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Mechanically induced sequential one-pot Wittig olefination–Diels–Alder reaction: a solvent-free approach to complex bicyclic scaffolds

Nina Biedermann [ID] and Michael Schnürch [ID] *

Herein we present a mechanically induced, solvent-free protocol that sequentially combines the Wittig olefination and Diels–Alder cycloaddition in one-pot and enables the synthesis of structurally complex bicyclic compounds. This method proceeds entirely under ball milling conditions without the requirement of any solvent while eliminating the need for intermediate purification. Careful optimization of the milling parameters and reagent addition enables efficient conversion of various α,β-unsaturated aldehydes and ketones with electron-deficient dienophiles to the corresponding cycloadducts *via* diene intermediates, demonstrating high stereoselectivity and yielding exclusively *endo* Diels–Alder adducts. Furthermore, the extension of the sequence by a solvent-free one-pot oxidation is exemplified, achieving a three-step synthesis in a single milling vessel without intermediate workup and purification, which exhibits excellent green metrics in comparison with solution-based methods. This operationally simple and sustainable approach demonstrates the potential of mechanochemistry to streamline multistep organic synthesis, while reducing solvent use and energy demand.

Introduction

The demand for more sustainable, efficient, and waste-reducing strategies in organic synthesis continues to drive innovation beyond traditional solution-based methodologies,[1] which typically suffer from one or more drawbacks such as high solvent usage, long reaction times, high energy demand, and elaborate purification procedures. Mechanochemical synthesis has emerged as a powerful alternative that enables chemical transformations through mechanical energy input and/or mechanical mixing such as grinding, ball milling, or extrusion.[2–5] Utilizing these techniques, reactions are typically performed under ambient conditions and with no or only minute amounts of solvent, drastically reducing both the energy demand and solvent usage which is in alignment with the principles of green chemistry.[6,7] Furthermore, mechanochemistry has been shown to enable reaction pathways that are inaccessible or inefficient, or differ completely in solution.[8–10]

In parallel, the development of one-pot synthetic methodologies, where multiple reaction steps are performed in a single reaction vessel without intermediate purification, has proven highly valuable for improving step economy, waste reduction, and streamlining workflows.[11–13] The combination of mechanochemistry and one-pot synthesis presents a synergistic platform for sustainable synthesis, merging solvent-free reactions and the operational efficiency of one-pot reaction sequences.

Institute of Applied Synthetic Chemistry, TU Wien, Getreidemarkt 9/163, 1060 Vienna, Austria. E-mail: michael.schnuerch@tuwien.ac.at

This dual strategy has recently been reviewed in detail by our group, highlighting the growing number of one-pot multistep transformations performed *via* milling or grinding.[14] However, despite these advances, one-pot multistep reactions under mechanochemical conditions remain rare, largely due to challenges in reagent compatibility, intermediate stability, and reactivity control in the solid state due to still lacking understanding of mechanistic pathways.

Among the most widely known name-reactions in organic synthesis are the Wittig olefination and the Diels–Alder (DA) reaction, both enabling access to molecular complexity from simple starting materials and of high importance, for example, in the synthesis of natural products.[15–23] The Wittig reaction facilitates the formation of carbon–carbon double bonds by the reaction of aldehydes or ketones with phosphonium ylides *via* a [2 + 2] pericyclic mechanism.[24] The Diels–Alder reaction, on the other hand, is a classic [4 + 2] cycloaddition that allows for the construction of six-membered rings, most commonly between an electron-rich diene and an electron-deficient dienophile.[25]

While both reactions have in principle been demonstrated independently under mechanochemical conditions,[26–34] their integration into a solvent-free one-pot protocol under mechanochemical conditions has not yet been reported. Our group recently developed a simple and robust mechanochemical protocol for the Wittig olefination of aldehydes and ketones, which proceeds cleanly and incredibly fast under solvent-free ball milling conditions[28] (Fig. 1, top left) and has also been demonstrated in a one-pot oxidation–Wittig olefination sequence and further applied in one-pot combination with a Heck cross-coupling reaction.[35]
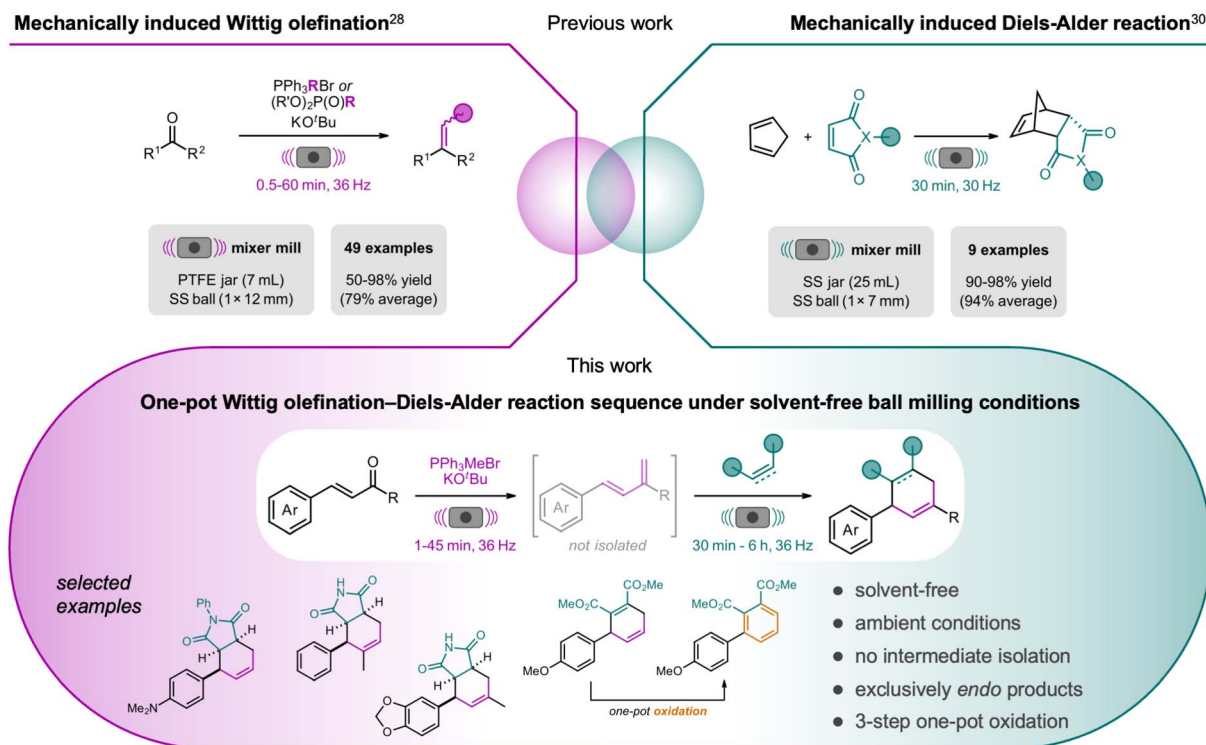
Fig. 1 Previous work on a mechanically induced Wittig olefination of aldehydes and ketones by Templ and Schnürch[28] (top, left), mechanically induced Diels–Alder reaction of cyclopentadiene with maleic anhydride and maleimide derivatives by Zhang et al.[30] (top right), and our herein presented work combining the Wittig olefination and Diels–Alder reaction in a solvent-free sequential one-pot approach, including selected examples and highlighting key aspects of our method (bottom).

Notably, the study on the solvent-free Wittig olefination included examples for conjugated dienes as products. Building upon this result, we identified an opportunity to explore further reactivity by employing the in situ-generated diene as a substrate for a solvent-free Diels–Alder reaction with electron-deficient dienophiles via ball milling, as it has been shown by Zhang et al.[30] with cyclopentadiene and maleic anhydride or maleimide derivatives (Fig. 1, top right).

Herein, we report a mechanochemically induced, solvent-free one-pot protocol that combines the Wittig olefination of α,β-unsaturated aldehydes and ketones with a subsequent Diels–Alder reaction using electron-deficient dienophiles (Fig. 1, bottom). The sequence is performed under solvent-free ball milling conditions with sequential addition of reagents, enabling a one-pot transformation. This operationally simple approach affords a diverse range of bicyclic products from readily available precursors. With our work, we do not only demonstrate the compatibility of these two classical reactions under mechanochemical conditions but also expand the current toolbox of mechanochemical multistep synthesis, contributing to the development of sustainable synthetic routes to complex scaffolds.
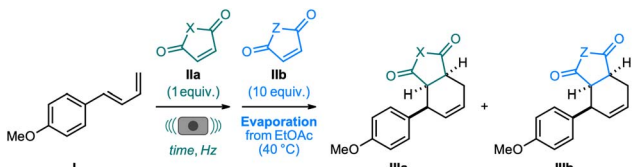
Results and discussion

Optimization of the mechanically induced, solvent-free Diels–Alder reaction

Our investigations started with the exploration of the Diels–Alder reaction under milling conditions with diene **I** and

electron-deficient dienophile *N*-phenylmaleimide (**IIa**, X = N-Ph). Initial experiments on the sequential Wittig olefination–Diels–Alder reaction, where an excess of dienophile (4 equiv.) was added to the reaction vessel after the Wittig olefination, revealed that the reaction also proceeds thermally induced in the isolation process via evaporation from EtOAc at 40 °C. To determine the reaction progress that is solely induced under mechanochemical agitation, optimization experiments were conducted as follows (Table 1): the Diels–Alder reaction of diene **I** was performed in a mixer mill with equimolar amount of dienophile **IIa**. After the milling process, an excess of a second dienophile **IIb** (10 equiv.), the quencher dienophile, was added to the milling jar before the addition of any solvent. Due to the large excess of the quencher dienophile, remaining diene should react preferentially with that one (Table 1, entry A1), allowing a differentiation between the solventless and thermally induced Diels–Alder reaction. Subsequently, the reaction mixture was evaporated from EtOAc at 40 °C water bath temperature to guarantee complete conversion of any unreacted diene intermediate to the quench-product. ^{1}H NMR was measured from the residue to determine the reaction progress in the ball mill (for details see SI). The reaction with *N*-phenylmaleimide (**IIa**, X = N-Ph) was optimized in terms of milling time and frequency (Table 1, entries A2–A5), showing complete conversion to **IIIa** in the mechanochemical process within 15 minutes at a frequency of 36 Hz (entry A5). Other milling parameters such as the material and size of the milling

Table 1   Optimization of the milling parameters for the mechanically induced Diels–Alder reaction of diene **I** under solvent-free conditions in a mixer mill[a]

Entry	**IIa**, X =	Frequency [Hz]	Time [min]	**IIb**, Z =	Ratio **IIIa** : **IIIb** (^{1}H NMR[b])	Yield **IIIa** [%]
A1[c]	N-Ph	In solution	45	NH	25 : 75	n.d.[d]
A2	N-Ph	30	30	NH	100 : 0	88
A3	N-Ph	30	15	NH	79 : 21	67
A4	**N-Ph**	**36**	**15**	**NH**	**100 : 0**	**91**
A5	N-Ph	36	10	NH	68 : 32	62
A6	NH	30	30	N-Ph	58 : 42	52
A7	**NH**	**36**	**30**	**N-Ph**	**100 : 0**	**97**
A8	**O**	**36**	**15**	**N-Ph**	**100 : 0**	**n.d.[d,e]**

[a] Reaction conditions: performed on 0.25 mmol scale at ambient temperature in a PTFE milling jar (7.5 mL) containing one hardened stainless-steel ball (∅ = 12 mm) in an IST636 mixer mill at 36 Hz. Diene **I** (1.0 equiv.) and dienophile **IIa** (X, 1.0 equiv.) were combined in the milling jar and milled for the indicated time at the indicated milling frequency. Workup: excess of a second dienophile **IIb** (Z, 10 equiv.) added to the milling jar; reaction mixture washed out with EtOAc and evaporated at 40 °C (water bath); isolated yields are reported. [b] Determined by integration of the CH2 group signals in ^{1}H NMR spectrum (for details see SI). [c] Diene **I** was added to a solution of dienophiles (1 : 10 mixture) in EtOAc (for details see SI). [d] n.d. = not determined. [e] Diminished yield upon isolation *via* column chromatography.

jar, or the number, size and material of the milling balls were not investigated further since the presented conditions using a 7.5 mL PTFE milling jar and one hardened stainless-steel ball with a diameter of 12 mm were the optimized reaction conditions for the Wittig olefination reported by our group.[28]

Other dienophiles, namely maleimide (**IIa**, X = NH) and maleic anhydride (**IIa**, X = O), were tested too, showing that the reaction with maleimide is slower, requiring 30 minutes of milling time at 36 Hz (entry A7). For maleic anhydride, milling for 15 minutes at 36 Hz was sufficient to obtain complete conversion of diene **I** to the respective DA product **IIIa** (entry A8). However, product **IIIa** with X = O could not be isolated efficiently *via* column chromatography, neither under standard column chromatography conditions nor under basic conditions (addition of 1% Et3N to the eluent), resulting in low isolated yields.

Optimization of the one-pot Wittig–Diels–Alder reaction sequence for (*E*)-4-methoxycinnamalaldehyde

Our optimization for the one-pot operation of the Wittig olefination and DA reaction (Table 2) started with the olefination conditions reported by our group.[28] Using PPh3MeBr (1.2 equiv.) and KO*t*Bu (1.4 equiv.), the Wittig olefination of (*E*)-4-methoxycinnamalaldehyde (**1**) was carried out by milling for 1 minute at 36 Hz, resulting in complete conversion to diene **I**. Subsequently, dienophile **2a** (1.0 equiv.) was added, and milling was continued for 15 minutes. However, under these conditions, the desired DA product **3a** was not obtained, and NMR analysis only showed the quench-product **3b** (Table 2, entry B1). Additional experiments on the DA reaction revealed that already

small amounts of KO*t*Bu present in the reaction mixture result in no or less conversion to the DA product (for details see SI), probably due to base-catalyzed hydrolysis of the dienophile. Therefore, the insertion of a base quenching step with solid NH4Cl between the Wittig and DA steps was investigated. After the Wittig olefination, solid NH4Cl (1 equiv.) was added to the jar and milling was conducted for 30 or 60 seconds, before the respective dienophile was added (entries B2–B3). Under these conditions, DA product **3a** was formed in the milling process, however only in low yield of maximum 17%, independent of the milling time for the quenching step. Switching the equivalents of PPh3MeBr and KO*t*Bu to avoid an excess of base resulted in better conversion in the mechanochemical process (entry B4) but still was not satisfactory, even when preformation of the Wittig ylide was performed to guaranty complete consumption of KO*t*Bu (entry B5). Including again a base quenching step with solid NH4Cl (1 equiv.), complete conversion to the DA product **3a** was observed performing the following sequence: first, the Wittig olefination was performed combining aldehyde **I** (1.0 equiv.), PPh3MeBr (1.4 equiv.) and KO*t*Bu (1.2 equiv.) in a milling jar and milling for 1 minute, followed by the addition of solid NH4Cl and additional milling for 1 minute. Subsequently, dienophile **2a** was added and milling was continued for 15 minutes (entry B7). In this case, only **3a** was observed when NMR analysis was conducted and **3a** was isolated in 84% yield which corresponds to the isolated yield for the Wittig olefination product **I**, reported by Templ and Schnürch,[28] indicating a quantitative Diels–Alder reaction. In order to rule out any catalytic effect of the grinding medium, the stainless-steel ball was replaced by an inert ZrO2 grinding ball, still affording product **3a** in a consistent yield of 85% (NMR yield) (entry B8).

Table 2 Optimization of the reaction conditions for the sequential one-pot Wittig olefination and Diels–Alder reaction of (E)-4-methoxy-cinnamalaldehyde (**1**)[a]
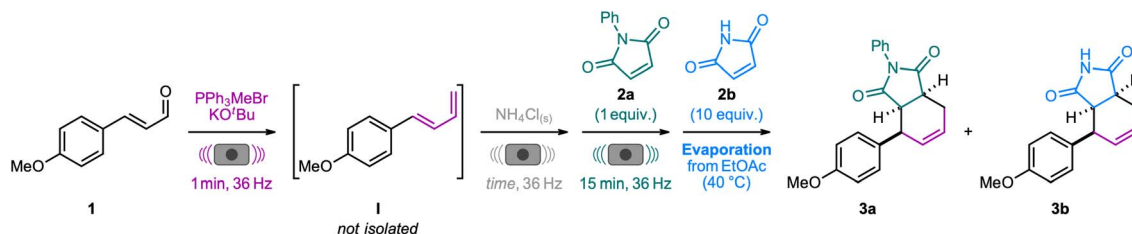
Entry	PPh$_3$MeBr [equiv.]	KO^{t}Bu [equiv.]	NH$_4$Cl [equiv.]	Time [min]	Ratio **3a** : **3b** (^{1}H NMR[b])	Yield **3a** [%]
B1	1.2	1.4	—	—	0 : 100	—
B2	1.2	1.4	1	0.5	22 : 78	16
B3	1.2	1.4	1	1	22 : 78	17
B4	1.4	1.2	—	—	40 : 60	n.d.[c]
B5[d]	1.8	1.6	—	—	66 : 33	n.d.[c]
B6	1.4	1.2	1	0.5	95 : 5	81
B7	**1.4**	**1.2**	**1**	**1**	**100 : 0**	**84**
B8[e]	1.4	1.2	1	1	100 : 0	85[f]

[a] Reaction conditions: performed on 0.3 mmol scale at ambient temperature in a PTFE milling jar (7.5 mL) containing one hardened stainless-steel ball (Ø = 12 mm) in an IST636 mixer mill at 36 Hz. Aldehyde **1** (1.0 equiv.), PPh$_3$MeBr (1.2 equiv.) and KO^{t}Bu (1.4 equiv.) were combined in the milling jar (1 minute); then addition of NH$_4$Cl (1.0 equiv.) (1 minute); subsequent addition of N-phenylmaleimide (**2a**, 1.0 equiv.) (15 minutes). Workup: excess of maleimide (**2b**, 10 equiv.) added to the milling jar; reaction mixture evaporated from EtOAc at 40 °C (water bath); isolated yields are reported. [b] Determined by integration of the CH$_2$ group signals in ^{1}H NMR spectrum (for details see SI). [c] n.d. = not determined. [d] Preformation of the ylide by milling of PPh$_3$MeBr and KO^{t}Bu for 1 minute at 36 Hz, then addition of aldehyde starting material **1** and milling for 1 minute; more equivalents of Wittig reagent and base were necessary to achieve complete conversion of aldehyde **1** within 1 minute of reaction time. [e] One ZrO$_2$ ball (Ø = 12 mm) used instead of stainless-steel ball. [f] NMR yield using 1,3,5-trioxane as internal standard.

Additionally, the stereochemistry of cycloadduct **3a** formed from reaction with dienophile **2a** was unambiguously confirmed as the *endo* conformer *via* NOESY NMR and single-crystal X-ray diffraction (for details see SI). Notably, only the *endo* product was observed, indicating that the Diels–Alder reaction proceeds with high *endo* selectivity under the employed solvent-free milling conditions.
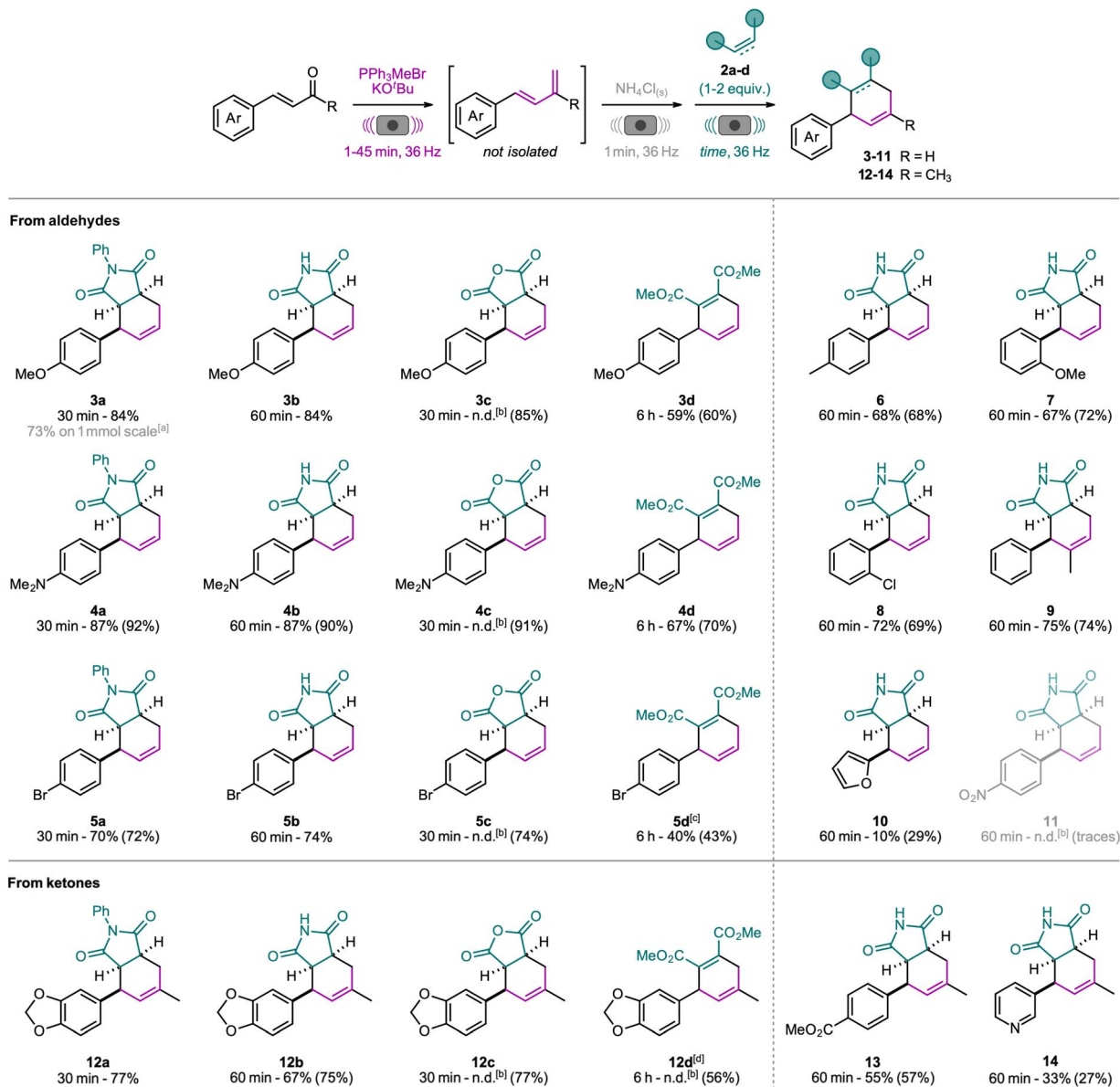
Scope of the one-pot Wittig olefination–Diels–Alder reaction sequence

With the optimized reaction conditions in hand, we explored the sequential one-pot Wittig olefination–Diels–Alder reaction with a range of α,β-unsaturated aldehydes and ketones, as well as various dienophiles (Scheme 1). In addition to the dienophiles presented in the optimization studies, a broader range of electron-deficient alkenes and alkynes was evaluated under the optimized mechanochemical conditions with substrate **1**. These included, for example, diethyl maleate, (E)-but-2-enedinitrile, a variety of sulfonyl-substituted alkenes, and acrylates. However, none of these investigated dienophiles afforded the corresponding Diels–Alder adducts within milling times of 30–60 minutes, and single experiments including Lewis acids to accelerate the DA reaction were unsuccessful too, suggesting polymerization of diene **I** (for details see SI). Notably, dimethyl acetylenedicarboxylate (DMAD, **2d**) was an additional dienophile found to participate in the cycloaddition under ball milling conditions. Nevertheless, its reactivity was significantly

lower compared to the maleimide-based dienophiles. In order to obtain complete conversion, a prolonged milling time of 6 hours and the use of 2 equivalents of DMAD were required (for optimization see SI), suggesting that reactivity under solvent-free conditions is highly dependent on the dienophile's electron deficiency.

In general, to ensure complete conversion across structurally diverse substrates and avoid the need for individual optimization, the reaction times for the DA step were slightly prolonged compared to the initial optimization studies. Specifically, milling durations were set to 30 minutes for reactions with N-phenylmaleimide (**2a**) and maleic anhydride (**2b**), 60 minutes for unsubstituted maleimide (**2c**), and 6 hours for DMAD (**2d**). With these dienophiles, the electronic influence of the substituent in *para* position on the phenyl ring of the diene was investigated starting the sequence from the respective α,β-unsaturated aldehyde. Electron-donating substituents (EDGs) such as methoxy and dimethylamino afforded products **3a–d** and **4a–d**, respectively, in moderate to high yield across all dienophiles, even on an increased scale which has been exemplified for compound **3a**, obtained in 84% (0.3 mmol) and 73% yield (1.0 mmol). In contrast, slightly diminished yields were obtained for their bromine-substituted analogue (products **5a–d**), an electron-withdrawing group (EWG). Notably, despite lower overall yields in the presence of an EWG, no residual diene and therefore the corresponding quench-product was observed in the crude ^{1}H NMR spectra (except in the case of

Scheme 1 Scope of the one-pot Wittig olefination–Diels–Alder reaction sequence of α,β-unsaturated aldehydes and ketones using different dienophiles. Isolated yields are shown (NMR yields in brackets using 1,3,5-trioxane as internal standard). Reaction conditions: Performed on 0.3 mmol scale at ambient temperature in a PTFE milling jar (7.5 mL) containing one hardened stainless-steel ball (∅ = 12 mm) in an IST636 or a Retsch MM500 vario mixer mill at 36 Hz or 35 Hz, respectively. In all cases, a "quencher" dienophile was added to the crude reaction mixture before the addition of solvents. If not stated otherwise, complete conversion to the desired product was observed in the milling process within the indicated time (for details see SI). From aldehyde: aldehyde (1.0 equiv.), PPh₃MeBr (1.2 equiv.) and KOᵗBu (1.4 equiv.) were combined in the milling jar (1 or 10 minute(s)); then addition of NH₄Cl (1.0 equiv.) (1 minute); subsequent addition of respective dienophile (1.0 equiv.; except for **3d**, **4d**, and **5d**: 2.0 equiv.) (indicated time). From ketone: PPh₃MeBr (1.8 equiv.) and KOᵗBu (1.6 equiv.) were combined in the milling jar (1 minute), then addition of ketone (1.0 equiv.) (45 minutes); then addition of NH₄Cl (2.0 equiv.) (1 minute); subsequent addition of respective dienophile (1.0 equiv.; except for **12d**: 2.0 equiv.) (indicated time). [a] Reaction was performed on a 1 mmol scale using one hardened stainless-steel ball (∅ = 12 mm) in a 25 mL PTFE milling jar; [b] n.d. = not determined – isolated yield was not determined due to isolation difficulties. [c] No complete conversion to **5d** in the milling process. [d] Product **12d** was obtained as a mixture with a byproduct which was inseparable via column chromatography (for details see SI).

substrate **5d**), indicating efficient consumption of the diene in the cycloaddition step. However, the Wittig olefination was found to proceed with lower efficiency for (E)-4-bromo-cinnamaldehyde (65% isolated yield, for details see SI) compared to the cinnamaldehyde derivatives with EDG. For

compound **5d**, bearing an electron-poor aryl ring, incomplete conversion to the desired Diels–Alder product was observed after 6 hours of milling with DMAD, consistent with reduced diene reactivity and in alignment with established frontier molecular orbital considerations for the Diels–Alder reaction:

electron-rich dienes (with elevated HOMO energies) engage more effectively with electron-poor dienophiles (lower LUMO), enabling favorable orbital overlap.[25,36]

The substrate scope was further expanded using maleimide (**2b**) as dienophile and α,β-unsaturated aldehydes with various substituents and aryl substitution patterns. Including methyl- and chloro-substituents, cycloaddition products **6–9** were obtained in good yields in the range of 68–75%, demonstrating tolerance toward moderate electronic variations. A furan-derived aldehyde afforded the corresponding cycloadduct **10** in only 10% isolated yield (29% NMR yield), despite complete conversion of the starting materials and no indication of residual diene intermediate. A control experiment excluding the dienophile **2b** confirmed that the diene decomposes upon extended milling (for details see SI). Similarly, nitro-substituted aldehyde failed to yield cycloadduct **11**, likely due to excessive electron deficiency of the diene intermediate. Although the diene was formed *via* Wittig olefination, only trace amounts of the desired product were detected. In both cases, compound **10** and **11**, ^{1}H NMR spectra of the crude reaction mixtures did not show signals consistent with the corresponding quench-products, suggesting degradation of the diene intermediate upon milling due to lacking reactivity with the dienophile.

Subsequently, α,β-unsaturated ketones were investigated as diene precursors, which were prepared from the respective benzaldehyde derivatives by Wittig olefination with dimethyl-2-oxopropylphosphate under milling conditions, following the previously reported protocol from our group (for details see SI).[28] Starting from these ketones, the reaction conditions for the Wittig methylenation to obtain the desired diene intermediates had to be adapted. Our investigations revealed that preformation of the Wittig ylide is essential to obtain high conversion to the diene, likely due to competitive enolate formation in the presence of base. Additionally, increased equivalents of Wittig salt and KO*t*Bu along with an extended

milling time of 45 minutes were necessary to drive the reaction to completion (for details see SI). However, with these refinements of the reaction conditions, the Wittig olefination–DA sequence could again be performed in one-pot fashion yielding the desired cycloaddition products. Compounds **12a–c** were obtained in good yield from a piperonal derivative and the respective dienophiles. In the case of DMAD, ^{1}H NMR analysis of the crude mixture indicated a yield of 56% of compound **12d**, although a minor inseparable byproduct was present and **12d** could not be obtained in pure form upon isolation (for details see SI). Expanding the ketone-based scope, compound **13** bearing a methyl ester substituent was obtained in moderate yield, whereas a pyridine-substituted diene displayed significantly lower reactivity due to the electron-poor nature of the pyridine moiety, affording the corresponding product **14** in only 33% yield.

It has to be mentioned that in all examples of the substrate scope 5 equiv. of a quencher dienophile were added before the isolation procedure. This ensured, that in all examples the isolated yield is derived from product formed during milling and not during workup. Even though important for the present study, this is not necessary when researchers of the scientific community apply our protocol, and alternative monitoring methods can be used such as TLC or NMR to track complete consumption of the starting materials.

It is further worth noting that although the reaction sequence was carried out without external heating, high-speed ball milling is known to generate heat through mechanical impact and friction, with temperature increases depending on various parameters (type of mill, milling frequency, time, material of the milling jar and balls *etc.*).[37–39] In addition, the physical state of the reaction mixture plays a significant role in temperature fluctuation upon milling.[38] Notably, all reactions turned into pastes after the Wittig olefination step due to the formation of *tert*-butanol, and after the subsequent Diels–Alder
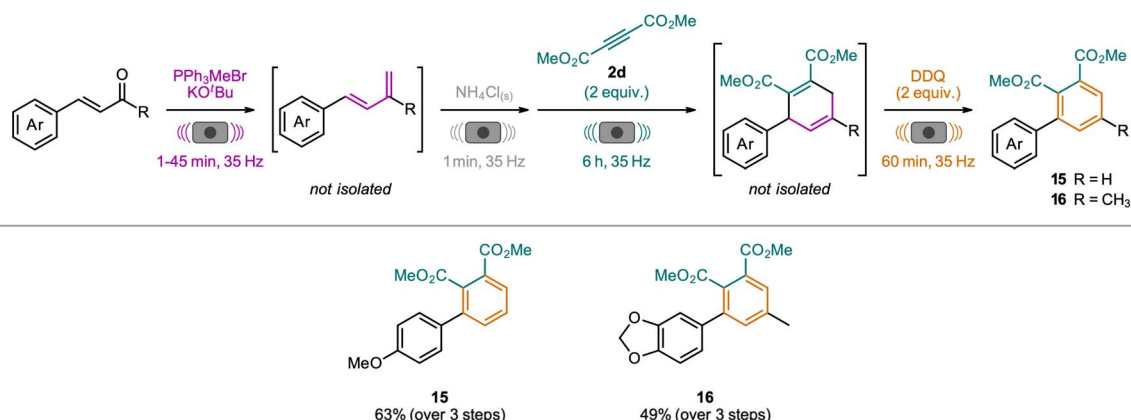
Scheme 2 One-pot Wittig olefination–Diels–Alder reaction–oxidation sequence to obtain the corresponding biaryl products. Reaction conditions: performed on 0.3 mmol scale at ambient temperature in a PTFE milling jar (7.5 mL) containing one hardened stainless-steel ball (Ø = 12 mm) in a Retsch MM500 vario mixer mill at 35 Hz. For **15**: aldehyde **1** (1.0 equiv.), PPh₃MeBr (1.2 equiv.) and KO*t*Bu (1.4 equiv.) were combined in the milling jar (1 minute); then addition of NH₄Cl (1.0 equiv.) (1 minute); subsequent addition of **2d** (2.0 equiv.) (6 hours); final addition of DDQ (2.0 equiv.) (60 minutes). For **16**: PPh₃MeBr (1.8 equiv.) and KO*t*Bu (1.6 equiv.) were combined in the milling jar (1 minute), then addition of ketone (1.0 equiv.) (45 minutes); then addition of NH₄Cl (2.0 equiv.) (1 minute); subsequent addition of **2d** (2.0 equiv.) (6 hours); final addition of DDQ (2.0 equiv.) (60 minutes) (for details see SI).

reaction oily residues were obtained, particularly for those involving liquid dienophile **2d** (for images see SI). However, the change in rheology upon the Wittig olefination is not expected to particularly influence the outcome of the Diels–Alder reaction, as in the first optimization experiments for the isolated DA (see Table 1) solely solid reaction mixtures were obtained even for reactions with complete conversion.

Furthermore, temperatures measurements were performed for representative examples throughout the scope to possibly explain the discrepancy in reaction times throughout the investigated dienophiles (for details see SI). In general, a consistent rise in temperature was observed during milling, with strong dependency on the milling time. For short milling steps of 1–10 minutes at 35 Hz, corresponding to the Wittig olefination and base-quenching steps, temperatures of ~30–40 °C were reached. For the subsequent DA reaction with **2a** with a milling time of 30 minutes, temperatures between 53 and 58 °C were measured, and extension of the time to 60 minutes (reactions with **2b**) resulted in a further rise to approximately 60 °C. Interestingly, significantly longer milling times of 6 hours (as required for reactions with **2d**) did not result in further heating, reaching a temperature plateau at ~60 °C.

These observations suggest that the temperature increase during milling likely contributes to faster reaction kinetics in the DA step, particularly for less reactive substrates such as **2b** and **2d**. Further investigations on the influence of milling frequency revealed that increasing the frequency stepwise from 10 to 35 Hz led to a continuous increase in product yields for **3a** and **3b**, accompanied by a rise in temperature from 27 to 44 °C (with constant milling times of 15 and 30 minutes, respectively; see SI). This suggests that both elevated temperatures and enhanced mechanical impact/friction could potentially contribute to the observed reactivity. However, as both parameters are intrinsically linked, their individual effects cannot be separated. A clear distinction between thermal and mechanical contributions would require experimental conditions where one variable could be independently controlled while keeping the other constant, which is not feasible with our current experimental setup.

One-pot Wittig olefination–Diels–Alder reaction–oxidation sequence

Finally, we aimed to perform a sequential one-pot oxidation of product **3d** to obtain the corresponding biaryl product **15** (Scheme 2). Under the conditions reported by Xu et al.[40] using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as oxidant, we achieved a fully solvent-free Wittig olefination–Diels–Alder–oxidation sequence without any intermediate workup. The one-pot oxidation of intermediate **3d**, obtained via the presented Wittig olefination–DA reaction sequence, proceeded smoothly by the addition of 2 equiv. of DDQ to the same milling jar and further milling for 60 minutes at 35 Hz (the use of only 1 equiv. DDQ resulted in incomplete conversion). The desired oxidation product **15** was obtained in 63% yield over three steps. The same route was further successful to transform compound **12d** into the corresponding biaryl **16** in a one-pot fashion, also allowing separation of the byproduct obtained in the Wittig–DA sequence as described earlier.

A comparable route towards compound **15** in solution has been demonstrated by Yasukawa et al.[41] (Scheme 3A). In this approach, diene **I** was synthesized by classical Wittig olefination of the aldehyde **1** and isolated by column chromatography (CC). The diene was then subjected to a neat DA reaction with **2d**, followed by a one-pot oxidation in water using Pd/C as catalyst and an excess of acrylic acid to regenerate Pd⁰, yielding **15**. Another protocol, reported by Huang et al.,[42] established the synthesis of **15** via iridium-catalyzed ortho-arylation of benzoic acid **IV** with diazonium salt **V** in acetone, followed by one-pot esterification of intermediate **VI** using methyl iodide in an acetone/acetonitrile (MeCN) mixture (Scheme 3B).

Comparing these two methods with our solvent-free, mechanochemical approach (Table 3), several advantages can be pointed out. First, our mechanochemical one-pot approach
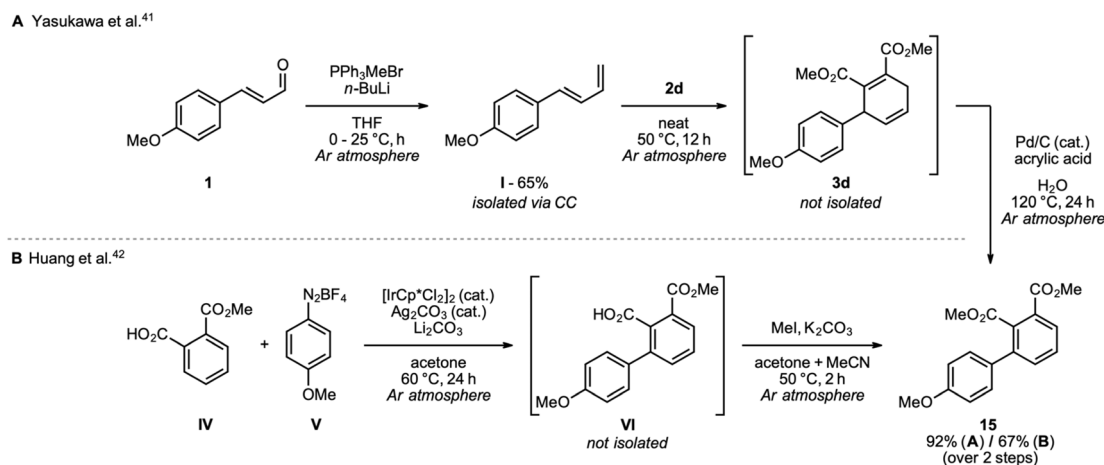
Scheme 3 Solution-based syntheses toward compound **15**; method (A): comparable approach via diene **I** and cycloadduct **3d**, reported by Yasukawa et al.;[41] method (B): one-pot approach based on iridium-catalyzed ortho-arylation of benzoic acid **IV** with diazonium salt **V**, reported by Huang et al.[42]

Table 3 Comparison of our mechanochemical approach and the solution-based methods A and B and for the synthesis of compound **15**, including comparison of the environmental factor (E-factor) and process mass intensity (PMI) (for calculation see SI)

Parameter	Mechanochemical approach	Solution method A	Solution method B
Yield [%]	63	60	67
Time [h]	7	>36	26
Atmosphere	Air	Argon	Argon
Temperature [°C]	Ambient	Up to 120	Up to 60
Solvent	None	THF, H_2O	Acetone, MeCN
No. isolation steps	1	2	1
Harmful reagents	DDQ	Acrylic acid	Iodomethane
E-factor[a]	7.4	72.5[b] 36.3[c]	26.5
PMI[a]	8.4	72.5[b] 37.3[c]	27.5

[a] Calculations were performed without consideration of solvents and mass separating agents used in the workup and isolation process. [b] Including H_2O used as solvent. [c] Excluding H_2O used as solvent.

stands out in terms of significantly shorter reaction times of only 7 hours *vs.* >36 hours (method A) and 26 hours (method B). Unlike the solution-based protocols, our process is operated without precautions from air and moisture, and without the need for an external heating source. While each of the three methods employs at least one hazardous reagent, the nature, amount, and associated risks vary significantly. Our mechanochemical approach makes use of DDQ (2 equiv.), which is classified as toxic if swallowed and should be handled with care. However, it is used under solvent-free conditions and in a closed system, reducing the risk of exposure. In contrast, solution method A requires a large excess (5 equiv.) of acrylic acid, a highly corrosive and volatile substance with serious health and environmental hazards, and aquatic toxicity. Solution method B involves methyl iodide (5 equiv.), a reagent known for its acute toxicity, mutagenicity, and suspected carcinogenicity, making it particularly concerning from a safety and regulatory point of view. Considering these factors, while none of the approaches is entirely free from hazardous reagents, the mechanochemical method offers a safer and more environmentally responsible alternative to the solution-based protocols by avoiding flammable solvents and highly toxic or carcinogenic reagents, and operating in a closed milling environment.

For comparison of the efficiency and environmental impact of the protocols, some relevant green metrics, namely the environmental factor (E-factor) and process mass intensity (PMI), were calculated (for details see SI). Our solvent-free one-pot three-step approach was found to exhibit an excellent E-factor of 7.4 and PMI score of 8.4, while significantly higher values were calculated for the solution methods A (E-factor/PMI: 72.5/73.5 (incl. H_2O), 36.3/37.3 (excl. H_2O)) and B (E-factor/PMI: 26.5/27.5). These values highlight the superior material economy and waste minimization achieved under solvent-free conditions.

Ultimately, the presented solvent-free one-pot three-step protocol represents an efficient and simple method for the synthesis of highly functionalized arenes, eliminating the need for any solvent or intermediate handling, thus contributing to the development of greener multistep synthesis.

Conclusions

In conclusion, we have developed a mechanically induced, solvent-free one-pot protocol that combines the Wittig olefination to obtain diene intermediates with a subsequent Diels–Alder reaction, providing an efficient and sustainable route to structurally complex bicyclic compounds. Through careful optimization of milling parameters and sequential addition of reactants and reagents, we established a method that proceeds under ball milling conditions without the need for intermediate purification.

The method shows broad applicability across a range of α,β-unsaturated aldehydes and ketones, as well as several electron-deficient dienophiles. Electronic effects on both the diene and dienophile components were found to significantly influence the reaction's efficiency, in line with established frontier molecular orbital principles. The ability to merge these two iconic reactions into an operationally simple and sustainable mechanochemical one-pot protocol underscores not only the compatibility of classic solution-phase transformations with solvent-free, mechanically induced synthesis, but also expands the repertoire of multistep mechanochemical methodologies. Moreover, we successfully extended the one-pot sequence by including a final oxidation step under solvent-free conditions, ultimately achieving a three-step synthesis in a single reaction

vessel without intermediate handling, which exhibits better green metrics than known solution methods.

Overall, the method's operational simplicity, efficiency, and environmentally friendly nature offers a distinct advantage over traditional methods, showing the potential of mechanochemistry to simplify synthetic processes and promote more sustainable practices in organic chemistry.

Author contributions

N. B. conducted synthetic experiments, optimizations and analytical characterization, and led the manuscript writing. M. S. performed the administration and supervision of the project as well as reviewing and editing of the manuscript. All authors have read and approved to the published version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

The metadata of this work (NMR spectra) is available *via* the TU Wien Research Data platform under DOI: **10.48436/ab694-b9p15**.

CCDC 2464570 (**3a**) contains the supplementary crystallographic data for this paper.[43]

Supplementary information (SI): all data supporting the findings of this study is available within the paper and its SI. General information, detailed description of NMR analysis of product mixtures and quant. NMR measurements, temperature measurements, further investigations and optimizations, detailed methods and characterization data for starting materials and compounds, green metrics calculations, NMR spectra, and X-ray analysis for **3a**. See DOI: **https://doi.org/10.1039/d5mr00087d**.

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