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One-pot organocatalytic domino Michael/α-alkylation reactions: highly enantioselective synthesis of functionalized cyclopentanones and cyclopentanols

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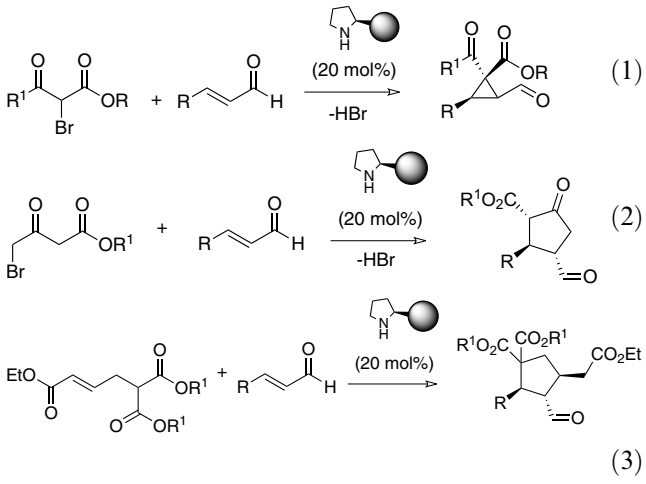
Abstract—A simple, highly enantioselective catalytic route to cyclopentanones is presented. The chiral amine catalyzed domino Michael/α-alkylation reaction gives access to functionalized cyclopentanones in good to high yields with 93 → 99% ee. The products were also reduced with high diastereoselectivity to the corresponding cyclopentanols.

Carbon–carbon bond-forming reactions are among the most important transformations in organic synthesis. Domino or cascade reactions, that involve the formation of multiple C–C bonds and stereocenters in one-pot, comprise a rapidly growing research field within the synthesis of small molecules with complex architectures.[1] The undeniable benefits of domino reactions include 'green chemistry' factors such as atom economy,[2] reduction of synthetic steps and minimization of solvents and waste.[3] Thus, significant efforts have been made in the development of asymmetric domino reactions using chiral precursors for stereocontrol.[1] However, the development of catalytic enantio- and diastereoselective domino reactions is still a challenging task. In this context, the development of organocatalytic asymmetric domino reactions has been intensely pursued.[4,5]

Recently, we developed a chiral amine catalyzed enantioselective cyclopropanation reaction between α,β-unsaturated aldehydes and 2-bromomalonates or 2-bromo-β-ketoesters (Eq. 1).[6] Based on this research and the importance of the cyclopentanone structural motif in natural products such as prostaglandins,[7–9] we became intrigued in whether highly substituted cyclopentanones could be assembled in an asymmetric fashion via a chiral amine catalyzed domino Michael/intramolecular α-alkylation reaction according to Eq. 2 and Scheme 1 (see later). Moreover, during the preparation of this manuscript Wang and co-workers reported an elegant organocatalytic route to cyclopentanes based on asymmetric double Michael reactions (Eq. 3).[10]



Herein, we describe a simple enantioselective catalytic route to highly functionalized cyclopentanones, which were obtained with 93 → 99% ee, via a chiral amine catalyzed domino Michael/α-alkylation reaction.

In initial experiments, we investigated chiral amines **4–10** for the asymmetric domino reaction between

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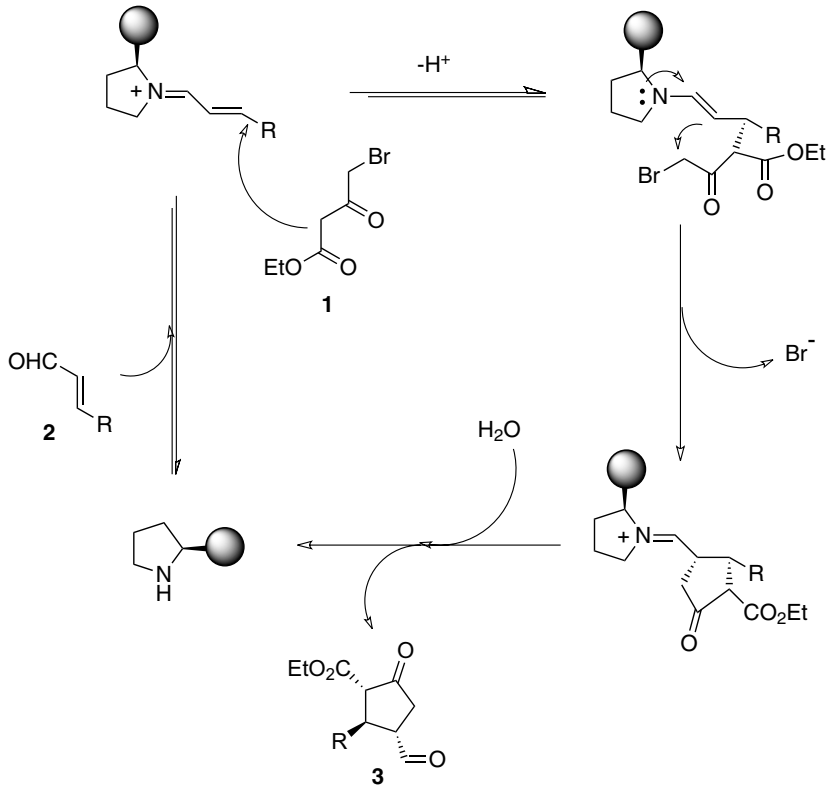
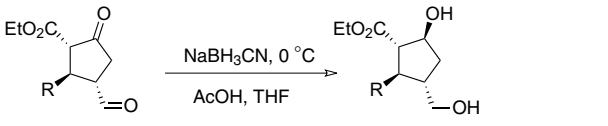


Scheme 1. A plausible reaction pathway for chiral amine catalyzed enantioselective cyclopentanone synthesis.

the ethyl ester of 4-bromo-acetoacetate **1** (0.3 mmol) and 2-heptenal **2a** (0.25 mmol) in an organic solvent (1 mL) under various reaction conditions (Table 1). 4-Bromo substituted β-ketoester **1** was chosen since the 4-chloro analogue gave only the Michael addition product.[5r]

We found that protected diphenylprolinol **5**[11] and (*S*)-proline **7** catalyzed the asymmetric formation of the trisubstituted cyclopentanones **3a** and *ent*-**3a**, respectively, in high yields with 97 and −53% ee, respectively (entries 2 and 4).[12] Of the four possible diastereoisomers, only two (**3a** and **3a′**) were formed in a ratio of 8:1. Chiral amine **5** also catalyzed the formation of a **3a** in other solvents with high enantioselectivity (entries 11–14). The presence of base was essential for the reaction to proceed. For example, the use of K_2CO_3 as the base enabled the catalytic asymmetric synthesis of **3a** in 88% yield, 8:1 dr and 98% ee (entry 9). Encouraged by these results, we decided to investigate the catalytic domino reaction between 4-bromo β-ketoester **1a** and different enals **2** with (*S*)-chiral amine **5** as the organocatalyst and K_2CO_3 as the proton sponge (Table 2).[13] In addition, we found that the diastereoselectivity of the reaction was increased at 4 °C (compare entries 1 and 2).

This novel methodology provided a simple entry to the chiral cyclopentanones **3a**–**e** possessing three new stereocenters in good to high yields with 6:1–12:1 dr and 93 → 99% ee. In the case of the domino reactions with enal **2c** as the acceptor, the best results were obtained at room temperature (entry 4). The chiral cyclopentanones **3** were also reduced with $NaBH_3CN$ to the corresponding diols **11** containing four stereocenters with excellent diastereoselectivity without affecting the enantiomeric excess. For example, diol **11d** was isolated in 63% yield as the predominant diastereomer with 98% ee (Eq. 4).[14] Thus, highly functionalized cyclopentanes containing primary and secondary alcohol groups can be synthesized via this organocatalytic domino reaction.



(4)

The relative stereochemistry of alcohols **11** was established by NOE experiments on **11d** and from the coupling constants of the ring-protons.[14] The experiments revealed that all the substituents in **11d** were *trans*.

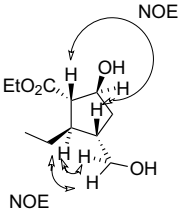
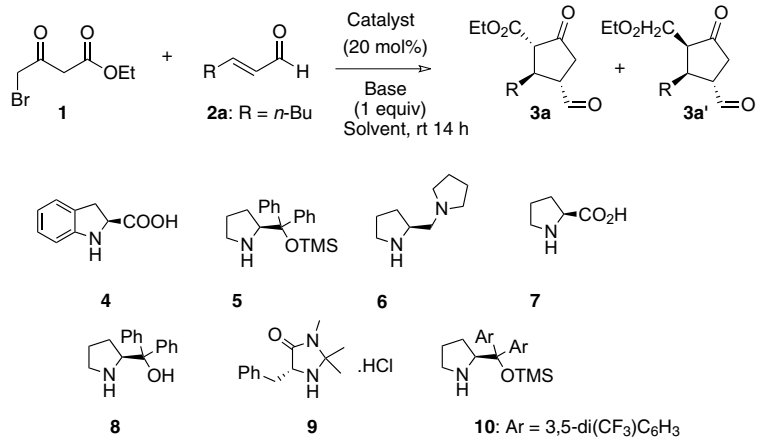


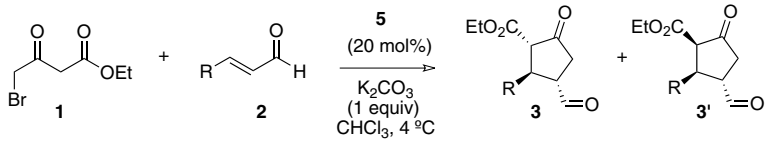
Table 1. Catalyst screen for the enantioselective reactions between **1** and **2a**[a]

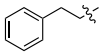


Entry	Catalyst	Solvent	Base	Yield[b]	dr[c]	ee[d]
1	**4**	$CHCl_3$	AcONa	0	—	—
2	**5**	$CHCl_3$	AcONa	67	8:1	97
3	**6**	$CHCl_3$	AcONa	0	—	—
4	**7**	$CHCl_3$	AcONa	74	8:1	−53
5	**8**	$CHCl_3$	AcONa	0	—	—
6	**9**	$CHCl_3$	AcONa	0	—	—
7	**10**	$CHCl_3$	AcONa	0	—	—
8	**5**	$CHCl_3$	Et_3N	0	—	—
9	**5**	$CHCl_3$	K_2CO_3	88	8:1	98
10	**5**	$CHCl_3$	KOH	55	8:1	96
11	**5**	CH_3CN	AcONa	77	8:1	91
12	**5**	Toluene	AcONa	62	8:1	96
13	**5**	THF	AcONa	55	8:1	96
14	**5**	MeOH	AcONa	80	8:1	88

[a] Experimental conditions: To a stirred solution of catalyst (20 mol %) in solvent (1.0 mL) were added α,β-unsaturated aldehyde **2a** (0.30 mmol), base (0.25 mmol) and ethyl 4-bromo-3-oxobutanoate **1** (0.25 mmol). The reaction was vigorously stirred for 14 h at room temperature. The crude product was purified by silica gel column chromatography (pentane:EtOAc-mixtures) to give cyclopentanones **3a** and **3a′**.
[b] Isolated yield of pure compounds **3a** and **3a′**.
[c] The ratio of **3a**:**3a′** as determined by ^{1}H NMR.
[d] Determined by chiral-phase HPLC analysis.

Table 2. Direct organocatalytic asymmetric domino reactions between 4-bromo β-ketoester **1** and enals **2**[a]



Entry	R	Prod.	Time (h)	Yield[b]	dr[c]	ee[d]
1	*n*-Bu	**3a**	14	72	10:1	99
2	*n*-Bu	**3a**	14[e]	88[e]	8:1[e]	98[e]
3	*n*-Pr	**3b**	14	83	10:1	>99
4		**3c**	3[e]	58[e]	12:1[e]	99[e]
5	Et	**3d**	14	70	9:1	98
6	Me	**3e**	14	76	6:1	93

[a] Experimental conditions: To a stirred solution of catalyst (20 mol %) in solvent (1.0 mL) were added α,β-unsaturated aldehyde **2** (0.30 mmol), K_2CO_3 (0.25 mmol) and ethyl 4-bromo-3-oxobutanoate **1** (0.25 mmol). The reaction was vigorously stirred for the time shown in the Table at 4 °C or at room temperature. Next, the crude product was purified by silica gel column chromatography (pentane:EtOAc-mixtures) to give the corresponding cyclopentanones **3**.
[b] Isolated yield of pure compounds **3** and **3′**.
[c] The ratio of **3**:**3′** as determined by ^{1}H NMR analysis.
[d] Determined by chiral-phase HPLC analysis.
[e] The reaction was run at room temperature.

Based on these experiments and previous reports on chiral pyrrolidine-catalyzed addition of β-keto esters to enals,[5k,r,6] we propose the following reaction mechanism. The reaction starts with iminium activation of the α,β-unsaturated aldehyde by the chiral pyrrolidine according to Scheme 1. Next, stereoselective nucleophilic conjugate attack on the β-carbon by the 4-bromo β-ketoester **1** results in a chiral enamine intermediate, which undergoes an intramolecular 5-*exo*-*tet* cyclization from the same face as the incoming **1**, followed by hydrolysis of the resulting iminium intermediate to give the cyclopentanone product **3**. In the case of (*S*)-proline **5** catalysis, the β-ketoester approached from the opposite face of the iminium intermediate to give cyclopentanone *ent*-**3**.

In summary, we have reported a simple, highly enantioselective, and organocatalytic asymmetric domino reaction. The chiral pyrrolidine catalyzed reactions between 4-bromo β-keto esters and α,β-unsaturated aldehydes proceeded with high chemo- and enantioselectivity to furnish the corresponding cyclopentanones in good to high yields with 6:1–12:1 dr and 93 → 99% ee. The cyclopentanones were also reduced to the corresponding tetra-substituted cyclopentanols with excellent diastereoselectivity. Further elaboration of this novel transformation, its synthetic application and mechanistic studies are ongoing in our laboratory.

Acknowledgement

We gratefully acknowledge the Swedish National Research Council and Carl-Trygger Foundation for financial support.

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12. Compound **3a**: Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 9.73$ (d, $J = 2.8$ Hz, 1H), 4.21 (q, $J = 7.2$ Hz, 2H), 3.05–2.45 (m, 4H), 1.76–1.60 (m, 2H),

1.60–1.43 (m, 2H), 1.40–1.20 (m, 6H), 0.88 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 207.7, 200.1, 168.6, 61.8, 61.2, 52.3, 41.6, 38.6, 34.0, 29.5, 22.6, 14.1, 13.8. $[\alpha]_D$ −65.5 (*c* 1.0, $CHCl_3$). HRMS (ESI): Calcd for $[M+Na]^+$ ($C_{13}H_{20}O_4$) requires *m*/*z* 263.1254; found, 263.1253. The enantiomeric excess was determined by GC on a chrompak CP-Chirasil-Dex CB-column. Temperature program: 5 min, 70 °C//2 °C min^{-1}//110 °C, 10 min//10 °C min^{-1}// 200, 10 min t_R = major enantiomer 11.3 min, minor enantiomer 11.6 min.

13. *Typical experimental procedure for the organocatalytic cyclopentanonation reactions*: To a stirred solution of catalyst **5** (0.05 mmol, 20 mol %) in $CHCl_3$ (1.0 mL), were added α,β-unsaturated aldehyde **2** (0.30 mmol, 1.2 equiv), K_2CO_3 (0.25 mmol, 1.0 equiv) and ethyl 4-bromo-3-oxo-butanoate **1** (0.25 mmol, 1.0 equiv). The reaction was vigorously stirred for the time and the temperature listed in Table 2. Next, the crude product was purified by silica gel column chromatography (pentane:EtOAc-mixtures) to give the corresponding cyclopentanone **3**. Compound **3d**: Colorless oil. IR (KBr): 2968, 2937, 2880, 1755, 1728, 1464, 1447, 1372, 1262, 1174, 1096, 1030, 854 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 9.74$ (d, $J = 2.4$ Hz, 1H), 4.21 (q, $J = 7.2$ Hz, 2H), 3.02–2.66 (m, 4H), 2.60–2.53 (m, 1H), 1.78–1.69 (m, 1H), 1.64–1.54 (m, 1H), 1.32–1.26 (m, 3H), 0.96 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 207.7, 200.2, 168.7, 62.0, 60.9, 52.0, 43.2, 38.8, 27.1, 14.3, 11.8. $[\alpha]_D$ +103.8 (*c* 1.0, $CHCl_3$). HRMS (ESI): Calcd for $[M+Na]^+$ ($C_{11}H_{16}O_4$) requires *m*/*z* 235.0941; found, 235.0939. The enantiomeric excess was determined by GC on a chrompak CP-Chirasil-Dex CB-column. Temperature program: 120 °C, 10 min, 120 °C// 3 °C min^{-1}//160 °C//80 °C min^{-1}//200 °C min^{-1}//5 min. t_R = major enantiomer 8.8 min, minor enantiomer 9.2 min.

14. *Procedure for the reduction of cyclopentanone* **3d**: To a stirred solution of cyclopentanone **3d** (42 mg, 0.20 mmol) in THF (1.0 mL) were added acetic acid (225 μL) and $NaBH_3CN$ (29 mg, 0.45 mmol) at 0 °C. The reaction was stirred at this temperature for 1 h and then at rt overnight. The crude product was purified by silica gel column chromatography (pentane:EtOAc-mixtures) to give the corresponding cyclopentanol **11d** (27 mg, 63% yield). Compound **11d**: colourless oil. IR (KBr): 3353, 2960, 2932, 2877, 1727, 1463, 1378, 1261, 1162, 1095, 1037, 914 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.37$ (dd, $J = 7.6$ Hz, 13.6 Hz, 1H, C*H*OH), 4.17 (q, $J = 7.2$ Hz, 2H, $COOCH_2CH_3$), 3.64 (dd, $J = 4.4$ Hz, 10.4 Hz, 1H, CH_2OH), 3.51 (dd, $J = 7.6$ Hz, 10.4 Hz, 1H, CH_2OH), 2.43 (dd, $J = 7.6$ Hz, 8.8 Hz, 1H, $CHCOOCH_2CH_3$), 2.10–2.01 (m, 1H, $CHCH_2CH_3$), 1.99–1.78 (m, 3H, CH_2, $CHCH_2OH$), 1.64–1.52 (m, 2H, CH_2CH_3), 1.27 (t, $J = 7.2$ Hz, 3H, CH_2CH_3), 0.92 (t, $J = 7.2$ Hz, 3H, $COOCH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 175.0, 75.6, 66.2, 60.9, 58.7, 44.9, 44.0, 37.1, 27.8, 14.4, 11.8. $[\alpha]_D$ −9.7 (*c* 1.0, $CHCl_3$). HRMS (ESI): Calcd for $[M+Na]^+$($C_{11}H_{20}O_4$) requires *m*/*z* 239.1254; found, 239.1262.