



Organocatalytic enantioselective domino synthesis of highly functionalized cyclohexanes with an all-carbon quaternary stereocenter

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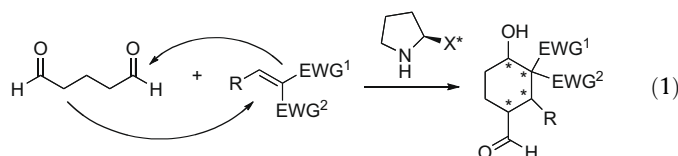
ABSTRACT

A highly enantioselective organocatalytic domino Michael/aldol reaction is presented. The reaction is catalyzed by chiral amines and gives access to highly functionalized cyclohexanes with one all-carbon quaternary stereocenter and multiple chiral stereocenters in high yields and 83–98% ee.

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Domino or cascade reactions, that involve the formation of multiple carbon-carbon bonds and stereocenters in one-pot, is a rapidly growing research field within the synthesis of small molecules with complex molecular scaffolds.¹ Domino reactions are advantageous since they include important ‘green’ chemistry factors such as atom economy,² reduction of synthetic steps, and minimization of solvents and waste.³ Another important factor that adds to the concept of domino reactions is asymmetric catalysis. In this context, the development of organocatalytic asymmetric one-pot domino reactions is an actively growing research area.^{4,5}

The stereoselective synthesis of all-carbon quaternary stereogenic centers in complex organic molecules is very important. However, this is a difficult task due to the inherent steric bias in the carbon-carbon bond-forming step.⁶ Thus, the development of enantioselective catalytic domino reactions that give access to small molecules containing all-carbon quaternary stereogenic centers is considered very challenging.⁷ Our group,^{8a} as well as Melchiorre and co-workers,^{7b} has recently reported the amine-catalyzed asymmetric conjugate addition of aldehydes to Michael acceptors derived from malonates and cyanoacetic acid, respectively.⁷ Prior to this, the amine-catalyzed addition of ketones to alkylidene malonates was reported.^{8c,d} Notably, Hayashi and co-workers have shown that glutaraldehyde can be used as a substrate in the construction of optically active cyclohexanes.⁹ They subsequently developed a catalytic domino Michael/nitro-aldol reaction. Based on these findings and our research interest in ‘green’ asymmetric catalysis,¹⁰ we envisioned a route to highly functionalized molecules with one quaternary all-carbon stereocenter and three additional stereocenters by a possible amine-catalyzed enantioselective domino Michael/aldol reaction (Eq. 1):



Herein, we demonstrate a highly enantioselective domino Michael/aldol one-pot synthesis of cyclohexane derivatives with a quaternary all-carbon stereocenter and cyano, formyl, hydroxy, and ester functional groups in 83–98% ee.

In an initial catalyst and solvent screening for the reaction between glutaraldehyde **1** and alkylidene malonate **2a** (Scheme 1), we found that of the investigated chiral amines, only protected diphenylprolinol **4**¹¹ catalyzed the asymmetric formation of cyclohexane derivative **3a** with a high level of stereoselectivity (>25:1 dr and 97% ee).

Encouraged by this result, we decided to investigate chiral amine **4** as a catalyst for the reaction between **1** and 2-cyanocinnamic acid ester **2b**, since a cyclohexane with an asymmetric quaternary stereocenter would be generated (Table 1). This type of compound is a valuable synthon for further synthetic manipulations.

This transformation resulted in the formation of the corresponding cyclohexane **3b** in high yields but with poor to high levels of diastereoselectivity (**3b**:**3b'**) and 37–79% ee at room temperature in all the solvents investigated (entries 1–4). The absolute stereochemistry of the product was switched in CH₃CN (entry 2). The switch in the enantioselectivity of the reaction in CH₃CN has also been observed in the chiral amine **4**-catalyzed α -selenylation of aldehydes.¹² Notably, increasing the reaction temperature improved the enantioselectivity significantly (entries 6–8) whereas decreasing it did not (entry 5). To our delight, decreasing the catalyst loading further improved the enantioselectivity in CHCl₃ and gave the corresponding cyclohexane **3b** with an

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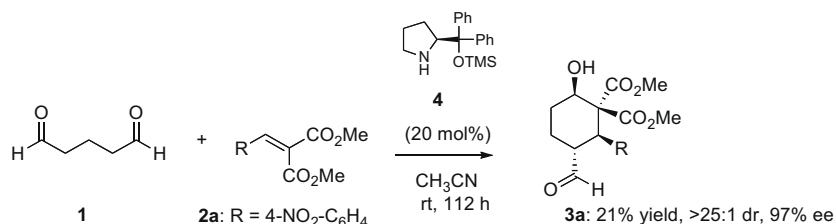
Scheme 1. Catalytic domino reaction between **1** and **2a**.

Table 1

Optimization of the conditions for the reaction between **1** and ester **2b**^a

Entry	Solvent	Temp (°C)	Time (h)	Yield ^b (%)	dr ^c	ee ^d (%)
1	CHCl ₃	23	3	80	7:1	79
2	CH ₃ CN	23	24	94	24:1	37 ^e
3	CH ₂ Cl ₂	23	21	51	12:1	38
4	Toluene	23	5	70	1:1	70
5	CHCl ₃	4	40	70	7:1	41
6	CHCl ₃	45	0.5	87	6:1	96
7	CH ₂ Cl ₂	40	0.3	96	6:1	87
8	CHCl ₃	45	0.8	94 ^f	6:1 ^f	98 ^f

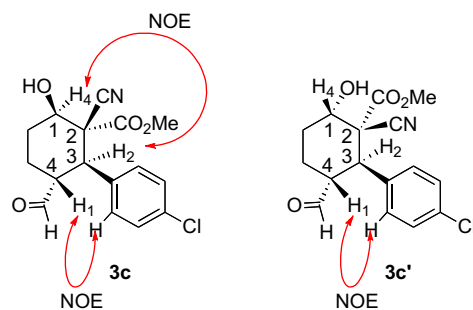
^a Experimental conditions: A mixture of **1** (0.5 mmol), **2b** (0.25 mmol), and catalyst (20 mol %) in 1 mL of solvent was stirred at the temperature and for the time indicated.^b Isolated yield of **3b** after silica gel column chromatography.^c Diastereomeric ratio of **3b**:**3b'** determined by ¹H NMR analysis of the crude reaction mixture.^d Ee of **3b** determined by chiral-phase HPLC analysis.^e The opposite enantiomer *ent*-**3b** was formed.^f 10 mol % of catalyst **4** was used at all stereocenters.

all-carbon quaternary stereocenter in 94% yield, a 6:1 dr and 98% ee (entry 8).

Based on these results, we decided to investigate the chiral amine **4**-catalyzed enantioselective domino reactions between dialdehyde **1** and various 2-cyanocinnamic acid esters **2** in CHCl₃ at 45 °C (Table 2).¹³

The organocatalytic asymmetric domino reactions gave the corresponding cyclohexanes **3b–i** in high yields (72–98%) as the predominant diastereoisomers (5:1–10:1 dr, **3**:**3'**), which could be separated readily from the minor diastereoisomers **3b'–i'** by silica gel column chromatography. The enantioselectivity of the reactions was high (83–98% ee). Thus, the one-pot procedure allows for the construction of four stereocenters with very high stereocontrol. The diastereoselectivity of this reaction is lower compared to when nitrostyrenes are used as substrates.⁹ This is due to the fact that a quaternary stereocenter is formed and that a higher temperature is employed compared to the reactions of nitrostyrenes at room temperature. This reaction was accelerated and the diastereoselectivity was slightly improved by the use of microwave irradiation without significantly affecting the enantioselectivity (entry 9).¹⁴ This could be due to a combination of the increased temperature and pressure. The corresponding acids **5**, diol **6**, and tri-ester **7** were synthesized in high yields from cyclohexanes **3** (Scheme 2).

The relative stereochemistry of **3c**¹⁵ was established by NOE experiments, which confirmed the relative configuration between all the neighboring substituents. The relative stereochemistry of the minor diastereoisomer was established by NOE experiments on compound **3c'**¹⁶ (93% ee).

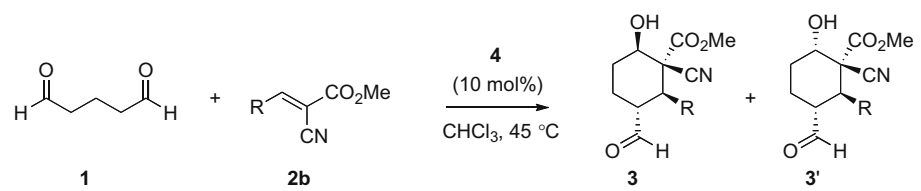


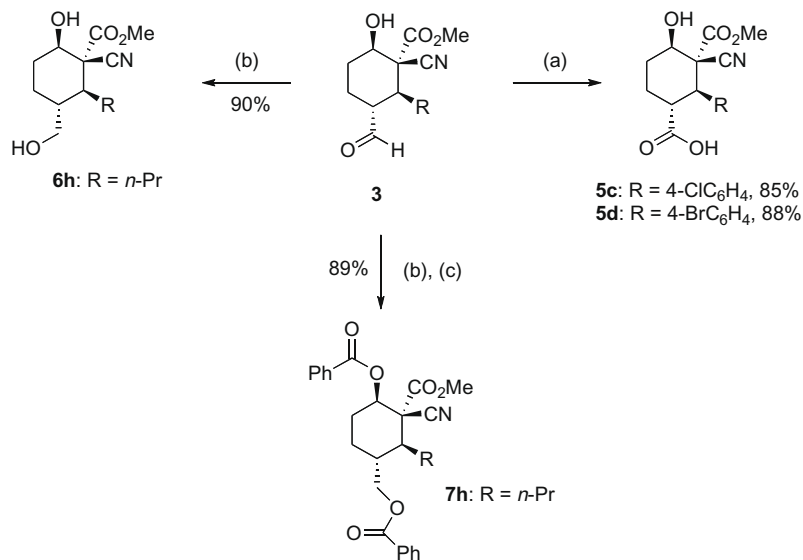
This was also confirmed by the X-ray analysis (Fig. 1) of acid **5c** (1*R*,2*R*,3*S*,4*R*).¹⁷

Based on these results and the chiral amine **4**-catalyzed aldehyde additions to Michael acceptors **2**,⁹ we propose the following domino reaction mechanism to account for the observed stereochemistry of the reaction (Scheme 3).

Thus, efficient shielding of the *Si*-face of the chiral enamine intermediate **I** by the bulky aryl groups of **4** leads to stereoselective *Re*-facial nucleophilic conjugate attack. Next, the in situ generated anion of the chiral iminium intermediate **II** undergoes a six-*exo-trig* intramolecular aldol addition on the aldehyde moiety to form iminium intermediate **III**. Hydrolysis gives the corresponding cyclohexane **3** and releases the chiral amine catalyst. The intermolecular aldol addition step was very fast since no free Michael

Table 2Catalytic asymmetric domino reactions between dialdehyde **1** and esters **2**^a

						
Entry	R	Product	Time (h)	Yield ^b (%)	dr ^c	ee ^d (%)
1		3b	0.8	94	6:1	98
2		3c	2	98	6:1	92
3		3d	2	95	9:1	85
4 ^e		3e	2	82	8:1	92
5 ^e		3f	2.5	78	5:1	93
6 ^e		3g	1	96	8:1	83
7 ^e		3h	2	89	6:1	95
8 ^e		3i	2	72	10:1	89
9 ^f		3c	1	97	7:1	89

^a Experimental conditions: A mixture of **1** (0.50 mmol), **2a** (0.25 mmol), and catalyst (10 mol %) in 1 mL of CHCl₃ was stirred at 45 °C for the time displayed.^b Isolated yield of **3** after silica gel column chromatography.^c Diastereomeric ratio of **3**:**3'** determined by ¹H NMR analysis of the crude reaction mixture.^d ee of **3** determined by chiral-phase HPLC analysis.^e 20 mol % of catalyst **4** was used.^f The reaction was performed in a sealed tube under microwave irradiation using a microwave synthesizer from personal systems (Biotage AB).**Scheme 2.** Reagents and conditions: (a) NaClO₂, KH₂PO₄, (CH₃)₂C=CHCH₃, *t*-BuOH/H₂O (5:1); (b) NaCNBH₃, THF, AcOH; (c) BzCl, CH₂Cl₂, Et₃N.

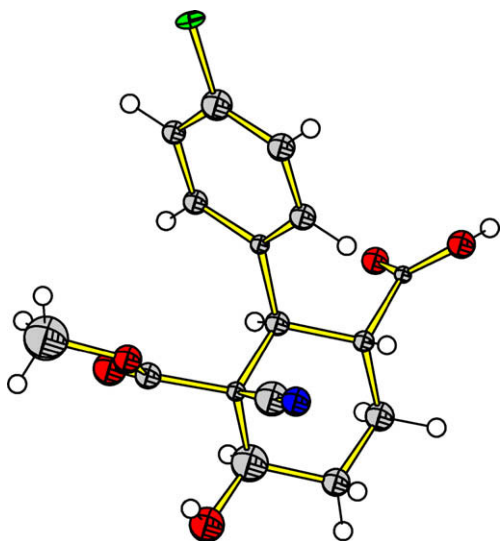


Figure 1. ORTEP picture of compound **5c**.

intermediate, which would have been formed by hydrolysis of iminium intermediate **II**, was observed. Moreover, this rapid equilibrium was also responsible for the time dependent conversion of the minor diastereoisomer **3'** to the more thermodynamically stable major diastereoisomer **3**.

In summary, we have developed a highly diastereo- and enantioselective one-pot domino Michael/aldol reaction for the synthesis of cyano, formyl, hydroxy, and ester functionalized cyclohexanes with one all-carbon stereocenter and three additional stereocenters. The reaction was accelerated by heating, can

be performed under microwave irradiation and the corresponding products can be used as scaffolds for further diversification. Further development of catalytic domino reactions that generate optically active molecules with an all carbon stereocenter is underway in our laboratory.

Acknowledgments

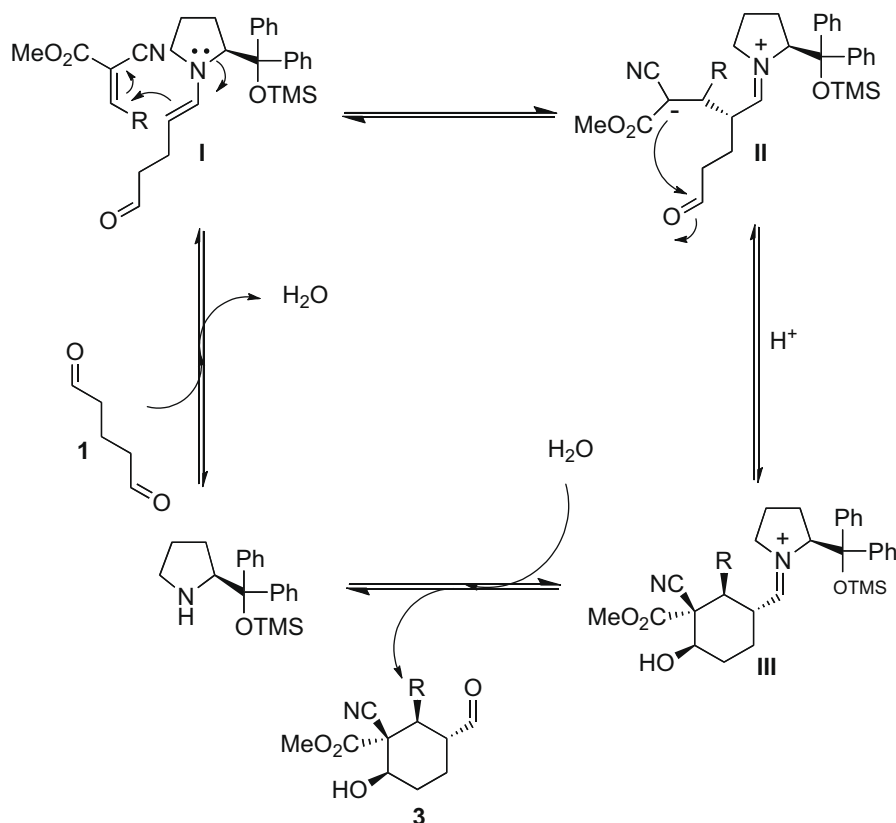
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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.02.209.

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13. To a stirred solution of the catalyst **4** (10 or 20 mol %) in CHCl_3 (1 mL) were added glutaraldehyde (100 mg, 0.5 mmol, 40% aqueous solution) and ester **2** (0.25 mmol) at 45 °C. Next, the reaction mixture was stirred vigorously and monitored by TLC. After the time shown in Table 2, the reaction mixture was allowed to cool and then extracted with EtOAc (3×15 mL). The organic layer was combined, dried over Na_2SO_4 , and the solvent was removed. The residue was purified by silica gel column chromatography (pentane/ethyl acetate = 4:1–1:1) to give the corresponding product **3**. (1S,2R,3R,6R)-Methyl 1-cyano-3-formyl-6-hydroxy-2-(4-nitrophenyl)cyclohexanecarboxylate **3b**: $[\alpha]_D^{25} + 16.1$ (c 1.0, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 9.46 (d, $J = 2.0$ Hz, 1H), 8.20 (d, $J = 8.8$ Hz, 2H), 7.51 (d, $J = 8.8$ Hz, 2H), 4.24 (dd, $J = 4.0, 12.0$ Hz, 1H), 3.59 (s, 3H), 3.50 (d, $J = 12.4$ Hz, 1H), 3.30 (ddt, $J = 2.0, 4.0, 12.4$ Hz, 1H), 2.44 (br s, 1H), 2.35–2.26 (m, 2H), 2.06–1.97 (m, 1H), 1.62–1.52 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 199.4, 167.5, 148.1, 143.0, 129.5, 124.2, 115.7, 73.7, 61.0, 53.9, 49.7, 47.9, 30.2, 24.3. The enantiomeric excess was determined by HPLC with an AD column (n -hexane/ i -PrOH = 90:10, $\lambda = 205$ nm), 0.5 mL/min; t_R = minor enantiomer 88.4 min, major enantiomer 99.7 min. HRMS (ESI): calcd for $[\text{M}+\text{Na}]^+$ ($\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_6\text{Na}$) requires m/z 355.0901, found 355.0897.
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15. Compound **3c**: $[\alpha]_D^{25} - 6.4$ (c 1.0, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 9.43 (d, $J = 2.0$ Hz, 1H), 7.34 (d, $J = 8.8$ Hz, 2H), 7.29–7.27 (m, 2H), 4.24 (d, $J = 12.0$ Hz, 1H), 3.61 (s, 3H), 3.35 (d, $J = 12.0$ Hz, 1H), 3.21 (ddt, $J = 2.0, 4.0, 12.0$ Hz, 1H), 2.40 (br s, 1H), 2.32–2.26 (m, 1H), 2.23–2.17 (m, 1H), 2.03–1.93 (m, 1H), 1.68–1.59 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 200.4, 167.7, 135.0, 133.8, 129.8, 129.5, 116.0, 73.6, 61.5, 53.8, 49.5, 48.0, 30.1, 24.2. The enantiomeric excess was determined by HPLC with an AD column (n -hexane/ i -PrOH = 90:10, $\lambda = 205$ nm), 0.5 mL/min; t_R = minor enantiomer 39.7 min, major enantiomer 44.1 min. HRMS (ESI): calcd for $[\text{M}+\text{Na}]^+$ ($\text{C}_{16}\text{H}_{16}\text{ClNO}_4\text{Na}$) requires m/z 344.0660, found 344.0657.
16. Compound **3c'**: $[\alpha]_D^{25} + 4.7$ (c 1.0, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 9.39 (d, $J = 2.0$ Hz, 1H), 7.33–7.28 (m, 4H), 4.40 (t, $J = 2.4$ Hz, 1H), 3.93 (br s, 1H), 3.82 (d, $J = 12.4$ Hz, 1H), 3.55 (s, 3H), 3.26–3.18 (m, 1H), 2.18–2.12 (m, 2H), 2.06–1.97 (m, 1H), 1.92–1.87 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 200.4, 169.3, 134.8, 134.7, 130.1, 129.3, 116.6, 69.1, 55.1, 53.9, 50.4, 41.9, 27.7, 19.7. The enantiomeric excess was determined by HPLC with an AD column (n -hexane/ i -PrOH = 90:10, $\lambda = 205$ nm), 0.5 mL/min; t_R = minor enantiomer 22.5 min, major enantiomer 29.4 min. HRMS (ESI): calcd for $[\text{M}+\text{Na}]^+$ ($\text{C}_{16}\text{H}_{16}\text{ClNO}_4\text{Na}$) requires m/z 344.0660, found 344.0658.
17. CCDC 704580 contains the supplementary crystallographic data for this Letter. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.