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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] organocatalysts[9] and aldolases[10] 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 alkylation[13] and chiral phosphoric acid-catalyzed addition to oxocarbenium ion[14] 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.

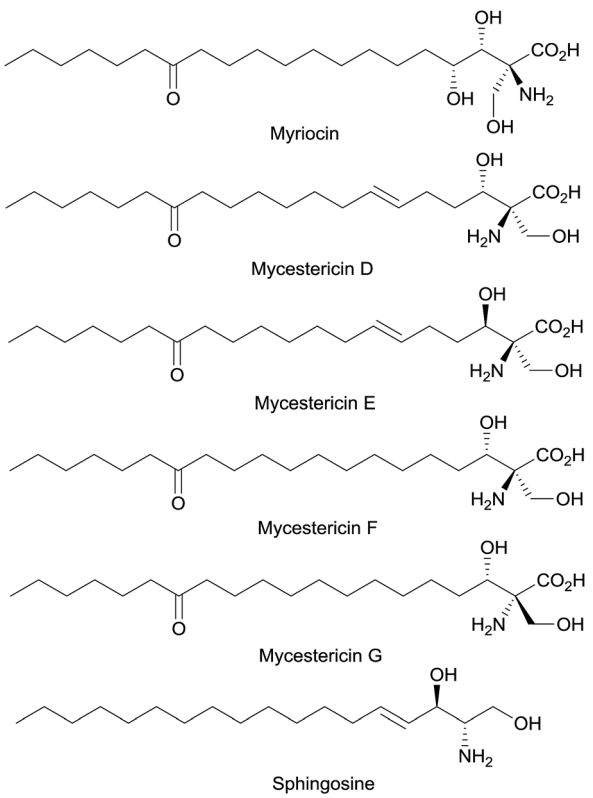
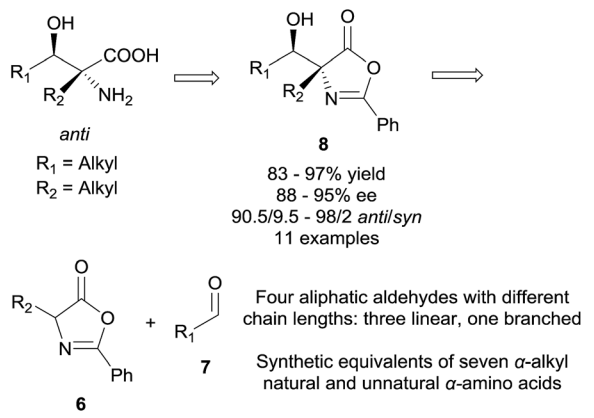



Fig. 1 Mycestericins: potent immunosuppressant natural products




Scheme 1 Reaction design

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

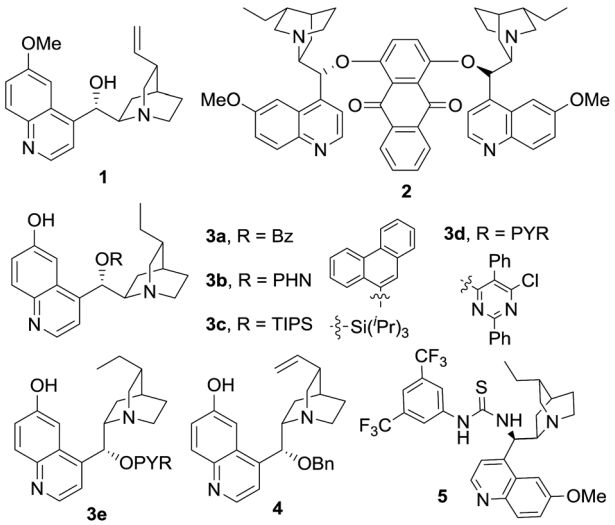
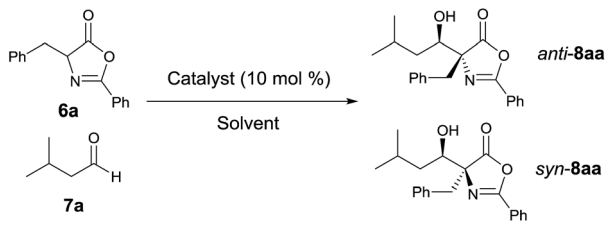



Fig. 2 Cinchona alkaloid catalysts

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 °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

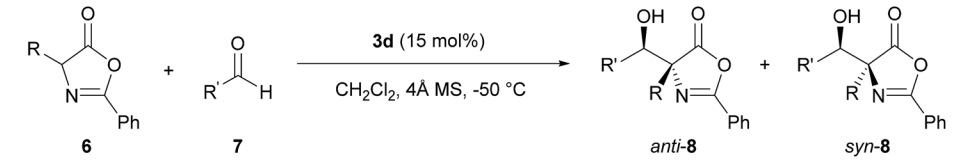
Table 1 Catalytic asymmetric aldol reaction of azlactone **6a** and aldehyde **7a**[a]




| Entry | Catalyst | Solvent | Temp (°C) | Time | Conv.[c] (%) | ee[cd] (%) | *anti*/*syn*[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** | $CH_2Cl_2$ (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** | $Et_2O$ (0.5 M) | −20 | 34 h | >95 | 53/−28 | 83/17 |
| 15 | **3d** | $CH_3CN$ (0.5 M) | −20 | 34 h | >95 | 72/−18 | 88/12 |
| 16[e,f] | **3d** | $CH_2Cl_2$ (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 chrial 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]




**6a**, R = Bn **6e**, R = $^{i}$Bu **7a**, R′ = $^{i}$Bu
**6b**, R = $^{n}$Bu **6f**, R = $CH_3SCH_2CH_2$ **7b**, R′ = Me
**6c**, R = Me **6g**, R = $CbzNH(CH_2)_4$ **7c**, R′ = $^{n}$Pr
**6d**, R= Allyl **7d**, R′ = $CH_3(CH_2)_{10}$

1 **8aa**
92% yield, 94% ee, anti/syn = 97.5/2.5, 88 h

2[d] **8ba**
98% yield, 95% ee, *anti*/*syn* = 98/2, 102 h (97% yield, -90% ee, *anti*/*syn* = 97.5/2.5, 142 h)

3 **8ca**
92% yield, 95% ee, *anti*/*syn* = 98/2, 103 h

4 **8da**
95% yield, 94% ee, *anti*/*syn* = 98/2, 109 h

5[c] **8ea**
89% yield, 93% ee, *anti*/*syn* = 97.5/2.5, 99 h

6 **8fa**
96% yield, 92% ee, *anti*/*syn* = 97/3, 120 h

7 **8ga**
95% yield, 94% ee, *anti*/*syn* = 97.5/2.5, 112 h

8[c] **8bb**
93% yield, 88% ee, *anti*/*syn* = 90.5/9.5, 114 h

9[d] **8bc**
95% yield, 94% ee, *anti*/*syn* = 97.5/2.5, 112 h (98% yield, -92% ee, *anti*/*syn* = 97/3,132 h)

10[d] **8dc**
97% yield, 94% ee, *anti*/*syn* = 97.5/2.5, 95 h (94% yield, -92% ee, *anti*/*syn* = 97/3, 136 h)

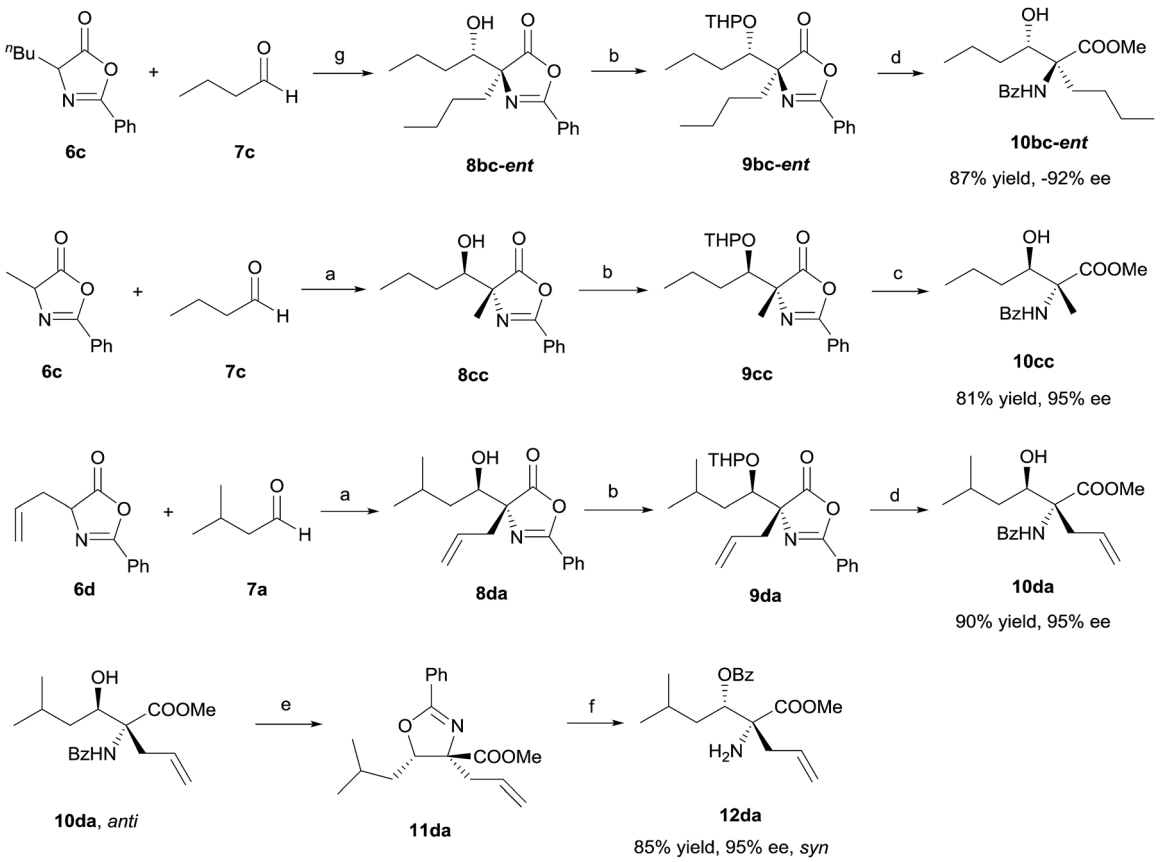
11 **8ad**
83% yield, 92% ee, *anti*/*syn* = 95.5/4.5, 131 h

[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 (~1.25 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 = pyridinum-*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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