for PhBr (entry 2), although no such effect was observed for the synthesis of **47d** from 2-phenylethyl bromide (entry 3). Interestingly, the classical Grignard synthesis in THF solution (conditions C) delivered nearly same yields of alcohols **47b–d** and their side-products compared to those obtained in the mechanochemical Barbier conditions with activated Mg (conditions A*). However, the latter was conducted under ambient air, whereas generally Grignard reactions typically demands an inert atmosphere.

Consistently, high yields of alcohols **47b–d** were achieved under mechanochemical conditions (conditions A) in the Barbier reactions of bromoethane (entry 1), bromobenzene (entry 2), and 2-phenylethyl bromide (entry 3) compared to their solution-phase counterparts (conditions B). The lower yields in the solution-based Barbier reactions was attributed to generation of side-products, majorly 2-naphthalenemethanol **48** in 11–20% yield, as well as additional by-products such as ketone **50b** in the case of EtBr (entry 1).

Table 1: Yields of alcohols **47b–d** and by-products in the Barbier reactions performed under mechanochemical conditions(A and A*), in THF solution(B), and in the Grignard reaction in THF solution(C).



entry	organic halide	product (by-product)	conditions, ^[a] yields (%) ^[b]			
			A	A*	B ^[c]	C
1	EtBr	47b	72	94	57	96
		48	11	2	20	3
		50b	7	0	5	0.5
2	PhBr	47c	83	92	57	— ^[d]
		48	6	3	20	—
3	Ph-CH ₂ -CH ₂ -Br	47d	88	85	52	90
		48	7	8	17	7

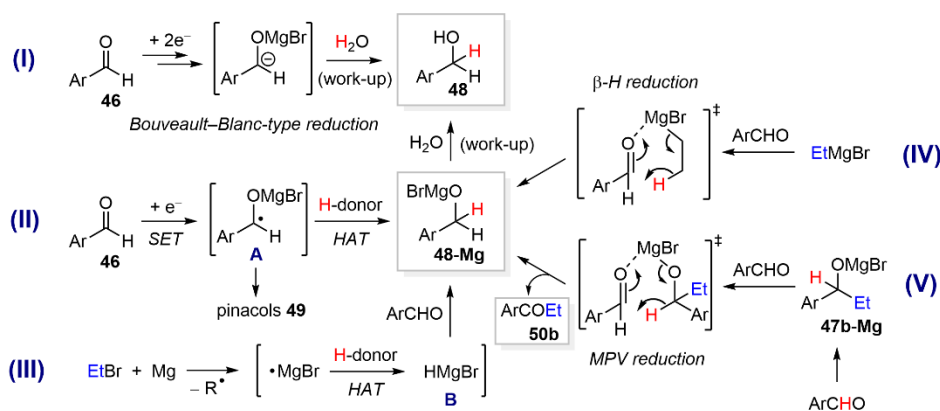
[a] **A**: ball milling, **46** (200 mg, 1.28 mmol), RX (1–1.2 equiv.), non-activated Mg powder, THF (3 equiv.), 30 Hz, 60 min, under air. **A***: same as A, but with Mg powder activated through prior ball milling (3 h at 30 Hz). **B**: in THF solution at stirring, same reactants as in A, under argon. **C**: in THF solution with RMgX (1 equiv.), under argon. [b] Yields are determined by ¹H NMR with internal standard after the hydrolytic workup (aq. NH₄Cl). [c] Performed with non-activated Mg powder. [d] Not performed. *The reaction with 2-phenylethyl bromide was performed by Tatsiana Nikonovich (entry 3).

3.1.2 Mechanistic study to elucidate the nature of the major side process

The model reaction between 2-naphthaldehyde **46** and EtBr was performed to elucidate the formation of main side products **48** and **50b**.

Five mechanistic hypotheses (Scheme 21, eqs. I–V) explaining the generation of the main side products 2-naphthalenemethanol **48** and **50b** were proposed based on literature precedents. The formation of ethyl ketone **50b** alongside with alcohol **48** pointed out on Meerwein-Ponndorf-Verley (MPV) reaction of alkoxide **47b-Mg** and aldehyde **46** as the most probable mechanism (eq. V). The following alternative pathways en route to **48** have been also considered: (eq. I), Bouveault-Blanc-type reduction of **46** with metallic Mg;^[192] (eq. II), hydrogen atom transfer (HAT) from THF or **46** to the ketyl radical anion A or (eq. III) via addition of transient magnesium hydride B^[193] to the carbonyl group of **46**; (eq. IV), β -hydride transfer from ethyl Grignard reagent.

Mechanistic hypotheses:

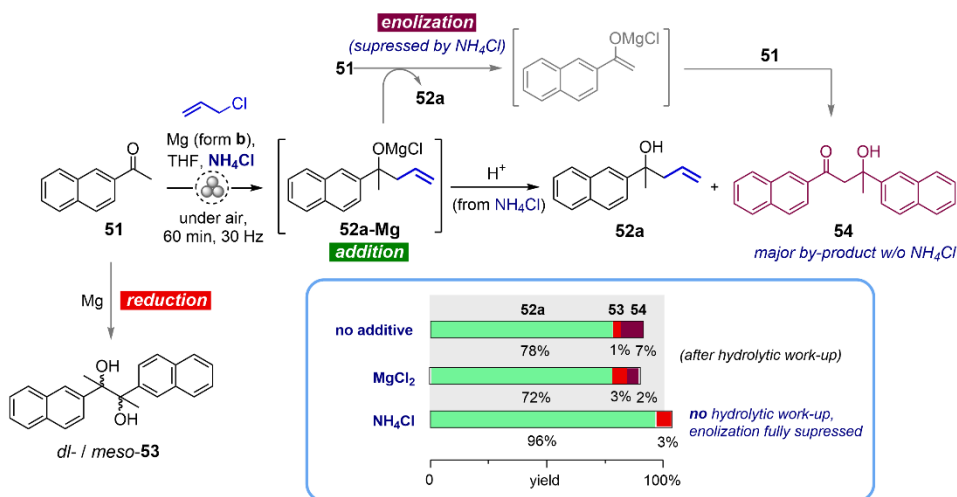


H-donor = THF or ArCHO; Ar = 2-naphthyl

SET = single electron transfer; HAT = hydrogen atom transfer; MPV = Meerwein-Ponndorf-Verley

Scheme 21. Mechanistic hypotheses explaining the formation of the side products **48** and **50b**.

The pathways shown in eq. (I–V) were distinguished experimentally by tracking the origin of α -hydrogen in alcohol **48** by means of deuterium-labelled reagents (Scheme 22): First, when the reaction was quenched with D_2O (a) or performed with $\text{THF-}d_8$ (b), $\text{EtBr-}d_6$ (c), no deuterium incorporation into alcohol **48** was observed. These results ruled out the possible pathways of (I) and (IV) or HAT from THF in the pathways (II) and (III). The absence of pinacols **49** among the by-products additionally indicated that the ketyl radical-anion A were unlikely generated. Second, the reaction of deuterated aldehyde **46-d** produced double deuterated alcohol **48-d₂** hence evidencing that α -hydrogens of **48** originate from the aldehyde hydrogen of **46** (eq. d). This result pointed out on operation of either HAT from aldehyde **46** (pathways II and III) or MPV reaction (V). But, through the MPV reaction pathway (V) stays in better agreement with the observed by-products and also explains the origin of **50b**. Further supporting evidence came from the successful MPV reaction between **47b-Mg** and 2-naphthaldehyde **46** under mechanochemical conditions (eq. e, the reaction was performed by Tatsiana Nikonovich).



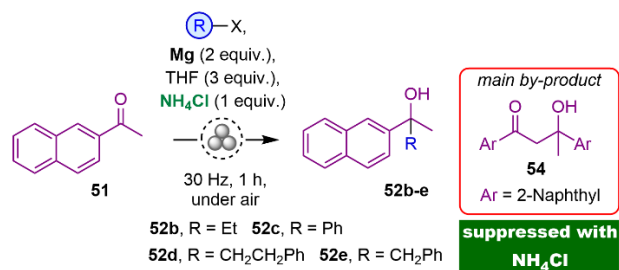
Scheme 23. The mechanochemical Barbier-Grignard reaction of allyl chloride with 2-acetylnaphthalene **51**. Suppression of enolization side process with solid ammonium chloride.

To suppress the enolization process, the reaction was carried out in the presence of various Lewis (like MgCl₂) and Brønsted acid (like NH₄Cl) as additives, aimed at quenching the basicity of the intermediate **52a-Mg** (Scheme 23). Among them, solid NH₄Cl (1 equiv.) proved surprisingly effective, completely inhibiting the enolization process **54** and yielding alcohol **52a** in an excellent 96% yield. In addition, alcohol **52a** could be isolated by simple filtration of the crude reaction mixture suspended in ethyl acetate, followed by solvent evaporation i.e., the conventional hydrolytic work-up was totally bypassed (see also the gram-scale preparation of **52a** discussed below). This suggests that alcohol **52a** was formed through three concurrent *in situ* steps: generation of Grignard reagent, Grignard addition and direct protonation of the resulting alkoxide **52a-Mg** with solid NH₄Cl, which streamlines the experimental protocol and offers a highly convenient approach.

Assuming generation of allylmagnesium chloride as an intermediate, the discovered high tolerance of the carbonyl addition process to a Brønsted acid additive looked extraordinary, since organomagnesium compounds are believed to act as eager proton acceptors. This result pointed out on two possibilities: (i) either the addition of the Grignard intermediate is extremely fast and can compete with the protonation rate, or (ii) the reaction occurred via radical intermediates and generation of transient organometallics is unlikely. Both hypotheses were credible and had literature precedents.^[194,195] Therefore, a more detailed study of the phenomenon was undertaken to gain a deeper understanding (see section 3.1.4).

In the similar way, the use of solid NH₄Cl significantly improved the yields of alcohols **52b-e** derived from other less reactive organic halides (Table 2, Entries 1–4), with the exception of **52d** (Entry 3). However, the yields remained lower compared to analogous reactions involving the more reactive 2-naphthaldehyde **46** (Table 1). Notably, the use of pre-activated magnesium did not enhance the outcome in the reaction of **51** with EtBr (for more details, see table S8 in the supporting information of publication I), suggesting that activated Mg may not be required for Barbier-type additions to ketones. However, no comparison experiments was performed for other organic halides.

Table 2: Synthesis of tertiary alcohols **52b-e** via mechanochemical Barbier reaction of ketone **51**.

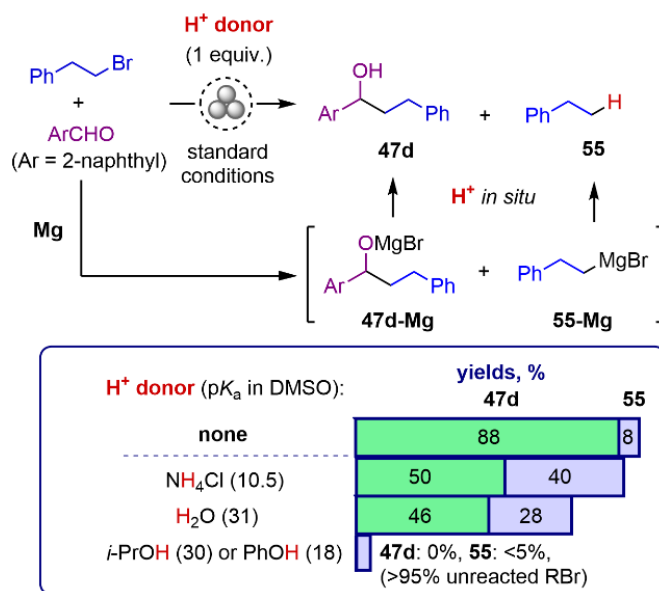


entry	organic halide	conditions, ^[a] yields (%) ^[b]			
		A , no additive		D , with NH ₄ Cl	
		52b-e	54	52b-e	54
1	EtBr	57	14	78	0
2	PhBr	33	11	68	0
3		53	15	49	0
4		67	7	82	0

[a] **A**: ball milling, **51**, RX (1.5 equiv.), non-activated Mg powder (2 equiv.), THF (3 equiv.), 30 Hz, 60 min, under air, followed by hydrolysis (aq. NH₄Cl). **D**: same as **A**, but with solid NH₄Cl (1 equiv.), followed by treatment with EtOAc, filtration and solvent evaporation. [b] Yields were determined by ¹H NMR with internal standard.

3.1.4 Tolerance to protic additives

The exceptional tolerance of the mechanochemical, presumably organomagnesium-mediated process to the solid Brønsted acid NH₄Cl was unexpected, given the well-known sensitivity of Grignard reagents to proton donors. This intriguing result encouraged us to conduct a more detailed investigation into the extent of this protic additives tolerance in reactions involving naphthaldehyde **46** with various organic halides (PhCH₂CH₂Br, EtBr, PhBr, allyl bromide, see Table 3, Scheme 24). We found that Barbier-type additions to naphthaldehyde **46** could proceed not only in the presence of solid NH₄Cl but also with H₂O. However, in these cases, the yields of the corresponding alcohols **47a–47d** were 10–40% lower compared to reactions performed without additives. In the presence of the protic additives, competitive protonation of organometallic intermediates took place, leading to reduced yields. In the case of PhCH₂CH₂Br, generation of ethyl benzene **55** (formed by protonation of **55-Mg**) was observed by ¹H NMR spectroscopy.



Scheme 24. Tolerance of the mechanochemical Barbier reaction of **46** and 2-phenylethyl bromide to protic additives. Proton quenching of alkoxide **47d-Mg** and a transient Grignard intermediate **55-Mg**.

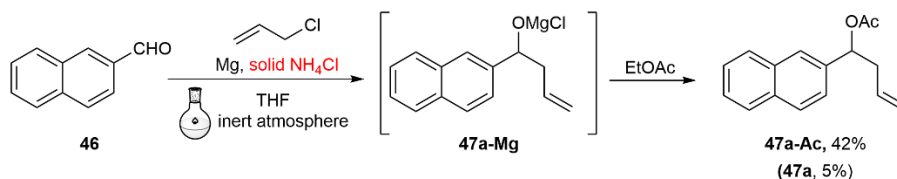
Table 3: Tolerance to protic additives in the mechanochemical Barbier reactions of aldehyde **46** with other organic halides.

entry	organic halide	product	yield (%) ^[a,b]			
			no additive	NH ₄ Cl	H ₂ O	<i>i</i> -PrOH
1		47a	98	62	65	37*
2	EtBr	47b	72	57	61	— ^[c]
3	PhBr	47c	83	53	46	— ^[c]

[a] Conditions: **46** (200 mg, 1.28 mmol), RBr (1.1 equiv.), non-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] Not performed.
 *the reaction was performed by Danylo Merzhyievskiy.

In stark contrast, the same reaction performed in THF solution were completely inhibited by the presence of H₂O (1 equiv.), showing no progress even after extended stirring for (24 h) at room temperature or upon heating. This failure could be attributed to the passivation of the magnesium surface by Mg(OH)₂,^[192] a barrier that is effectively overcome under mechanochemical conditions due to continuous removal of surface layers through ball milling. In addition, the similar solution-based experiment using aldehyde **46** and allyl chloride in the presence of solid NH₄Cl in THF solution under inert atmosphere, failed to protonate *in situ* generated magnesium alkoxide intermediate **47a-Mg** (Scheme 25). This was evidenced by treating the crude reaction mixture directly

with EtOAc, resulting in acetate **47a-Ac** (42% yield), with alcohol **47a** only as a minor product (5% yield). This result highlights the importance of mechanochemical activation in revealing the hidden reactivity of solid reactants.



Scheme 25. The solution-phase Barbier-Grignard reaction of allyl chloride with 2-naphthaldehyde **46** in presence of solid NH₄Cl.

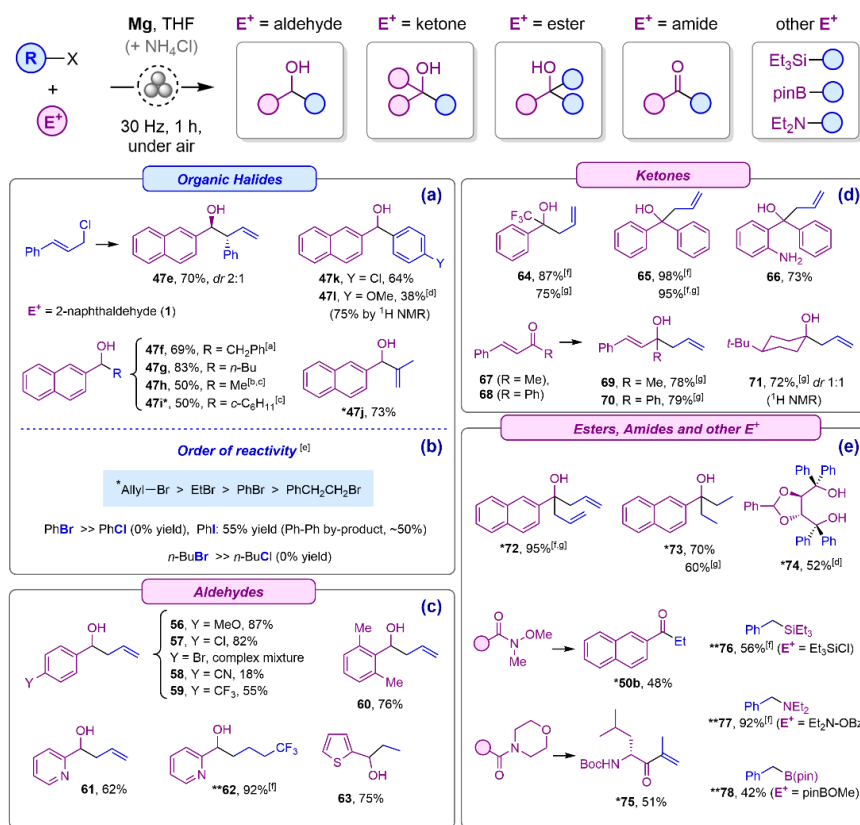
The obtained mechanochemical results suggest that the use of NH₄Cl for *in situ* release of the alcoholic product from the respective Mg alkoxide could be justified only when (i) the use of highly reactive Grignard reagents towards carbonyl additions such as allyl magnesium chloride,^[196] because as we go to less reactive organometallics, significant competitive protonation of Grignard reagent may occur; (ii) undesired enolization needs to be suppressed, or (iii) a simplified work-up procedure is desired. Interestingly, both liquid H₂O and solid NH₄Cl exhibited similar effects under mechanochemical conditions (Table 3), a phenomenon possibly explained by coordination of water to Mg²⁺ ions in the solid phase, which may reduce water's effective reactivity.^[194] A broad range of additional protic sources, beyond those already mentioned, was screened by Tatsiana Nikonovich (Table S9, Supporting Information of publication I). The screening showed the lack of correlation between the degree of protonation of organomagnesium compound **55-Mg** and the pK_a values of the proton donors. This suggests that Brønsted acidity alone does not govern the reactivity. Instead, these differences are more likely due to kinetic factors. For example, phenol and isopropanol, both miscible with the liquid organic phase completely suppressed the reaction. This behaviour is likely because of rapid protonation of organometallics in liquid organic phase and concurrent reaction between Mg and these alcohols. These results indicate that solid aggregate state and ionic character of NH₄Cl might be responsible for the reduced protonation rate of organometallic intermediates.

3.1.5 Substrate scope of organic halides and electrophiles

With the optimized conditions in hand for the synthesis of alcohols from aldehydes and ketones, the broader range of scope of organic halides and electrophiles were evaluated. In addition to various functionalized aldehydes and ketones, we also explored esters, amides, and several non-carbonyl electrophiles capable of forming C–Si, C–B, and C–N bonds (Scheme 26). We opted to use activated magnesium for all the reactions, as it consistently delivered similar or improved yields compared to non-activated magnesium during optimization and can be easily prepared on the gram scale (see Section 1, Supporting Information of publication I).

In reactions with 2-naphthaldehyde **46**, cinnamyl chloride reacted almost exclusively via allylic rearrangement, yielding alcohol **47e** in 70% isolated yield as a 2:1 mixture of *anti*- and *syn*-diastereomers (Scheme 26, a). Benzyl bromide smoothly delivers **47f** in 69% yield. Among aliphatic halides, *n*-butyl bromide was highly effective, producing **47g** in 83% yield, while methyl iodide gave the corresponding carbinol **47h** in a modest 50% yield. Notably, this result demonstrates that methyl iodide reacts under mechanochemical

conditions, even though the iodide passivates Mg in THF, which typically hinders the formation of Grignard reagents. The reaction of 2-naphthaldehyde **46** with bromocyclohexane required an excess of activated Mg (12 equiv.) to deliver **47i** in 50% yield, similar yield was obtained from using *c*-C₆H₁₁MgBr in THF. In contrast, 2-bromopropene delivers alcohol **47j** in 73% yield, showing that vinyl bromides are more compatible with this protocol (**47i**, **47j** were synthesized by Tatsiana Nikonovich). Functionalized aryl bromides, such as *p*-methoxy- and *p*-chloro bromobenzenes, also reacted successfully, delivered **47l** and **47k** in moderate yields, respectively. These transformations required pre-activation of Mg using a crystal of iodine. In the case of **47k**, the chemoselectivity was notable, the less reactive C–Cl bond remained untouched while the C–Br bond reacted. This selectivity is consistent with the established reactivity trend for halides in Grignard reagent formation in solution (C–I > C–Br > C–Cl > C–F).^[90] In line with earlier mechanochemical Grignard studies,^[106,128] we observed that bromides outperformed chlorides and iodides.



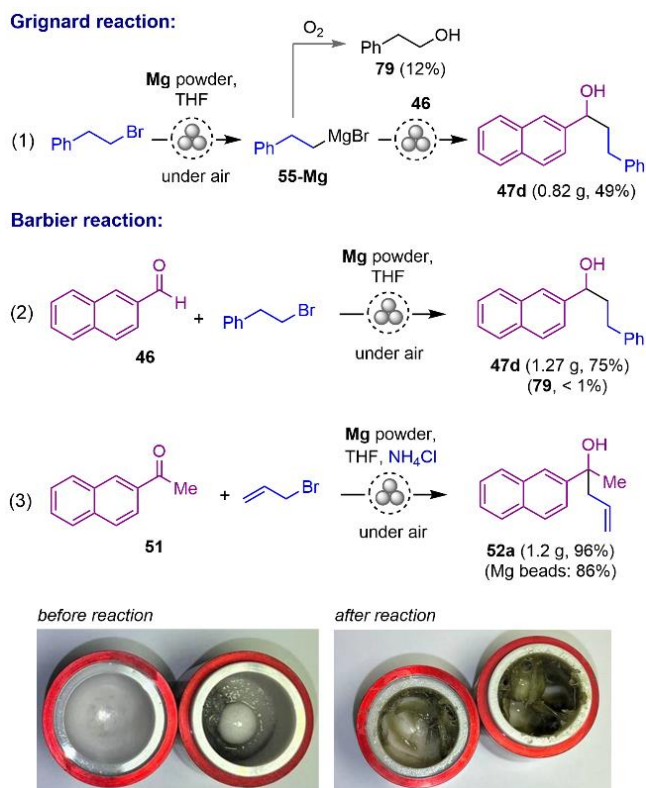
Scheme 26. Synthetic applications of *in situ* generated organomagnesium nucleophiles. General conditions: E⁺ (0.6–3 mmol), RX (1.1–1.5 equiv.), activated Mg powder (2 equiv.), THF (3 equiv.), ball milling at 30 Hz, 1hr, under air, followed by hydrolytic work-up (aq. NH₄Cl). The reactions were performed with bromides (X = Br) except for R = allyl and benzyl (X = Cl). Yields of isolated products are shown. [a] X = Br. [b] X = I. [c] With 12 equiv. of activated Mg powder. The same yield of **47i** was obtained in reaction with *c*-C₆H₁₁MgBr in THF solution. [d] Yield after purification by crystallization. [e] Based on competition experiments. [f] No column chromatography was carried out. [g] With NH₄Cl (1 equiv.) as an additive, without hydrolytic work-up. *Reactions were performed by Tatsiana Nikonovich. **Reactions were performed by Danylo Merzhyievskiy.

Aliphatic and aromatic chlorides were generally unreactive in the mechanochemical Barbier reaction (Scheme 26, b), whereas benzylic and allylic chlorides were highly reactive, comparable to their respective bromide analogues. Iodobenzene delivered a lower yield of **47c** (55%) compared to bromobenzene (92%) due to competitive Wurtz coupling, which led to the formation of biphenyl in ~50% yield. For better understanding of the relative reactivity of organic bromides under these mechanochemical conditions, a series of competition experiments was conducted by Tatsiana Nikonovich (more details can be found in Section 2.7, Supporting Information of publication I). These experiments revealed the reactivity order of $\text{CH}_2 = \text{CHCH}_2\text{Br} > \text{EtBr} > \text{PhBr} > \text{PhCH}_2\text{CH}_2\text{Br}$. This order is also similar to the one observed in classical Grignard reagent formation in diethyl ether solution.^[90]

In the series of *para*-substituted benzaldehydes (Scheme 26, c), electronic effects significantly influenced the reaction results. The electron-donating methoxy group in *p*-anisaldehyde favoured a smooth transformation, produced alcohol **56** in 87% yield. In contrast, benzaldehydes bearing electron-withdrawing substituents such as *p*-Cl and *p*-CF₃ led to increased formation of arylmethanol and pinacol by-products, resulting in lower yields of alcohols **57** and **59** in 82% and 55%, respectively. Aldehydes with *p*-CN and *p*-Br substituents proved incompatible, resulted complex mixtures of products. Steric hindrance from *ortho*-substitution had a lower impact, alcohol **60** was successfully delivered in 76% yield from the corresponding 2,6-dimethylbenzaldehyde, indicating that bulky groups near the formyl function do not significantly impede the allylation reaction. Heteroaromatic aldehydes also proved to be compatible substrates. Reactions of pyridine and thiophene based aldehydes with allylchloride, 4-bromo-1,1,1-trifluorobutane (performed by Danylo Merzhyievskiy), and ethyl bromide delivered alcohols of **61**, **62**, and **63** in 62–92% yields. The successful formation of **61** is particularly noteworthy, as 2-pyridinecarboxaldehyde has previously been reported as unreactive in mechanochemical Barbier reactions using zinc.^[117]

Coming to the scope of ketones (Scheme 26, d), non-enolizable ketones such as 2,2,2-trifluoroacetophenone and benzophenone reacted effectively with allyl chloride under mechanochemical conditions, without requiring solid NH₄Cl as an additive. The corresponding alcohols **64** and **65** were obtained in high yields of 87% and 98%, respectively. When solid NH₄Cl (1 equiv.) was included, the yields remained high (75% and 95%), indicating good tolerance toward this Brønsted acid. Notably, the unprotected-NH₂ group was also well-tolerated, as shown by the successful synthesis of amino alcohol **66**. The reactions of α,β -unsaturated ketones such as benzylideneacetone **67** and chalcone **68** occurred exclusively as 1,2-addition, yielding the corresponding alcohols **69** and **70** without detectable 1,4-addition products. Diastereoselectivity was evaluated in the synthesis of alcohol **71**, which was obtained in 75% yield as a 1:1 mixture of diastereomers, similar to the analogous allylation reactions using allyl magnesium chloride under conventional conditions in solution.^[196]

In addition, Tatsiana Nikonovich demonstrated that the optimised conditions are suitable for the synthesis of tertiary alcohols from various esters and ketones from amides. Danylo Merzhyievskiy showed that the reactions are suitable for C–B, C–N and C–Si bond formation with the corresponding electrophiles (Scheme 26, e).



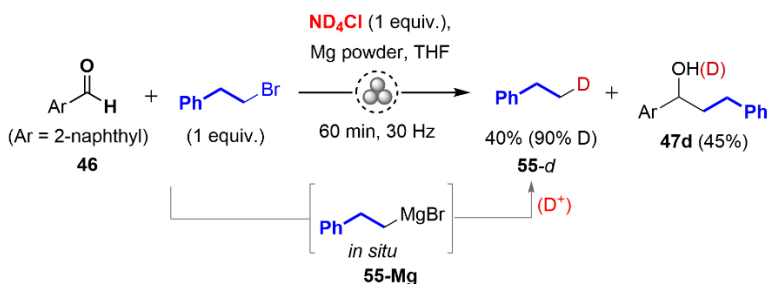
Scheme 27. Gram-scale preparations and a comparison of mechanochemical Grignard and Barbier protocols.

A gram-scale synthesis of alcohol **47d** (Scheme 27) was performed to compare the performance of the developed Barbier method (one-step) with the mechanochemical Grignard (two-step) approach, both performed under air. The Barbier method significantly outperformed the Grignard reaction, produced **47d** in 75% yield compared to 49% with the Grignard approach, using stoichiometric amounts of 2-naphthaldehyde **46** and 2-phenylethyl bromide. The lower yield in the Grignard method (two-step procedure) was attributed to the partial oxidation of the organomagnesium intermediate (**55-Mg**) by atmospheric oxygen, leading to the formation of alcohol **79** in 12% yield. In contrast, the Barbier reaction exhibited stronger resistance to the oxidative degradation. In addition, we also successfully scaled up the allylation of 2-acetylnaphthalene **51** using solid NH_4Cl as an additive, isolating alcohol **52a** in 96% yield after direct treatment with ethyl acetate, filtration and solvent evaporation. While no major safety issues were encountered when using Mg powder, the use of less reactive Mg beads is recommended for scale-up, offering a safer alternative. Keeping in mind that larger Mg surface area is key to achieving optimal yields, we repeated the gram-scale synthesis of **52a** using a 10-fold excess of Mg beads, which delivered the product in a still high yield of 86%. Additionally, excess Mg beads were collected and approximately 8.7 equivalents were recovered out of the 10 equivalents used.

3.1.6 Mechanistic experiments and the role of mechanical energy

In general, the mechanistic processes behind the seemingly straightforward Barbier reaction and the related formation of Grignard reagents are in fact intricate and not fully understood.^[73] Many aspects of these transformations remain debated because of controversial experimental results. It is currently adopted that the alcohol product could form either by the reaction of a carbonyl compound with a transient Grignard reagent or alternative radical-mediated pathway.

Firstly, a deuteration experiment was conducted using 2-naphthaldehyde **46** and 2-phenylethyl bromide in the presence of ND₄Cl to trap the *in situ* generated transient Grignard intermediate. After the reaction, the crude mixture was directly analyzed by ¹H NMR in CDCl₃, showing the formation of (ethyl-2-*d*)benzene **55-d** in 40% yield, along with 45% of product **47d** (Scheme 28). Deuterium incorporation was determined to be 90%, as evidenced by ¹H and ¹³C NMR data (more details can be found in section 4.1 in the Supporting Information of Publication I). In the ¹H NMR spectrum, the integral intensity of the methyl proton signal at δ 1.22 ppm was reduced (2H vs 3H in the non-deuterated material). Additionally, a characteristic triplet was observed in the ¹³C NMR spectrum at δ 15.4 ppm ($J_{CD} = 19.4$ Hz). This result clearly indicating both the generation and deuteration of a transient Grignard intermediate **55-Mg**.

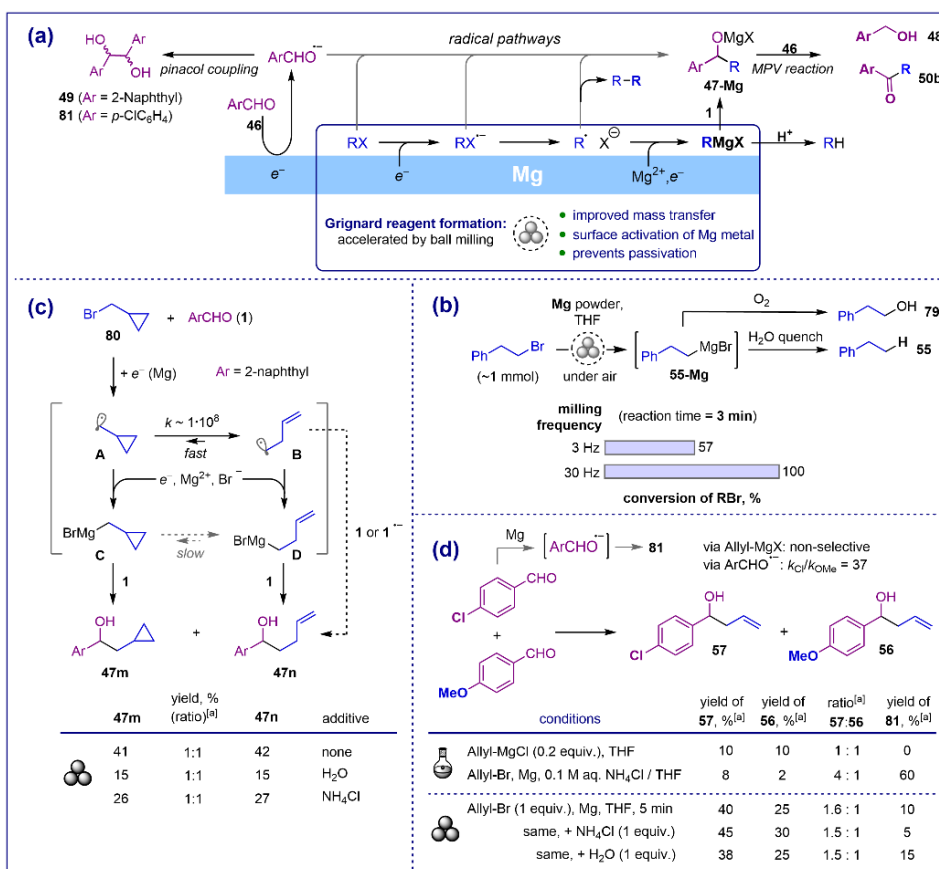


Scheme 28. Trapping of organomagnesium intermediate **55-Mg** in a deuterium quenching experiment.

Secondly as we know, the addition of Grignard reagents to the carbonyl group of **46** forms magnesium alkoxide products **47-Mg** (Scheme 29, a). However, side products such as pinacols **49** and MPV-type reduction products **48** and **50b** may arise from competing reactions of naphthaldehyde **46**, particularly if the consumption of **46** during its reaction with the Grignard reagent is relatively slow. Since the Grignard additions to carbonyl compounds are typically very fast,^[196,197] we concluded that the Grignard reagent formation (GRF) is the rate-limiting step in the entire process. To suppress undesired side-reactions, it is important to accelerate the Grignard reagent formation (GRF) under mechanochemical conditions, thereby ensuring fast consumption of aldehyde **46**. This conclusion aligns with previous kinetic studies in solution, which have demonstrated that GRF rates are strongly influenced by the area and physical properties of magnesium surface, the viscosity of the medium, and the stirring rate.^[90,91] The latter two factors are particularly important because the reaction of organic bromides with magnesium often occurs at transport-controlled rate,^[90,91] where the delivery of the organic halide to the magnesium surface is the rate-limiting step.

Therefore, the rapid agitation of ball mill, which significantly enhances mass transfer,^[198] and is expected to accelerate rate of Grignard reagent formation (GRF), improves yields at higher milling frequencies. However, these are only hypotheses and more mechanistic studies, preferably with real time *in situ* monitoring, are required.

As a supporting evidence, we observed a clear acceleration in the rate of Grignard reagent **55-Mg** formation at higher milling frequency (30 Hz) compared to lower milling frequency (3 Hz) (Scheme 29, b). At 30 Hz, the starting phenylethyl bromide was fully consumed within just 3 minutes, whereas the reaction proceeded noticeably slower at 3 Hz. The second key factor might be the mechanical activation of the magnesium surface during milling.^[79,189] This process continuously exposes fresh reactive metallic sites and prevents the surface passivation, allowing the reaction to initiate even in the presence of H₂O. Additionally, this factor not only increase the rate of GRF but also minimizes the induction delay.



Scheme 29. (a) Mechanistic interpretation and supporting experiments; (b) dependence of rate on milling frequency for generation of Grignard reagent **55-Mg**; (c) radical clock experiment; (d) competitive allylation of *p*-OMe and *p*-Cl benzaldehydes. [a] Determined by ¹H NMR. *Reactions were performed by Tatsiana Nikonovich. **Reactions were performed together with Danylo Merzhyevskyy.

Although the formation of organomagnesium intermediates was evident (Scheme 28), the involvement of alternative radical-mediated pathways en route to **47-Mg** (Scheme 29, a) could not be entirely ruled out.^[199] Such radical mechanisms are known to be formed in related mechanochemical Minisci-type reactions^[130,131] and are predominant in aqueous Barbier reactions with magnesium.^[192,195,200] Therefore, additional mechanistic experiments have been performed with the aim of detecting the contribution of the radical mechanisms.

Firstly, Tatsiana Nikonovich conducted the radical clock experiment by using cyclopropylmethyl bromide **80** as a radical clock probe (Scheme 29, c), yielding a near 1:1 mixture of alcohols **47m** and **47n**, regardless of protic additives. These results indicate the rapid formation^[189] of Grignard reagent **C** from the cyclopropylmethyl radical **A**, occurring at the same high rate as its fast intramolecular rearrangement into **B** ($k \sim 10^8 \text{ s}^{-1}$)^[201] suggesting a fast organometallic pathway. The lower yields with protic sources were attributed to competitive protonation of organometallic intermediates. Radical mechanism would have favoured dominant formation of **47n**, which was not observed.

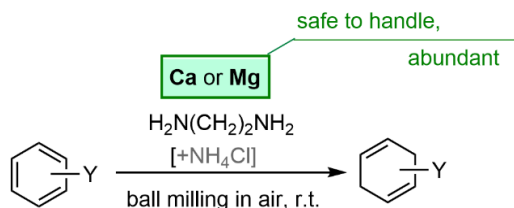
Secondly, based on these findings, we anticipated that substrates that generate more stable and long-lived radical or radical anion species, such as electron-deficient aromatic aldehydes and allyl halides, may be more prone to react via the radical mechanism. To test this hypothesis, a series of experiments have been performed together with Danylo Merzhyievskiy. The competitive allylation reactions of *p*-methoxy and *p*-chlorobenzaldehyde (Scheme 29, d) were selected based on the distinct electronic properties of these substrates and differ in their tendency to form radical anions.^[200] Under mechanochemical conditions, the allylation to *p*-Cl-substituted alcohol **57** was slightly favoured (ratio **57:56** = 1.5:1), with minor formation of pinacol by-products, implying insignificant generation of the corresponding anion-radical from *p*-chlorobenzaldehyde. For comparison, the Barbier reaction in aqueous THF produced *p*-Cl-substituted alcohol **57** as the kinetic product (ratio **57:56** = 4:1) but in low yield (~8%), whereas pinacols **81** were dominant (60% yield). This reaction was shown to proceed via anion-radical species.^[200] Expectedly, addition of allylmagnesium chloride in THF solution was non-selective (ratio **57:56** = 1:1), no pinacol products was observed.

These obtained results suggest that the radical pathway contributes to a minor extent under mechanochemical conditions, mostly with electron-deficient carbonyl substrates. Nevertheless, these results do not rule out the possibility of a major contribution of the radical mechanism for other substrates that are more prone to producing stabilized radical species upon single electron reduction.

3.2 Mechanochemical Birch Reduction with Low Reactive Alkaline Earth Metals (Publication II)

This work was inspired by advances in mechanochemical organometallic synthesis with Group II metals. In particular, following the development of the mechanochemical Barbier-Grignard reaction (Section 3.1), in which single-electron transfer (SET) from magnesium metal to an organic halide initiates Grignard reagent formation, we hypothesized that ball milling could similarly facilitate SET from Group II metals to other organic compounds, especially aromatic systems, thus enabling Birch reduction with these low-reactive metals. Additional inspiration came from the work of Ito, Kubota, and co-workers,^[107] who demonstrated the facile generation of organocalcium reagents from mechanochemically activated calcium metal. We aimed to take advantage of

mechanochemistry to enhance the reductive properties of calcium and magnesium, thereby addressing the known limitations of this chemistry in solution. Moreover, calcium and especially magnesium appeared to be safer alternatives to hazardous alkali metals, and more sustainable alternatives to scarce lithium. At the time this work was initiated, no mechanochemical analogues of Birch reduction had yet been reported in the literature.



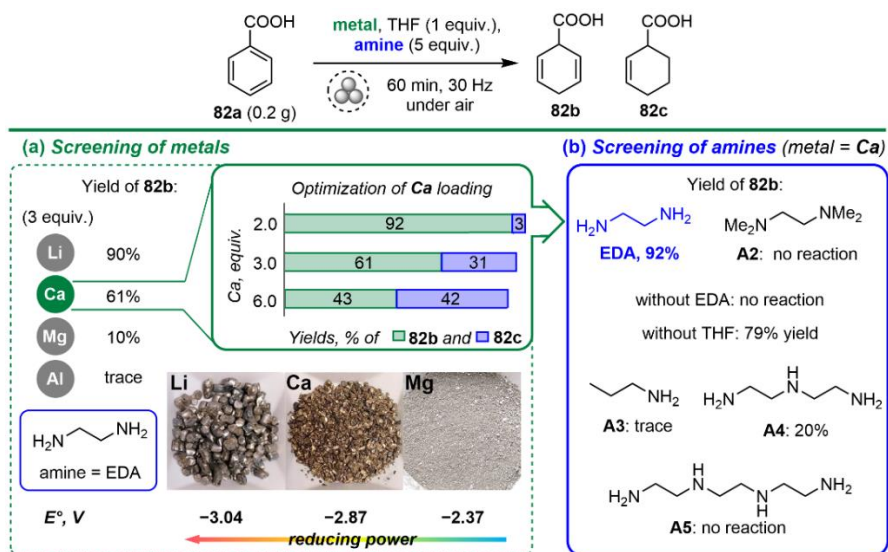
Scheme 30: Mechanochemical Birch reduction with Group II metals.

3.2.1 Optimization studies with calcium

The experiments were performed using a Form-Tech Scientific FTS-1000 shaker mill, operating at 30 Hz maximal milling frequency in 15 mL ZrO₂ jars containing a single 10-mm ZrO₂ milling ball. The study began with the screening of metals (3 equiv.) for the Birch reduction of benzoic acid **82a**, employing ethylenediamine (EDA, 5 equiv.) as a substitute for liquid ammonia and tetrahydrofuran (THF, 1 equiv.) as an additive (Scheme 31, a). These conditions were adapted from a previously reported solution-based protocol with lithium metal, developed by Koide and co-workers.^[165] As we opted to develop an operationally simple and safer protocol than conventional Birch reduction, we excluded highly hazardous K and Na, focusing only on metals that are safer to handle: Li (from Group I), Ca and Mg (Group II), and Al (Group III). In these preliminary experiments, granular lithium (4–10 mesh) produced the Birch reduction product **82b** in 90% yield after 60 minutes of milling at 30 Hz under ambient conditions. To our delight, granular calcium (~9 mesh) also demonstrated strong reducing ability, affording **82b** in 61% yield along with 31% of the over-reduced alkene product **82c**. In contrast, magnesium powder (< 75 μm) gave very low 10% yield of **82b**, and aluminium showed negligible reactivity. These results identified calcium as a feasible alternative to lithium metal, though it exhibited a tendency for over-reduction. We attributed this to excessive metal loading, as the formation of **82b** (in its calcium salt form) demands only 1.5 equivalents of calcium, based on a 2 e⁻ transfer to the arene and a 1 e⁻ transfer to the carboxylic proton. Supporting this, increased calcium loading (6 equiv.) enhanced the yield of **82c** to 42%. Conversely, reducing the loading close to stoichiometric levels (2 equiv.) resulted in a high 92% yield of **82b**, comparable to the lithium-mediated reaction. These results highlight calcium's potential as a reductant in Birch reductions, provided its reactivity is carefully controlled through precise stoichiometry adjustment.

Encouraged by these results, we turned our attention to understand the role of the amine, a key component in Birch chemistry. In liquid ammonia or low-molecular weight amines, alkali metals generate blue solutions containing solvated electrons, electrides, and alkalides all act as powerful reducing agents. Screening of amines (Scheme 31, b) revealed that a primary bidentate diamine such as ethylenediamine (EDA) is essential for achieving high yields of **82b**. The reaction was failed to proceed in the absence of EDA or when it was replaced with its tetramethylated analogue, TMEDA (**A2**), highlighting the importance of primary amine groups. Other amines, including mono-, tri-, and tetra-

amines (**A3–A5**), produced poor results, despite previous success in solution-based Birch reductions using lithium in THF.^[165] These results highlight the significance of EDA under mechanochemical conditions, acting both as an optimal ligand for Ca²⁺ to facilitate electron transfer and as a proton donor. However, the reason for this optimal performance remains unclear and warrants further investigation. Furthermore, we observed that the addition of THF (1 equiv.) enhanced yields in the calcium-mediated reduction. When THF was omitted, the yield of **82b** dropped slightly to 79%.

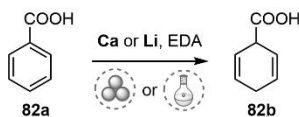


Scheme 31. Mechanochemical Birch Reduction of benzoic acid: screening of metals and amines in the reaction with Ca metal. Yields were determined by ¹H NMR with an internal standard after the hydrolytic workup (aq. HCl). More details can be found in Supporting Information of publication II.

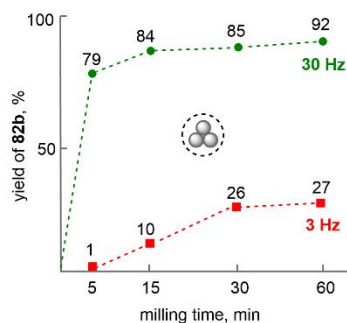
3.2.2 Reaction kinetics and comparison with the solvent-based method

Ex situ monitoring of the reaction kinetics (Scheme 32, a) showed that the high 92% yield of **82b** was achieved within one hour at a milling frequency of 30 Hz, while approximately 80% conversion happened within the first 5 minutes. Lowering the milling frequency to 3 Hz significantly diminished both the yield of **82b** and the reaction rate, highlighting the significant role of mechanical activation in amplifying the reaction. This effect was attributed to the continuous exposure of active metal surface through frequent ball collisions, which prevent surface passivation and improves mass transfer in the organic phase.^[198]

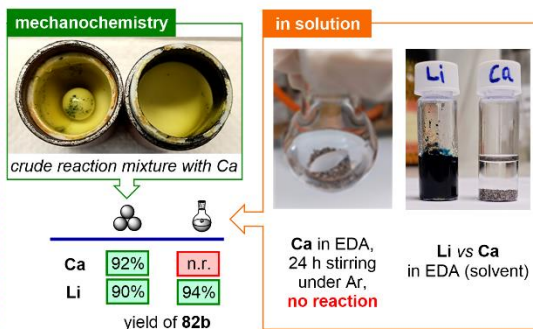
The importance of ball milling was further underscored by comparing solution-state and mechanochemical conditions (Scheme 32, b). Unlike in the mixer mill, calcium failed to produce any Birch reduction product after over 20 hours of stirring in EDA under argon at room temperature. In contrast, lithium in EDA solution produced **82b** in a high 94% yield, rapidly forming a deep blue solution indicating the generation of solvated electrons and/or metal electrides. In comparison, Calcium remained undissolved with no visible colour change even after two days. In the mechanochemical experiments, however, we observed the blue patches in the reaction mixture immediately after opening the jars, which quickly turned yellow colour upon air exposure. This observation suggests that the ball impacts greatly expedite the generation of solvated electrons and/or metal electrides from calcium metal.



(a) Kinetics and effect of milling frequency



(b) Comparison with Birch reduction in solution



Scheme 32. (a) Effect of the milling frequency on the reaction rate with calcium. (b) Comparison with Birch reduction in solution (n.r. = no reaction).

3.2.3 The role of protic source and reduction of electron-rich arenes

In a subsequent study, the developed optimized conditions were applied to the Birch reduction of a representative electron-rich aromatic substrate, *n*-butoxybenzene as a model substrate **83a** (Table 4, entry 1). Under these conditions, the result was unsatisfactory, yielding the mixture of isomeric dienes **83b** (7%) and **83c** (37%), as well as the enol ether **83d** (24%). In the classical Birch reductions, stepwise protonation sequences are essential alongside single-electron transfers (see Scheme 1.3.1 in the literature overview). For electron-deficient arenes (e.g., **82a**), protonation typically occurs after the addition of two electrons, with the resulting carbanion sufficiently basic to abstract a proton from the medium (e.g., liquid ammonia or amines).^[153] In contrast, electron-rich arenes (e.g., **83a**) protic additive (like alcohol) is essential, because the second electron is not transferred until after the weakly basic radical anion is protonated.^[202]

Interestingly, the reduction of **83a** under mechanochemical conditions proceeded even without an alcohol, indicating that EDA was able to act as a proton source (entry 1). However, due to suboptimal selectivity and moderate yields, we explored the addition of traditional *tert*-butanol as a protic additive, in search of improved outcomes. While this increased the overall conversion of **83a**, product yields and selectivity saw only minor improvement (entry 2). The conjugated diene **83c**, which is thermodynamically more stable isomer, became the predominant product (49% yield), likely due to base-catalysed isomerization of **83b**.

To suppress this rearrangement, we sought to select a more suitable protic source. The unique advantage of mechanochemistry is the compatibility with solid inorganic additives. Reflecting from our previous success using solid ammonium chloride to enhance yields in the Mg-mediated Barbier reaction of ketones,^[203] we tested solid NH₄Cl (entry 3). Interestingly, the formation of 1,3-diene isomer **83c** was completely suppressed, and the yield of the desired diene **83b** increased significantly to 82%, with only minor formation of the over-reduced product **83d** (7%). Notably, a similar improvement of result was observed in the lithium-mediated reduction, where NH₄Cl led to a 74% yield of **83b**. Historically, solid NH₄Cl has been used in classical Birch reductions

of biaryls in liquid ammonia to prevent isomerization and complex product mixtures, but as a quenching agent rather than a proton source.^[204,205] Beyond improved chemoselectivity, solid NH₄Cl offers practical advantages as a non-flammable, inexpensive and easy-to-handle solid, well-suited for mechanochemical applications. It also acts as a grinding additive, maintaining the mixture in a powder state throughout milling.

Table 4. Ca-Mediated mechanochemical Birch reduction of *n*-butoxybenzene (**83a**) and influence of the protic source.

entry	protic source (3 equiv.) ^[a]	yield (%)			
		83a	83b	83c	83d
1	no protic source	28	7	37	24
2	<i>tert</i> -butanol	2	22	49	15
3	solid NH ₄ Cl ^[a]	8	82 ^[b]	0	7
4	<i>n</i> -PrNH ₂ ^[c]	38	0	0	37
5	<i>n</i> -PrNH ₂	0	0	0	54 ^[d]

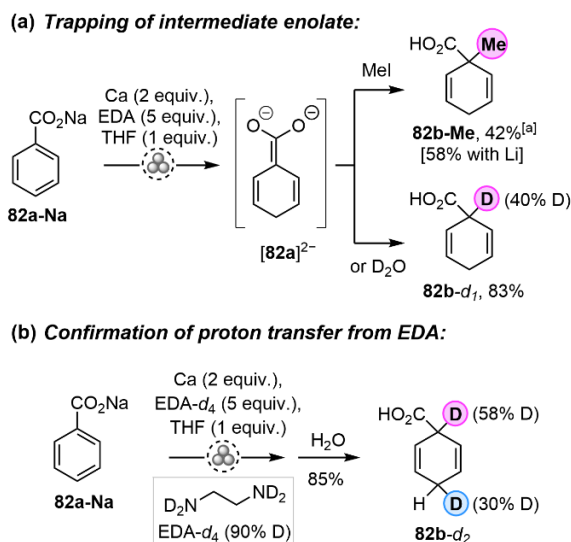
[a] No reaction occurred with ammonium salts such as MeNH₃Cl and EDA•2HCl. [b] Produced in 74% yield with Li metal (3 equiv.). [c] Isopropylamine showed the same outcome. [d] With 4 equiv. of Ca. No reaction occurred without EDA (performed by Danylo Merzhyevskiy). Yields were determined by ¹H NMR with an internal standard after the hydrolytic workup (aq. NH₄Cl).

The reactions involving electron rich arenes were mainly performed by using crystalline NH₄Cl, and we observed the evolution of ammonia gas upon contact with ethylenediamine (EDA). Thus, using NH₄Cl pellets which has lower surface area instead of crystalline form is much more convenient during loading reagents for upscale operations. In addition, other tested additives like KH₂PO₄, glycine, NH₃ were suboptimal and EDA•2HCl, MeNH₃Cl were ineffective. But, in the case of using *n*-propyl amine and isopropylamine, we managed to optimize the conditions yielding exclusively **83d** in 54% (performed by Dr. Danylo Merzhyevskiy).

These results suggest that as like in the case of Barbier-Grignard reaction,^[203] the performance of the protic source is influenced not only by Brønsted acidity, but also likely by kinetic factors and their aggregate state.

3.2.4 Deuterium labelling experiments

To investigate the origin of the C-1 (ipso) and C-4 (para) hydrogens in the reduction of benzoic acid, a series of mechanistic experiments, including deuterium labelling studies, have been performed (Scheme 33). According to the classic mechanism,^[153] the formation of an enolate dianion intermediate **[82a]**²⁻ leads to proton incorporation specifically at the C-1 and C-4 positions (Scheme 33, a). The addition of methyl iodide to the reaction mixture prior to the hydrolysis led to the formation of the ipso-methylated product **82b-Me** in 42% yield (Scheme 33, a). This yield was notably lower than that occurred in the analogous Lithium-mediated reaction, which afforded **82b-Me** in 58% yield. The difference between the Li- and Ca-mediated reactions is likely caused by either reduced reactivity of the calcium enolate or, more likely, a greater extent of proton transfer from EDA. In support, quenching with deuterium oxide resulted in 40% deuterium incorporation at the C-1 position, with no deuterium incorporation at C-4 position. Furthermore, when deuterium-labelled EDA (90% D) was used, the product **82b** delivers 58% and 30% deuterium incorporation at C-1 and C-4, respectively (Scheme 33, b). These deuterium incorporation levels were lower than 90% D in EDA. Based on previous studies, we believe that it might be caused by the kinetic isotope effect, which can be substantial in the Birch reaction (e.g. $k_H/k_D = 9.9$ for the reduction of benzene).^[206] The obtained results suggests that in the Ca-mediated reaction EDA donates protons more readily than in the Li-mediated process. A similar observation was noted previously in liquid ammonia and was attributed to the increased acidity of ammonia coordinated to calcium cations, as well as to the low solubility of calcium amide.^[207]

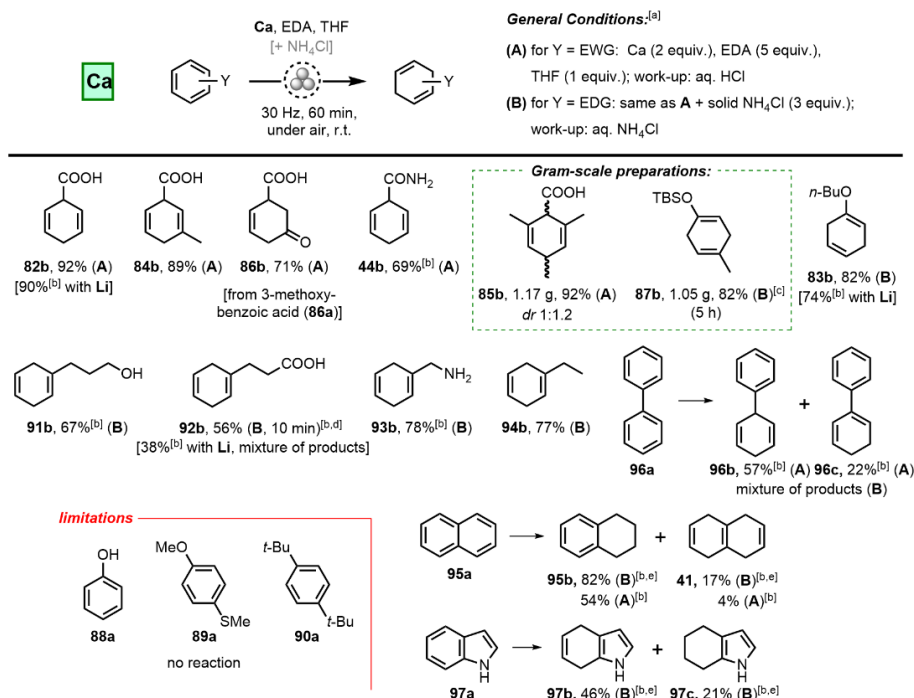


Scheme 33. (a) Trapping of intermediate enolate **[82a]**²⁻ in the Birch reduction of **82a** and its sodium salt. (b) Confirmation of proton transfer from EDA. Yields were determined by ¹H NMR with an internal standard. [a] The reaction was performed starting from benzoic acid **82a** instead of sodium benzoate **82a-Na**.

3.2.5 Substrate scope and limitations

With the optimised conditions in hand, we established two general protocols A and B (Scheme 34), tailored for the Ca-mediated Birch reduction of electron-poor and electron-rich arenes, respectively and tested the range of compatible substrates. Initially,

Benzoic acid consistently afforded **82b** in 92% yield, and this result extended to *m*-toluic acid, which provided 3-methyl-substituted cyclohexadiene **84b** in 89% yield. Similarly, mesitoic acid gave the 2,4,6-trimethyl derivative **85b** as an approximately equimolar mixture of *cis* and *trans* isomers in 92% combined yield. Notably, **4b** was prepared on a gram scale, demonstrating the scalability of the method. 3-Methoxybenzoic acid delivers **86b** in a slightly reduced 71% yield, mainly due to incomplete conversion. Beyond carboxylic acids, benzamide was successfully reduced to cyclohexadiene **44b** with a 69% yield.



Scheme 34. Mechanochemical Birch reduction of arenes with Ca. [a] The reactions were performed at a 1–2.6 mmol scale. Any deviations from the general conditions are specified in the Scheme and footnotes below. Unless stated otherwise, yields of isolated products are given, corrected for ¹H NMR purity. The products are prone to slow oxidation with air, recovering the starting arene. [b] Yields were determined by ¹H NMR with an internal standard after the hydrolytic workup (aq. HCl for conditions A and aq. NH₄Cl for conditions B). [c] Ca (4 equiv.), EDA (6 equiv.), NH₄Cl (3 equiv.), THF (2 equiv.). Same reaction at 200 mg scale produced **87b** in 89% yield after 3 h. [d] The yield of **92b** did not increase with additional milling time, the rest was mostly unconverted starting material. Only 1 equiv. of NH₄Cl was used. [e] With 3 equiv. of Ca and 1.5 h of milling.

Next, we turned our attention to electron-rich arenes, including phenols, their derivatives, alkylbenzenes, polycyclic aromatics, and heterocycles. Among phenol derivatives, TBS-protected *p*-cresol **87a** delivers clean reduction to **87b** in 82% yield on gram scale, aligning with previous reports using electrochemical^[208] and Li-mediated Birch methods.^[97,165] However, the reaction proceeded more slowly, requiring 3–5 hours compared to the typical 1 hour duration for other substrates. Unprotected phenol **88a** was unreactive, consistent with previous reports attributing this to the high energy barrier for electron addition to the phenolate anion.^[209] Similarly, 4-methoxyphenyl methyl sulfide **89a** and 1,4-di-*tert*-butylbenzene **90a** were unsuccessful, likely due to

their low electron affinities, as previously observed in the potassium electride-based mechanochemical reduction.^[166] Alkyl substituted benzenes **91–94a**, featuring terminal hydroxyl, amino, or carboxylic acid groups, reacted smoothly and affords 1,4-cyclohexadienes **91–94b** in 56–78% yields. Nonetheless, incomplete conversion was observed for **91b** and **92b**, while over-reduction byproducts appeared in the case of benzyl amine **93b**. Next, the reduction of polycyclic aromatic hydrocarbons, such as naphthalene **95a** and biphenyl **96a**, were tested. Similarly to benzoic acid derivatives, these substrates can produce dicarbanion intermediates, therefore both conditions A and B were tried and compared. The reduction of naphthalene under conditions B produced hydrocarbon **95b** in 82% yield and its isomer **41** in 17% yield after 90 min milling, while the condition A delivers poor yields of the same products due to lower conversion of the starting material. On the contrary, biphenyl **96a** affords a mixture of 1,4-dihydrobiphenyl **96b** and 3,4-dihydrobiphenyl **96c** in 57% and 22% yields, respectively, under conditions A. while the conditions B were unsuccessful and afforded complex mixture of products at incomplete conversion approx. 50% of **96a**. Finally, reduction of the heterocyclic substrate indole **97a** under conditions B produced two major products **97b** and **97c** obtained in 46% and 21% yields, respectively.

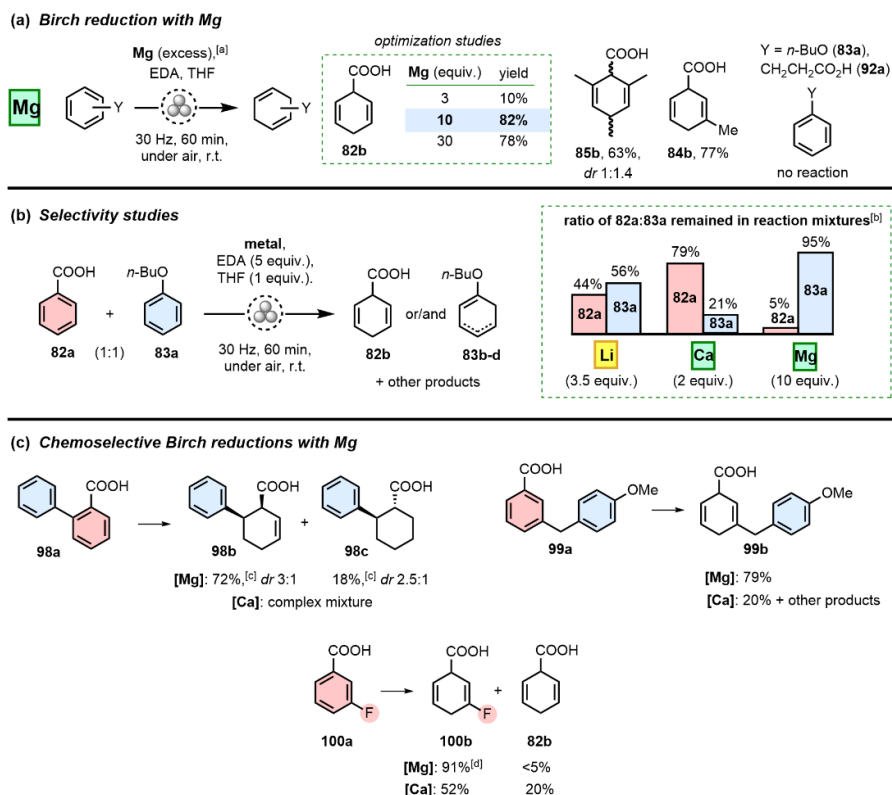
The diverse substrate scope explored in this study showing close similarity of the results to that of classic alkali metal reductants,^[97,165] underscoring mechanochemically activated calcium as a practical and effective alternative. In several cases, including the formation of **82b** and **83b**, comparable yields were achieved with both calcium and lithium. Notably, the reduction of 3-phenylpropionic acid to diene **92b** proceeded with a slightly higher yield 56% and full conversion using calcium metal, compared to a 38% yield and a mixture of reduction products observed with lithium (for more details, see Section 6.15 in the Supporting Information of publication II). Shortly after this work was published, the group of Ito and Kubota reported similar findings with calcium metal.^[210]

3.2.6 The Birch reduction with magnesium

During the initial metals screening (Scheme 31), magnesium showed promise and delivered approximately 10% yield of **82b** from the reduction of benzoic acid using 3 equiv. of the metal. Considering magnesium's practical advantages, such as its relative stability toward air and moisture and our previous findings that its reactivity under mechanochemical conditions improves with the larger surface area provided by excess of the metal,^[203] we explored the use of excessive loadings. When benzoic acid **82a** was treated with a large excess of magnesium powder (10 and 30 equiv., Scheme 35, a), the yield of diene **82b** significantly improved, and delivers up to 82%. Similarly, 2,4,6-trimethyl- and 3-methylbenzoic acids gave the corresponding Birch products **85b** and **84b** in 63% (1:1.4 dr) and 77% yields, respectively. In contrast, electron-rich arenes such as **83a** and **92a** remained unreactive, indicating that the scope of the Mg-mediated reduction is restricted to electron-deficient arenes.

Considering magnesium's lower reactivity compared to calcium, we explored its potential for achieving chemoselective Birch reductive transformations often complicated by over-reduction when using more reactive metals like calcium. To assess this, we first conducted competitive reduction experiments with an equimolar mixture of electron-deficient arene (benzoic acid, **82a**) and electron-rich arene (*n*-butylphenyl ether, **83a**) (Scheme 35, b). Magnesium selectively reduced only **82a**, leaving **83a** completely unreacted. In contrast, both substrates were reduced with calcium or lithium.

Further evidence of the highly chemoselective reductive properties of magnesium was obtained in intramolecular experiments, using bifunctional substrates **98a** and **99a**, which contain both electron-poor and electron-rich arene moieties (Scheme 35, c). In the case of 2-phenylbenzoic acid **98a**, magnesium selectively reduced the benzoic acid ring to afford cyclohexene derivative **98b** as the major product in 72% yield, *cis:trans* = 3:1, with minor formation of the fully reduced compound **98c** in 18% yield, *cis:trans* = 1:2.5. In contrast, the reduction with calcium led to a complex mixture, likely due to accompanying reduction of the phenyl substituent. Similarly, diarylmethane **99a** delivers selective reduction with Mg to give **99b** in 79% yield, while Ca delivers only 20% of **99b**, and mixture of other unidentified byproducts. Remarkably, Mg also demonstrated excellent functional group tolerance. For example, 3-fluorobenzoic acid **100a** was smoothly reduced to the fluorinated diene **100b** in 91% yield, with no significant dehalogenation observed. In contrast, the same substrate results in partial defluorination with calcium metal, forming diene **82b** as a side product. These findings open the door to achieve chemoselective Birch reductions, which are uncommon.



Scheme 35. Mechanochemical Birch reduction of arenes with Mg and its limitations (a), selectivity studies (b) and chemoselective Birch reductions (c). Unless stated otherwise, yields were determined by ¹H NMR with an internal standard after the hydrolytic workup (aq. HCl or aq. NH₄Cl). [a] Optimal conditions: Mg powder (10 equiv.), EDA (5 equiv.), THF (1 equiv.). [b] Determined by HPLC analysis of the crude reaction mixtures (HPLC analysis was performed by Tatsiana Jarg). ¹H NMR with an internal standard showed a similar outcome. [c] With 30 equiv. of Mg and 1.5 h of milling. Relative configuration is depicted for the major diastereomer (*cis*-**98b** and *trans*-**98c**). [d] The product **100b** was isolated by column chromatography on silica gel in 78% yield. *Compound **99a** was synthesized by Danylo Merzhyevskiy.

3.2.7 Other dissolved metal-type reductive transformations

Next, we explored the applicability of Ca- and Mg-based protocols in a range of other reductive transformations beyond the classic Birch reductions^[170] (eqs. a–m, Scheme 36). This investigation not only demonstrates the versatility of the developed methods but also gives important insights into the functional group tolerance of the protocols, particularly regarding functional groups that are typically sensitive to reductive conditions.

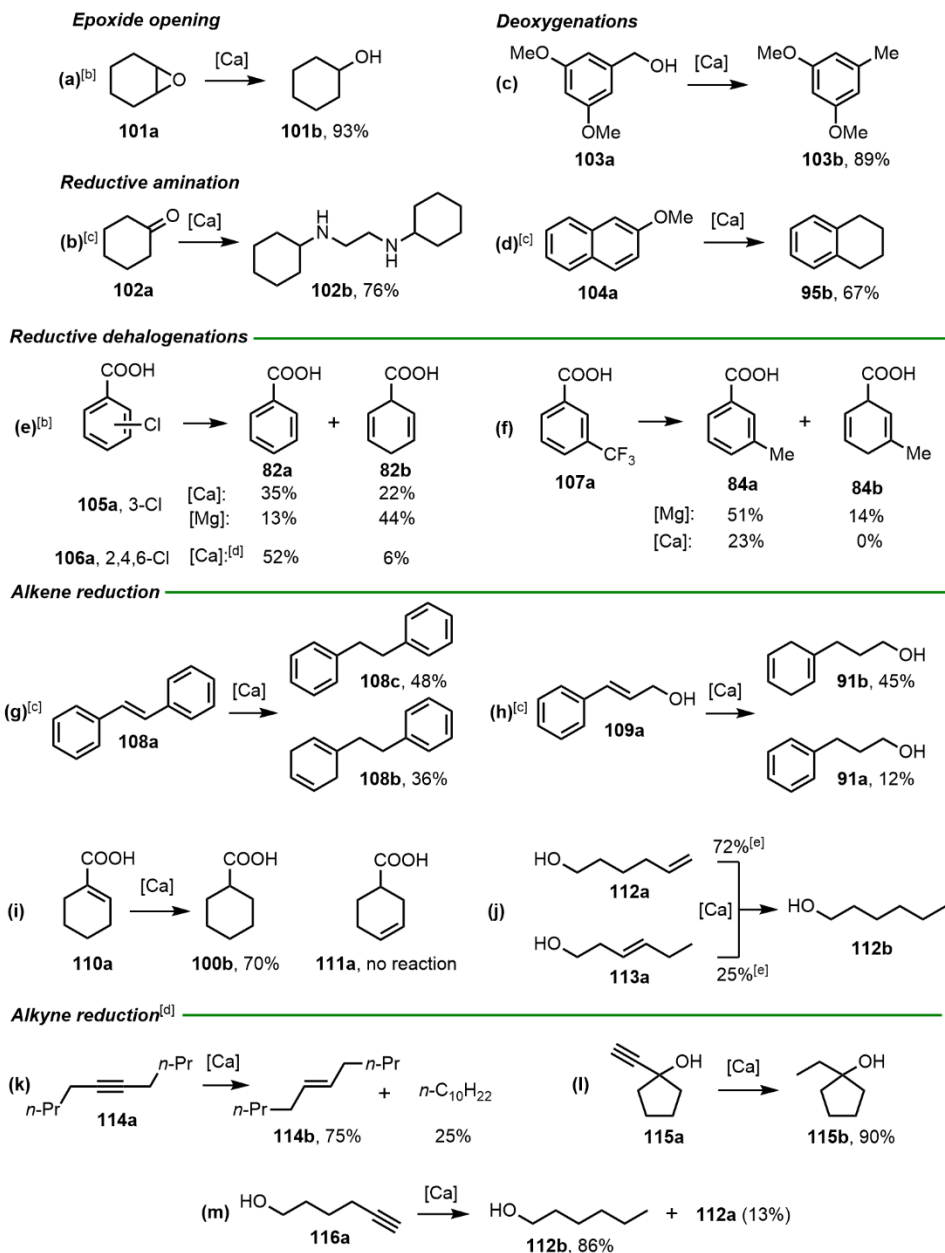
Reductive cleavage of epoxides and ethers using calcium has previously been demonstrated in solvents such as liquid ammonia or EDA.^[211] Under the mechanochemical conditions with calcium metal, both the reductive ring-opening of cyclohexene oxide **101a** (eq. a)^[211] and the reductive amination of cyclohexanone **102a** (eq. b) proceeded efficiently and delivers 93% and 76% yields respectively. Benzylic deoxygenation of alcohol **103a** (eq. c) occurred in high yield 89%, with no reduction of the electron-rich arene ring, indicating that benzylic deoxygenation is particularly favourable under these conditions. Similarly, the Ca-mediated Birch reduction of 2-methoxynaphthalene **104a** was dominated by reductive deoxygenation, resulting hydrocarbon **95b** as the major product in 67% yield (eq. d).

Reductive dehalogenations of 3-chlorobenzoic acid **105a** and 2,4,6-trichlorobenzoic acids **106a** proceeded smoothly with 3 equiv. of Ca metal, yielding benzoic acid **82a** in 35–52% yields along with up to 22% of the Birch product **82b** (eq. e), demonstrating that dechlorination precedes arene reduction. When **106a** was treated with excess Mg (10 equiv.), the reaction favoured Birch reduction, delivering **82b** as the major product in 44% yield. These results align with prior findings by Rowland^[123,124] and Birke on the mechanochemical degradation of chlorinated compounds.

Similarly, Mg-mediated dehalogenation of 3-(trifluoromethyl) benzoic acid **107a** delivers a mixture of **84a** and **84b** in 51% and 14% respectively (eq. f). Calcium shows similar reactivity, but under standard conditions with only 2 equiv. of calcium metal, the reaction produced **84a** in 23% with incomplete conversion. These findings demonstrated that, apart from fluorine substituent which tolerated in the Birch reduction of **100a** with Mg metal (see Scheme 35, c), other halogenated substituents are generally incompatible and readily undergo dehalogenation. This reactivity profile suggests potential applications of Mg and Ca metals in the remediation of halogenated environmental pollutants.^[123]

General conditions:^[a][Ca]: Ca (2 equiv.), EDA (5 equiv.), NH₄Cl (3 equiv.), THF (1 equiv.), ball milling in air at 30 Hz, 60–90 min, r.t.

[Mg]: Mg (10 equiv.), EDA (5 equiv.), THF (1 equiv.), ball milling in air at 30 Hz, 60 min, r.t.



Scheme 36. Other dissolved metal-type reductive transformations with Ca and Mg. [a] The reactions were performed at 1–1.5 mmol scale with 200 mg of the starting material. Any deviation from the general conditions are specified in the Scheme and footnotes below. Yields were determined by ¹H NMR with an internal standard after the hydrolytic workup (aq. HCl). [b] Without NH₄Cl additive. [c] With 3 equiv. of Ca. [d] Ca (4 equiv.), EDA (6–7 equiv.). [e] Indicates conversion of the starting material into the product.

Since calcium metal has been known to reduce olefins^[212] and alkynes^[213] in liquid ammonia and amines, we investigated the tolerance of unsaturated bonds under our developed mechanochemical conditions and assessed their preparative utility. Alkenes featuring a double bond conjugated to an aromatic ring such as stilbene **108a** and cinnamic alcohol **109a**, result in complete reduction of the olefin along with partial reduction of the arene ring, yielding mixtures of two main products (eqs. g and h). Similarly, the conjugated double bond in 1-cyclohexene-1-carboxylic acid **110a** was fully reduced, delivering cyclohexanecarboxylic acid **110b** as the major product in 70% yield (eq. i), alongside minor by-products such as the corresponding aldehyde and alcohol, accompanying from the partial reduction of the carboxylic group (more details can be found in Supporting Information in section 9.5.3 of publication II). In contrast, isolated endocyclic olefins were inert under these conditions. For instance, the isomeric acid **111a** remained unreacted, consistent with the resistance of 2-cyclohexene-1-carboxylic acid **82c** observed during the initial optimization experiments (Scheme 31). These findings demonstrate that olefins conjugated with aromatic or carbonyl groups are particularly susceptible to reduction, whereas isolated cyclic double bonds are significantly more resistant. For acyclic substrates, reactivity depends on the position of the double bond. In the case of, isomeric alkenols **112a** and **113a** (eq. j), the terminal double bond in **112a** was readily reduced, delivering 1-hexanol **112b** in 72% yield. Conversely, the internal double bond in **113a** proved more resistant, and produced only 25% conversion to **112b** under identical conditions.

The reduction of internal alkynes to (*E*)-alkenes using alkali metals in liquid ammonia is well-established in the literature,^[214] with a rare example of a calcium-mediated reaction in liquid amines.^[213] Similarly, our developed mechanochemical conditions converted 5-decyne **114a** to (*E*)-decene **114b** in 75% yield (eq. k), though this reaction was accompanied by over-reduction to *n*-decane (25% yield). In contrast, propargylic alcohol **115a** results complete reduction to ethyl carbinol **115b** with a high yield of 90% (eq. l). In addition, the terminal alkyne **116a** gave 1-hexanol **112b** in 86% yield, along with 13% of the intermediate 5-hexen-1-ol **112a** (eq. m). Overall, these results demonstrates that alkynes are readily reduced to the corresponding alkenes, which are then further reduced to alkanes, except in the case of more resistant internal olefins.

4 Conclusions

The primary objectives of this thesis were to develop the mechanochemical protocols that utilize calcium and magnesium metals for synthetically valuable chemical transformations, both through the generation of polar organometallic reagents and in reductive processes. The key outcomes of this research are summarized as follows:

- Mechanochemical activation of magnesium allows for the efficient generation of organomagnesium nucleophiles *in situ* under Barbier conditions, expanding the reaction scope beyond traditional allylations. This solvent-free, operationally simple protocol demonstrates broad substrate compatibility (38 examples) and achieves moderate to high yields (42–98%), comparable to those achieved with classic Grignard chemistry.
- The mechanochemical Barbier-Grignard reaction exhibits remarkable tolerance to air, moisture, and solid proton donors, improving reaction outcomes. Solid Brønsted acid such as NH_4Cl notably enhance performance by suppressing side reactions of ketones, releasing alcohol products directly from magnesium alkoxides, and simplifying the reaction work-up, thus increasing both efficiency and practicality.
- Mechanochemical activation transforms calcium into an effective reductant for Birch reduction and related dissolved metal-type reductive transformations. This approach reduces both electron-deficient and electron-rich arenes, affording products in yields of up to 92%, similar to those obtained with classical alkali metal reductants. Solid NH_4Cl , used as a protic source, outperformed traditional alcohol additives under mechanochemical conditions in the reduction of electron-rich arenes.
- Mechanochemical activation significantly boosts the reducing power of otherwise low-reactive magnesium in the Birch reduction, enabling efficient reduction of electron-poor aromatic carboxylic acids. The lowest reactivity of magnesium among the alkaline earth metals allows for chemoselective reductions, which are relatively uncommon in traditional Birch chemistry.
- Overall, mechanochemistry effectively amplifies the reactivity of alkaline earth metals, enabling reactions that are challenging under solution conditions. This innovative approach enhances operational simplicity, safety, and sustainability, offering viable alternatives to classical solution-based organometallic synthesis and reductive transformations, and demonstrating potential for industrial-scale chemical manufacturing and the discovery of unprecedented transformations.

References

- [1] A. Stolle, T. Szuppa, S. E. S. Leonhardt, B. Ondruschka, *Chem. Soc. Rev.* **2011**, *40*, 2317–2329.
- [2] J.-L. Do, T. Frišćić, *ACS Cent. Sci.* **2017**, *3*, 13–19.
- [3] S. Mateti, M. Mathesh, Z. Liu, T. Tao, T. Ramireddy, A. M. Glushenkov, W. Yang, Y. I. Chen, *Chem. Commun.* **2021**, *57*, 1080–1092.
- [4] J. L. Howard, Q. Cao, D. L. Browne, *Chem. Sci.* **2018**, *9*, 3080–3094.
- [5] A. Casagrande, A. Niidu, R. Aav, D. Kananovich, E. Colacino, in *Encyclopedia of Green Chemistry (First Edition)* (Ed.: B. Török), Elsevier, Oxford, **2025**, pp. 550–571.
- [6] S. Arfelis, A. I. Martín-Perales, R. Nguyen, A. Pérez, I. Cherubin, C. Len, I. Malpartida, A. Bala, P. Fullana-i-Palmer, *Heliyon* **2024**, *10*, e34655.
- [7] A. C. Jones, J. A. Leitch, S. E. Raby-Buck, D. L. Browne, *Nature Synthesis* **2022**, *1*, 763–775.
- [8] *Chem. Rev.* **2016**, *116*, 9629–9630.
- [9] M. Yan, Y. Kawamata, P. S. Baran, *Chem. Rev.* **2017**, *117*, 13230–13319.
- [10] L. Takacs, *Journal of Materials Science* **2018**, *53*, 13324–13330.
- [11] N. Shan, F. Toda, W. Jones, *Chem. Commun.* **2002**, 2372–2373.
- [12] L. Takacs, *Chem. Soc. Rev.* **2013**, *42*, 7649–7659.
- [13] International Union of Pure and Applied Chemistry (IUPAC), DOI 10.1351/goldbook.MT07141.
- [14] S. L. James, C. J. Adams, C. Bolm, D. Braga, P. Collier, T. Frišćić, 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, D. C. Waddell, *Chem. Soc. Rev.* **2012**, *41*, 413–447.
- [15] D. J. C. Constable, P. J. Dunn, J. D. Hayler, G. R. Humphrey, Jr. Leazer Johnnie L., R. J. Linderman, K. Lorenz, J. Manley, B. A. Pearlman, A. Wells, A. Zaks, T. Y. Zhang, *Green Chem.* **2007**, *9*, 411–420.
- [16] M. C. Bryan, P. J. Dunn, D. Entwistle, F. Gallou, S. G. Koenig, J. D. Hayler, M. R. Hickey, S. Hughes, M. E. Kopach, G. Moine, P. Richardson, F. Roschangar, A. Steven, F. J. Weiberth, *Green Chem.* **2018**, *20*, 5082–5103.
- [17] L. Takacs, *Journal of Thermal Analysis and Calorimetry* **2007**, *90*, 81–84.
- [18] D. Tan, F. García, *Chem. Soc. Rev.* **2019**, *48*, 2274–2292.
- [19] T. Frišćić, C. Mottillo, H. M. Titi, *Angewandte Chemie International Edition* **2020**, *59*, 1018–1029.
- [20] Y. S. Zholdassov, R. W. Kwok, M. A. Shlain, M. Patel, M. Marianski, A. B. Braunschweig, *RSC Mechanochem.* **2024**, *1*, 11–32.
- [21] G. R. Kumar, K. Jayasankar, S. K. Das, T. Dash, A. Dash, B. K. Jena, B. K. Mishra, *RSC Adv.* **2016**, *6*, 20067–20073.
- [22] E. Suut-Tuule, E. Schults, T. Jarg, J. Adamson, D. Kananovich, R. Aav, *ChemSusChem* **2025**, *18*, e202402354.
- [23] D. E. Crawford, C. K. G. Miskimmin, A. B. Albadarin, G. Walker, S. L. James, *Green Chem.* **2017**, *19*, 1507–1518.
- [24] E. Colacino, A. Porcheddu, I. Halasz, C. Charnay, F. Delogu, R. Guerra, J. Fullenwarth, *Green Chem.* **2018**, *20*, 2973–2977.
- [25] R. S. Atapalkar, A. A. Kulkarni, *React. Chem. Eng.* **2024**, *9*, 10–25.
- [26] Y. Quan, R. Shen, R. Ma, Z. Zhang, Q. Wang, *ACS Sustainable Chem. Eng.* **2022**, *10*, 7216–7222.

- [27] L. Gonnet, C. B. Lennox, J.-L. Do, I. Malvestiti, S. G. Koenig, K. Nagapudi, T. Friščić, *Angewandte Chemie International Edition* **2022**, *61*, e202115030.
- [28] R. Geib, E. Colacino, L. Gremaud, *ChemSusChem* **2024**, *17*, e202301921.
- [29] M. Carta, L. Vugrin, G. Miletić, M. J. Kulcsár, P. C. Ricci, I. Halasz, F. Delogu, *Angewandte Chemie International Edition* **2023**, *62*, e202308046.
- [30] J. Andersen, J. Mack, *Angewandte Chemie International Edition* **2018**, *57*, 13062–13065.
- [31] T. Seo, N. Toyoshima, K. Kubota, H. Ito, *J. Am. Chem. Soc.* **2021**, *143*, 6165–6175.
- [32] A. A. L. Michalchuk, I. A. Tumanov, V. A. Drebushchak, E. V. Boldyreva, *Faraday Discuss.* **2014**, *170*, 311–335.
- [33] L. Dong, L. Li, H. Chen, Y. Cao, H. Lei, *Advanced Science* **2024**, *n/a*, 2403949.
- [34] S. Garrido Nuñez, D. L. Schott, J. T. Padding, *Powder Technology* **2025**, *457*, 120919.
- [35] N. Kumar, K. Biswas, *Review of Scientific Instruments* **2015**, *86*, 083903.
- [36] R. Thorwirth, F. Bernhardt, A. Stolle, B. Ondruschka, J. Asghari, *Chemistry – A European Journal* **2010**, *16*, 13236–13242.
- [37] J. G. Hernández, C. Bolm, *J. Org. Chem.* **2017**, *82*, 4007–4019.
- [38] C. F. Burmeister, R. Schmidt, K. Jacob, S. Breitung-Faes, A. Stolle, A. Kwade, *Chemical Engineering Journal* **2020**, *396*, 124578.
- [39] D. Margetić, V. Štrukil, in *Mechanochemical Organic Synthesis* (Eds.: D. Margetić, V. Štrukil), Elsevier, Boston, **2016**, pp. 1–54.
- [40] F. Basoccu, P. Caboni, A. Porcheddu, *ChemSusChem* **2025**, *18*, e202402547.
- [41] D. A. Fulmer, W. C. Shearouse, S. T. Medonza, J. Mack, *Green Chem.* **2009**, *11*, 1821–1825.
- [42] R. A. Haley, J. Mack, H. Guan, *Inorg. Chem. Front.* **2017**, *4*, 52–55.
- [43] S. Hwang, S. Grätz, L. Borchardt, *Chem. Commun.* **2022**, *58*, 1661–1671.
- [44] O. F. Jafter, S. Lee, J. Park, C. Cabanetos, D. Lungerich, *Angewandte Chemie International Edition* **2024**, *63*, e202409731.
- [45] C. J. Taylor, A. Pomberger, K. C. Felton, R. Grainger, M. Barecka, T. W. Chamberlain, R. A. Bourne, C. N. Johnson, A. A. Lapkin, *Chem. Rev.* **2023**, *123*, 3089–3126.
- [46] P. Ying, J. Yu, W. Su, *Advanced Synthesis & Catalysis* **2021**, *363*, 1246–1271.
- [47] J. L. Howard, Y. Sagatov, L. Repousseau, C. Schotten, D. L. Browne, *Green Chem.* **2017**, *19*, 2798–2802.
- [48] M. E. Skala, S. M. Zeitler, M. R. Golder, *Chem. Sci.* **2024**, *15*, 10900–10907.
- [49] M. M. Haskins, M. J. Zaworotko, *Crystal Growth & Design* **2021**, *21*, 4141–4150.
- [50] A. M. Belenguer, G. I. Lampronti, A. J. Cruz-Cabeza, C. A. Hunter, J. K. M. Sanders, *Chem. Sci.* **2016**, *7*, 6617–6627.
- [51] J.-L. Do, C. Mottillo, D. Tan, V. Štrukil, T. Friščić, *J. Am. Chem. Soc.* **2015**, *137*, 2476–2479.
- [52] W. C. Shearouse, J. Mack, *Green Chem.* **2012**, *14*, 2771–2775.
- [53] R. Thorwirth, A. Stolle, B. Ondruschka, *Green Chem.* **2010**, *12*, 985–991.
- [54] A. C. Jones, W. I. Nicholson, H. R. Smallman, D. L. Browne, *Org. Lett.* **2020**, *22*, 7433–7438.
- [55] X. Zhu, J. Liu, T. Chen, W. Su, *Applied Organometallic Chemistry* **2012**, *26*, 145–147.
- [56] J. Li, Y. Wu, *Lubricants* **2014**, *2*, 21–43.
- [57] J. Bonnamour, T.-X. Métro, J. Martinez, F. Lamaty, *Green Chem.* **2013**, *15*, 1116–1120.
- [58] S. A. Weissman, N. G. Anderson, *Org. Process Res. Dev.* **2015**, *19*, 1605–1633.

- [59] D. J. C. Constable, C. Jimenez-Gonzalez, R. K. Henderson, *Org. Process Res. Dev.* **2007**, *11*, 133–137.
- [60] T. Dalidovich, K. A. Mishra, T. Shalima, M. Kudrjašova, D. G. Kananovich, R. Aav, *ACS Sustainable Chem. Eng.* **2020**, *8*, 15703–15715.
- [61] N. Fantozzi, J.-N. Volle, A. Porcheddu, D. Virieux, F. García, E. Colacino, *Chem. Soc. Rev.* **2023**, *52*, 6680–6714.
- [62] G. Kaupp, *CrystEngComm* **2009**, *11*, 388–403.
- [63] A. Porcheddu, E. Colacino, L. De Luca, F. Delogu, *ACS Catal.* **2020**, *10*, 8344–8394.
- [64] K. Kubota, H. Ito, *Trends in Chemistry* **2020**, *2*, 1066–1081.
- [65] S. Zhao, Y. Li, C. Liu, Y. Zhao, *Tetrahedron Letters* **2018**, *59*, 317–324.
- [66] M. T. J. Williams, L. C. Morrill, D. L. Browne, *ChemSusChem* **2022**, *15*, e202102157.
- [67] F. Cuccu, L. De Luca, F. Delogu, E. Colacino, N. Solin, R. Mocci, A. Porcheddu, *ChemSusChem* **2022**, *15*, e202200362.
- [68] L. E. Wenger, T. P. Hanusa, *Chem. Commun.* **2023**, *59*, 14210–14222.
- [69] J. G. Hernández, N. A. J. Macdonald, C. Mottillo, I. S. Butler, T. Frišić, *Green Chem.* **2014**, *16*, 1087–1092.
- [70] D. Seyferth, *Organometallics* **2001**, *20*, 2940–2955.
- [71] K. Ziegler, H. Colonius, *Justus Liebigs Annalen der Chemie* **1930**, *479*, 135–149.
- [72] U. Wietelmann, J. Klett, *Zeitschrift für anorganische und allgemeine Chemie* **2018**, *644*, 194–204.
- [74] L. Gössl, K. Dahms, G. Menges-Flanagan, M. Maskos, *Org. Process Res. Dev.* **2024**, *28*, 2028–2040.
- [75] G. Wu, M. Huang, *Chem. Rev.* **2006**, *106*, 2596–2616.
- [76] T. Banno, Y. Hayakawa, M. Umeno, *Journal of Organometallic Chemistry* **2002**, *653*, 288–291.
- [77] D. G. Brown, J. Boström, *J. Med. Chem.* **2016**, *59*, 4443–4458.
- [78] S. D. Roughley, A. M. Jordan, *J. Med. Chem.* **2011**, *54*, 3451–3479.
- [79] A. Fürstner, *Angewandte Chemie International Edition in English* **1993**, *32*, 164–189.
- [80] R. D. Rieke, P. T.-J. Li, T. P. Burns, S. T. Uhm, *J. Org. Chem.* **1981**, *46*, 4323–4324.
- [81] V. Birke, C. Schütt, W. K. L. Ruck, in *Environmental Applications of Nanoscale and Microscale Reactive Metal Particles*, American Chemical Society, **2009**, pp. 39–54.
- [82] P. Hasler, W. Richarz, *Ind. Eng. Chem. Res.* **1989**, *28*, 38–43.
- [83] S. E. Koon, C. E. Oyler, J. H. M. Hill, W. J. Bowyer, *J. Org. Chem.* **1993**, *58*, 3225–3226.
- [84] G. Picotin, P. Miginiac, *J. Org. Chem.* **1987**, *52*, 4796–4798.
- [85] M. Kimura, M. Seki, *Tetrahedron Letters* **2004**, *45*, 1635–1637.
- [86] R. D. Rieke, P. M. Hudnall, *J. Am. Chem. Soc.* **1972**, *94*, 7178–7179.
- [87] P. Cintas, J.-L. Luche, in *Synthetic Organic Sonochemistry* (Ed.: J.-L. Luche), Springer US, Boston, MA, **1998**, pp. 167–234.
- [88] K. V. Baker, J. M. Brown, N. Hughes, A. J. Skarnulis, A. Sexton, *J. Org. Chem.* **1991**, *56*, 698–703.
- [89] H. Amii, K. Uneyama, *Chem. Rev.* **2009**, *109*, 2119–2183.
- [90] H. R. Rogers, C. L. Hill, Y. Fujiwara, R. J. Rogers, H. L. Mitchell, G. M. Whitesides, *J. Am. Chem. Soc.* **1980**, *102*, 217–226.
- [91] H. R. Rogers, J. Deutch, G. M. Whitesides, *J. Am. Chem. Soc.* **1980**, *102*, 226–231.
- [92] M. Kumasaki, K. Tanaka, T. Otsuka, *Journal of Thermal Analysis and Calorimetry* **2015**, *120*, 633–639.
- [93] H. Kryk, G. Hessel, W. Schmitt, N. Tefera, *Chemical Engineering Science* **2007**, *62*, 5198–5200.

- [94] Z. Cheng, L. Ni, J. Wang, J. Jiang, H. Yao, Q. Chen, F. Cui, W. Jiang, S. Ye, *Process Safety and Environmental Protection* **2021**, *147*, 654–673.
- [95] S. E. García-Garrido, A. Presa Soto, E. Hevia, J. García-Álvarez, *European Journal of Inorganic Chemistry* **2021**, *2021*, 3116–3130.
- [96] D. Seyferth, *Organometallics* **2009**, *28*, 1598–1605.
- [97] Y. Gao, K. Kubota, H. Ito, *Angewandte Chemie International Edition* **2023**, e202217723.
- [98] D. Wittenberg, *Justus Liebigs Annalen der Chemie* **1962**, *654*, 23–26.
- [99] K. Tanaka, S. Kishigami, F. Toda, *J. Org. Chem.* **1991**, *56*, 4333–4334.
- [100] G.-W. Wang, Y. Murata, K. Komatsu, T. S. M. Wan, *Chem. Commun.* **1996**, 2059– 2060.
- [101] J. M. Harrowfield, R. J. Hart, C. R. Whitaker, *Aust. J. Chem.* **2001**, *54*, 423–425.
- [102] S. Wada, N. Hayashi, H. Suzuki, *Org. Biomol. Chem.* **2003**, *1*, 2160–2163.
- [103] R. A. Haley, A. R. Zellner, J. A. Krause, H. Guan, J. Mack, *ACS Sustainable Chem. Eng.* **2016**, *4*, 2464–2469.
- [104] Q. Cao, J. L. Howard, E. Wheatley, D. L. Browne, *Angewandte Chemie International Edition* **2018**, *57*, 11339–11343.
- [105] K. Kondo, K. Kubota, H. Ito, *Nature Synthesis* **2025**, DOI 10.1038/s44160-025-00753-3.
- [106] V. S. Pfennig, R. C. Vilella, J. Nikodemus, C. Bolm, *Angewandte Chemie International Edition* **2022**, *61*, e202116514.
- [107] P. Gao, J. Jiang, S. Maeda, K. Kubota, H. Ito, *Angewandte Chemie International Edition* **2022**, *61*, e202207118.
- [108] K. Kubota, S. Kawamura, J. Jiang, S. Maeda, H. Ito, *Chem. Sci.* **2024**, *15*, 17453–17459.
- [109] W. I. Nicholson, J. L. Howard, G. Magri, A. C. Seastram, A. Khan, R. R. A. Bolt, L. C. Morrill, E. Richards, D. L. Browne, *Angewandte Chemie International Edition* **2021**, *60*, 23128–23133.
- [110] L. K. Wei, S. Z. Abd Rahim, M. M. Al Bakri Abdullah, A. T. Yin, M. F. Ghazali, M. F. Omar, O. Nemeş, A. V. Sandu, P. Vizureanu, A. E. Abdellah, *Materials* **2023**, *16*, DOI 10.3390/ma16134635.
- [111] C. Suryanarayana, E. Ivanov, in *Advances in Powder Metallurgy* (Eds.: I. Chang, Y. Zhao), Woodhead Publishing, **2013**, pp. 42–68.
- [112] H. Zhang, N. Davison, E. Lu, *RSC Mechanochem.* **2025**, *2*, 370–388.
- [113] D. C. Waddell, T. D. Clark, J. Mack, *Tetrahedron Letters* **2012**, *53*, 4510–4513.
- [114] T. Vilaivan, *ACS Chem. Health Saf.* **2022**, *29*, 132–134.
- [115] C. Falenczyk, P. Benjamin, H. Petra, B. König, *Synthetic Communications* **2015**, *45*, 348–354.
- [116] Q. Cao, R. T. Stark, I. A. Fallis, D. L. Browne, *ChemSusChem* **2019**, *12*, 2554–2557.
- [117] J. Yin, R. T. Stark, I. A. Fallis, D. L. Browne, *J. Org. Chem.* **2020**, *85*, 2347–2354.
- [118] L. Pontini, J. A. Leitch, D. L. Browne, *Green Chem.* **2023**, *25*, 4319–4325.
- [119] A. C. Jones, M. T. J. Williams, L. C. Morrill, D. L. Browne, *ACS Catal.* **2022**, *12*, 13681–13689.
- [120] T. Čarný, M. Mart, M. Blauciak, B. Steinhübllová, R. Šebesta, *ChemCatChem* **2025**, *17*, e202500373.
- [121] T. Čarný, D. Mravcová, B. Steinhübllová, R. Šebesta, *Advanced Synthesis & Catalysis* **2025**, *367*, e202401403.
- [122] A. Nanni, D. Kong, C. Zhu, M. Rueping, *Green Chem.* **2024**, *26*, 8341–8347.

- [123] S. A. Rowlands, A. K. Hall, P. G. McCormick, R. Street, R. J. Hart, G. F. Ebell, P. Donecker, *Nature* **1994**, *367*, 223–223.
- [124] V. Birke, J. Mattik, D. Runne, *Journal of Materials Science* **2004**, *39*, 5111–5116.
- [125] V. Birke, C. Schütt, H. Burmeier, W. Ruck, *Fresenius Environmental Bulletin* **2011**, *20*, 2794–2805.
- [126] H. Chen, J. Fan, Y. Fu, C.-L. Do-Thanh, X. Suo, T. Wang, I. Popovs, D. Jiang, Y. Yuan, Z. Yang, S. Dai, *Advanced Materials* **2021**, *33*, 2008685.
- [127] I. R. Speight, T. P. Hanusa, *Molecules* **2020**, *25*, DOI 10.3390/molecules25030570.
- [128] R. Takahashi, A. Hu, P. Gao, Y. Gao, Y. Pang, T. Seo, J. Jiang, S. Maeda, H. Takaya, K. Kubota, H. Ito, *Nature Communications* **2021**, *12*, 6691.
- [129] D. Jędrzkiewicz, J. Langer, S. Harder, *Zeitschrift für anorganische und allgemeine Chemie* **2022**, *648*, e202200138.
- [130] C. Wu, T. Ying, H. Fan, C. Hu, W. Su, J. Yu, *Org. Lett.* **2023**, *25*, 2531–2536.
- [131] C. Wu, T. Ying, X. Yang, W. Su, A. V. Dushkin, J. Yu, *Org. Lett.* **2021**, *23*, 6423–6428.
- [132] L. Zong, R. Sun, X. Hu, J. Zhang, Y. Luan, Zhengbao. Xu, C. Xie, X. Li, F.-G. Sun, H. Liu, Z.-Q. Liu, Z. Zhao, L. Zhang, *Advanced Synthesis & Catalysis* **2024**, *366*, 1509–1516.
- [133] S. Chen, C. Fan, Z. Xu, M. Pei, J. Wang, J. Zhang, Y. Zhang, J. Li, J. Lu, C. Peng, X. Wei, *Nature Communications* **2024**, *15*, 769.
- [134] C. Wu, J. Lv, H. Fan, W. Su, X. Cai, J. Yu, *Chemistry – A European Journal* **2024**, *30*, e202304231.
- [135] T. Liu, X. Zhang, Q. Wang, Z. Lian, *Angewandte Chemie International Edition* **2025**, *64*, e202424186.
- [136] M. Westerhausen, *Angewandte Chemie International Edition* **2001**, *40*, 2975–2977.
- [137] M. Westerhausen, *Zeitschrift für anorganische und allgemeine Chemie* **2009**, *635*, 13–32.
- [138] M. Westerhausen, M. Gärtner, R. Fischer, J. Langer, L. Yu, M. Reiher, *Chemistry – A European Journal* **2007**, *13*, 6292–6306.
- [139] N. N. Greenwood, A. Earnshaw, Eds., in *Chemistry of the Elements (Second Edition)*, Butterworth-Heinemann, Oxford, **1997**, pp. 107–138.
- [140] T. P. Hanusa, *Chem. Rev.* **1993**, *93*, 1023–1036.
- [141] T. P. Hanusa, *Polyhedron* **1990**, *9*, 1345–1362.
- [142] A. Koch, Q. Dufrois, M. Wirgenings, H. Görls, S. Kriek, M. Etienne, G. Pohnert, M. Westerhausen, *Chemistry – A European Journal* **2018**, *24*, 16840–16850.
- [143] H. Gilman, F. Schulze, *J. Am. Chem. Soc.* **1926**, *48*, 2463–2467.
- [144] A. Cortés-Lobo, J. G. Hernández, *ChemPlusChem* **2024**, *89*, e202400257.
- [145] P. Gao, J. Jiang, Y. Fukuzawa, S. Maeda, K. Kubota, H. Ito, *RSC Mechanochem.* **2024**, *1*, 486–491.
- [146] M. Power, E. Alcock, G. P. McGlacken, *Org. Process Res. Dev.* **2020**, *24*, 1814–1838.
- [147] P. R. Carlier, *J. Am. Chem. Soc.* **2003**, *125*, 12057–12057.
- [148] P. Gao, Y. Li, D. Zhang, G. Zhang, L. Gao, F. Chen, *Chemistry – A European Journal* **2024**, *30*, e202400963.
- [149] A. J. Birch, *J. Chem. Soc.* **1944**, 430–436.
- [150] A. E. Goetz, J. Arcari, S. W. Bagley, R. Hicklin, L. Jin, Z. Jin, X. Li, Z. Liu, J. C. McWilliams, M. D. Parikh, T. Potter, W. J. Smith, L. Sun, J. Trujillo, P. Wang, X. Zhao, *Org. Process Res. Dev.* **2023**, DOI 10.1021/acs.oprd.3c00141.
- [151] X.-G. Si, S.-X. Feng, Z.-Y. Wang, X. Chen, M.-M. Xu, Y.-Z. Zhang, J.-X. He, L. Yang, Q. Cai, *Angewandte Chemie International Edition* **2023**, *62*, e202303876.
- [152] J. M. Hook, L. N. Mander, *Nat. Prod. Rep.* **1986**, *3*, 35–85.

- [153] H. E. Zimmerman, *Acc. Chem. Res.* **2012**, *45*, 164–170.
- [154] R. A. Benkeser, C. Arnold Jr, R. F. Lambert, O. H. Thomas, *J. Am. Chem. Soc.* **1955**, *77*, 6042–6045.
- [155] R. A. Benkeser, R. E. Robinson, D. M. Sauve, O. H. Thomas, *Journal of the American Chemical Society* **1955**, *77*, 3230–3233.
- [156] L. Reggel, R. A. Friedel, I. Wender, *J. Org. Chem.* **1957**, *22*, 891–894.
- [157] M. E. Garst, L. J. Dolby, S. Esfandiari, N. A. Fedoruk, N. C. Chamberlain, A. A. Avey, *J. Org. Chem.* **2000**, *65*, 7098–7104.
- [158] B. K. Peters, K. X. Rodriguez, S. H. Reisberg, S. B. Beil, D. P. Hickey, Y. Kawamata, M. Collins, J. Starr, L. Chen, S. Udyavara, K. Klunder, T. J. Gorey, S. L. Anderson, M. Neurock, S. D. Minter, P. S. Baran, *Science* **2019**, *363*, 838–845.
- [159] A. Chatterjee, B. König, *Angewandte Chemie International Edition* **2019**, *58*, 14289–14294.
- [160] O. Tiedt, J. Fuchs, W. Eisenreich, M. Boll, *Journal of Biological Chemistry* **2018**, *293*, 10264–10274.
- [161] J. L. Dye, K. D. Cram, S. A. Urbin, M. Y. Redko, J. E. Jackson, M. Lefenfeld, *J. Am. Chem. Soc.* **2005**, *127*, 9338–9339.
- [162] P. Lei, Y. Ding, X. Zhang, A. Adijiang, H. Li, Y. Ling, J. An, *Org. Lett.* **2018**, *20*, 3439–3442.
- [163] S. Asako, I. Takahashi, T. Kurogi, Y. Murakami, L. Ilies, K. Takai, *Chem. Lett.* **2022**, *51*, 38–40.
- [164] S. Asako, H. Nakajima, K. Takai, *Nature Catalysis* **2019**, *2*, 297–303.
- [165] J. Burrows, S. Kamo, K. Koide, *Science* **2021**, *374*, 741–746.
- [166] N. Davison, J. A. Quirk, F. Tuna, D. Collison, C. L. McMullin, H. Michaels, G. H. Morritt, P. G. Waddell, J. A. Gould, M. Freitag, J. A. Dawson, E. Lu, *Chem* **2023**, *9*, 576–591.
- [167] K. Fujishiro, Y. Morinaka, Y. Ono, T. Tanaka, L. T. Scott, H. Ito, K. Itami, *J. Am. Chem. Soc.* **2023**, *145*, 8163–8175.
- [168] K. Kondo, K. Kubota, H. Ito, *Chem. Sci.* **2024**, DOI 10.1039/D3SC06052G.
- [169] M. Winter, *WebElements Periodic Table*, can be found under <https://www.web-elements.com> (accessed July **2025**).
- [170] J. R. Hwu, Y. S. Wein, Y.-J. Leu, *J. Org. Chem.* **1996**, *61*, 1493–1499.
- [171] C. Combellas, F. Kanoufi, A. Thiébault, *Journal of Electroanalytical Chemistry* **2001**, *499*, 144–151.
- [172] R. A. Benkeser, J. Kang, *J. Org. Chem.* **1979**, *44*, 3737–3739.
- [173] K. N. Campbell, L. T. Eby, *J. Am. Chem. Soc.* **1941**, *63*, 2683–2685.
- [174] D. F. Lindow, C. N. Cortez, R. G. Harvey, *J. Am. Chem. Soc.* **1972**, *94*, 5406–5412.
- [175] R. A. Benkeser, F. G. Belmente, M.-H. Yang, *Synthetic Communications* **1983**, *13*, 1103–1116.
- [176] R. A. Benkeser, J. A. Laugal, A. Rappa, *Tetrahedron Letters* **1984**, *25*, 2089–2092.
- [177] C. Pétrier, K. Suslick, *Ultrasonics Sonochemistry* **2000**, *7*, 53–61.
- [178] K. N. Campbell, J. P. McDermott, *J. Am. Chem. Soc.* **1945**, *67*, 282–283.
- [179] P. Markov, C. Ivanoff, *Tetrahedron Letters* **1962**, *3*, 1139–1141.
- [180] J. F. Reynes, V. Isoni, F. García, *Angewandte Chemie International Edition* **2023**, *62*, e202300819.
- [181] D. E. Crawford, A. Porcheddu, A. S. McCalmont, F. Delogu, S. L. James, E. Colacino, *ACS Sustainable Chem. Eng.* **2020**, *8*, 12230–12238.
- [182] V. Isoni, K. Mendoza, E. Lim, S. K. Teoh, *Org. Process Res. Dev.* **2017**, *21*, 992–1002.

- [183] R. R. A. Bolt, H. R. Smallman, J. A. Leitch, G. W. Bluck, F. Barreateau, A. V. Iosub, D. Constable, O. Dapremont, P. Richardson, D. L. Browne, *Angewandte Chemie International Edition* **2024**, *63*, e202408315.
- [184] I. Priestley, C. Battilocchio, A. Iosub, F. Barreateau, G. W. Bluck, K. B. Ling, K. Ingram, M. Ciaccia, J. A. Leitch, D. L. Browne, *Org. Process Res. Dev.* **2023**, *27*, 1154–1154.
- [185] P. Slavík, B. R. Trowse, P. O'Brien, D. K. Smith, *Nature Chemistry* **2023**, *15*, 319–325.
- [186] C. Blomberg, *The Barbier Reaction and Related One-Step Processes*, Springer-Verlag, **1993**.
- [187] S. Li, J.-X. Wang, X. Wen, X. Ma, *Tetrahedron* **2011**, *67*, 849–855.
- [188] V. Sarathy, A. J. Salter, J. T. Nurmi, G. O'Brien Johnson, R. L. Johnson, P. G. Tratnyek, *Environ. Sci. Technol.* **2010**, *44*, 787–793.
- [189] J. F. Garst, M. P. Soriaga, *Coordination Chemistry Reviews* **2004**, *248*, 623–652.
- [190] P. Sobota, B. Duda, *Journal of Organometallic Chemistry* **1987**, *332*, 239–245.
- [191] A. Kadam, M. Nguyen, M. Kopach, P. Richardson, F. Gallou, Z.-K. Wan, W. Zhang, *Green Chem.* **2013**, *15*, 1880–1888.
- [192] W.-C. Zhang, C.-J. Li, *J. Org. Chem.* **1999**, *64*, 3230–3236.
- [193] E. Ashby, J. Buhler, I. Lopp, T. Wiesemann, J. Bowers Jr, J. Laemmle, *J. Am. Chem. Soc.* **1976**, *98*, 6561–6570.
- [194] G. Osztrovszky, T. Holm, R. Madsen, *Org. Biomol. Chem.* **2010**, *8*, 3402–3404.
- [195] C.-J. Li, W.-C. Zhang, *J. Am. Chem. Soc.* **1998**, *120*, 9102–9103.
- [196] N. D. Bartolo, J. A. Read, E. M. Valentín, K. A. Woerpel, *Chem. Rev.* **2020**, *120*, 1513–1619.
- [197] T. Holm, *J. Org. Chem.* **2000**, *65*, 1188–1192.
- [198] G. A. Bowmaker, *Chem. Commun.* **2013**, *49*, 334–348.
- [199] E. C. Ashby, *Q. Rev. Chem. Soc.* **1967**, *21*, 259–285.
- [200] J. H. Dam, P. Fristrup, R. Madsen, *J. Org. Chem.* **2008**, *73*, 3228–3235.
- [201] D. Griller, K. U. Ingold, *Acc. Chem. Res.* **1980**, *13*, 317–323.
- [202] P. W. Rabideau, *Tetrahedron* **1989**, *45*, 1579–1603.
- [203] J. V. Nallaparaju, T. Nikonovich, T. Jarg, D. Merzhyievskiy, R. Aav, D. G. Kananovich, *Angewandte Chemie International Edition* **2023**, e202305775.
- [204] B. J. Arnold, S. M. Mellows, P. G. Sammes, T. W. Wallace, *J. Chem. Soc., Perkin Trans. 1* **1974**, 401–409.
- [205] K. Koide, *Synthesis* **2022**, *55*, 707–718.
- [206] H. E. Zimmerman, P. A. Wang, *J. Am. Chem. Soc.* **1993**, *115*, 2205–2216.
- [207] D. Caine, *Org. React.* 1976, **23**, 1–85, p. 14 and references therein.
- [208] B. K. Peters, K. X. Rodriguez, S. H. Reisberg, S. B. Beil, D. P. Hickey, Y. Kawamata, M. Collins, J. Starr, L. Chen, S. Udyavara, K. Klunder, T. J. Gorey, S. L. Anderson, M. Neurock, S. D. Minter, P. S. Baran, *Science* **2019**, *363*, 838–845.
- [209] Josef. Fried, N. A. Abraham, T. S. Santhanakrishnan, *J. Am. Chem. Soc.* **1967**, *89*, 1044–1045.
- [210] K. Kubota, Y. Fukuzawa, K. Kondo, Y. Gao, H. Ito, *Chemistry Letters* **2024**, *53*, upae060.
- [211] R. A. Benkeser, A. Rappa, L. A. Wolsieffer, *J. Org. Chem.* **1986**, *51*, 3391–3393.
- [212] H. Gilman, J. C. Bailie, *J. Am. Chem. Soc.* **1943**, *65*, 267–268.
- [213] R. A. Benkeser, F. G. Belmonte, *J. Org. Chem.* **1984**, *49*, 1662–1664.
- [214] K. N. Campbell, L. T. Eby, *J. Am. Chem. Soc.* **1941**, *63*, 216–219.

Acknowledgements

This work was conducted in the Department of Chemistry and Biotechnology of the School of Science at Tallinn University of Technology. The work was supported by the Estonian Ministry of Education and Research (Grant No PRG399), the European Union H2020-FETOPEN grant 828779 (INITIO), COST Action CA18112 “Mechanochemistry for Sustainable Industry”, the ASTRA “TUT Institutional Development Programme for 2016-2022” Graduate School of Functional Materials and Technologies (2014–2020.4.01.16–0032), Erasmus+ and ESF Dora programs.

The work in this thesis would not have been possible without the continuous support of many individuals, to whom I will be forever grateful.

First and foremost, I would like to express my deepest gratitude to my supervisor Dr. Dzmitry Kananovich for his unwavering support over the past 5 years and has helped me to grow and develop my scientific skills for which I am incredibly grateful. I am especially thankful for the fruitful scientific discussions we had during this journey and for your constant motivation to achieve my full potential. I am equally grateful to my co-supervisor, Prof. Riina Aav, who has been the driving force behind the supramolecular chemistry group. Her constant guidance, insightful suggestions, and continuous encouragement have been invaluable throughout this study. I am especially thankful for her patience and the way she supports and appreciates her students, which builds our confidence and motivates us to perform at our best. In addition, I would also like to express my sincere appreciation to Dr. Khalil Yamani and Dr. Benjamin Martin for hosting me at A.G. Novartis in Basel, Switzerland, and for their encouragement in pursuing exciting scientific work during my time there.

I am sincerely grateful to my colleagues Dr. Tatsiana Nikonovich, Riin Satsi, Dr. Tatsiana Jarg, Dr. Danylo Merzhyievskiy, and Dr. Marina Kudrjašova for their valuable contributions to my research and publications. Their support, collaboration, and shared expertise have been truly appreciated. I also thankful to all of my former and present co-workers from the 429 lab: Dr. Kamini Mishra, Marek, Kristi, Suman, Andrea, Elina Suut and Dr. Elena Prigorchenko for all your help and for providing a good working atmosphere in the lab. In addition, I would like to extend my sincere thanks to all the members of the Supramolecular group Nele, Marko, Jevgenija, Kristjan, Ngan, Eve, Ander, Ketrin, Elina Bugrōšov, Ece, Rauno, Mari-Liis, Dr. Mario Öeren, Dr. Lukaš Ustrnul, Dr. Karin Valmsen and Liisa Rebane for the inspiring group meetings, memorable trips, engaging conversations and above all, for being such wonderful colleagues. A special thanks to Marko, Nele and Mahendra for the many good times we shared throughout this journey.

In addition, I would like to express my thanks to all the past and present colleagues from the fourth floor for being very kind and supportive colleagues, especially to Dr. Kristin Erkman for her support and patience on wide range of challenges, from chemical to administrative issues. I am thankful to Dr. Mikk Kaasik for reviewing my thesis and providing valuable comments.

Finally, I am extremely thankful to all my family members Mum, Dad, Krishna, Hyndhavi and Lahari, without them none of these would have been possible. I am also deeply grateful to all my friends, especially to Dr. Sai Srinivas Ponugoti for all your support and for being beside me throughout my studies.

Abstract

Mechanochemical Activation of Alkaline Earth Metals and Its Applications in Organic Synthesis

In recent years, there has been growing interest in the use of mechanochemistry, through ball milling and other mechanochemical devices, to boost the reactivity of metals in organic synthesis, including the generation of polar organometallic reagents and reductive transformations. The advantages of mechanochemistry include reduced use of hazardous organic solvents and operationally simpler that can be performed under ambient conditions and in air. These benefits highlight mechanochemistry as an attractive alternative to traditional organometallic synthesis in solution, which often suffer from several practical shortcomings. In this thesis, applications of mechanochemistry to address two long-standing challenges in organic synthesis are presented: (i) an efficient and broad-scope of Barbier-Grignard reaction with magnesium metal, and (ii) the Birch reduction with low-reactive calcium and magnesium.

The first chapter describes the mechanochemical adaptation of the magnesium-mediated Barbier reaction. This approach overcomes long-standing limitations of traditional Barbier-Grignard chemistry, enabling the coupling of a wide variety of organic halides (allylic, vinylic, aromatic, and aliphatic) with a broad range of electrophiles (including aromatic aldehydes, ketones, esters, amides, O-benzoyl hydroxylamine, chlorosilane, and borate esters) to form C–C, C–N, C–Si, and C–B bonds. The developed method offers the advantages of being operationally simple, tolerant to air, and unexpectedly resistant to water and some weak Brønsted acids. Notably, the addition of solid NH_4Cl was found to increase yields in reactions with ketones by inhibiting base-mediated side processes. Mechanistic investigations revealed that the reaction proceeds predominantly through transient polar organomagnesium species, with a minor contribution from a radical pathway, facilitated by improved mass transfer and activation of the magnesium surface under ball-milling conditions. Gram-scale examples have been demonstrated, highlighting the method's scalability.

The second chapter describes a novel mechanochemical approach to the Birch reduction, leveraging the reactivity of less-reactive alkaline earth metals (Ca, Mg). By employing ethylenediamine (EDA) and tetrahydrofuran (THF) as liquid additives, Ca and Mg metals are transformed into powerful reductants under ball milling conditions. This methodology enables calcium to effectively reduce both electron-poor and electron-rich aromatic systems and delivers good yields even on gram scale, comparable to those obtained with traditionally used alkali metal reductants. Notably, solid NH_4Cl was employed as an affordable protic source, outperforming traditional alcoholic additives in terms of both yield and product selectivity. In addition, magnesium exhibits enhanced reducing capabilities, facilitating the reduction of benzoic acids while preserving electron-rich aromatic rings, thus allowing for chemoselective reductions. Finally, the versatility of this approach extends to other dissolved metal-type reductive transformations, including the reduction of alkenes and alkynes.

Finally, this research presents an alternative methodology to conventional organometallic synthesis in solution. The established mechanistic insights and reactivity trends lay the groundwork for further innovations toward sustainable and safer implementation of organometallic processes and the discovery of new reactions.

Lühikokkuvõte

Mehhanokeemiline leelismuldmetallide aktiveerimine ja selle rakendused orgaanilises sünteesis

Viimastel aastatel on kasvanud huvi mehaanokeemia abil suurendada metallide reaktsioonivõimet orgaanilises sünteesis, kasutades näiteks kuulveskeid või teisti mehaanokeemilisi seadmeid. Mehhanokeemiliselt võib genereerida ka polaarseid organometallilisi reagente ja teostada orgaaniliste ainete taandamist. Mehaanokeemia eelisteks on ohtlike orgaaniliste lahustite kasutuse vähendamine ningreaktsioonisegude lihtsam töötlus tavatingimustes ja õhu juuresolekul. Need eelised muudavad mehaanokeemia atraktiivseks alternatiiviks traditsioonilisele lahuses toimuvale organometallilisele sünteesile, millel on sageli mitmeid praktilisi puudusi. Käesolevas töös on näidatud mehaanokeemia rakendust kahe orgaanilise sünteesi pikaajalise probleemi lahendamiseks: (i) efektiivne ja laiaulatuslik Barbier-Grignard'i reaktsioon magneesiumiga ning (ii) Birch'i redutseerimine väheaktiivsete kaltsiumi ja magneesiumi abil.

Esimeses peatükis kirjeldatakse magneesiumil põhineva Barbier' reaktsiooni mehaanokeemilist kohandamist. See lähenemine ületab traditsioonilise Barbier-Grignardi keemia pikaajalised piirangud, võimaldades laias valikus orgaaniliste halogeniidide (alüül-, vinüül-, aromaatsed ja alifaatsed) sidumist mitmesuguste elektrofiilidega (sealhulgas aromaatsed aldehüüdid, ketoonid, estrid, amiidid, O-bensioüülhüdrosüülamiin, klorosilaan ja boraatestrid), et moodustada C–C, C–N, C–Si ja C–B sidemeid. Väljatöötatud meetod on lihtne, talub kokkupuudet õhuga ning on üllatavalt vastupidav vee ja mõnede nõrkade Brønsted'i hapete suhtes. Märkimisväärne on see, et tahke NH_4Cl lisamine suurendas ketoonidega toimuvate reaktsioonide saagiseid, pärssides aluselist kõrvalprotsesside toimumist. Mehhanistlikud uuringud näitasid, et reaktsioon toimub peamiselt lühiealiste polaarsete organomagneesiumühendite kaudu, ja väheses ulatuses radikaalse mehhanismi kaudu, mida soodustavad metallpinna aktiveerimine ja paranenud massiülekanne kuuljahvatuse tingimustes. On näidatud ka grammiskaalas toimivaid reaktsioone, mis tõstab esile meetodi skaleeritavuse.

Teine peatükk kirjeldab uutset mehaanokeemilist lähenemist Birchi taandamisele, kasutades vähemreaktiivseid leelismuldmetalle (Ca, Mg). Kaltsium ja magneesium muundatakse vedelate lisandite etüleendiamiini (EDA) ja tetrahüdrofuraani (THF) juuresolekul ja mehhanilise töötluse abil võimsateks redutseerijateks. See meetod võimaldab kaltsiumil efektiivselt redutseerida nii elektronvaeseid kui ka elektronirikkaid aromaatsed süsteeme, andes häid saagiseid ka grammiskaalal, võrreldes traditsiooniliselt kasutatavate leelismetallidega. Märkimisväärselt kasutati protolüütilise allikana odavat tahket NH_4Cl -i, mis ületas traditsioonilised alkohoolsed lisandid nii saagise kui ka selektiivsuse osas. Lisaks näitab magneesium suurenenud redutseerimisvõimet, võimaldades bensoehapete taandamist, säilitades samal ajal elektronirikka aromaatses tuuma, võimaldades seeläbi kemoselektiivseid taandamisi. Lisaks saab selle meetodiga teostada ka alkeenide ja alüünide redutseerimist. Käesolev töö pakub teostuselt oluliselt mugavat alternatiivi tavapärasele lahuses toimuvale organometallilisele sünteesile. Kasvanud arusaam uuritud reaktsioonide mehhanismidest ja reaktsioonitrendidest loovad hea aluse organometalliliste protsesside jätkusuutlikumale ja ohutumale rakendamisele ning uute reaktsioonide avastamisele.

Appendix 1

Publication I

J. V. Nallaparaju, T. Nikonovich, T. Jarg, D. Merzhyievskiy, R. Aav, D. G. Kananovich. Mechanochemistry-Amended Barbier Reaction as an Expedient Alternative to Grignard Synthesis. *Angewandte Chemie International Edition*, **2023**, *62*, e202305775.

Reproduced by permission of John Wiley and Sons.

Appendix 2

Publication II

J. V. Nallaparaju, R. Satsi, D. Merzhyievskiy, T. Jarg, R. Aav, D. G. Kananovich. Mechanochemical Birch Reduction with Low Reactive Alkaline Earth Metals *Angewandte Chemie International Edition* **2024**, *63*, e202319449.

Reproduced by permission of John Wiley and Sons.

Curriculum vitae

Personal data

Name: Jagadeesh Varma Nallaparaju
Date of birth: 20.10.1996
Place of birth: Andhra Pradesh, India
Citizenship: Indian

Contact data

E-mail: jagadeesh.nallaparaju@outlook.com

Education

2020–2025 Ph.D., Tallinn University of Technology, Department of Chemistry and Biotechnology, Tallinn, Estonia
2017–2019 M.Sc., Andhra University, Andhra Pradesh, India
2014–2017 B.Sc., Krishna University, Andhra Pradesh, India

Language competence

Telugu native
English advanced
Hindi basic

Professional employment

2021–2025 Early-Stage Researcher, Tallinn University of Technology, Department of Chemistry and Biotechnology, Estonia
2024 Internship (August – November), Novartis AG, Basel, Switzerland
2017–2018 Industrial student, Chemist, AVRA Laboratories Pvt. Ltd, India

Honours and awards

2025 Erkki Truve Doctoral Study Scholarship, Tallinn University of Technology, Estonia
2024 9th EuChemS Chemistry Congress (ECC 9) Poster Prize, Dublin, Ireland
2024 18th Belgian Organic Synthesis Symposium (BOSS) Poster Prize, Liège, Belgium
2023 Tallinn University of Technology best research article of the year in natural, exact and health sciences: J. V. Nallaparaju et al., *Angewandte Chemie International Edition* **2023**, 62, e202305775
2022 Symposium of Department of Chemistry and Biotechnology Flash presentation award, Tallinn University of Technology, Estonia

Supervised theses

2023, Riin Satsi, B. Sc. Mechanochemical Birch Reduction with Calcium Metal (Tallinn University of Technology, Department of Chemistry and Biotechnology)

Elulookirjeldus

Isikuandmed

Nimi: Jagadeesh Varma Nallaparaju
Sünniaeg: 20.10.1996
Sünnikoht: Andhra Pradesh, India
Kodakondsus: India

Kontaktandmed

E-post: jagadeesh.nallaparaju@outlook.com

Hariduskäik

2020–2025 PhD, Tallinna Tehnikaülikool, Keemia ja biotehnoloogiainstituut, Tallinn, Eesti
2017–2019 MSc, Andhra Ülikool, Andhra Pradesh, India
2014–2017 BSc, Krishna Ülikool, Andhra Pradesh, India

Keelteoskus

Telugu keel emakeel
Inglise keel kõrgtase
Hindi keel algtase

Teenistuskäik

2021–2025 Nooremteadur, Tallinna Tehnikaülikool, Keemia ja biotehnoloogia instituut, Eesti
2024 Praktika, mehhanokeemik, Novartis A.G., Basel, Šveits
2017–2018 Tööstuspraktikant, keemik, AVRA Laboratories Pvt. Ltd., India

Teaduspreemiad ja tunnustused

2025 Erkki Truve doktorantuuri stipendium, Tallinna Tehnikaülikool, Eesti
2024 9th EuChemS Chemistry Congress (ECC 9) posterettekande auhind, Dublin, Iirimaa
2024 18th Belgian Organic Synthesis Symposium (BOSS) posterettekande auhind, Liège, Belgia
2023 Tallinna Tehnikaülikooli parim teadusartikkel loodus-, täppis- ja terviseteaduste valdkonnas: J. V. Nallaparaju et al., *Angewandte Chemie International Edition* **2023**, 62, e202305775
2022 Keemia ja biotehnoloogiainstituudi sümpoosium, välkettekande auhind, Tallinna Tehnikaülikool, Eesti

Juhendatud lõputööd

2023, Riin Satsi, B. Sc. *Mehhanokeemiline Birchi taandamine kaltsiumi metalliga* (Tallinna Tehnikaülikool, Keemia ja biotehnoloogia instituut)