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Catalytic asymmetric direct aldol reaction of α -alkyl azlactones and aliphatic aldehydes†

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

Optically active β -hydroxy- α -amino acids are an important class of amino acids as they are structural motifs in many biologically active natural products such as vancomycin,¹ katanosins,²

cyclosporin,³ myriocin,^{4a,b} mycestericins,^{4c,d} sphingosine and threonine (Fig. 1). Furthermore, these amino acids are also useful chiral building blocks in organic synthesis as precursors to β -lactams,⁵ β -halo- α -amino acids,⁶ and aziridines.⁷ A variety of catalytic asymmetric approaches for the synthesis of β -hydroxy- α -amino acids has been reported.^{8–14} In a pioneering study,^{8a} Ito, Hayashi and coworkers reported a gold-catalyzed highly diastereoselective and enantioselective aldol reaction for the generation of β -hydroxy- α -amino acids containing tertiary α -carbons. Since then other groups have also reported asymmetric direct aldol reactions with chiral transition-metal catalysts,^{8c–h} organocatalysts⁹ and aldolases¹⁰ for the synthesis of β -hydroxy- α -amino acids and their derivatives. In addition, Sharpless asymmetric aminohydroxylation,¹¹ transition-metal-catalyzed asymmetric hydrogenation,¹² palladium-catalyzed allylic alkylation¹³ and chiral phosphoric acid-catalyzed addition to oxocarbenium ion¹⁴ have been utilized to achieve the same goal.

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

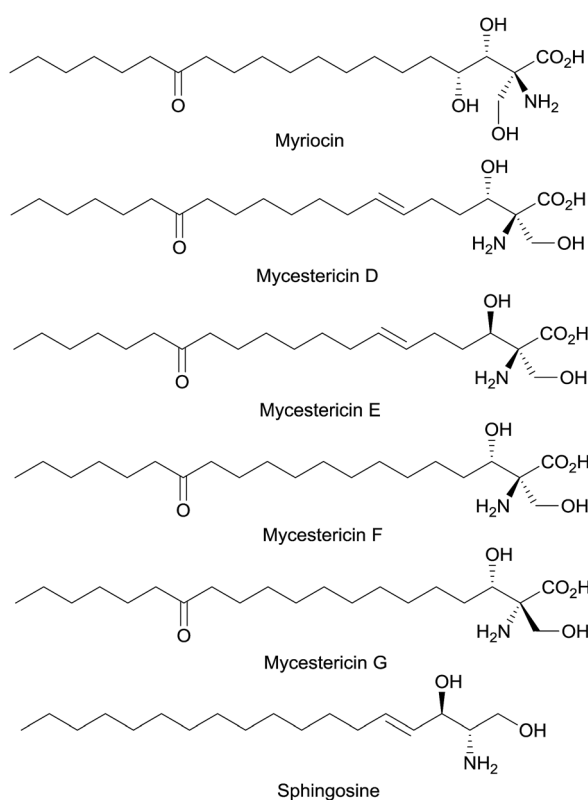
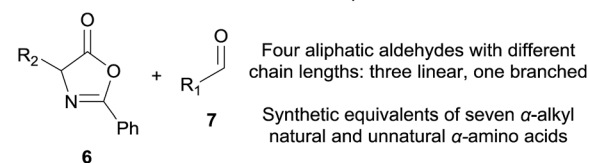
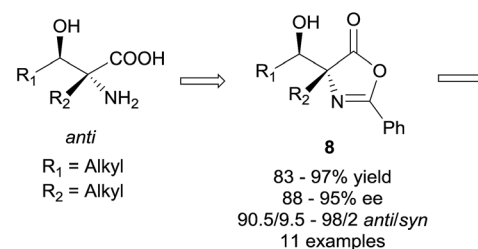


Fig. 1 Mycestericins: potent immunosuppressant natural products

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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



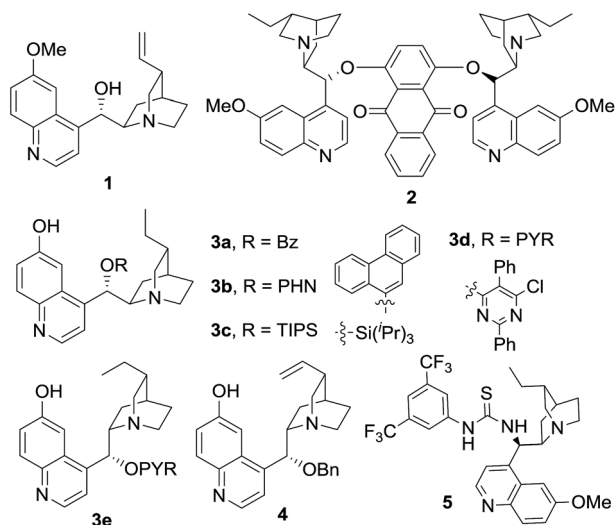
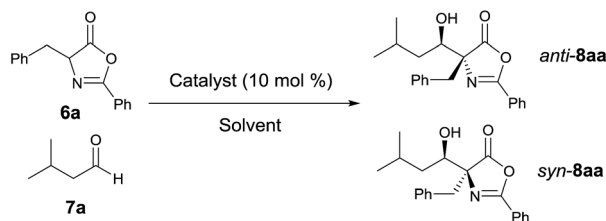


Fig. 2 Cinchona alkaloid catalysts

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

available. Herein, we report the first efficient catalytic asymmetric direct aldol reaction of α -alkyl azlactones **6** and aliphatic aldehydes **7** (Scheme 1), which provides, to our knowledge, the first useful asymmetric catalytic access toward β -hydroxy- α -amino acids bearing alkyl substituents at both the tertiary β -stereocenter and the quaternary α -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 β -hydroxy- α -amino acids.

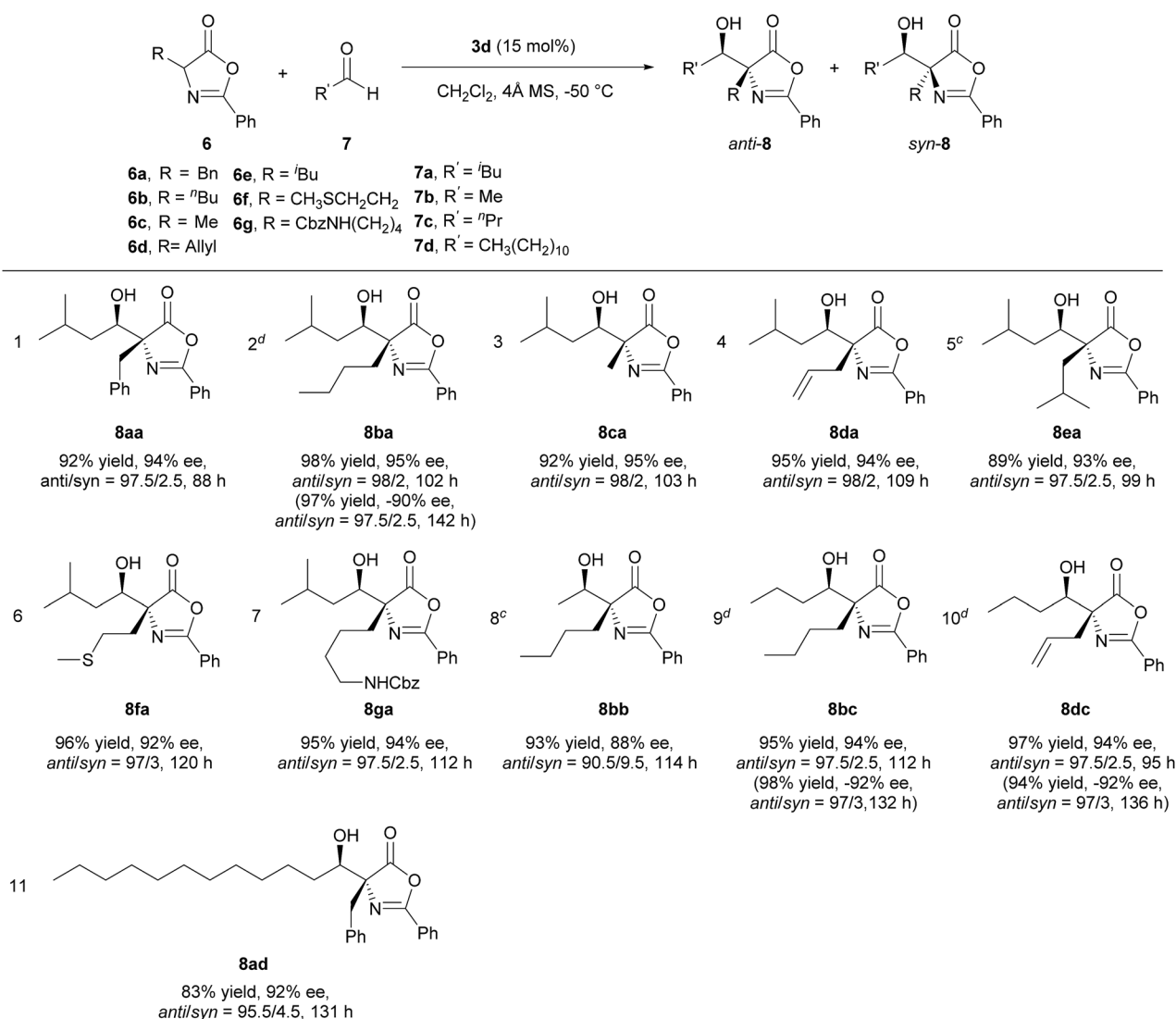
We initiated our study by reacting azlactone **6a** and aldehyde **7a** in the presence of a stoichiometric amount of triethylamine. After considerable experiments, we found that a reaction could be reasonably fast and clean at $-20\text{ }^\circ\text{C}$ in chloroform. We next investigated the possibility 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**^a

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

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



Table 2 Scope of reaction^{abe}

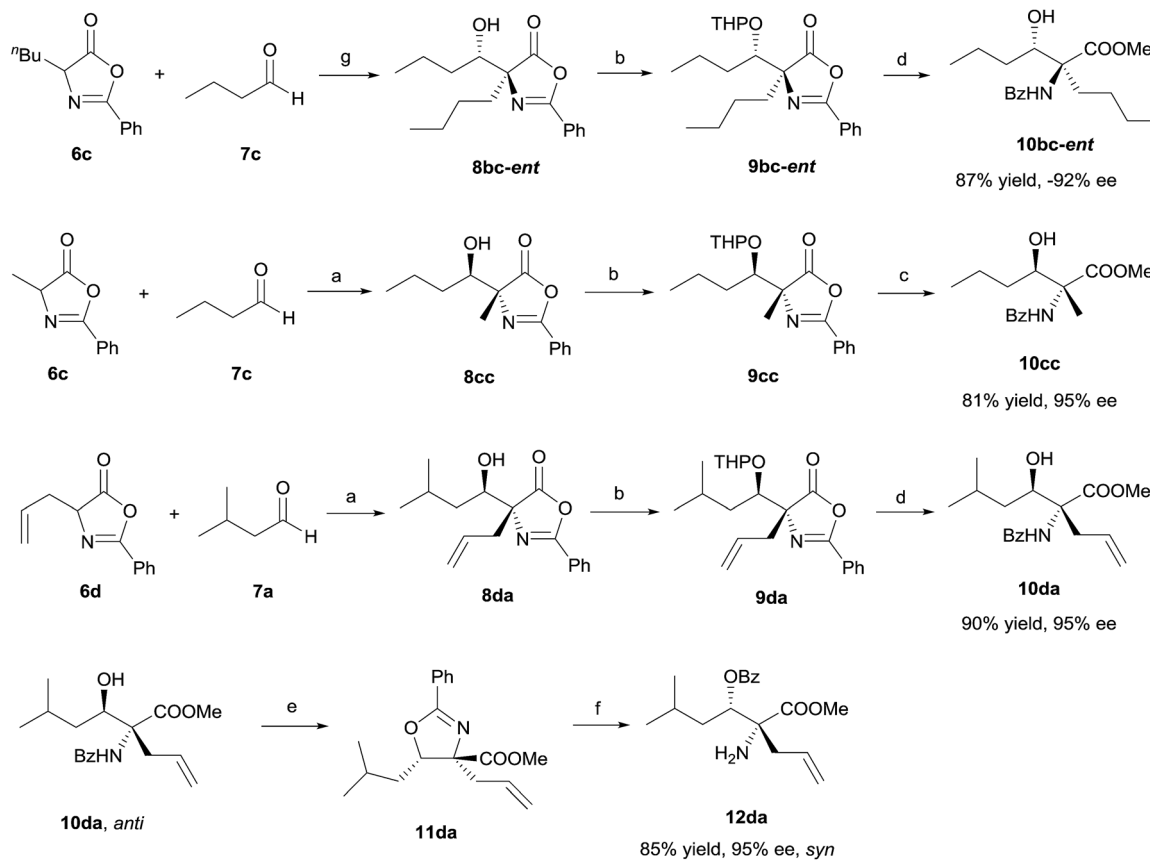
^a Unless noted, reactions were carried out with 0.1 mmol of **6**, 0.15 mmol of **7**, 0.015 mmol of **3d**, 10 mg of 4 Å molecular sieves in 1 mL of dichloromethane. ^b ee value and *anti/syn* ratio determined by chiral HPLC analysis. ^c 0.2 mmol of **7b**. ^d Results in parentheses obtained using **3e** (15 mol%) as catalyst. ^e 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 α -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%), CH_2Cl_2 , 4 Å MS, -50°C ; (b) PPTS, DHP, CH_2Cl_2 , rt; then K_2CO_3 , Na_2SO_4 , MeOH, rt; (c) 2 N HCl, MeOH, rt; (d) HCl in MeOH ($\sim 1.25\text{ M}$), rt; (e) SOCl_2 , THF, rt; (f) 2 N HCl, THF, rt; (g) **3e** (15 mol%), CH_2Cl_2 , 4 Å MS, -50°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,[†] the relative and absolute configurations of aldol products **8** were determined by 1D NOESY experiment and a modified Mosher's method, respectively.¹⁶

To demonstrate the potential synthetic utility of the chiral aldol adduct **8**, ring opening transformations converting **8** into useful β -hydroxy- α -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 β -hydroxy- α -aminoester **10** (Scheme 2). Critical to the development of this useful conversion was the experimental discovery that the THP protected β -hydroxy- α -alkylazlactones **9**, unlike **8**, is inert toward retro-aldol decompositions.¹⁷ It should be noted that the four-step enantioselective preparations of β -hydroxy- α -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 β -hydroxy- α -amino acid derivative **10**, we developed a one-pot conversion of *anti*- β -hydroxy- α -amino acid **10da** into the corresponding *syn*- β -hydroxy- α -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 α -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 β -hydroxy- α -amino acids bearing alkyl substituents at both the tertiary β -stereocenter and the quaternary α -stereocenter, this new catalytic asymmetric aldol reaction should find applications in natural product synthesis and medicinal chemistry.¹⁸

Acknowledgements

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