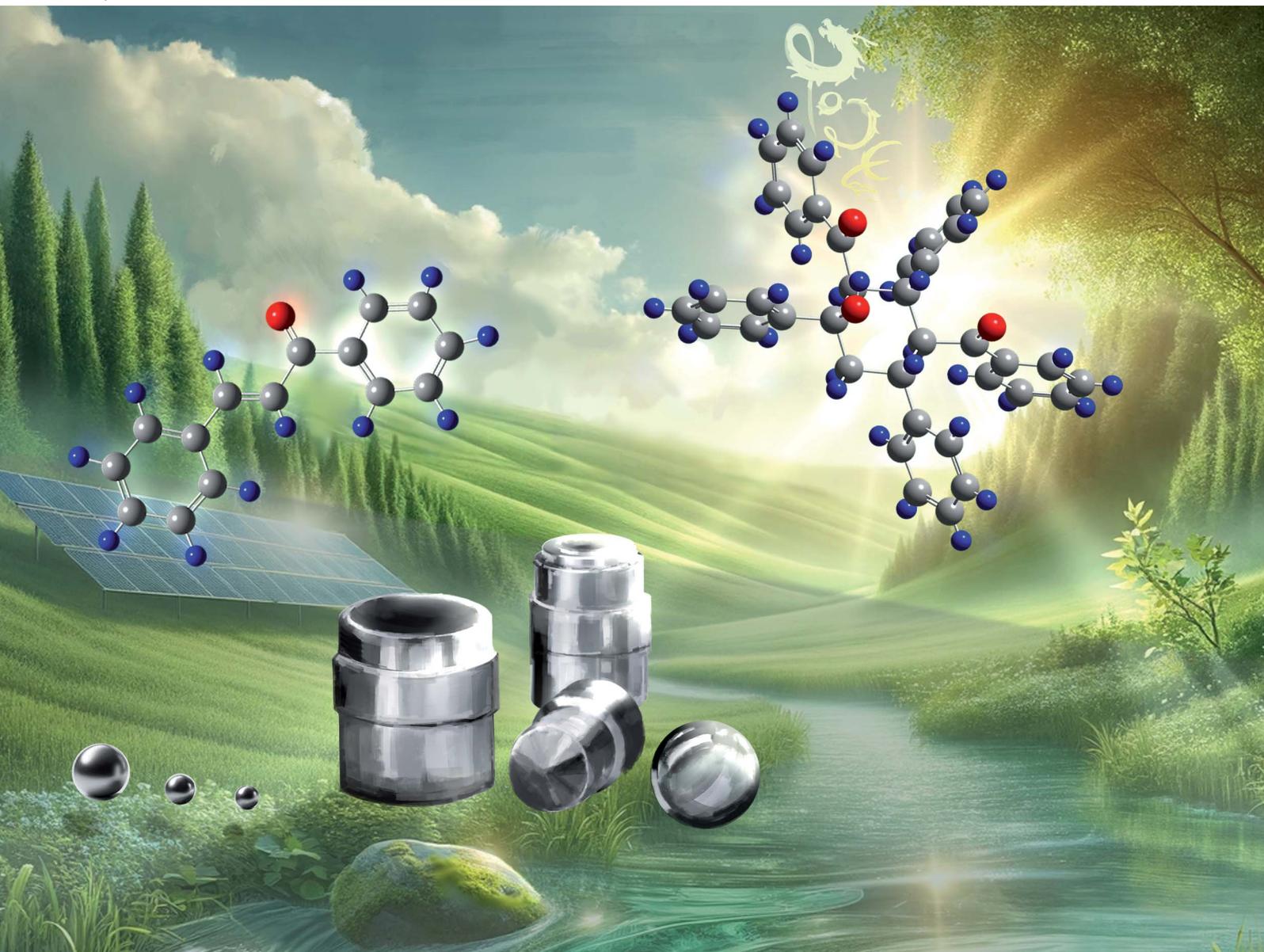


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PAPER

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Base-mediated trimerization of enones under solvent-free
and ball-milling conditions

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Base-mediated trimerization of enones under solvent-free and ball-milling conditions†

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An efficient mechanochemical trimerization of enones with KO^tBu as the base and water as the proton source under solvent-free and ambient conditions has been developed. This protocol provides novel, simple, rapid and scalable access to 1,3,5-triaryl-2,4-acyl-cyclohexanols, which exist as chair conformations with all bulky substituents located at equatorial positions. In addition, the formed cyclohexanol derivatives can be further dehydrated to afford the corresponding cyclohexene derivatives with β,γ -unsaturation. By changing the type or amount of the employed base, another type of stereoisomer, where the 4-acyl group is situated at the axial position, can be favorably generated as the major product.

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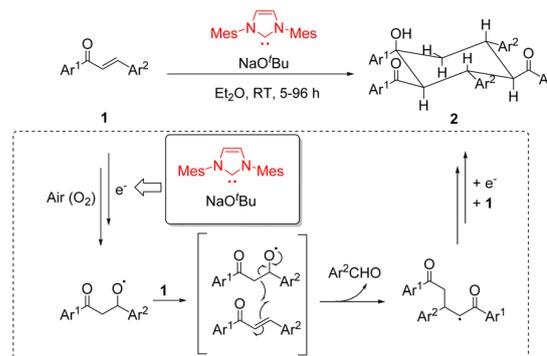
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Mechanochemical organic transformations have drawn increasing attention over the past few decades.¹ Apart from providing efficient and ambient organic processes in modern synthetic chemistry, mechanochemical reactions can even alter the chemical selectivity, providing unexpected products that cannot be generated by their solution-based counterparts.²

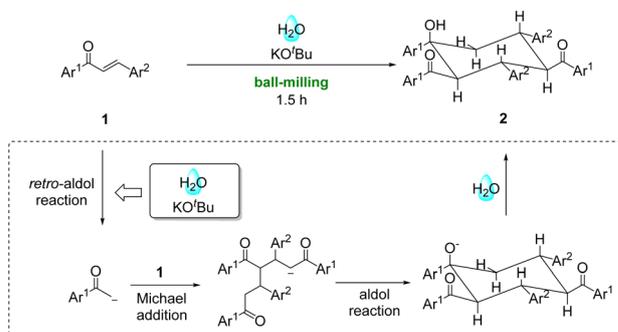
Over the past two decades, enones have been frequently applied in the area of mechanochemistry, such as Michael additions,³ aminohalogenations,⁴ Mn(OAc)₃-mediated radical reactions⁵ and cascade reactions.⁶ Recently, the trimerization of enones was realized using N-heterocyclic carbene (NHC)/NaO^tBu/O₂ in ether for 5–96 h *via* an initial single-electron-transfer (SET) step, subsequent reaction with O₂, radical coupling and homolytic O–O bond breaking to generate the key alkoxy radical, followed by reactions with two other enones through multiple steps (Scheme 1a).⁷ This reaction required the combination of NHC and NaO^tBu to generate radical intermediates from enones for further reactions. In continuation of our interest in mechanochemistry,⁸ we herein disclose our finding that enones can undergo mechanochemical solvent-free trimerization with KO^tBu as the base and water as the proton source

through a cascade process of the *retro*-aldol reaction of enones, followed by double Michael additions and a final intramolecular aldol reaction (Scheme 1b).

Previous work

a) NaO^tBu/NHC-enabled trimerization of enones *via* radical pathway

This work

b) KO^tBu/H₂O-enabled trimerization of enones *via* domino reaction

Scheme 1 Strategies for the trimerization of enones.

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† Electronic supplementary information (ESI) available: Detailed experimental procedures and characterization data, NMR spectra of products 2a–2v, 2a', 3a, 4a and 4q, and X-ray data of product 2a. CCDC 2277780. For ESI and crystallographic data in CIF or other electronic format see DOI: <https://doi.org/10.1039/d3mr00010a>



Chalcone **1a** was chosen as the model substrate to determine the optimal reaction conditions. Initially, 0.20 mmol of **1a** and 2 equiv. of KO^tBu were added into a stainless steel jar (5 mL) together with 4 stainless steel balls (5 mm in diameter) under solvent-free and ambient conditions and mixed at a milling frequency of 1800 rounds per minute (rpm) in a Retsch MM 400 mixer mill at room temperature for 1.5 h. Unfortunately, 2,4-dibenzoyl-1,3,5-triphenylcyclohexanol (**2a**) could be observed only in a trace amount, together with its stereoisomer **2a'** in 34% yield (Table 1, entry 1). The stereochemistry of **2a** was determined from its NMR spectra⁷ and unambiguously established by single-crystal X-ray crystallography (Fig. 1), while the stereochemistry of **2a'** was confirmed by comparison of its NMR data with those reported in the previous literature.⁹ The single-crystal structure of **2a** clearly showed that all bulky phenyl and benzoyl groups were located at equatorial positions in the chair conformation. In contrast, most bulky substituents of **2a'** were situated at equatorial sites except for the axial 4-benzoyl group. To our satisfaction, the outcome was dramatically changed when 2 equiv. of H₂O was added as the proton source, and **2a** was obtained selectively and efficiently in 86% yield (Table 1, entry 2). These results indicated that H₂O was crucial in promoting this reaction. With the increase in the amount of

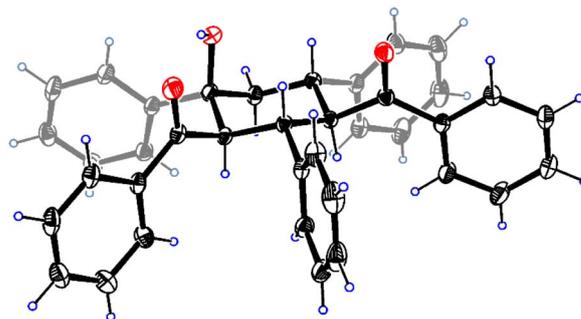


Fig. 1 ORTEP diagram for one enantiomer of racemic **2a** with 15% thermal ellipsoids. The solvent molecule CHCl₃ is omitted for clarity.

H₂O to 3 equiv., the product yield was enhanced to 95%, yet further increasing the amount of H₂O to 4 equiv. did not improve the efficiency of the reaction (Table 1, entries 3 and 4). In addition, no benefit to the yield of **2a** could be achieved by increasing the amount of KO^tBu from 2 equiv. to 3 equiv. (Table 1, entry 5). Reducing the amount of KO^tBu to 1 equiv. gave **2a** in only 21% yield, yet its stereoisomer **2a'** could be favorably obtained in 58% yield (Table 1, entry 6). Reducing the reaction time from 1.5 h to 1 h resulted in a lower product yield, while increasing the reaction time to 2 h led to a similar yield (Table 1, entries 7 and 8 vs. entry 3). Product **2a** could also be efficiently obtained by replacing KO^tBu with KOH or NaOH in the presence of 18-crown-6 or 15-crown-5, respectively (Table 1, entries 9 and 10). Thus, the combination of alkali hydroxide with a crown ether was an alternative way to obtain **2a** efficiently under mechanochemical conditions. However, when KOH or NaOH was used alone, **2a'** became the major product, and **2a** was the minor product (Table 1, entries 11 and 12). These results showed that stronger bases (KO^tBu) under mechanochemical conditions resulted in more efficient formation of product **2a**, while relatively weaker bases (KOH or NaOH alone) favored the generation of its stereoisomer **2a'**. In the solid state, the different tightness of the arrangement between the cations and anions of bases might lead to different effective sizes, resulting in different reactivities of the anions. The utilization of a double-component solid base system⁹ consisting of NaOH and K₂CO₃ in a ratio of 2 : 1 led to a similar result to that of using NaOH only, and no reaction occurred when K₂CO₃ was employed alone (Table 1, entries 13 and 14). Other inorganic and organic bases, such as Cs₂CO₃, KOAc and Et₃N, were also examined. Nevertheless, all these bases were ineffective in this reaction (Table 1, entries 15–17). The above experimental results showed that the type and amount of the employed base exhibited strong influences on the reaction efficiency, stereo-selectivity and product distribution. The exact reason remains to be clarified. To compare the present solvent-free reaction with its solution-based counterpart, the reaction of **1a** (0.20 mmol) with KO^tBu (0.40 mmol) and H₂O (0.60 mmol) performed in 1.5 mL of diethyl ether (Et₂O) at 25 °C for 48 h provided **2a** (22%), 1,3,5-tribenzoyl-2,4,6-triphenylcyclohexane⁷ (**3a**, 27%) and other unidentified byproducts, showing much lower selectivity (Table 1, entry 18). Other solvents, including

Table 1 Optimization of the reaction conditions^a

Entry	Base	Molar ratio ^b	Yield of 2a (%)	Yield of 2a' (%)
1	KO ^t Bu	1 : 2 : 0	Trace	34
2	KO ^t Bu	1 : 2 : 2	86	Trace
3	KO ^t Bu	1 : 2 : 3	95	Trace
4	KO ^t Bu	1 : 2 : 4	89	Trace
5	KO ^t Bu	1 : 3 : 3	82	Trace
6	KO ^t Bu	1 : 1 : 3	21	58
7 ^c	KO ^t Bu	1 : 2 : 3	87	Trace
8 ^d	KO ^t Bu	1 : 2 : 3	96	Trace
9 ^e	KOH	1 : 2 : 3	90	Trace
10 ^f	NaOH	1 : 2 : 3	87	Trace
11	KOH	1 : 2 : 3	13	41
12	NaOH	1 : 2 : 3	16	37
13	NaOH/K ₂ CO ₃	1 : 2 : 1 : 3 ^g	11	34
14	K ₂ CO ₃	1 : 2 : 3	n.r.	n.r.
15	Cs ₂ CO ₃	1 : 2 : 3	n.r.	n.r.
16	KOAc	1 : 2 : 3	n.r.	n.r.
17	Et ₃ N	1 : 2 : 3	n.r.	n.r.
18 ^h	KO ^t Bu	1 : 2 : 3	22	0

^a Unless otherwise noted, all reactions were performed with 0.20 mmol of chalcone, KO^tBu and H₂O together with 4 stainless steel balls (5 mm in diameter) in a stainless steel jar (5 mL) and milled vigorously (1800 rpm) in a Retsch MM 400 mixer mill at room temperature for 1.5 h.

^b Molar ratio referred to chalcone/KO^tBu/H₂O. ^c The reaction time was 1 h. ^d The reaction time was 2 h. ^e 0.20 mmol of 18-crown-6 was added as the additive. ^f 0.20 mmol of 15-crown-5 was added as the additive. ^g Molar ratio referred to chalcone/NaOH/K₂CO₃/H₂O. ^h The reaction was performed in Et₂O at 25 °C for 48 h.



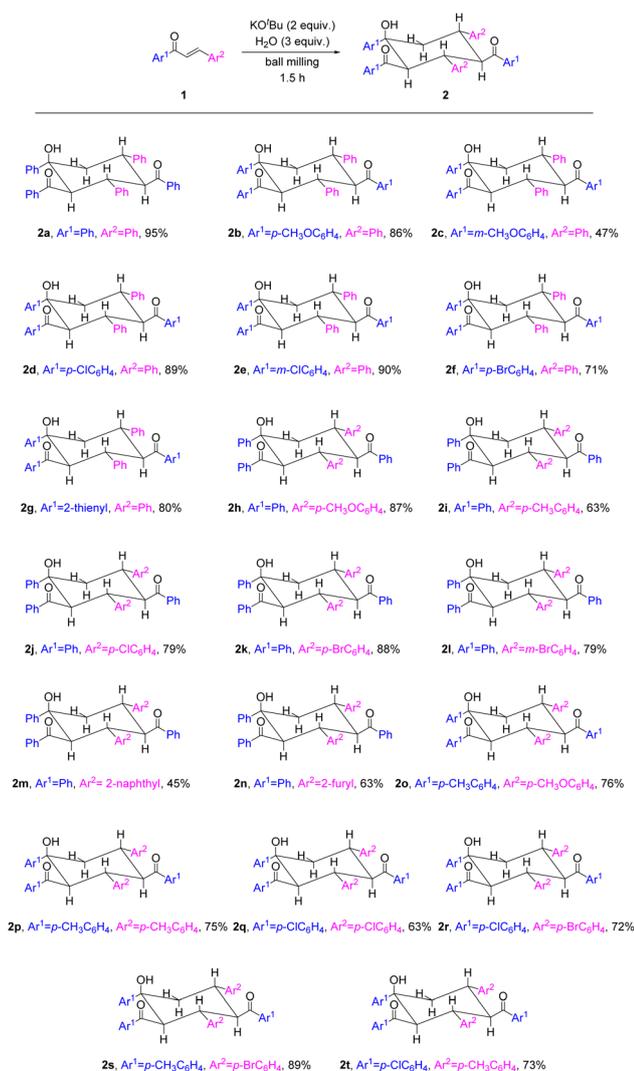
toluene, dimethyl sulfoxide (DMSO), tetrahydrofuran (THF) and acetonitrile (CH_3CN), were also screened. However, all of them led to lower product yields. Thus, it is obvious that the present mechanochemical solvent-free protocol shows advantages and uniqueness compared to the corresponding liquid-phase reaction in terms of product yield, reaction time and selectivity, likely due to more intimate and efficient intermolecular interactions of the “highly concentrated” reagents and/or absence of the solvation effect under the current ball-milling conditions. On the basis of the above results, the optimized conditions were determined as follows: **1a** (0.20 mmol), KO^tBu (0.40 mmol), H_2O (0.60 mmol), a milling frequency of 1800 rpm and a milling time of 1.5 h at room temperature.

With the optimized reaction conditions in hand, we proceeded to study the substrate scope of the trimerization of enones to provide 1,3,5-triaryl-2,4-acyl-cyclohexanols (Scheme 2). Enones

with different functional groups on the aromatic substituent (Ar^1) next to the carbonyl group and the β -aryl substituent (Ar^2) as the same phenyl group (**1b–1g**) were investigated. Chalcones with Ar^1 bearing electron-donating (*p*-OMe and *m*-OMe) groups afforded trimers **2b** and **2c** in yields of 86% and 47%, respectively. Enones with Ar^1 containing electron-withdrawing (*p*-Cl, *m*-Cl and *p*-Br) groups proceeded well and provided products **2d–2f** in 71–90% yields. Furthermore, the enone with Ar^1 as a heteroaryl (2-thienyl) group was also suitable and gave product **2g** in 80% yield. We then studied chalcones with Ar^1 as the same phenyl group and different Ar^2 substituents (**1h–1n**) and found that the reactions proceeded smoothly to afford trimers **2h–2n** in moderate to good yields. Chalcones with Ar^2 bearing electron-donating groups (*p*-OMe and *p*-Me) afforded products **2h** and **2i** in 87% and 63% yields, respectively. Substrates with Ar^2 containing electron-withdrawing groups (*p*-Cl, *p*-Br and *m*-Br) underwent trimerization and generated cyclohexanols **2j–2l** in 79–88% yields. In addition, chalcones with Ar^2 as the naphthyl or heteroaryl (2-furyl) group were compatible and provided products **2m** and **2n** in 45% and 63% yields, respectively. Alternatively, enones with both Ar^1 and Ar^2 carrying an electron-donating *p*-Me or *p*-OMe group gave products **2o** and **2p** in 76% and 75% yields, respectively. Substrates with both Ar^1 and Ar^2 containing an electron-withdrawing *p*-Cl or *p*-Br group could be used and converted into trimers **2q** and **2r** in 63% and 72% yields, respectively. Finally, enones with Ar^1 and Ar^2 as a combination of an electron-donating group and an electron-withdrawing group were examined, and products **2s** and **2t** could be obtained in 89% and 73% yields, respectively.

To further evaluate the practicability of the present mechanochemical protocol, a scale-up trimerization of chalcone **1a** (1 mmol) was carried out under our optimal reaction conditions for 1.5 h. To our delight, trimer **2a** was obtained in a satisfactory yield of 74%, indicating that the present method could be performed for a larger-scale preparation.

To gain insights into the reaction pathway, we performed several control experiments (Table 2). When 3 equiv. of the radical scavenger 2,2,6,6-tetramethylpiperidinoxy (TEMPO) was added to the reaction mixture of **1a**, KO^tBu and H_2O under the optimized conditions, the yield of **2a** was 47% (Table 2, entry



Scheme 2 Results for the mechanochemical trimerization of enones **1a–1t** mediated by KO^tBu . All reactions were performed with 0.20 mmol of **1**, KO^tBu (2 equiv.) and H_2O (3 equiv.) together with 4 stainless steel balls (5 mm in diameter) in a stainless steel jar (5 mL) and milled (1800 rpm) at room temperature for 1.5 h.

Table 2 Control experiments to elucidate the reaction mechanism^a

Entry	Condition	Yield of 2a (%)
1	3 equiv. of TEMPO	47
2	10 equiv. of TEMPO	41
3	Nitrogen atmosphere	83

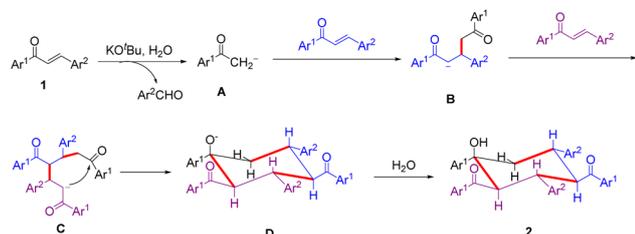
^a All reactions were performed with 0.20 mmol of **1a**, KO^tBu (2 equiv.) and H_2O (3 equiv.) together with 4 stainless steel balls (5 mm in diameter) in a stainless steel jar (5 mL) and milled (1800 rpm) at room temperature for 1.5 h.



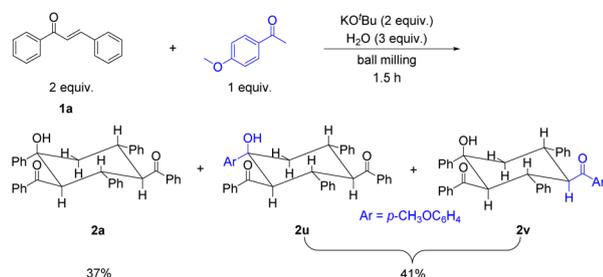
1). Increasing the amount of TEMPO to 10 equiv. led to a similar yield of 41% (Table 2, entry 2). These experiments with TEMPO suggested that our reaction was significantly different from the previous solution reaction, which occurred through SET radical pathways.⁷ To explore whether molecular oxygen under an air atmosphere played a role during the milling process, the jar containing **1a**, KO^tBu and H₂O was filled with nitrogen (N₂) and tightened in a glovebox. Then, the reaction mixture was milled under the optimal conditions, and **2a** was isolated in 83% yield (Table 2, entry 3). There was no obvious effect on the reaction, indicating that oxygen was not involved in our reaction.

The rarely investigated *retro*-aldol reaction of chalcones could take place in the presence of water, a secondary amine as an organocatalyst and trifluoroacetic acid as a cocatalyst in MeCN^{10a} or catalyzed by tetrabutylammonium hydroxide at 150 °C under microwave irradiation in aqueous solution.^{10b} Benzaldehyde was detected from the solvent-free reaction of **1a** with KO^tBu and H₂O in a molar ratio of 1 : 2 : 3 after milling for 0.5 h (Fig. S1†), hinting that the challenging *retro*-aldol reaction could be facilitated solely by the inorganic base and water under mechanochemical conditions.

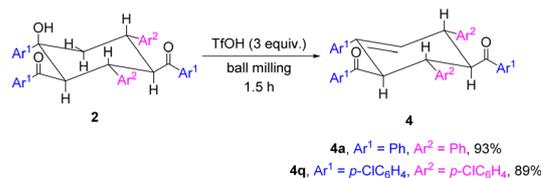
Based on the above experimental results and previous literature,¹¹ a plausible reaction mechanism is proposed and shown in Scheme 3. Initially, the *retro*-aldol reaction of enone **1** with the aid of KO^tBu and H₂O generates an aldehyde and the carboanionic species **A**. The latter undergoes Michael addition to the second enone **1**. The resulting intermediate **B** undergoes a second Michael addition to the third enone **1** to afford intermediate **C**. Subsequently, intermediate **C** cyclizes *via* an



Scheme 3 Proposed reaction mechanism.



Scheme 4 Mechanochemical reaction of **1a** and 4'-methoxyacetophenone with KO^tBu and H₂O. The reaction was performed with **1a** (0.20 mmol), 4'-methoxyacetophenone (0.10 mmol), KO^tBu (0.40 mmol) and H₂O (0.60 mmol) together with 4 stainless steel balls (5 mm in diameter) in a stainless steel jar (5 mL) at 1800 rpm and room temperature for 1.5 h.



Scheme 5 Dehydration reactions. Both reactions were performed with 0.10 mmol of **2** and TfOH (3 equiv.) together with 4 stainless steel balls (5 mm in diameter) in a stainless steel jar (5 mL) and milled (1800 rpm) at room temperature for 1.5 h.

intramolecular aldol reaction to give anion **D**, followed by protonation with H₂O to afford trimer **2**.

To verify whether the carboanionic species **A** can indeed be generated from the *retro*-aldol reaction of enones, 4'-methoxyacetophenone was added as the competing precursor to the reaction mixture of **1a**, KO^tBu and H₂O. Interestingly, **2a** (37%) and inseparable isomeric products **2u** and **2v** in a 1 : 1 ratio (a combined yield of 41%) were obtained (Scheme 4). In this case, **2a** could still be formed in a comparable yield to the combined yield of **2u** and **2v**. 4'-Methoxyacetophenone could be deprotonated by KO^tBu to give a similar carboanionic **A**, which underwent Michael addition to **1a**, resulting in anion **B** and equally stable anion **B'** by 1,3-proton transfer. The following steps were the same as those shown in Scheme 3 and provided isomeric products **2u** and **2v** (for details, see Scheme S1†).

In the cyclohexene rings of trimers **2**, there exists an axial hydroxyl group, which can be eliminated by further dehydration. Trimers **2a** and **2q** were employed as representative examples (Scheme 5). As desired, cyclohexene derivative **4a** was obtained in 93% yield when **2a** was treated with 3 equiv. of trifluoromethanesulfonic acid (TfOH) for 1.5 h under ball-milling conditions.^{6d} Similarly, **4q** could be successfully isolated in 89% yield. The dehydration of **2a** and **2q** caused an unusual stereoselective elimination, resulting in the formation of β,γ -unsaturated cyclohexenes instead of the more stable α,β -unsaturated cyclohexenes. This regioselectivity may be a result of the axial positioning of the hydroxyl group in the cyclohexanols, which preferentially underwent elimination with an equatorial hydrogen to form a six-membered transition state. In addition, the dehydration reaction under basic conditions, including KO^tBu, KOAc, K₂CO₃ or 4-dimethylaminopyridine (DMAP), was attempted to afford the more stable α,β -unsaturated cyclohexenes. However, the desired dehydration products could not be produced.

Conclusions

In summary, we have developed a solvent-free stereoselective trimerization of enones with KO^tBu as the base and water as the proton source under ball-milling conditions, affording 1,3,5-triaryl-2,4-acyl-cyclohexanols with all bulky substituents located at equatorial positions. These unusual trimerization products can be straightforwardly obtained from enones by a cascade process of a *retro*-aldol reaction, double Michael additions and intramolecular aldol reaction. Other stereoisomers with most



bulky substituents situated at equatorial sites except for a 4-acyl group at the axial position can also be obtained in moderate yields by reducing the amount of KO^tBu or changing KO^tBu to a relatively weaker base KOH or NaOH. It should be noted that the challenging *retro*-aldol reaction can be mechanochemically achieved solely with an inorganic base and water and is the critical initiation step. In addition, the formed cyclohexanol derivatives can be efficiently transformed into the corresponding cyclohexene derivatives *via* a dehydration reaction with TfOH. Our protocol features solvent-free and ambient conditions, a short reaction time, and easily available and inexpensive reagents.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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