DOI: 10.1002/chem.200901541

Chiral Primary–Secondary Diamines Catalyzed Michael–Aldol–Dehydration Reaction between Benzoylacetates and α,β-Unsaturated Ketones: Highly Enantioselective Synthesis of Functionalized Chiral Cyclohexenones

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Functionalized chiral cyclohexenones are an important class of scaffolds found in numerous naturally occurring and synthetic molecules possessing a broad spectrum of biological activities.[1] Several methodologies have been utilized to access this kind of compounds, including kinetic resolution of racemic substituted cyclohexenones by catalytic asymmetric reactions[2] and various multistep synthesis.[3] Nevertheless, these systems more or less suffer from several drawbacks such as only half of the starting material could be used in kinetic resolution to obtain products with the desired configuration and low efficiency for multi-step synthesis.

Recently, the application of organocatalysis to this field has afforded a valuable alternative access to these useful compounds, which usually features readily available starting materials, good atom- and step-economy, mild reaction conditions and high stereo-/enantioselectivities.[4–8] List et al. realized a highly enantioselective desymmetrizing intramolecular aldol reaction of 4-substituted-2,6-heptanediones to enantiomerically enriched 5-substituted-3-methyl-2-cyclohexene-1-ones using a quinine-derived primary catalyst.[5] Using α,β-unsaturated aldehydes as the Michael acceptors, Jørgensen et al.[6] and Hayashi et al.[7] have successfully utilized diarylprolinol silyl ether as the organocatalyst and various nucleophilic donors to prepare different chiral cyclohexenones with excellent enantioselectivities. On the other hand, α,β-unsaturated ketones as the Michael acceptors have received less attention probably due to their reduced reactivities compared with enals. Using a phenylalanine-derived imidazolidine catalyst, Jørgensen et al.[8] were among the first to visualize a highly enantio- and diastereoselective Michael–aldol reaction of ketoesters and enones to provide functionalized chiral cyclohexanes, which after dehydration in the presence of an acid could be converted to chiral cyclohexenones. However, long reaction times were generally required (95–240 h). Chen et al.[9] also applied Cinchona alkaloid-derived primary amine catalysts to catalyze the Michael addition of dicyanoalkenes to enones; the products could be converted to chiral cyclohexenones in high enantioselectivities in one step. In the view of these results, there is still room for the development of organocatalysts for the highly enantioselective synthesis of functionalized chiral cyclohexenones.

Recently, we have developed a novel readily available primary–secondary diamine catalyst system for the Michael additions of malonates to enones with excellent yields and enantioselectivities.[10] We disclosed herein that a similar catalyst system could also efficiently catalyze the Michael–aldol–dehydration reaction between benzoylacetates and α,β-unsaturated ketones to provide functionalized chiral cyclohexenones in excellent enantioselectivities.

Initially, the reaction of ethyl benzoylacetate **1a** with benzylideneacetone **2a** was selected as a model reaction for the catalyst evaluation (Table 1). In the presence of 20 mol% of catalyst **3a** (Figure 1) and 20 mol% of additive TFA, the reaction was completed within 72 h to provide the desired products in 90% yield with moderate diastereoselectivity and excellent enantioselectivities for both diastereoisomers (Table 1, entry 1). However, neither elongating the alkyl chain of the second amine moiety in **3a** nor increasing its

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200901541.

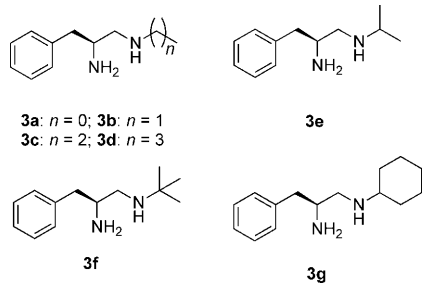
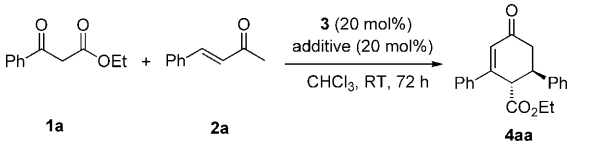


Figure 1. Structures of the catalysts studied.

steric hindrance could improve the results (Table 1, entries 2–7).

Of note is the key role the acid additive played in this transformation: the reaction did not proceed in the absence of additives (Table 2, entry 1) and only trace product was obtained when HOAc, TsOH and D-CSA[11] were used as the additives (Table 2, entries 2–4). Finally, D-*N*-Boc-phenylglycine turned out to be the additive of choice, which provided the desired product in 91% yield and 99% *ee* for both diastereoisomers, albeit without improvement in the diastereoselectivity (Table 2, entry 7). Less satisfactory results were obtained using the racemic D,L-*N*-Boc-phenylglycine as an additive (Table 2, entry 8).[12]

Table 1. Screening of catalysts for the Michael–aldol–dehydration reaction between ethyl benzoylacetate **1a** and benzylideneacetone **2a**.[a]

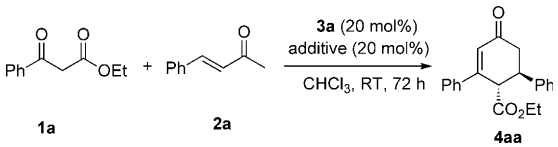


1a **2a** **4aa**

Entry	Catalyst **3**	Additive	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	**3a**	TFA	90	77:23	95/95
2	**3b**	TFA	89	78.22	90/89
3	**3c**	TFA	93	74:26	90/89
4	**3d**	TFA	96	70:30	90/89
5	**3e**	TFA	89	73:27	94/91
6	**3f**	TFA	92	67:33	95/95
7	**3g**	TFA	89	74:26	93/94

[a] Reaction conditions: **2a** (1.0 equiv), **1a** (2.0 equiv), **3** (20 mol%), $CHCl_3$ (2.0 mL). The relative configuration of **4aa** was determined by NOE experiments. For details of the reaction process, please see the Supporting Information [b] Yield of the isolated product after column chromatography. [c] Determined by ^{1}H NMR analysis; major isomer: *trans*. [d] The *ee* value was determined by chiral HPLC.

Table 2. Screening of acid additive for the Michael–aldol–dehydration reaction between ethyl benzoylacetate **1a** and benzylideneacetone **2a**.[a]



1a **2a** **4aa**

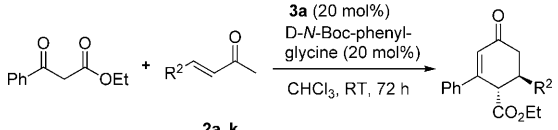
Entry	Additive	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	none	0	–	–
2	HOAc	trace	–	–
3	TsOH	trace	–	–
4	D-CSA	trace	–	–
5	CF_3SO_3H	90	77:23	98/96
6	L-*N*-Boc phenylglycine	93	75:25	97/95
7	D-*N*-Boc phenylglycine	91	77:23	99/99
8	D,L-*N*-Boc phenylglycine	86	72:28	96/91
9[e]	D-*N*-Boc phenylglycine	65	73:27	98/94

[a] Reaction conditions: **2a** (1.0 equiv), **1a** (2.0 equiv), **3a** (20 mol%), $CHCl_3$ (2.0 mL). [b] Yield of the isolated product after column chromatography. [c] Determined by ^{1}H NMR analysis; major isomer: *trans*. [d] The *ee* value was determined by chiral HPLC . [e] CH_2Cl_2 was used as solvent. D-CSA: D-camphor sulfonic acid.

With the optimized reaction conditions at hand, the scope of the tandem Michael–aldol–dehydration reaction between ethyl benzoylacetate **1a** and enones **2** was explored (Table 3). Overall, all examined substrates could provide the desired products in moderate to excellent yields and 99% *ee* for both diastereoisomers. For enones **2a–j** with different substituted benzene rings, while only negligible difference was observed in chemical yields and enantioselectivities, slightly higher d.r. values were obtained for substrates bearing electron-donating substituents (Table 3, entry 8 and 9). Heterocyclic furan enone **2k** also performed well to give the desired product albeit with a decrease in the yield (Table 3, entry 11). Good results were also obtained when the aliphatic enone **2l** was used (Table 3, entry 12).

Similarly, no significant difference in chemical yield and enantioselectivity was observed for other benzoylacetates **1b–e** bearing different ester moieties while a slight better diastereoselectivity was obtained with **1d** bearing a bulky *tert*-butyl group (Table 4, entries 1–4). The effective system could also be extended to the aliphatic substrate (Table 4, entry 5).

Table 3. Enantioselective Michael–aldol–dehydration reaction between ethyl benzoylacetate **1a** and enones **2** catalyzed by the **3a**/D-*N*-Boc phenylglycine combination.[a]

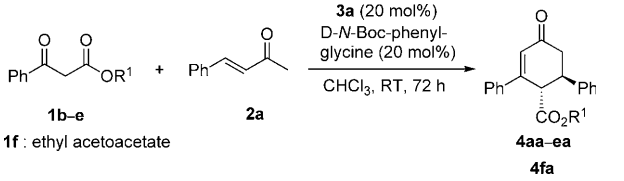


1a **2a–k** **4aa–ea**

Entry	R^2	Product	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	Ph, **2a**	**4aa**	91	77:23	99/99
2	2-naphthyl, **2b**	**4ab**	85	77:23	99/>99
3	4-FC_6H_4, **2c**	**4ac**	84	77:23	>99/99
4	4-ClC_6H_4, **2d**	**4ad**	76	76:24	99/>99
5	3-ClC_6H_4, **2e**	**4ae**	82	71:29	>99/>99
6	2-ClC_6H_4, **2f**	**4af**	79	71:29	>99/>99
7	4-BrC_6H_4, **2g**	**4ag**	78	74:26	99/>99
8	4-MeC_6H_4, **2h**	**4ah**	77	81:19	99/99
9	4-$MeOC_6H_4$, **2i**	**4ai**	81	78:22	99/99
10	4-$NO_2C_6H_4$, **2j**	**4aj**	87	62:38	99/99
11	2-furyl, **2k**	**4ak**	55	80:20	>99/>99
12	*n*Pr, **2l**	**4al**	98	78:22	99/99

[a] Reaction conditions: **2** (1.0 equiv), **1a** (2.0 equiv), **3a**/D-*N*-Boc-phenylglycine (20 mol%), $CHCl_3$ (2.0 mL). [b] Yield of the isolated product after column chromatography. [c] Determined by ^{1}H NMR analysis; major isomer: *trans*. [d] The *ee* value was determined by chiral HPLC.

Table 4. Enantioselective Michael–aldol–dehydration reaction between benzoylacetates **1** and enones **2a** catalyzed by the **3a**/D-*N*-Boc phenylglycine combination.[a]



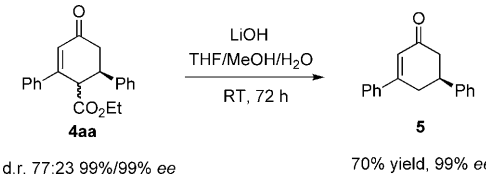
Entry	R^1	Product	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	Me, **1b**	**4ba**	85	73:27	99/>99
2	allyl, **1c**	**4ca**	73	77:23	99/99
3	*t*Bu, **1d**	**4da**	71	85:15	>99/99
4	Bn, **1e**	**4ea**	90	66:34	>99/>99
5	**1f**	**4fa**	65	75:25	97/98

[a] Reaction conditions: **2a** (1.0 equiv), **1** (2.0 equiv), **3a**/D-*N*-Boc-phenylglycine (20 mol%), $CHCl_3$ (2.0 mL). [b] Yield of the isolated product after column chromatography. [c] Determined by ^1H NMR analysis; major isomer: *trans*. [d] The *ee* value was determined by chiral HPLC.

As shown in Scheme 1, the absolute configuration of **4aa** was determined by conversion to the known compound **5** via a simple decarboxylation reaction while maintaining the stereochemical integrity at C-5. Of note is that **5** has previously been procured via multistep synthesis.[13] Thus, the present method may be one of the most convenient ways to this kind of chiral 3,5-substituted cyclohexenones.

The proposed mechanism for the Michael–aldol–dehydration reaction is outlined in Scheme 2. In the first step, α,β-unsaturated ketone **2** is activated by the formation of iminium ion with catalyst **3a**. The *Re* face of the enone in this intermediate is shielded by the bulky group of the chiral catalyst allowing the benzoylacetate **1** to attack the *Si* face of the enone **2**. Next, the generated chiral enamine intermediate performs an intramolecular aldol addition to form the cyclohexane ring **6**. After dehydration, chiral cyclohexenones **4** were obtained. Since the concentration of the intermediate **6** is very low at all stages of the reaction, the detection of the intermediate does not rule out alternative mechanisms such as Mannich–Knoevenagel-type mechanism.[14]

In summary, we have developed a novel highly enantioselective organocatalytic tandem Michael–aldol–dehydration reaction that provides an expedited access to highly functionalized chiral cyclohexenone derivatives by using a simple amine catalyst. Efforts are currently underway on further application of the catalyst system to other related reactions as well as a more detailed mechanistic understanding of the reaction.



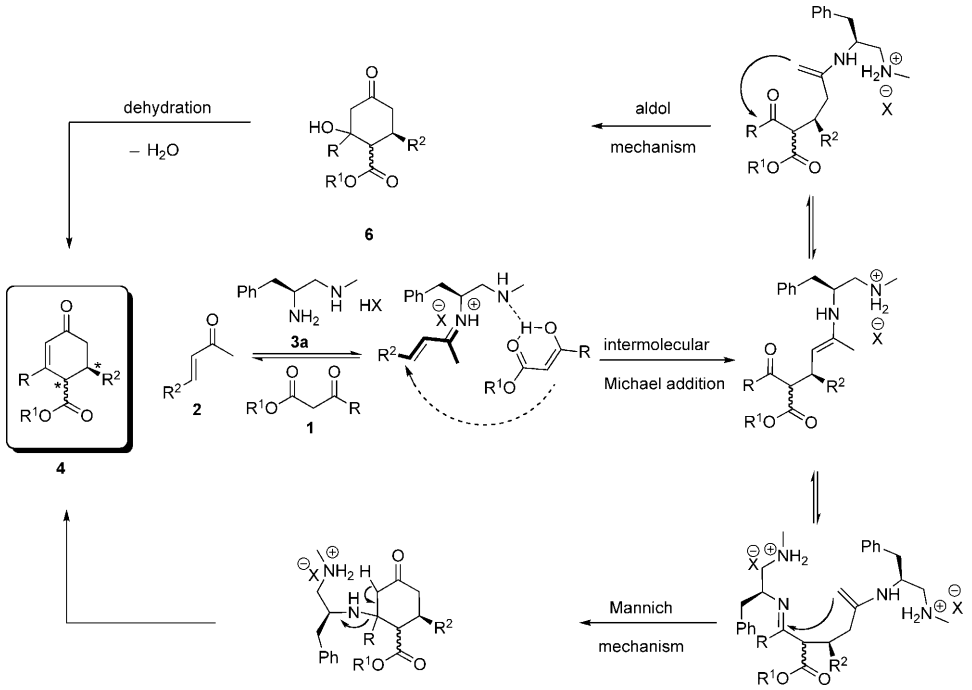
Scheme 1. Conversion of **4aa** to 3,5-disubstituted cyclohexenone **5**.

Experimental Section

General: Unless otherwise indicated, all compounds and reagents were purchased from commercial suppliers and used without further purification. Proton nuclear magnetic resonance spectra are recorded at 300 MHz. All chemical shifts (δ) are given in ppm. NMR spectra were recorded on Varian EM-360 A, Varian EM90 or Bruker AMX-300 NMR spectrometer. IR spectra were recorded on a Perkin–Elmer 983G instrument. MS or HRMS was recorded on a HP-5989 A spectrometer. Melting points were determined on a Mettler-Toledo FP62 melting point apparatus and are uncorrected. HPLC analysis was carried out on WATERS equipment. Catalysts **3a–d**,[10] **3e**,[15] **3f**,[16] and **3g**[17] were prepared from known procedure.

General procedure for the Michael–aldol–dehydration reaction: To a mixture of enone **2** (0.25 mmol), catalyst **3** (0.05 mmol) and D-*N*-Boc phenylglycine (0.05 mmol) in $CHCl_3$ (2.0 mL) was added benzoylacetate (**1**; 0.5 mmol) at ambient temperature. After stirring for 72 h, the reaction mixture was quenched with 1 M aqueous HCl solution and extracted with EtOAc. The combined organic layer was dried over Na_2SO_4, filtered, and concentrated to afford the desired product **4** after flash column chromatography on silica gel (petroleum ether/Et_2O).

Further details are available in the Supporting Information.



Scheme 2. Proposed reaction mechanism for the Michael–aldol–dehydration reaction.

Acknowledgements

The generous financial support from the National Natural Science Foundation of China, QT Program, Shanghai Natural Science Council, and Excellent Young Scholars Foundation of NNSF are gratefully acknowledged.

Keywords: aldol reaction · asymmetric catalysis · enones · Michael reaction · organocatalysis

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Received: June 6, 2009
Revised: August 10, 2009
Published online: November 11, 2009

