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# Catalytic asymmetric direct aldol reaction of $\alpha$ -alkyl azlactones and aliphatic aldehydes†

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An unprecedented highly diastereoselective and enantioselective aldol reaction of  $\alpha$ -alkyl azlactones and aliphatic aldehydes was achieved with cinchona alkaloid catalysts. To our knowledge, this reaction provides the first useful catalytic asymmetric access toward  $\beta$ -hydroxy- $\alpha$ -amino acids bearing alkyl substituents, which are structural motifs embedded in many natural products.

Optically active  $\beta$ -hydroxy- $\alpha$ -amino acids are an important class of amino acids as they are structural motifs in many biologically active natural products such as vancomycin,<sup>1</sup> katanosins,<sup>2</sup>

cyclosporin,<sup>3</sup> myriocin,<sup>4a,b</sup> mycestericins,<sup>4c,d</sup> sphingosine and threonine (Fig. 1). Furthermore, these amino acids are also useful chiral building blocks in organic synthesis as precursors to  $\beta$ -lactams,<sup>5</sup>  $\beta$ -halo- $\alpha$ -amino acids,<sup>6</sup> and aziridines.<sup>7</sup> A variety of catalytic asymmetric approaches for the synthesis of  $\beta$ -hydroxy- $\alpha$ -amino acids has been reported.<sup>8–14</sup> In a pioneering study,<sup>8a</sup> Ito, Hayashi and coworkers reported a gold-catalyzed highly diastereoselective and enantioselective aldol reaction for the generation of  $\beta$ -hydroxy- $\alpha$ -amino acids containing tertiary  $\alpha$ -carbons. Since then other groups have also reported asymmetric direct aldol reactions with chiral transition-metal catalysts,<sup>8c–h</sup> organocatalysts<sup>9</sup> and aldolases<sup>10</sup> for the synthesis of  $\beta$ -hydroxy- $\alpha$ -amino acids and their derivatives. In addition, Sharpless asymmetric aminohydroxylation,<sup>11</sup> transition-metal-catalyzed asymmetric hydrogenation,<sup>12</sup> palladium-catalyzed allylic alkylation<sup>13</sup> and chiral phosphoric acid-catalyzed addition to oxocarbenium ion<sup>14</sup> have been utilized to achieve the same goal.

We became interested in the development of catalytic asymmetric synthesis of  $\beta$ -hydroxy- $\alpha$ -amino acids because biologically interesting natural products such as mycestericins contain a chiral  $\beta$ -hydroxy- $\alpha$ -amino acid motif that could not be constructed from existing catalytic asymmetric aldol reactions.

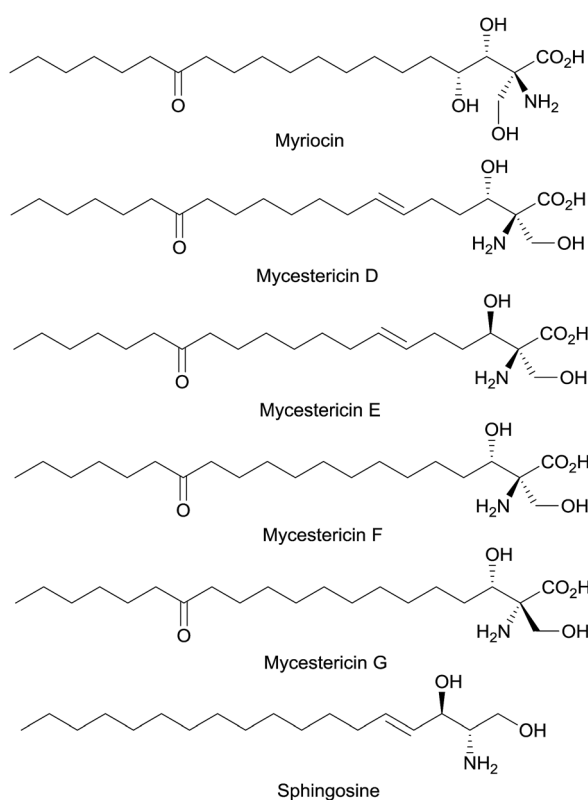
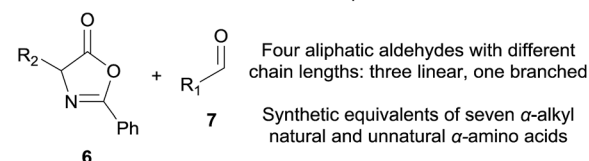
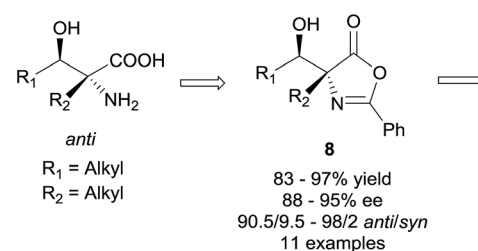


Fig. 1 Mycestericins: potent immunosuppressant natural products

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† Electronic supplementary information (ESI) available: Experimental procedures and characterization for new compounds are provided. See DOI: 10.1039/c5sc02116b



Scheme 1 Reaction design



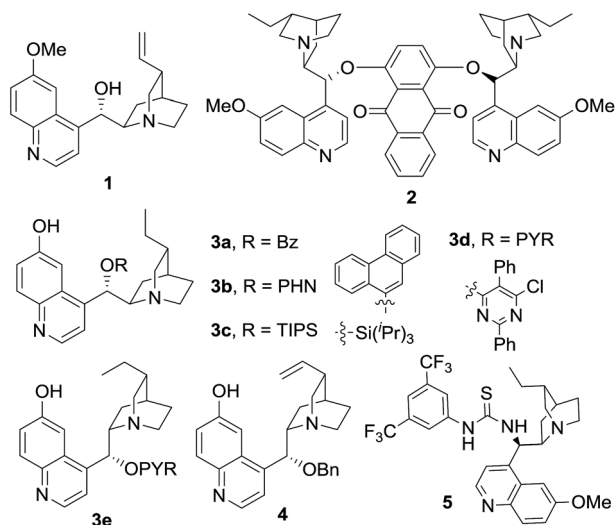
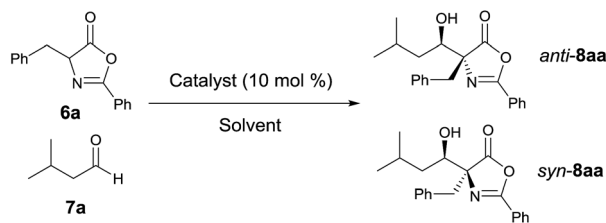


Fig. 2 Cinchona alkaloid catalysts

In particular this motif presents both a tertiary  $\beta$ -stereocenter and a quaternary  $\alpha$ -stereocenter with alkyl substituents. In principle, an efficient catalytic asymmetric aldol reaction of  $\alpha$ -alkyl enolates or the equivalents with aliphatic aldehydes could provide a direct access to this structural motif.<sup>15</sup> However, to our knowledge, such an asymmetric transformation was not

available. Herein, we report the first efficient catalytic asymmetric direct aldol reaction of  $\alpha$ -alkyl azlactones **6** and aliphatic aldehydes **7** (Scheme 1), which provides, to our knowledge, the first useful asymmetric catalytic access toward  $\beta$ -hydroxy- $\alpha$ -amino acids bearing alkyl substituents at both the tertiary  $\beta$ -stereocenter and the quaternary  $\alpha$ -stereocenter. The high *anti*-diastereoselectivity in combination with a broad substrate scope allows the reaction to complement existing methods to form a general strategy for the asymmetric synthesis of  $\beta$ -hydroxy- $\alpha$ -amino acids.

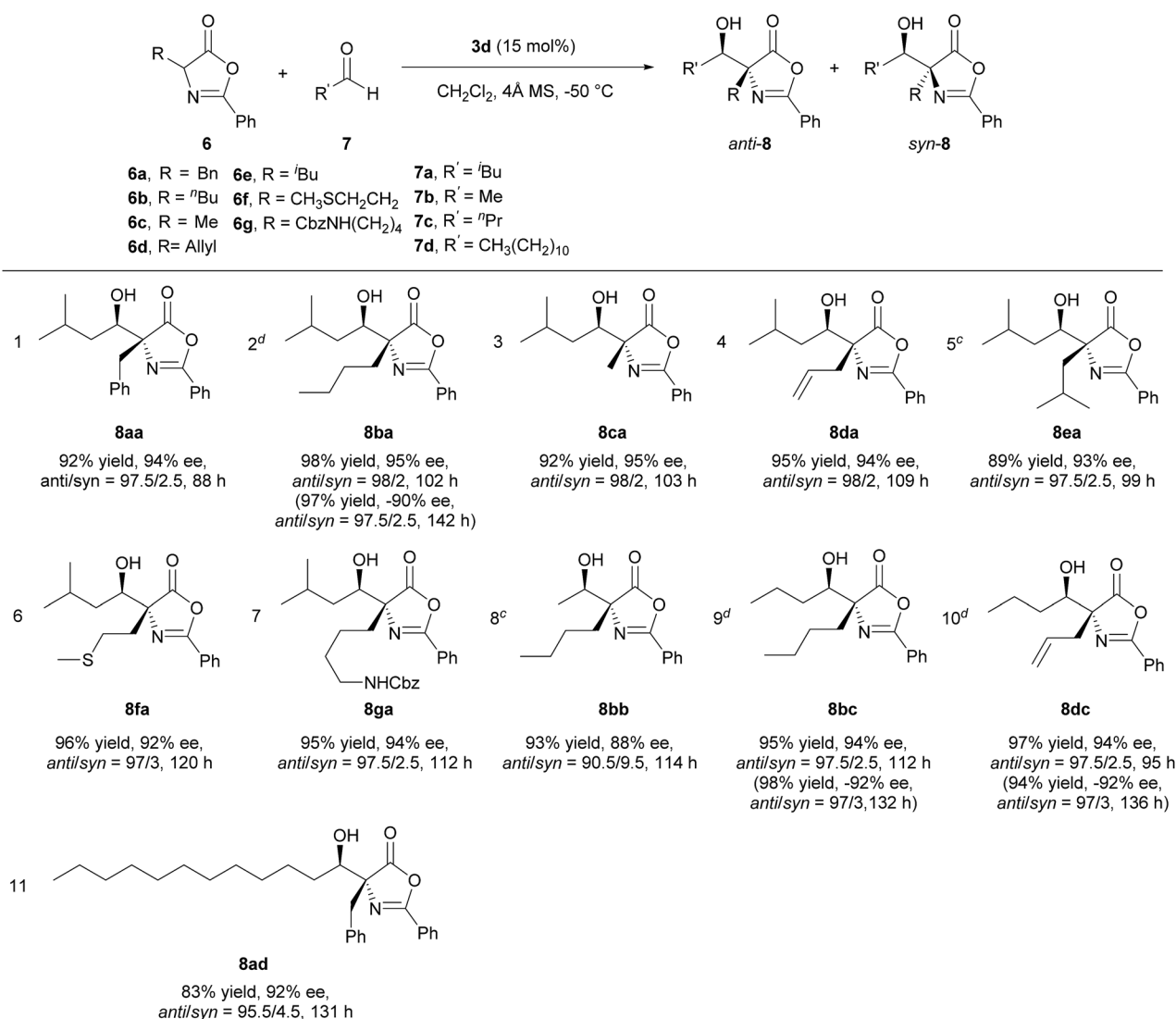
We initiated our study by reacting azlactone **6a** and aldehyde **7a** in the presence of a stoichiometric amount of triethylamine. After considerable experiments, we found that a reaction could be reasonably fast and clean at  $-20\text{ }^\circ\text{C}$  in chloroform. We next investigated the possibility of promoting an asymmetric variant of this reaction with cinchona alkaloid-derived catalysts (Fig. 2). Upon first screening of a series cinchona alkaloid derivatives, (entries 1–9, Table 1), we identified the 6'-OH cinchona alkaloid **3d** as the most promising catalyst in terms of affording high diastereoselectivity and enantioselectivity (entry 6, Table 1). Catalyst **3e**, the pseudo-enantiomer of **3d**, gave comparable results with an expected reverse sense of asymmetric induction (entry 7, Table 1). Following these results, we carried out the **3d**-promoted aldol reaction in a variety of solvents with azlactone **6a** at a significantly decreased concentration of 0.5 M (entry 10–15). We found that the reaction at the reduced

Table 1 Catalytic asymmetric aldol reaction of azlactone **6a** and aldehyde **7a**<sup>a</sup>

Entry	Catalyst	Solvent	Temp ( $^\circ\text{C}$ )	Time	Conv. <sup>c</sup> (%)	ee <sup>cd</sup> (%)	<i>anti</i> / <i>syn</i> <sup>c</sup>
1	<b>1</b>	CHCl <sub>3</sub> (2 M)	-20	15 h	>95	29/22	43.5/56.5
2	<b>2</b>	CHCl <sub>3</sub> (2 M)	-20	15 h	93	43/12	40.5/59.5
3	<b>3a</b>	CHCl <sub>3</sub> (2 M)	-20	15 h	>95	57/25	81/19
4	<b>3b</b>	CHCl <sub>3</sub> (2 M)	-20	15 h	>95	51/19	73/27
5	<b>3c</b>	CHCl <sub>3</sub> (2 M)	-20	15 h	92	-7/18	71/29
6	<b>3d</b>	CHCl <sub>3</sub> (2 M)	-20	15 h	>95	75/13	88/12
7	<b>3e</b>	CHCl <sub>3</sub> (2 M)	-20	15 h	>95	-73/16	90/10
8	<b>4</b>	CHCl <sub>3</sub> (2 M)	-20	15 h	91	-64/-6	82/18
9	<b>5</b>	CHCl <sub>3</sub> (2 M)	-20	15 h	>95	-71/22	66/34
10	<b>3d</b>	CHCl <sub>3</sub> (0.5 M)	-20	34 h	95	86/-11	91/9
11	<b>3d</b>	CH <sub>2</sub> Cl <sub>2</sub> (0.5 M)	-20	34 h	93	86/-39	93.5/6.5
12	<b>3d</b>	PhCH <sub>3</sub> (0.5 M)	-20	34 h	80	48/-28	80/20
13	<b>3d</b>	THF (0.5 M)	-20	34 h	>95	50/-28	79.5/20.5
14	<b>3d</b>	Et <sub>2</sub> O (0.5 M)	-20	34 h	>95	53/-28	83/17
15	<b>3d</b>	CH <sub>3</sub> CN (0.5 M)	-20	34 h	>95	72/-18	88/12
16 <sup>e,f</sup>	<b>3d</b>	CH <sub>2</sub> Cl <sub>2</sub> (0.1 M)	-50	88 h	>95 (92) <sup>b</sup>	94/ND	97.5/2.5

<sup>a</sup> Reactions were carried out with 0.1 mmol of **6a** and 0.15 mmol of **7a**. <sup>b</sup> Isolated yield. <sup>c</sup> Determined by chiral HPLC analysis. <sup>d</sup> ee (*anti*/*syn*). <sup>e</sup> 10 mg of 4 Å molecular sieves were added. <sup>f</sup> 15 mol% of **3d**.



Table 2 Scope of reaction<sup>abe</sup>

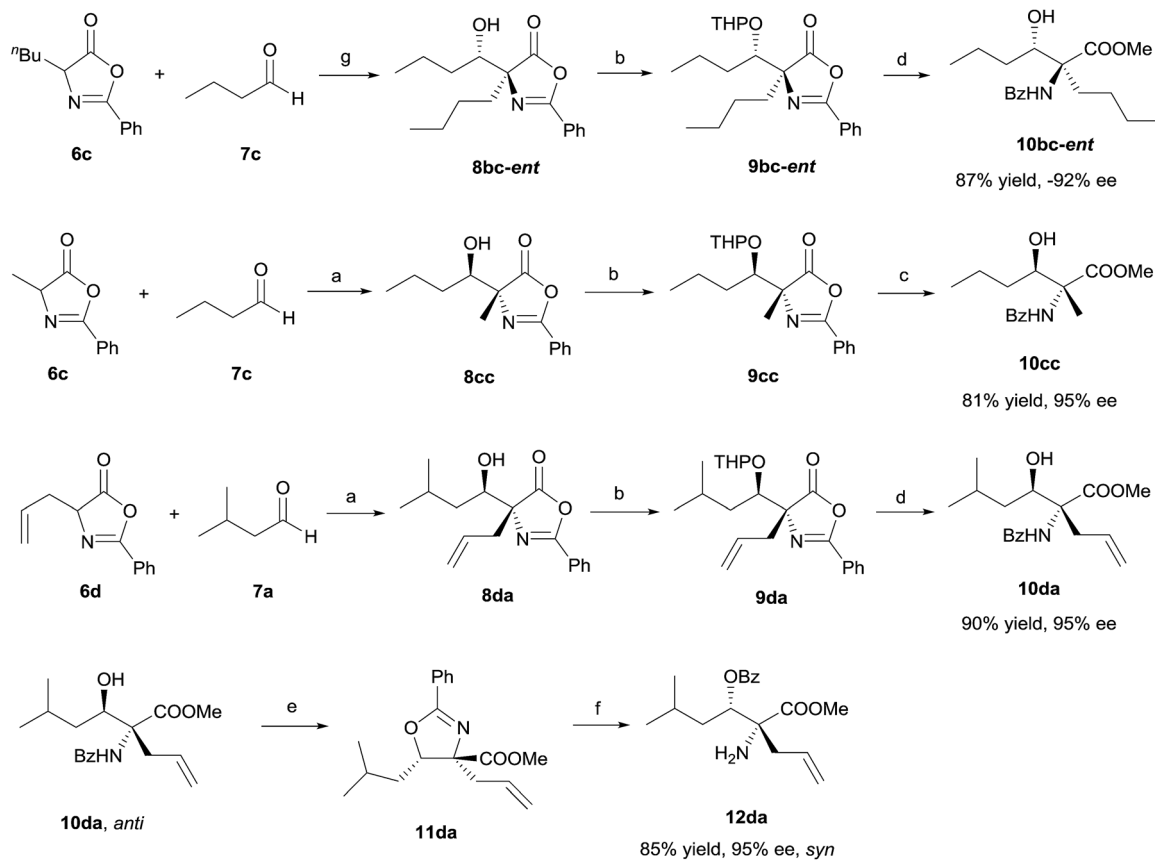
<sup>a</sup> Unless noted, reactions were carried out with 0.1 mmol of **6**, 0.15 mmol of **7**, 0.015 mmol of **3d**, 10 mg of 4 Å molecular sieves in 1 mL of dichloromethane. <sup>b</sup> ee value and *anti/syn* ratio determined by chiral HPLC analysis. <sup>c</sup> 0.2 mmol of **7b**. <sup>d</sup> Results in parentheses obtained using **3e** (15 mol%) as catalyst. <sup>e</sup> See ESI for determination of relative and absolute configurations.

concentration proceeded in higher diastereo- and enantioselectivity (entry 10 vs. 6). Moreover, the reaction in dichloromethane occurred in a slightly higher diastereoselectivity than and the same enantioselectivity as the reaction in chloroform (entries 11–10, Table 1). Both the diastereoselectivity and enantioselectivity afforded by catalyst **3d** could be improved significantly when the reaction was performed at significantly reduced temperature and concentration (entry 16 vs. 11), although a higher catalyst loading and an extended reaction time were required for the reaction to proceed to completion. Importantly, under these conditions, a highly diastereoselective and enantioselective aldol reaction was established to generate the desired aldol product **8aa** in 92% isolated yield, 94% ee and 97.5/2.5 *anti/syn* ratio. It should be noted that no product

resulted from the self-aldol reaction by aldehyde **7a** was detected by NMR analysis.

Applying the optimized reaction conditions for the model reaction, we investigated the substrate scope of this asymmetric aldol reaction (Table 2). The reactions of aldehyde **7a** and azlactones **6a–g** bearing different  $\alpha$ -alkyl substituents gave consistently excellent yields, enantioselectivity and *anti*-selective diastereoselectivity (entries 1–7, Table 2). The catalyst could also accommodate variations in aliphatic aldehydes as shown by its high efficiency in the promotion of asymmetric aldol reactions involving a series of aliphatic aldehydes (entries 8–11, Table 2). The tolerance of aldehyde **7d**, which bears a linear C12 alkyl chain, is noteworthy. With catalyst **3e**, the reaction provide equally efficient access to the other enantiomer of the aldol





**Scheme 2** Transformation of aldol product **8**. Reagents and conditions: (a) **3d** (15 mol%),  $\text{CH}_2\text{Cl}_2$ , 4 Å MS,  $-50^\circ\text{C}$ ; (b) PPTS, DHP,  $\text{CH}_2\text{Cl}_2$ , rt; then  $\text{K}_2\text{CO}_3$ ,  $\text{Na}_2\text{SO}_4$ , MeOH, rt; (c) 2 N HCl, MeOH, rt; (d) HCl in MeOH ( $\sim 1.25\text{ M}$ ), rt; (e)  $\text{SOCl}_2$ , THF, rt; (f) 2 N HCl, THF, rt; (g) **3e** (15 mol%),  $\text{CH}_2\text{Cl}_2$ , 4 Å MS,  $-50^\circ\text{C}$ . PPTS = pyridinium-*p*-toluenesulfonate; DHP = 3,4-dihydro-2-*H*-pyran.

product, as shown in the formation of aldol adduct *ent*-**8ba**, *ent*-**8bc** and *ent*-**8dc** (entries 2, 9, 10, Table 2). As detailed in the ESI,<sup>†</sup> the relative and absolute configurations of aldol products **8** were determined by 1D NOESY experiment and a modified Mosher's method, respectively.<sup>16</sup>

To demonstrate the potential synthetic utility of the chiral aldol adduct **8**, ring opening transformations converting **8** into useful  $\beta$ -hydroxy- $\alpha$ -amino acid derivative **10** must be developed. We found that **8** were liable toward retro-aldol initiated decompositions under a variety of reaction conditions. After extensive experimental explorations, we were able to establish a high yield, three-step protocol to convert **8** into  $\beta$ -hydroxy- $\alpha$ -aminoester **10** (Scheme 2). Critical to the development of this useful conversion was the experimental discovery that the THP protected  $\beta$ -hydroxy- $\alpha$ -alkylazlactones **9**, unlike **8**, is inert toward retro-aldol decompositions.<sup>17</sup> It should be noted that the four-step enantioselective preparations of  $\beta$ -hydroxy- $\alpha$ -aminoester **10** from azlactones **6** and aldehydes **7** require only a single purification for the isolation of **10**, both intermediates **8** and **9** were used for the next step without subjecting to purifications. To establish enantioselective access to all four stereoisomers of  $\beta$ -hydroxy- $\alpha$ -amino acid derivative **10**, we developed a one-pot conversion of *anti*- $\beta$ -hydroxy- $\alpha$ -amino acid **10da** into the corresponding *syn*- $\beta$ -hydroxy- $\alpha$ -amino acid *syn*-**12da** involving the treatment

of *anti*-**10da** with thionyl chloride followed by HCl in THF (Scheme 2).

## Conclusions

In summary, we have developed a highly enantioselective and diastereoselective direct aldol reaction of  $\alpha$ -alkyl azlactones with aliphatic aldehydes catalyzed by cinchona alkaloid catalysts **3d** and **3e**. To our knowledge, this is the first efficient asymmetric direct aldol reaction of azlactones and aliphatic aldehydes. Providing an efficient catalytic asymmetric access to  $\beta$ -hydroxy- $\alpha$ -amino acids bearing alkyl substituents at both the tertiary  $\beta$ -stereocenter and the quaternary  $\alpha$ -stereocenter, this new catalytic asymmetric aldol reaction should find applications in natural product synthesis and medicinal chemistry.<sup>18</sup>

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