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Grinding-Assisted Asymmetric Organocatalysis: A Solvent-free Approach to the Formation of Vicinal Quaternary and Tertiary Stereocenters

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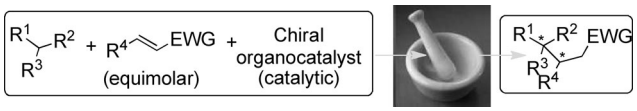
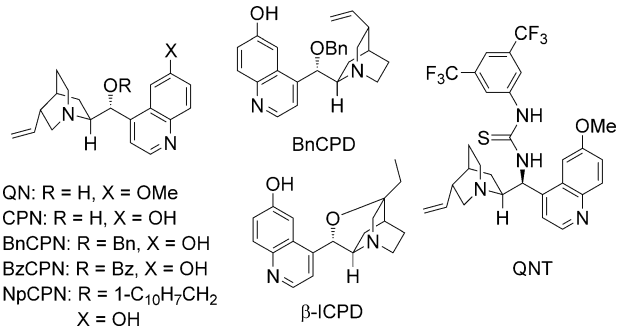
Mechanochemical techniques, such as grinding and ball-milling, are widely applied to pulverize minerals into fine particles in the preparation and modification of inorganic solids. Recently, their use in synthetic organic chemistry has increased because of environmental considerations, and such techniques have been widely used in solvent-free non-asymmetric transformations.[1] In asymmetric transformations the applications of mechanochemical techniques has been limited. Bolm and co-workers have developed a cinchona-alkaloid-mediated asymmetric opening of a cyclic *meso*-anhydride[2] and a proline-catalyzed asymmetric direct aldol reaction[3] by using a ball-milling technique. Recently, Xu and co-workers have reported a solvent-free asymmetric Michael addition that uses a ball mill.[4] To our knowledge, there is no report in literature which involves the use of grinding with pestle and mortar for performing catalytic asymmetric transformations.[5]

Avoiding the use of organic solvents in chemical synthesis is an important step towards developing environmentally benign chemical technologies. There are many alternatives for the replacement of organic solvents as reaction media, which include ionic liquids, liquid or supercritical CO_2, and water. Another alternative is to perform reactions in solvent-free conditions.[6] Most of the asymmetric transformations conducted in solvent-free conditions require an excess amount of one reactant for proper mixing of reactants and catalyst. In such cases the reactant itself acts as a solvent, which results in wastage of costly materials and may cause problems for disposal.[7] Designing a solvent-free asymmetric catalytic reaction that involves an equimolar amount of substrate remains a great challenge in organic chemistry. We envisaged that this challenge can be addressed by the use of mechanochemical techniques, such as grinding (Scheme 1).

In the last decades, asymmetric organocatalysis has emerged as the backbone of asymmetric synthesis.[8] Recent progress in asymmetric organocatalysis has been accompanied by the development of numerous synthetic transformations that use different organocatalysts, including cinchona alkaloids and their derivatives.[9] Among different cinchona alkaloid derivatives, the 6′-OH cinchona alkaloids have made their mark as powerful bifunctional hydrogen-bonding organocatalysts for wide array of asymmetric reactions (Scheme 2).[10–11]



Scheme 1. Grinding-assisted solvent-free asymmetric organocatalysis.



Scheme 2. Structure of cinchona-derived organocatalysts used. β-ICPD = β-isocupreidine; BnCPN = 9-*O*-benzylcupreine; BzCPN = 9-*O*-benzoylcupreine; CPN = cupreine; NpCPN = 9-*O*-(1′-naphthylmethyl)cupreine; QN = quinine; QNT = 9-thiourea epi-quinine.

Asymmetric conjugate addition to nitroolefins has been widely studied since the emergence of organocatalysis, as the nitro group of the corresponding nitroalkanes can be converted into various functional groups.[12–13] Asymmetric organocatalytic addition of trisubstituted β-keto esters to nitroolefins provides easy access to Michael adducts that contain adjacent tertiary and quaternary stereocenters.[14] The stereoselective formation of quaternary stereocenters still remains a formidable challenge because of steric hindrance.[15] Because of the synthetic challenge of synthesizing quaternary stereocenters and designing a solvent-free asymmetric catalytic transformation in which equimolar amounts of reactants can be used, we have developed a solvent-free organocatalytic asymmetric Michael addition reaction by grinding with a pestle and mortar.

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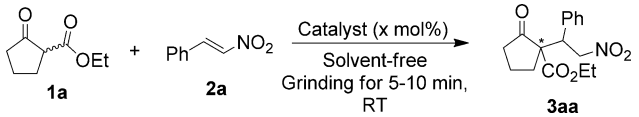
Initially, an equimolar mixture of **1a** (liquid) and **2a** (solid) was ground with 1 mol% of cupreine (CPN; solid) as catalyst in a pestle and mortar for 5 min under aerobic conditions. During this period the reaction mixture immediately formed a homogeneous liquid, which thickened on further grinding. After 5 min the reaction mixture was left undisturbed at room temperature and the progress of the reaction was monitored by TLC at regular intervals. On complete consumption of the reactants (30 min) the product was purified by chromatography. To our delight, the addition product **3aa** was isolated in 92% yield, 91:9 diastereomeric ratio (d.r.), and 92% *ee* (Table 1, entry 1). The reaction was repeated three times to evaluate the reproducibility of the method, and the results were consistent in terms of yield and stereoselectivity. Furthermore, screening of different cinchona derived organocatalysts (Table 1, entry 2-8) showed that the reaction with BnCPN affords **3aa** in 92% yield and the highest stereoselectivity (91:9 d.r. and 97% *ee*; Table 1, entry 2). By using BnCPN (5 mol%), adduct **3aa** was isolated in 98% yield in 15 min (Table 1, entry 10). In contrast, BnCPN catalyzed reactions of **1a** with **2a** proceed at a slower rate when performed in toluene or neat with traditional stirring (Table 1, entries 11–14). Adduct **3aa** was isolated in lower yield (78%) from the reaction in toluene after 24 h with comparable stereoselectivity to that of the grinding-assisted reaction (Table 1, entry 12). The remarkably higher rate of reaction with grinding is probably a result of the proper mixing of reactants and catalyst, as well as additional pressure.

Table 1. Catalyst screening and optimization for grinding-assisted Michael reaction of β-ketoester (**1a**) with nitrostyrene (**2a**).[a]



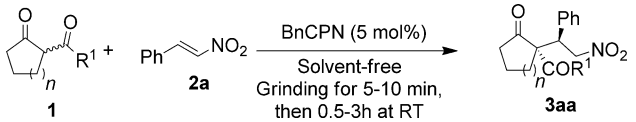
1a 2a 3aa

Entry	Catalyst (mol%)	*t* [h]	Yield [%][b]	d.r.	*ee* [%][c]
1	CPN (1)	0.5	92	91:9	92
2	BnCPN (1)	0.5	92	91:9	97
3	NpCPN (1)	0.5	91	93:7	93
4	BzCPN (1)	0.5	89	83:17	96
5	BnCPD (1)	0.5	91	91:9	−95
6	β-ICPD (1)	0.5	91	91:9	−91
7	QNT (1)	0.5	94	95:5	84
8	QN (1)	0.5	87	86:14	−28
9	BnCPN (2)	0.5	94	91:9	97
10	BnCPN (5)	0.3	98	91:9	97
11[d]	BnCPN (5)	0.5	31	90:10	97
12[d]	BnCPN (5)	24	78	89:11	98
13[e]	BnCPN (5)	0.5	29	91:9	97
14[e]	BnCPN (5)	24	86	90:10	96

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.2 mmol), and catalyst were ground for 5–10 min at RT. [b] Yield of both diastereomers after purification. [c] *ee* value of major diastereomer. [d] Reaction was carried out in toluene. [e] Reaction was carried out neat by stirring.

The substrate scope of the grinding-assisted Michael addition was evaluated by screening the reactions of different β-ketoesters with **2a** and BnCPN (5 mol%, Table 2). The Michael reactions of different five-membered β-ketoesters with nitrostyrene catalyzed by BnCPN provide the corresponding Michael adducts in high yield and high stereoselectivity (83:17–98:2 d.r. and 89–95% *ee*; Table 2, entries 2–5). The six membered cyclic β-ketoester **1f** reacted with **2a** to give adduct **3fa** in 87% yield, 99:1 d.r., and 94% *ee* (Table 2, entry 6). The cyclic diketone **1g** reacted rapidly with **2a** and gave **3ga** in 96% yield with moderate diastereoselectivity (70:30 d.r.) and high enantioselectivity (84% *ee*) for the major diastereomer (Table 2, entry 7).

Table 2. Grinding-assisted stereoselective Michael reaction of nitrostyrene (**2a**) with various β-ketoesters and a diketone.[a]



1 2a 3aa

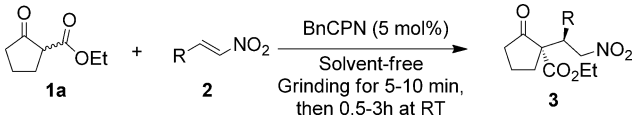
Entry	R^1, n	*t* [h]	**3**	Yield [%][b]	d.r.	*ee* [%][c]
1	R^1=OEt, *n*=1 (**1a**)	0.5	**3aa**	99	91:9	97
2	R^1=OMe, *n*=1 (**1b**)	0.5	**3ba**	98	84:16	95
3	R^1=O*i*Pr, *n*=1 (**1c**)	1.0	**3ca**	92	94:6	92
4	R^1=O*t*Bu, *n*=1 (**1d**)	3.0	**3da**	93	98:2	91
5	R^1=OBn, *n*=1 (**1e**)	3.0	**3ea**	90	83:17	89
6	R^1=OEt, *n*=2 (**1f**)	3.0	**3fa**	87	99:1	94
7	R^1=Me, *n*=1 (**1g**)	0.6	**3ga**	96	70:30	84

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.2 mmol), and BnCPN (5 mol%) were ground for 5-10 min at RT. [b] Yield of both diastereomers after purification. [c] *ee* value of major diastereomer.

After the successful application of the grinding method for different β-ketoesters and a diketone, different nitroalkene derivatives were screened with **1a** as the nucleophile (Table 3). Nitroalkenes with electron-withdrawing substituents on the aromatic ring reacted efficiently with **1a** to provide the corresponding adducts **3ab–3af** in high yield (85–98%), high diastereoselectivity (89:11–99:1 d.r.) and high enantioselectivity (90–94% *ee*, Table 3, entries 1–5). The reactions with nitroalkenes that contain electron-donating groups on the phenyl ring also provided 1,4-adducts **3ag–3ai** in high yield (72-86%) and high stereoselectivity (87:13–92:8 d.r. and 85–97% *ee*, Table 3, entries 6–8). The reactions of nitroalkenes substituted with naphthyl groups resulted in the formation of Michael adducts **3aj** and **3ak** in high yield and high stereoselectivity (Table 3, entries 9–10). Not only aromatic, but heteroaromatic nitroalkenes **2l** and **2m** also undergo the Michael addition with **1a** in the presence of BnCPN to give **3al** and **3am**, respectively in high yield (up to 93%) as well as high enantioselectivity (up to 98% *ee*) and good diastereoselectivity (up to 95:5 d.r.) (Table 3, entries 11–12).

The substrate scope of this grinding-assisted asymmetric organocatalysis was further extended for the conjugate addition of **1a** to nitrodiene derivatives. The reactions with unsubstituted and substituted nitrodienes resulted in the formation of **2an–2ar** in 81-97% yield and 86-95% *ee*

Table 3. Grinding assisted stereoselective Michael reaction of nitroolefins with β-ketoester (**1a**).[a]



1a 2 3

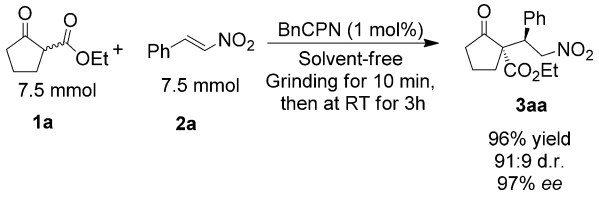
Entry	R	*t* [h]	3	Yield [%][b]	d.r.	*ee* [%][c]
1	4-FC_6H_4 (**2b**)	1.0	**3ab**	98	99:1	92
2	2-ClC_6H_4 (**2c**)	3.0	**3ac**	85	92:8	94
3	3-ClC_6H_4 (**2d**)	2.0	**3ad**	89	91:9	92
4	4-ClC_6H_4 (**2e**)	1.0	**3ae**	91	89:11	93
5	4-$NO_2C_6H_4$ (**2f**)	0.5	**3af**	95	91:9	90
6	4-MeC_6H_4 (**2g**)	1.5	**3ag**	86	92:8	97
7	4-$MeOC_6H_4$ (**2h**)	1.5	**3ah**	81	87:13	85
8	3,4-$(MeO)_2C_6H_3$ (**2i**)	3.0	**3ai**	72	87:13	92
9	1-$C_{10}H_7$ (**2j**)	1.0	**3aj**	91	91:9	93
10	2-$C_{10}H_7$ (**2k**)	1.0	**3ak**	90	92:8	93
11	2-furanyl (**2l**)	1.0	**3al**	93	95:5	98
12	2-thienyl (**2m**)	0.6	**3am**	91	94:6	94
13	PhCH=CH (**2n**)	0.5	**3an**	97	91:9	92
14	2-$NO_2C_6H_4$CH=CH (**2o**)	1.0	**3ao**	93	96:4	95
15	4-$NO_2C_6H_4$CH=CH (**2p**)	1.0	**3ap**	95	92:8	89
16	2-$MeOC_6H_4$CH=CH (**2q**)	3.0	**3aq**	82	93:7	93
17	4-$MeOC_6H_4$CH=CH (**2r**)	3.0	**3ar**	81	84:16	86
18	cyclohexyl (**2s**)	3.0	**3as**	85	76:24	97

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.2 mmol), and BnCPN (5 mol%) were ground for 5-10 min at RT. [b] Yield of both diastereomers after purification. [c] *ee* value of major diastereomer.

(Table 3, entries 13–17). Aliphatic nitroalkene **2s** also reacted efficiently with **1a** in the presence of BnCPN to give **3as** in 85% yield with 97% *ee* and 76:24 d.r. (Table 3, entry 18).

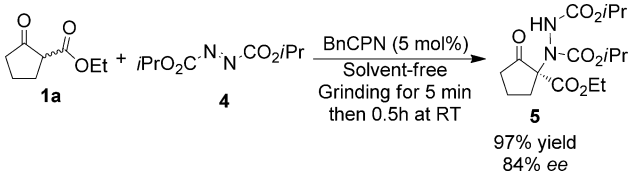
The absolute configuration of the Michael adducts obtained was assigned as 1*S*,2′*R* on the basis of a comparison of the specific rotation and HPLC chromatogram of **3ba** with that reported in the literature.[14a]

In this grinding process BnCPN has a high turnover number, as lowering of the catalyst loading did not affect the stereochemistry of Michael adduct **3aa**. Hence, scaling up the reaction of **1a** with **2a** to a one-gram scale with only 1 mol% of BnCPN gave **3aa** in 96% yield with 91:9 d.r. and 97% *ee* (Scheme 3).



Scheme 3. Gram-scale organocatalytic stereoselective Michael reaction with grinding.

After the successful application of organocatalysis with grinding for asymmetric conjugate addition reactions, we further extended the scope of this method for enantioselective amination reactions to generate aminated quaternary stereocenters.[16–17] Grinding equimolar amount of **1a** with diisopropyl azodicarboxylate (**4**) in the presence of 5 mol% of BnCPN resulted in the formation of adduct **5** in a short reaction time (0.5 h) with 97% yield and 84% *ee* (Scheme 4).



Scheme 4. Grinding-assisted enantioselective amination.

In conclusion, we have developed the application of grinding with a pestle and mortar in asymmetric organocatalysis. This protocol provides a rapid, convenient, and environmentally benign route for the synthesis of vicinal tertiary and quaternary stereocenters in high yield (72–99%) and high stereoselectivity (up to 98% *ee* and up to 99:1 d.r.). This method uses equimolar amounts of reactants at a low loading of readily available chiral catalyst under solvent-free aerobic reaction conditions. Grinding-assisted organocatalysis was not only successful for asymmetric conjugate addition reactions, but also for enantioselective amination of a β-ketoester to generate a quaternary amino stereogenic center. Further evaluation of the substrate scope of grinding-assisted organocatalysis is under investigation and the results will be published in due course.

Experimental Section

General procedure for BnCPN catalyzed asymmetric organocatalytic conjugate addition reaction with grinding

The β-ketoester (**1**, 0.2 mmol), nitroalkene (**2**, 0.2 mmol) and BnCPN (5 mol%), were ground with a pestle and mortar for 5–10 min. The reaction mixture was kept at room temperature until TLC indicated the completion of the reaction. After completion, the product was purified by chromatography on a silica gel column (hexane/ethyl acetate 9:1–8:2).

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Keywords: Michael reaction · nitroalkenes · organocatalysis · quaternary stereocenters · solvent-free

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