High-speed Ball Milling Enables an Ultra-fast Wittig Olefination Under Ambient and Solvent-free Conditions Without Ylide Pre-formation.

Johanna Templ[a] and Michael Schnürch*[a]

[a] J. Templ, M. Schnürch
Institute of Applied Synthetic Chemistry, TU Wien
Getreidemarkt 9/E163
1060 Vienna (Austria)
E-mail: michael.schnuerch@tuwien.ac.at

Abstract:

30 Seconds to success! – The Wittig reaction, a fundamental and extensively utilized reaction in organic chemistry, enables the efficient conversion of carbonyl compounds to olefins using phosphonium salts. Traditionally, meticulous reaction setup, including the pre-formation of a reactive ylide species *via* deprotonation of a phosphonium salt, is crucial for achieving high-yielding reactions under classical solution-based conditions. In this report, we present an unprecedented protocol for an ultra-fast mechanochemically driven Wittig reaction under solvent-free and ambient conditions, eliminating the need for tedious ylide pre-formation under strict air and moisture exclusion. A range of aldehydes and ketones were reacted with diverse phosphonium salts under high-speed ball milling conditions, giving access to the respective olefins in only 30 seconds.

Introduction:

Seventy years ago, Georg Wittig reported a ground-breaking reaction that revolutionized synthetic organic chemistry: the Wittig olefination.[1-3] This reaction, which converts carbonyl compounds into their unsaturated analogues *via* a [2+2] pericyclic mechanism, remains one of the most fundamental and extensively utilized transformations for the synthesis of functional alkenes.[3-6] Despite numerous adaptations, the classical Wittig reaction continues to be crucial in modern synthetic chemistry, with applications ranging from polymer chemistry[7-9] and material sciences[10,11] to drug and natural product synthesis.[12-17] Even on an industrial scale, the Wittig reaction is frequently pivotal; a prominent example is BASF's ton-scale synthesis of vitamin A and its derivatives.[5,18-23]

In light of growing environmental concerns, there is an urgent need for more sustainable and greener modifications of this widely used reaction.[23] Recent efforts have focused on developing catalytic versions of the Wittig reaction, using strategies to regenerate phosphine *via* chemical or electrochemical reduction of the resulting phosphine oxide.[24-28] Although these methods can recycle by-products, they often generate wasteful by-products themselves, for example when using chemical reductants like phenyl silane (PhSiH₃).[24] Additionally, attempts to use water as a reaction medium have been made,[29-34] but the energy-intensive process of treating aqueous chemical waste often mitigates any environmental and cost benefits.[35,36] Thus, the development of more sustainable and environmentally benign olefination processes remains a significant challenge.

Mechanochemistry has emerged as a transformative approach in this regard significantly advancing greener practices in academia and industry.[37-40] This method uses mechanical force and friction to drive chemical reactions, often resulting in rapid reaction kinetics and either eliminating the need for solvents

entirely or minimizing their use to a bare minimum—a strategy known as liquid-assisted grinding (LAG).[41-43] Mechanochemistry frequently enables reactions that are highly air and/or moisture sensitive in solution to proceed smoothly under ambient conditions.[44-46] These features make mechanochemistry an attractive and suitable strategy for modern synthetic chemistry.[47-50]

Despite its potential, solvent-free or LAG Wittig-type reactions are relatively underexplored in the literature (Figure 1). Most reports focus on stabilized phosphonium ylides in the Horner-Wadsworth-Emmons (HWE) modification of the Wittig reaction[51-56] or semi-stabilized ylides from benzyl phosphonium salts.[57-60] While these reactions are conducted under neat conditions, some protocols still require external heating, such as conventional heating *via* an oil bath or microwave irradiation, to provide the necessary energy.[51,53] Reports relying solely on mechanical force to drive the reaction are scarce.[52,54,57-59,61]

In 2018, Mack explored the diastereoselectivity of the Wittig reaction on benzaldehyde under LAG using benzyltriphenylphosphonium bromide.[57] And very recently Friščić reported a hexameric supramolecular cage assembly constructed from (dibromomethyl)triphenylphosphonium bromide units.[61] This assembly can encapsulate small carbonyl compounds and, upon mechanical impact, yield the respective 1,1-dibromoolefins *via* a base-activated host (PPh$_3$CHBr$_2$) - guest (aldehyde/ketone) directed Wittig olefination.

In 2002, Balema and Pecharsky explored the mechanochemical generation of phosphonium ylides under a helium atmosphere using K$_2$CO$_3$ as a base.[59] However, their study was limited, focusing on only three phosphonium salts reacted with three aromatic aldehydes. This investigation presented the exclusive example to date of a solvent-free methenylation reaction using a trimethylphenylphosphonium salt. Notably, employing 2-naphthyl aldehyde as a substrate, they obtained the respective vinyl derivative in a 73% yield after an extensive milling time of 20 hours.
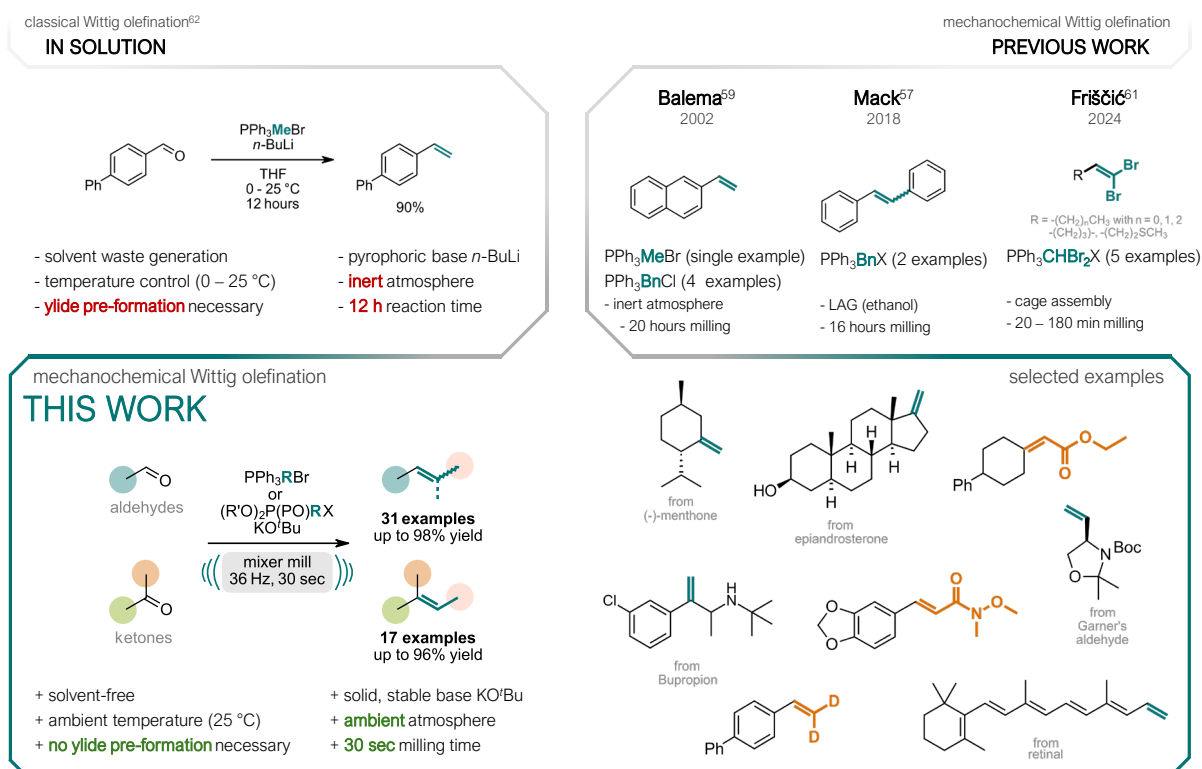

Figure 1. Typical reaction conditions for the Wittig reaction of 4-phenyl benzaldehyde with PPh$_3$MeBr in solution (top, left), previous work on mechanochemical Wittig reactions by Balema, Mack, and Friščić (top, right), and our herein presented work with its advantages compared to reactions in solution (bottom, left) and selected examples thereof (bottom, right).

These findings led us to hypothesize that a Wittig reaction using non-stabilized phosphonium ylides under ball milling conditions is feasible. However, a general and broadly applicable protocol for a solvent-free mechanochemical Wittig reaction using non-stabilized phosphonium ylides and a diverse set of carbonyl compounds has not yet been established. This gap in the literature prompted us to further investigate conditions for fast and high-yielding mechanochemically driven aldehyde-to-olefin conversions. Our newly presented method is unprecedented and outstanding in terms of ease of reaction setup and reaction time, representing a significant advancement in the field of mechanochemical synthesis.

Results & Discussion

Optimization of Reaction Conditions

Throughout our optimization studies, 4-phenyl benzaldehyde (I), methyltriphenylphosphonium bromide (a, PPh$_3$MeBr), and a solid base were ball-milled in a 7 mL Teflon™ milling vessel containing one 12 mm stainless steel ball. The reactions were carried out at a defined frequency using an IST636 mixer mill (for detailed optimization data, see SI).

We commenced by testing two solid bases, K$_2$CO$_3$ (1.6 equiv.) and KO^{t}Bu (1.6 equiv.), which are frequently employed in Wittig reactions in solution, for the solvent-free methenylation of I (0.5 mmol) using PPh$_3$MeBr (1.4 equiv.) with a milling time of 45 minutes at 30 Hz (Figure 2, entry B7 and A1). Although previous protocols demonstrated that K$_2$CO$_3$ enables ylide formation with prolonged milling times (20 hours), this base was ineffective with a 45-minutes milling time in our protocol (entry B7).[59] Gratifyingly, employing KO^{t}Bu as the base lead to full conversion of I, giving the desired vinyl derivative (1) in 70% isolated yield (entry A1).

Further optimization showed that the milling time could be reduced to as short as 30 seconds, with the aldehyde (I) still showing full conversion (entry A6). Consequently, 30 seconds was selected as the preferred reaction time, despite giving a lower yield compared to the other data points (entry A2- A5).
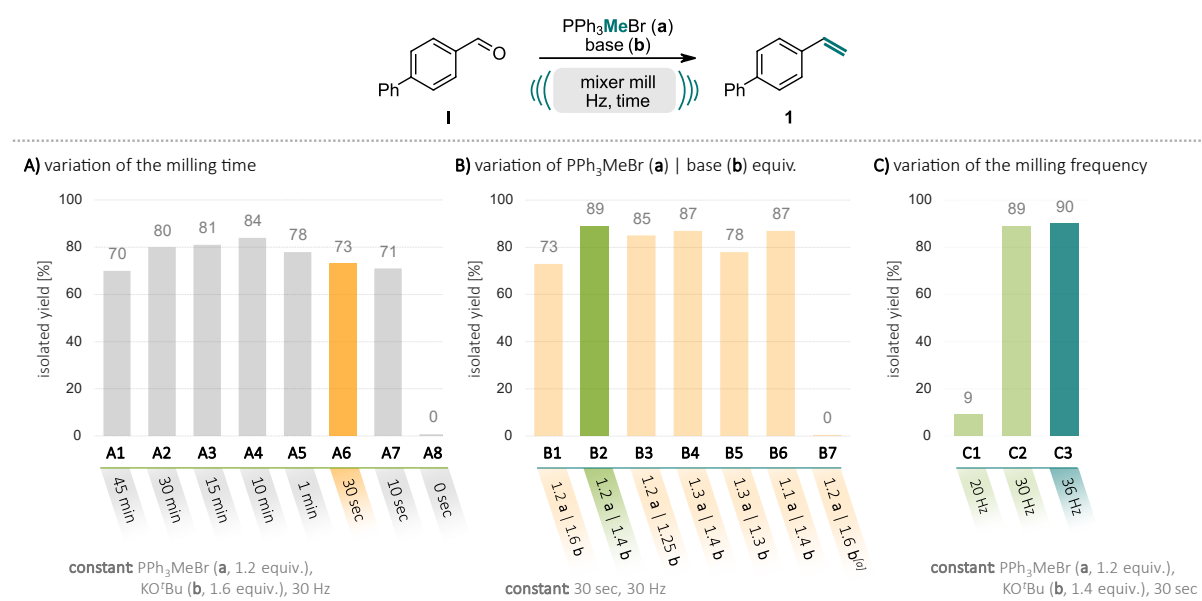

Figure 2. Optimization of reaction conditions for the mechanochemical Wittig olefination. Reactions were performed on a 0.5 mmol scale under air in an IST636 mixer mill, using a Teflon™ milling jar (7 mL) and one stainless steel milling ball (12 mm). 4-Phenyl benzaldehyde (I) (96 mg, 0.5 mmol) was used as substrate, KO^{t}Bu as the base (b) (except for entry B7, where K$_2$CO$_3$ was used) and PPh$_3$MeBr (a) as the alkenylating agent. For details, see SI. [a] K$_2$CO$_3$ was used as a base with a milling time of 45 min.

3

At a shorter milling time of 10 seconds, unreacted aldehyde was still present in the reaction mixture (entry A7). Without mechanical impact (0 seconds) starting material could be quantitatively recovered (entry A8). This blank experiment confirms that the reaction is not taking place during workup procedures, but that the conversion of **I** to **1** is indeed mechanochemically induced.

Careful finetuning of the phosphonium salt and base equivalents significantly improved the yield of the product (**1**) from 73% to 89% (entries B1 − B6). Additionally, variation in milling frequency showed that a threshold frequency of at least 30 Hz is necessary (entries C2 and C3); at lower frequencies, only minimal product formation was observed, with unreacted starting material being recovered (entry C1). Finally, we established a protocol that excels in ease of reaction setup and rapid reaction times (entry C3).

An olefination in solution using the same substrates and achieving a similar yield of 90% is described in the literature (Figure 1, top, left).[62] In this conventional method, the ylide from PPh_3MeBr is pre-formed at 0 °C in THF under an inert atmosphere, using an excess of the highly pyrophoric and oxygen-sensitive base *n*-BuLi. The resulting solution is stirred for 30 minutes at 0 °C. After the addition of aldehyde **I**, the reaction is allowed to reach room temperature and stirred for 12 hours until complete conversion.

In contrast, our protocol involves combining all reactants- the carbonyl compound, the phosphonium salt and solid, easy-to-handle base KO^tBu- in a Teflon™ milling vessel containing one milling ball, without the need for air or moisture exclusion (Figure 1, bottom, left). The vessel is closed, mounted in a mixer mill, and ground for only 30 seconds at a frequency of 36 Hz. Typically, no pre-formation of the phosphonium ylide or sequential aldehyde addition is necessary to ensure a high-yielding olefination reaction. However, for highly base-sensitive substrates, ylide pre-formation with lower base-to-phosphonium amounts can be conducted. In this modified approach, KO^tBu (1.2 equiv.) and PPh_3MeBr (1.4 equiv.) are ground for 1 minute at 36 Hz to form a yellow paste. The vessel is then opened, the carbonyl compound is added, and milling is continued until the reaction is complete.

Notably, the progress of the reaction can be easily monitored by opening the reaction vessel multiple times to take small samples, without negatively affecting the reaction outcome. This flexibility and ease of monitoring further underscore the practicality and efficiency of our mechanochemical protocol.

Substrate Scope

With the optimized reaction conditions in hand, we evaluated the generality of this protocol by converting a diverse set of carbonyl compounds into their respective olefins (Figure 3). Benzaldehyde derivatives (**1**- **9**, **11**, and **13**) consistently yielded good to excellent results, ranging from 50% to 95%, regardless of their substitution patterns. Electron-donating (**2**, **3**, **7** − **9**) and electron-withdrawing (**5**, **6**, **13**) groups, as well as combinations thereof (**4**), were well tolerated on various positions on the aromatic ring. Interestingly, under standard conditions without ylide pre-formation, product **9** was isolated in a moderate yield of 58%, with 16% of the dealkylated by-product *N*-methyl-4-vinylaniline. However, using the modified procedure with ylide pre-formation (1.2 equiv. of KO^tBu and 1.4 equiv. of PPh_3MeBr), the reaction proceeded smoothly, yielding product **9** in 80% with no observable dealkylation. A pinacol boronate-substituted aldehyde, which is highly useful for subsequent Suzuki-Miyaura coupling, reacted more reluctantly. But, after a prolonged milling time of 1 hour, the desired product **11** was obtained in 80% yield. This protocol is not limited to benzaldehyde derivatives; for example, 4-methoxycinnamaldehyde reacted smoothly, even on an increased scale, yielding product **12** in 84% (0.5 mmol scale) and 80% (2 mmol scale). Garner's aldehyde, a valuable chiral building block in natural
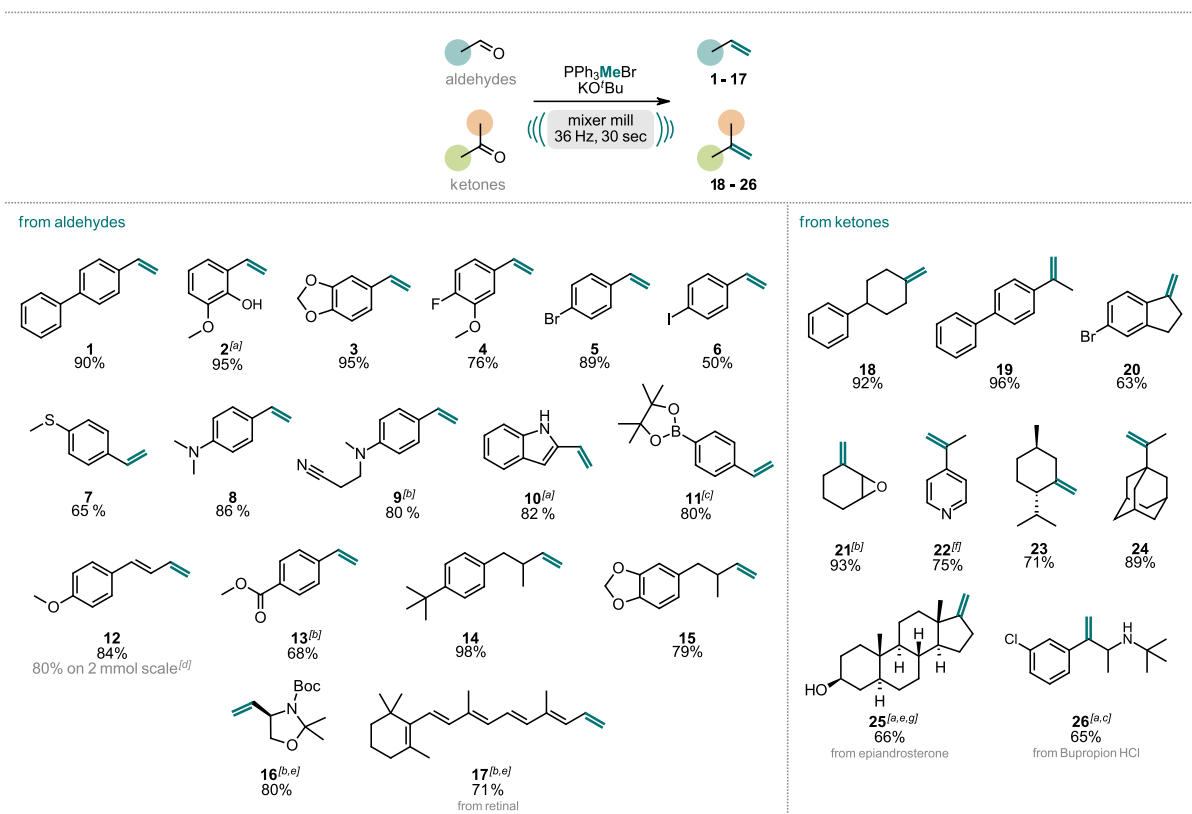
Figure 3. Scope of the Wittig olefination of aldehydes and ketones using PPh₃MeBr. Reactions were performed on a 0.5 mmol scale under air in an IST636 mixer mill, using a Teflon™ milling jar (7 mL) and one stainless steel milling ball (12 mm) at a milling frequency of 36 Hz. If not stated otherwise, milling was conducted for 30 seconds using KO^{t}Bu (0.7 mmol, 1.4 equiv.) and PPh₃MeBr (0.6 mmol, 1.2 equiv.). Isolated yields are shown. [a] 2.4 equiv. KO^{t}Bu were used. [b] Ylide pre-formation was conducted milling KO^{t}Bu (1.2 equiv.) and PPh₃MeBr (1.4 equiv.) for 1 minute before aldehyde/ketone addition (for details, see SI). [c] 1 hour milling time. [d] Reaction was performed on a 2 mmol scale using two 12 mm stainless steel milling balls in a 25 mL Teflon™ milling jar. [e] 5 minutes milling time. [f] 1 minute milling time. [g] Reaction was performed on a 0.2 mmol scale.

product synthesis, underwent olefination readily, yielding 80% of its vinylated analogue **16**.[63] Notably, highly conjugated *all-trans*-retinal was methenylated in 71% yield (product **17**), underscoring the potential of this method for future industrial applications in carotenoid synthesis.[23]

Beyond aldehydes, ketones also performed exceptionally well under the optimized reaction conditions (products **18**–**26**). Cyclohexanone-derived substrates yielded products **18** (92%) and **21** (93%). Notably, the latter is highly base-sensitive, necessitating ylide pre-formation to ensure high yields. A pyridinyl moiety was readily tolerated (product **22**), and natural product (−)-menthone, along with an adamantane-derived substrate, were converted to the vinylated products **23** and **24** in 71% and 89% yield, respectively. Remarkably, the complex steroid epiandrosterone was successfully converted to product **25**, with the newly formed double bond positioned at C-17. Additionally, we demonstrated the feasibility of this approach for the late-stage olefination of the atypical antidepressant and nicotine antagonist Bupropion, yielding product **26** in 65%.[64,65] This showcases the protocol's potential for application in the synthesis and late-stage functionalization of complex and bioactive molecules.

Subsequently, we explored the versatility of various phosphonium salts with aldehydes and ketones (Figure 4). We selected piperonal as a model aldehyde substrate due to the benzodioxole motif's frequent presence in pharmaceutically active compounds and promising drug candidates.[66-68] Generally, reactions with non-stabilized and semi-stabilized ylides (yielding products **28**-**33**, **37**, **38**) gave mixtures of isomers, as expected. Stabilized ylides (yielding products **34**-**36**) exclusively gave the *E*-isomers in yields ranging from 68% to 92%. Some substrates required slightly longer milling times due to increased steric hindrance affecting reaction rates as the substitution on the Wittig reagent increased, but no
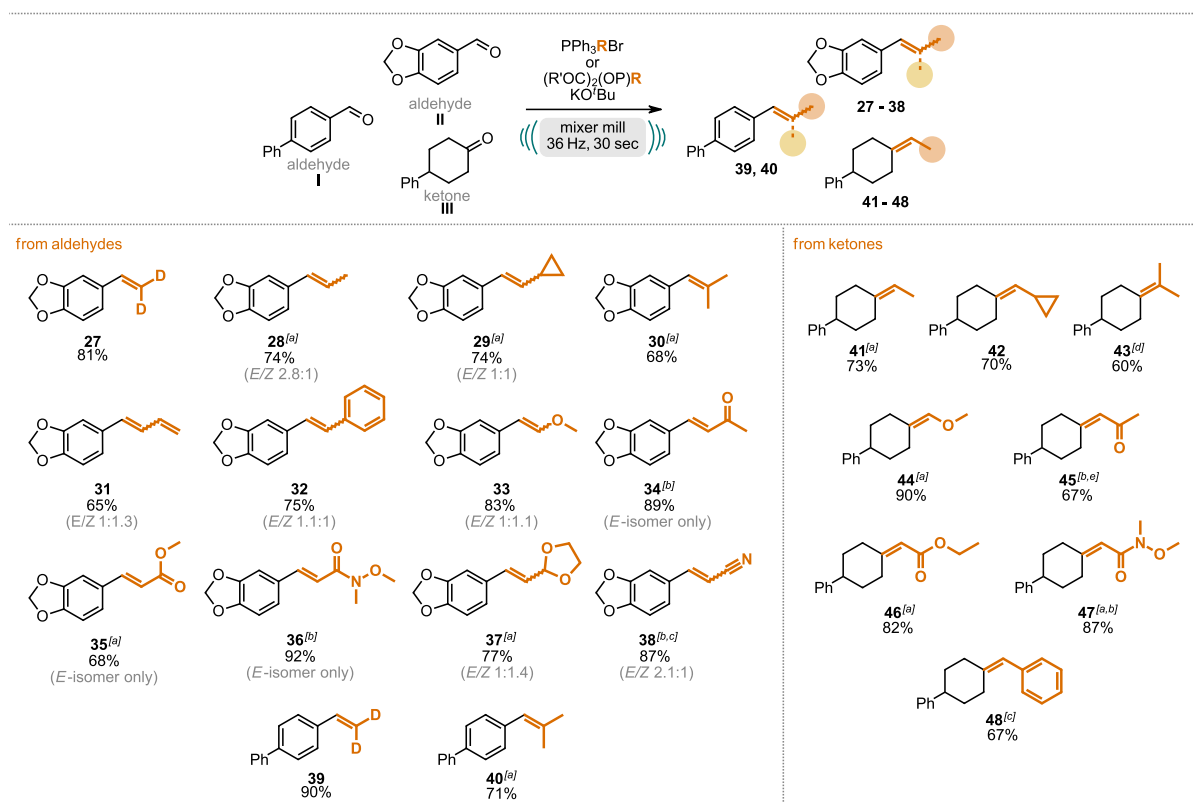
5

Figure 4. Scope of the Wittig olefination on aldehydes **I** and **II**, and ketone **III** using different phosphonium halides. Reactions were performed on a 0.5 mmol scale under air in an IST636 mixer mill, using a Teflon™ milling jar (7 mL) and one stainless steel milling ball (12 mm) at a milling frequency of 36 Hz. If not stated otherwise, milling was conducted for 30 seconds using KO^{t}Bu (0.7 mmol, 1.4 equiv.) and the respective phosphonium halide (0.6 mmol, 1.2 equiv.). Isolated yields are shown. [a] 5 minutes milling time. [b] Ylide pre-formation was conducted milling KO^{t}Bu (1.2 equiv.) and the phosphonium halide (1.4 equiv.) for 1 minute before aldehyde/ketone addition (for details, see SI). [c] 15 minutes milling time. [d] 30 minutes milling time. [e] 1 hour milling time.

reaction was conducted for longer than 1 hour. Deuteromethenylation using PPh$_3$CD$_3$I was feasible under the given reaction conditions, yielding deuterovinylated products **27** and **39** in 81% and 90%, respectively. Remarkably, this protocol allowed for the introduction of several valuable functional groups *via* the respective phosphonium salts: Weinreb amide (**36** and **47**), dioxolane (**37**), ester (**35** and **46**), and nitrile derivative (**38**). This versatility underscores the method's broad applicability and potential for generating a wide array of functionalized products.

Sequential One-pot Oxidation-Olefination

Finally, we aimed to test the method's compatibility with a preceding oxidation of a primary alcohol to an aldehyde in a solvent-free, sequential one-pot conversion (Figure 5; for details, see SI). Initially, we used Dess-Martin periodinane (DMP) to oxidize 4-biphenyl methanol (**IV**) to 4-phenyl benzaldehyde (**I**), giving 93% isolated product in just 30 seconds at 36 Hz. However, attempts to couple this oxidation with a Wittig olefination in a one-pot conversion gave a maximum of 31% for olefin **1**, likely due to incompatibility between Dess-Martin oxidation by-products and the phosphonium species (Figure 5, top).

Gratifyingly, using a solvent-free Stahl oxidation protocol by Porcheddu *et al.*[69] involving catalytic amounts of (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO), *N*-methyl imidazole (NMI), 2,2'-bipyridine (bpy) ligand, and cheap [Cu(CN)$_4$](OTf), we achieved a fully solvent-free, mechanochemical oxidation-olefination sequence without intermediate workup (Figure 5, bottom). The catalytic active species for
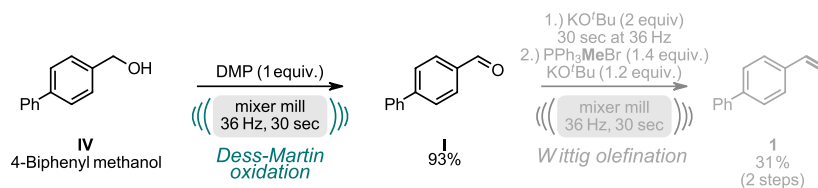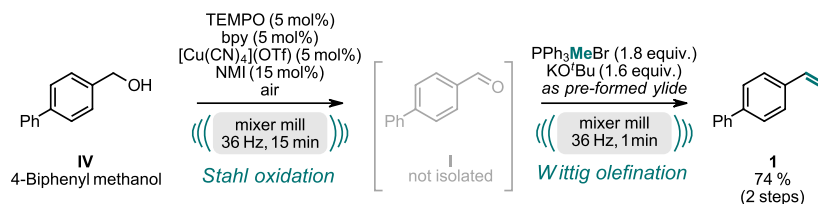
Figure 5. Sequential one-pot oxidation-olefination approach. Reactions were performed in an IST636 mixer mill, using a Teflon™ milling jar (7 mL) and one stainless steel milling ball (12 mm). Isolated yields are shown. **A)** Dess-Matin oxidation was performed on a 0.3 mmol scale under air with **IV** and Dess-Martin periodinane (0.3 mmol, 1 equiv.) at a milling frequency of 36 Hz and 30 seconds milling time. **B)** Stahl oxidation – Wittig olefination was performed on a 0.5 mmol scale. TEMPO (5 mol%), bpy (5 mol%), [Cu(CN)$_4$](OTf) (5 mol%), and NMI (15 mol%) were ball milled for 1 minute, then **IV** was added and shaking was continued for 3 x 5 minutes at 36 Hz, with opening the vessels every 5 minutes. The pre-formed ylide (obtained by milling PPh$_3$MeBr (0.9 mmol, 1.8 equiv.) and KO^{t}Bu (0.8 mmol, 1.6 equiv.) for 1 min at 36 Hz) was added and milling was continued for 1 minute at 36 Hz (for details, see SI).

oxidation was pre-formed for 1 minute at 36 Hz, after which the primary alcohol was added. The oxidation, using air as the oxidant, proceeded at 36 Hz for 15 minutes. As soon as TLC indicated complete oxidation of **IV**, a pre-formed ylide—created by milling the phosphonium halide and base for one minute—was added as a yellow paste to the aldehyde-containing vessel. The mixture was then milled for one minute, yielding the desired olefin **1** in 74% over two steps. This one-pot protocol is remarkable for its efficiency and simplicity, eliminating the need for solvent and minimize intermediate handling, thus paving the way for greener multi-step syntheses.

Conclusion

The mechanochemical Wittig olefination protocol presented in this study offers a highly efficient and environmentally friendly alternative to conventional solution-phase methods. By eliminating the need for solvents and air- or moisture-sensitive conditions, this protocol significantly simplifies the reaction setup. The method is remarkably fast, achieving complete conversion in as little as 30 seconds, and avoids the use of highly pyrophoric bases such as *n*-BuLi. The ability to conduct the reaction without pre-forming the phosphonium ylide further underscores the practicality and efficiency of this approach.

Our results demonstrate that this protocol is broadly applicable, converting a diverse array of carbonyl compounds into their corresponding olefins with high yields. The use of different phosphonium salts to introduce various functional groups highlights the method's flexibility and potential for generating a wide array of structurally diverse products.

The simplicity and effectiveness of this mechanochemical approach make it a promising tool for advancing greener synthetic practices in both academic and industrial settings. Its rapidity, efficiency, and environmentally friendly nature offer a distinct advantage over traditional methods, contributing to a more sustainable future in synthetic chemistry.

Methods

General procedure for Wittig olefination without ylide pre-formation

A 7 mL Teflon™ milling vessel equipped with one 12 mm stainless steel ball, was charged with the aldehyde/ketone substrate (0.5 mmol, 1 equiv.), the respective phosphonium halide (0.6 mmol, 1.2 equiv.), and potassium tert-butoxide (0.7 mmol, 1.4 equiv.). The closed Teflon™ vessel was mounted into the holding station of an IST636 mixer mill and milling was conducted at a frequency of 36 Hz for 30 seconds.

After the milling process, the reaction was quenched by adding 6 mL of a sat. $NH_4Cl(aq.)$ solution directly to the milling vessel. Subsequently, ether was added, and the contents were transferred to a separation funnel. The product was extracted three times with ether and the combined organic phases were washed once with sat. $NH_4Cl_{(aq.)}$ solution, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was further purified via column chromatography.

General procedure for Wittig olefination with ylide pre-formation

A 7 mL Teflon™ milling vessel equipped with one 12 mm stainless steel ball, was charged with the respective phosphonium halide (0.7 mmol, 1.4 equiv.), and potassium tert-butoxide (0.6 mmol, 1.2 equiv.). The closed Teflon™ vessel was mounted into the holding station of an IST636 mixer mill and milling was conducted at a frequency of 36 Hz for 1 minute. Subsequently, the milling vessel was opened, and the aldehyde/ketone substrate (0.5 mmol, 1 equiv.) was added to vessel. The vessel was closed and mounted again into the mixer mill's holding station and milling process was continued at 36 Hz for additional 30 seconds.

After the milling process, the reaction was quenched by adding 6 mL of a sat. $NH_4Cl_{(aq.)}$ solution directly to the milling vessel. Subsequently, ether was added, and the contents were transferred to a separation funnel. The product was extracted three times with ether and the combined organic phases were washed once with sat. $NH_4Cl_{(aq.)}$ solution, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was further purified via column chromatography.

Procedure for sequential one-pot oxidation-olefination reaction:

A 7 mL Teflon™ milling vessel equipped with one 12 mm stainless steel ball, was charged with (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO, 5 mol%), N-methyl imidazole (NMI, 15 mol%), 2,2'-bipyridine (bpy) ligand (5 mol%), and [Cu(CN)4](OTf) (5 mol%). The closed Teflon™ vessel was mounted into the holding station of an IST636 mixer mill and milling was conducted at a frequency of 36 Hz for 1 minute. Subsequently, the milling vessel was opened, and 4-biphenyl methanol (IV) (0.5 mmol, 1 equiv.) was added to the vessel. The vessel was closed and mounted again into the mixer mill's holding station and milling was continued for 15 minutes in total. After each 5 minutes, the milling process was interrupted, and the vessel was opened for 2 minutes to allow for air exchange. After complete oxidation, the pre-formed ylide—created by milling the PPh$_3$MeBr (0.9 mmol, 1.8 equiv.) and KO^{t}Bu (0.8 mmol, 1.6 equiv.) for one minute in a separate vessel—was added as a yellow paste to the aldehyde-containing vessel. Subsequently, milling was continued for 1 minute.

After the milling process, the reaction was quenched by adding 6 mL of a sat. $NH_4Cl_{(aq.)}$ solution directly to the milling vessel. Subsequently, ether was added, and the contents were transferred to a separation funnel. The product was extracted three times with ether and the combined organic phases were washed once with sat. $NH_4Cl_{(aq.)}$ solution, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was further purified via column chromatography.

9

References

1   Wittig, G. & Geissler, G. Zur Reaktionsweise des Pentaphenyl-phosphors und einiger Derivate. *Justus Liebigs Annalen der Chemie* **580**, 44-57 (1953).

2   Wittig, G. & Schöllkopf, U. Über Triphenyl-phosphin-methylene als olefinbildende Reagenzien (I. Mitteil. *Chemische Berichte* **87**, 1318-1330 (1954). https://doi.org/https://doi.org/10.1002/cber.19540870919

3   Maercker, A. in *Organic Reactions*   270-490 (John Wiley & Sons, Ltd., 2011).

4   Murphy, P. J. & Brennan, J. The Wittig olefination reaction with carbonyl compounds other than aldehydes and ketones. *Chemical Society Reviews* **17**, 1-30 (1988). https://doi.org/10.1039/CS9881700001

5   McNulty, J., McLeod, D., Das, P. & Zepeda-Velázquez, C. Wittig Reactions of Trialkylphosphine-derived Ylides: New Directions and Applications in Organic Synthesis. *Phosphorus, Sulfur, and Silicon and the Related Elements* **190**, 619-632 (2015). https://doi.org/10.1080/10426507.2014.980907

6   Byrne, P. A. & Gilheany, D. G. The modern interpretation of the Wittig reaction mechanism. *Chemical Society Reviews* **42**, 6670-6696 (2013). https://doi.org/10.1039/C3CS60105F

7   Smith, R. C., Chen, X. & Protasiewicz, J. D. A Fluorescent (E)-Poly(p-phenylenephosphaalkene) Prepared by a Phospha-Wittig Reaction. *Inorganic Chemistry* **42**, 5468-5470 (2003). https://doi.org/10.1021/ic0345471

8   Pinto, M. R., Hu, B., Karasz, F. E. & Akcelrud, L. Emitting polymers containing cyano groups. Synthesis and photophysical properties of a fully conjugated polymer obtained by Wittig reaction. *Polymer* **41**, 8095-8102 (2000). https://doi.org/https://doi.org/10.1016/S0032-3861(00)00162-2

9   Mallavarapu, L. X. & Ravve, A. Modification of polymers via the Wittig reaction. *Journal of Polymer Science Part A: General Papers* **3**, 593-603 (1965). https://doi.org/https://doi.org/10.1002/pol.1965.100030216

10   Liu, Y. *et al.* Vinylene-Linked 2D Conjugated Covalent Organic Frameworks by Wittig Reactions. *Angewandte Chemie International Edition* **61**, e202209762 (2022). https://doi.org/https://doi.org/10.1002/anie.202209762

11   Hou, J. *et al.* Wittig reaction constructed an alkaline stable anion exchange membrane. *Journal of Membrane Science* **518**, 282-288 (2016). https://doi.org/https://doi.org/10.1016/j.memsci.2016.07.020

12   Valizadeh, H. & Vaghefi, S. One-Pot Wittig and Knoevenagel Reactions in Ionic Liquid as Convenient Methods for the Synthesis of Coumarin Derivatives. *Synthetic Communications* **39**, 1666-1678 (2009). https://doi.org/10.1080/00397910802573163

13   Rocha, D. H. A., Pinto, D. C. G. A. & Silva, A. M. S. Applications of the Wittig Reaction on the Synthesis of Natural and Natural-Analogue Heterocyclic Compounds. *European Journal of Organic Chemistry* **2018**, 2443-2457 (2018). https://doi.org/https://doi.org/10.1002/ejoc.201800523

14   Nicolaou, K. C., Härter, M. W., Gunzner, J. L. & Nadin, A. The Wittig and Related Reactions in Natural Product Synthesis. *Liebigs Annalen* **1997**, 1283-1301 (1997). https://doi.org/https://doi.org/10.1002/jlac.199719970704

15   Heravi, M. M., Zadsirjan, V., Daraie, M. & Ghanbarian, M. Applications of Wittig Reaction in the Total Synthesis of Natural Macrolides. *ChemistrySelect* **5**, 9654-9690 (2020). https://doi.org/https://doi.org/10.1002/slct.202002192

16   Heravi, M. M., Ghanbarian, M., Zadsirjan, V. & Alimadadi Jani, B. Recent advances in the applications of Wittig reaction in the total synthesis of natural products containing lactone, pyrone, and lactam as a scaffold. *Monatshefte für Chemie - Chemical Monthly* **150**, 1365-1407 (2019). https://doi.org/10.1007/s00706-019-02465-9

17   Bestmann, H. J. & Vostrowsky, O. in *Wittig Chemistry.* 85-163 (Springer Berlin Heidelberg).

18   Pommer, H. & Thieme, P. C. in *Wittig Chemistry.* 165-188 (Springer Berlin Heidelberg).

19   Pommer, H. The Wittig Reaction in Industrial Practice. *Angewandte Chemie International Edition in English* **16**, 423-429 (1977). https://doi.org/https://doi.org/10.1002/anie.197704233

20   Parker, G. L., Smith, L. K. & Baxendale, I. R. Development of the industrial synthesis of vitamin A. *Tetrahedron* **72**, 1645-1652 (2016). https://doi.org/https://doi.org/10.1016/j.tet.2016.02.029

21   Kolodiazhnyi, O. in *Phosphorus Ylides: Chemistry and Application in Organic Synthesis* 359-538 (Johan Wiley & Sons, Ltd., 1999).

22   Ernst, H. Recent advances in industrial carotenoid synthesis. **74**, 2213-2226 (2002). https://doi.org/doi:10.1351/pac200274112213

23   Bonrath, W. *et al.* 75 Years of Vitamin A Production: A Historical and Scientific Overview of the Development of New Methodologies in Chemistry, Formulation, and Biotechnology. *Organic Process Research & Development* **27**, 1557-1584 (2023). https://doi.org/10.1021/acs.oprd.3c00161

24   Schirmer, M.-L., Adomeit, S. & Werner, T. First Base-Free Catalytic Wittig Reaction. *Organic Letters* **17**, 3078-3081 (2015). https://doi.org/10.1021/acs.orglett.5b01352

25   O'Brien, C. J. *et al.* Part I: The Development of the Catalytic Wittig Reaction. *Chemistry – A European Journal* **19**, 15281-15289 (2013). https://doi.org/https://doi.org/10.1002/chem.201301444

26   Lao, Z. & Toy, P. H. Catalytic Wittig and aza-Wittig reactions. *Beilstein Journal of Organic Chemistry* **12**, 2577-2587 (2016). https://doi.org/10.3762/bjoc.12.253

27   Chakraborty, B., Kostenko, A., Menezes, P. W. & Driess, M. A Systems Approach to a One-Pot Electrochemical Wittig Olefination Avoiding the Use of Chemical Reductant or Sacrificial Electrode. *Chemistry – A European Journal* **26**, 11829-11834 (2020). https://doi.org/https://doi.org/10.1002/chem.202001654

28   Cao, J.-J., Zhou, F. & Zhou, J. Improving the Atom Efficiency of the Wittig Reaction by a "Waste as Catalyst/Co-catalyst" Strategy. *Angewandte Chemie International Edition* **49**, 4976-4980 (2010). https://doi.org/https://doi.org/10.1002/anie.201000896

29   Russell, M. G. & Warren, S. Wittig reactions in water. Synthesis of new water-soluble phosphonium salts and their reactions with substituted benzaldehydes. *Tetrahedron Letters* **39**, 7995-7998 (1998). https://doi.org/https://doi.org/10.1016/S0040-4039(98)01740-7

30   Orsini, F., Sello, G. & Fumagalli, T. One-Pot Wittig Reactions in Water and in the Presence of a Surfactant. *Synlett* **2006**, 1717-1718 (2006). https://doi.org/10.1055/s-2006-947323

31   Odinets, I. L. & Matveeva, E. V. Ionic Liquids and Water as “Green” Solvents in Organophosphorus Synthesis. *Current Organic Chemistry* **14**, 1171-1184 (2010). https://doi.org/http://dx.doi.org/10.2174/138527210791330486

32   El-Batta, A. *et al.* Wittig Reactions in Water Media Employing Stabilized Ylides with Aldehydes. Synthesis of α,β-Unsaturated Esters from Mixing Aldehydes, α-Bromoesters, and Ph3P in Aqueous NaHCO3. *The Journal of Organic Chemistry* **72**, 5244-5259 (2007). https://doi.org/10.1021/jo070665k

33   Das, J. & Ghosh, S. A new synthesis of flavones and pyranoflavone by intramolecular photochemical Wittig reaction in water. *Tetrahedron Letters* **52**, 7189-7194 (2011). https://doi.org/https://doi.org/10.1016/j.tetlet.2011.10.134

34   Dambacher, J. *et al.* Water is an efficient medium for Wittig reactions employing stabilized ylides and aldehydes. *Tetrahedron Letters* **46**, 4473-4477 (2005). https://doi.org/https://doi.org/10.1016/j.tetlet.2005.04.105

35   Winterton, N. The green solvent: a critical perspective. *Clean Technologies and Environmental Policy* **23**, 2499-2522 (2021). https://doi.org/10.1007/s10098-021-02188-8

36   Blackmond, D. G., Armstrong, A., Coombe, V. & Wells, A. Water in Organocatalytic Processes: Debunking the Myths. *Angewandte Chemie International Edition* **46**, 3798-3800 (2007). https://doi.org/https://doi.org/10.1002/anie.200604952

37   Margetić, D. Mechanochemistry as a green method in organic chemistry and its applications. *Physical Sciences Reviews* (2023). https://doi.org/doi:10.1515/psr-2022-0351

38   James, S. L. *et al.* Mechanochemistry: opportunities for new and cleaner synthesis. *Chemical Society Reviews* **41**, 413-447 (2012). https://doi.org/10.1039/C1CS15171A

39   Colacino, E. & García, F. Mechanochemistry and Emerging Technologies for Sustainable Chemical Manufacturing. (2023).

40   Ardila-Fierro, K. J. & Hernández, J. G. Sustainability Assessment of Mechanochemistry by Using the Twelve Principles of Green Chemistry. *ChemSusChem* **14**, 2145-2162 (2021). https://doi.org/https://doi.org/10.1002/cssc.202100478

41   Ying, P., Yu, J. & Su, W. Liquid-Assisted Grinding Mechanochemistry in the Synthesis of Pharmaceuticals. *Advanced Synthesis & Catalysis* **363**, 1246-1271 (2021). https://doi.org/https://doi.org/10.1002/adsc.202001245

42   Wohlgemuth, M. *et al.* Milling Medium-Free Suzuki Coupling by Direct Mechanocatalysis: From Mixer Mills to Resonant Acoustic Mixers**. *Chemistry – A European Journal* **29**, e202301714 (2023). https://doi.org/https://doi.org/10.1002/chem.202301714

43   Howard, J. L., Sagatov, Y., Repusseau, L., Schotten, C. & Browne, D. L. Controlling reactivity through liquid assisted grinding: the curious case of mechanochemical fluorination. *Green Chemistry* **19**, 2798-2802 (2017). https://doi.org/10.1039/C6GC03139K

44   Templ, J. & Schnürch, M. Allylation of C-, N-, and O-Nucleophiles via a Mechanochemically-Driven Tsuji–Trost Reaction Suitable for Late-Stage Modification of Bioactive Molecules. *Angewandte Chemie International Edition* **63**, e202314637 (2024). https://doi.org/https://doi.org/10.1002/anie.202314637

45   Takahashi, R. *et al.* Mechanochemical synthesis of magnesium-based carbon nucleophiles in air and their use in organic synthesis. *Nature Communications* **12**, 6691 (2021). https://doi.org/10.1038/s41467-021-26962-w

46   Gao, Y., Kubota, K. & Ito, H. Mechanochemical Approach for Air-Tolerant and Extremely Fast Lithium-Based Birch Reductions in Minutes. *Angewandte Chemie International Edition* **62**, e202217723 (2023). https://doi.org/https://doi.org/10.1002/anie.202217723

47   Wang, G.-W. Mechanochemical organic synthesis. *Chemical Society Reviews* **42**, 7668-7700 (2013). https://doi.org/10.1039/C3CS35526H

48   Tan, D. & García, F. Main group mechanochemistry: from curiosity to established protocols. *Chemical Society Reviews* **48**, 2274-2292 (2019). https://doi.org/10.1039/C7CS00813A

49   Takacs, L. The historical development of mechanochemistry. *Chemical Society Reviews* **42**, 7649-7659 (2013). https://doi.org/10.1039/C2CS35442J

50   Howard, Joseph L., Cao, Q. & Browne, D. L. Mechanochemistry as an emerging tool for molecular synthesis: what can it offer? *Chemical Science* **9**, 3080-3094 (2018). https://doi.org/10.1039/C7SC05371A

51   Thiemann, T., Watanabe, M., Tanaka, Y. & Mataka, S. Solvent-free Wittig olefination with stabilized phosphoranes—scope and limitations. *New Journal of Chemistry* **28**, 578-584 (2004). https://doi.org/10.1039/B311894K

52   Ramírez-Marroquín, O. A. *et al.* First mechanosynthesis of piperlotines A, C, and derivatives through solvent-free Horner-Wadsworth-Emmons reaction. *Synthetic Communications* **49**, 244-255 (2019). https://doi.org/10.1080/00397911.2018.1550204

53   Nguyen, K. C. & Weizman, H. Greening Wittig Reactions: Solvent-Free Synthesis of Ethyl trans-Cinnamate and trans-3- (9-Anthryl)-2-Propenoic Acid Ethyl Ester. *Journal of Chemical Education* **84**, 119 (2007). https://doi.org/10.1021/ed084p119

54   Jiménez-Arellanes, M. A. *et al.* Mechanosynthesis of phosphonocinnamic esters through solvent-free Horner-Wadsworth-Emmons reaction. *Phosphorus, Sulfur, and Silicon and the Related Elements* **197**, 1045-1054 (2022). https://doi.org/10.1080/10426507.2022.2053976

55   Ando, K. & Yamada, K. Highly E-selective solvent-free Horner–Wadsworth–Emmons reaction catalyzed by DBU. *Green Chemistry* **13**, 1143-1146 (2011). https://doi.org/10.1039/C1GC15134G

56   Ando, K. & Yamada, K. Solvent-free Horner–Wadsworth–Emmons reaction using DBU. *Tetrahedron Letters* **51**, 3297-3299 (2010). https://doi.org/https://doi.org/10.1016/j.tetlet.2010.04.072

57   Denlinger, K. L. *et al.* Liquid-assisted grinding and ion pairing regulates percentage conversion and diastereoselectivity of the Wittig reaction under mechanochemical conditions. *Beilstein Journal of Organic Chemistry* **14**, 688-696 (2018). https://doi.org/10.3762/bjoc.14.57

58   Leung, S. H. & Angel, S. A. Solvent-Free Wittig Reaction: A Green Organic Chemistry Laboratory Experiment. *Journal of Chemical Education* **81**, 1492 (2004). https://doi.org/10.1021/ed081p1492

59   Balema, V. P., Wiench, J. W., Pruski, M. & Pecharsky, V. K. Mechanically Induced Solid-State Generation of Phosphorus Ylides and the Solvent-Free Wittig Reaction. *Journal of the American Chemical Society* **124**, 6244-6245 (2002). https://doi.org/10.1021/ja017908p

60   Yan, J. & Jiang, C. Mechanochemical Synthesis of Rosuvastatin Intermediates by Liquid-Assisted Wittig Reaction. *Open Access Library Journal* **7**, 1-7 (2020).

61   Marrett, J. M., Titi, H. M., Teoh, Y. & Friščić, T. Supramolecular "baking powder": a hexameric halogen-bonded phosphonium salt cage encapsulates and functionalises small-molecule carbonyl compounds. *Chemical Science* **15**, 298-306 (2024). https://doi.org/10.1039/D2SC04615F

62   Tang, M., Han, S., Huang, S., Huang, S. & Xie, L.-G. Carbosulfenylation of Alkenes with Organozinc Reagents and Dimethyl(methylthio)sulfonium Trifluoromethanesulfonate. *Organic Letters* **22**, 9729-9734 (2020). https://doi.org/10.1021/acs.orglett.0c03810

63   Liang, X., Andersch, J. & Bols, M. Garner's aldehyde. *Journal of the Chemical Society, Perkin Transactions 1*, 2136-2157 (2001). https://doi.org/10.1039/B101054I

64   Richmond, R. & Zwar, N. Review of bupropion for smoking cessation. *Drug and Alcohol Review* **22**, 203-220 (2003). https://doi.org/10.1080/09595230100100642

65   Dhillon, S., Yang, L. P. H. & Curran, M. P. Bupropion. *Drugs* **68**, 653-689 (2008). https://doi.org/10.2165/00003495-200868050-00011

66   Silva, W. L. *et al.* Synthesis, thermal behavior and biological evaluation of benzodioxole derivatives as potential cytotoxic and antiparasitic agents. *Medicinal Chemistry Research* **32**, 944-956 (2023). https://doi.org/10.1007/s00044-023-03047-5

67   Hawash, M. *et al.* Evaluating the Neuroprotective Potential of Novel Benzodioxole Derivatives in Parkinson's Disease via AMPA Receptor Modulation. *ACS Chemical Neuroscience* (2024). https://doi.org/10.1021/acschemneuro.4c00163

68   Hawash, M., Jaradat, N., Hameedi, S. & Mousa, A. Design, synthesis and biological evaluation of novel benzodioxole derivatives as COX inhibitors and cytotoxic agents. *BMC Chemistry* **14**, 54 (2020). https://doi.org/10.1186/s13065-020-00706-1

69   Porcheddu, A., Colacino, E., Cravotto, G., Delogu, F. & De Luca, L. Mechanically induced oxidation of alcohols to aldehydes and ketones in ambient air: Revisiting TEMPO-assisted oxidations. *Beilstein Journal of Organic Chemistry* **13**, 2049-2055 (2017). https://doi.org/10.3762/bjoc.13.202