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Catalytic Asymmetric Direct Aldol Reaction of α-Alkyl Azlactones and Aliphatic Aldehydes

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Abstract

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–c], mycestericins[4d–e], sphingosine and threonine (Figure 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, Hayahsi 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. 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

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Electronic Supplementary Information (ESI) available: Experimental procedures and characterization for new compounds are provided. See DOI: 10.1039/c000000x/

asymmetric transformation was not available. Herein, we report the first efficient catalytic asymmetric direct aldol reaction of α-alkyl azlactone **6** and aliphatic aldehyde **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 (Figure 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 **3**-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 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 are 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 7 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 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 supporting information, 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].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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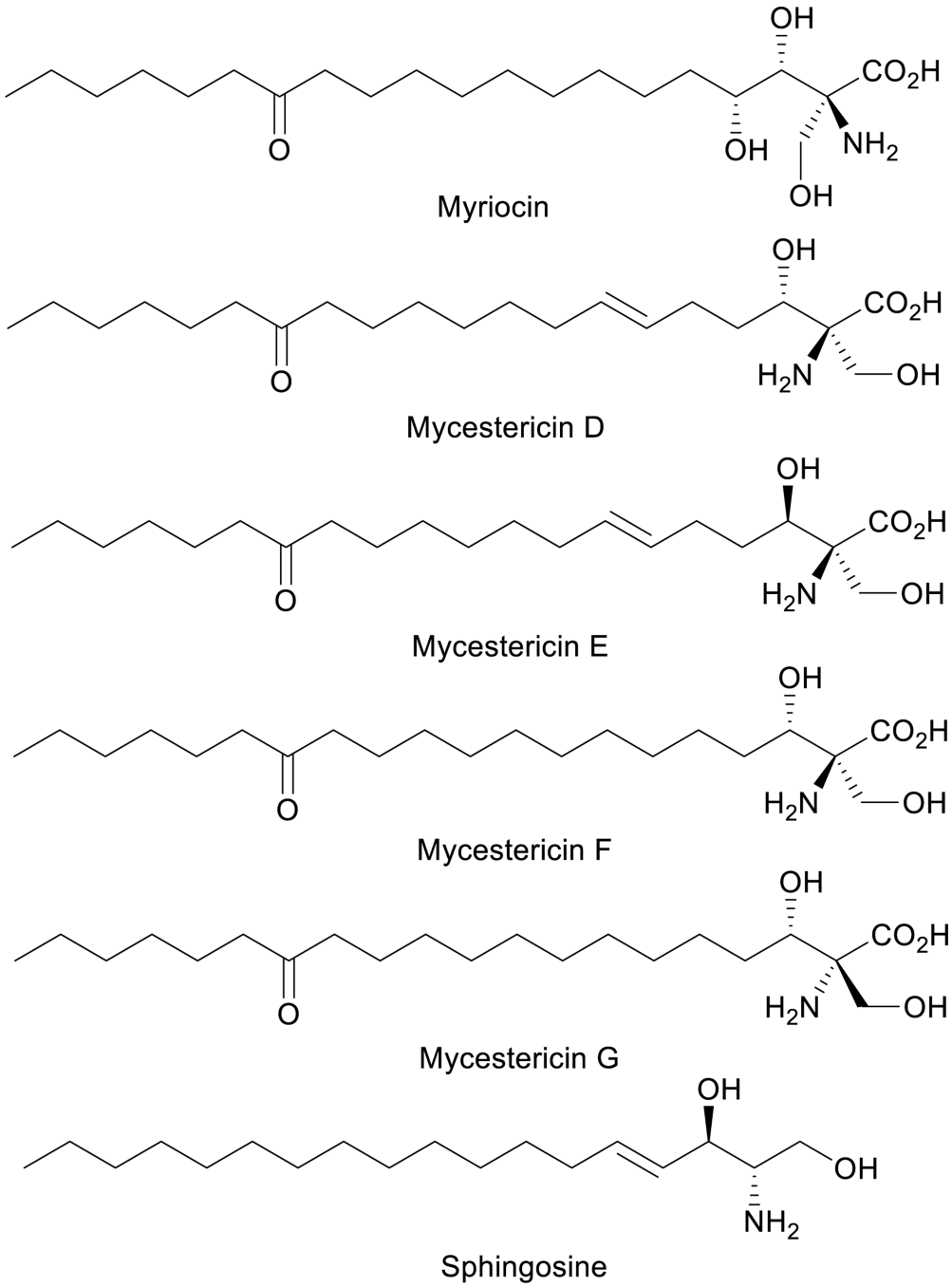


Figure 1.

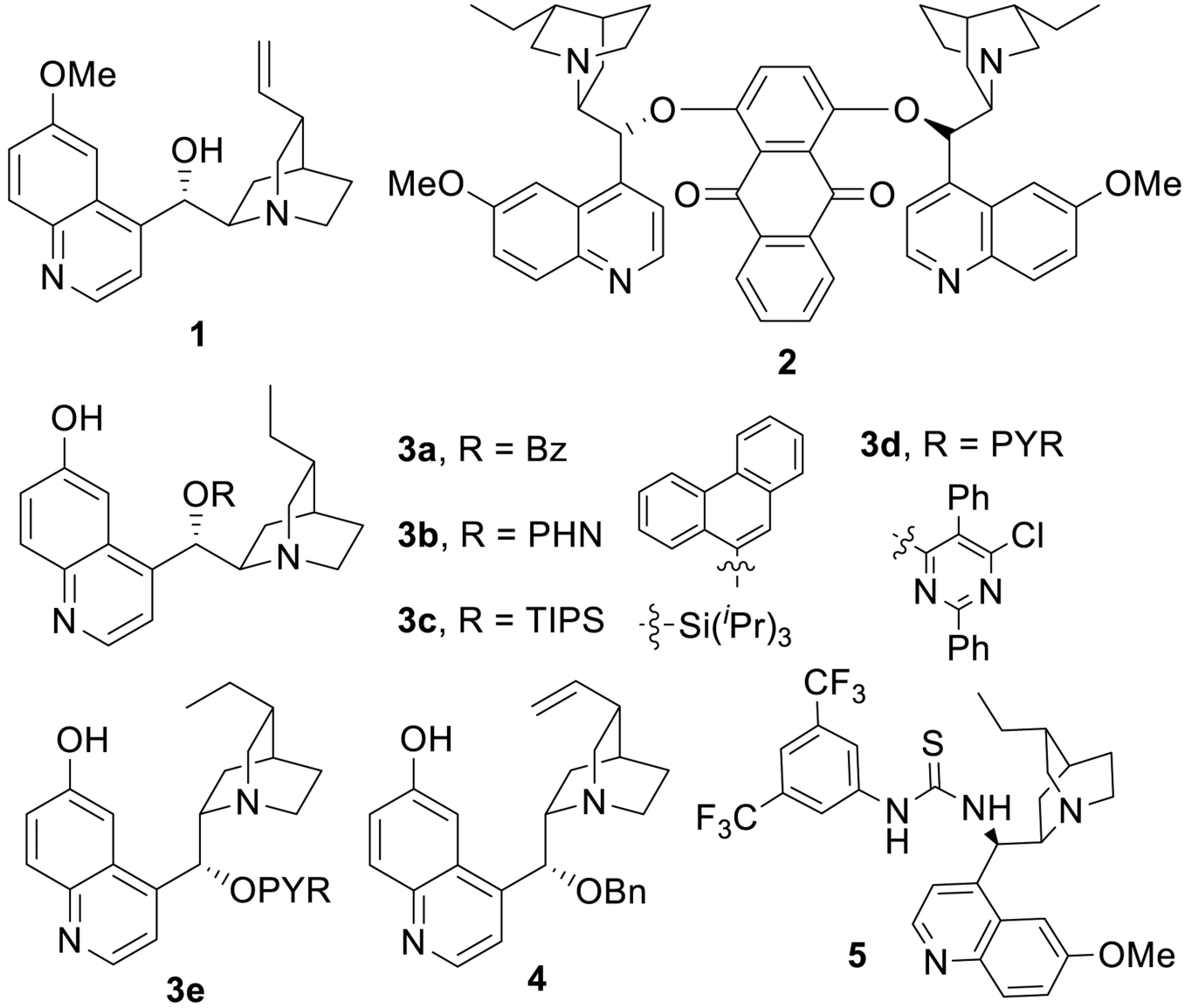
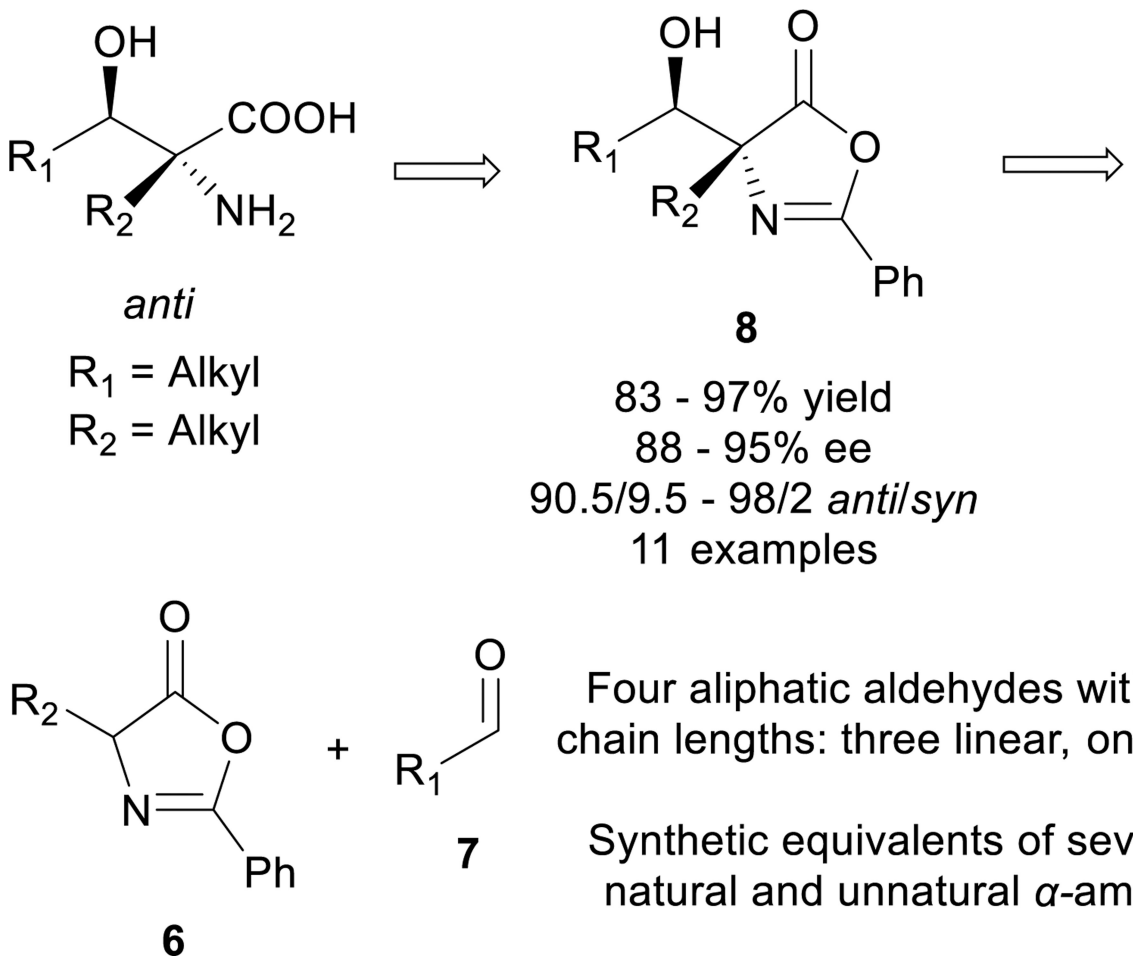
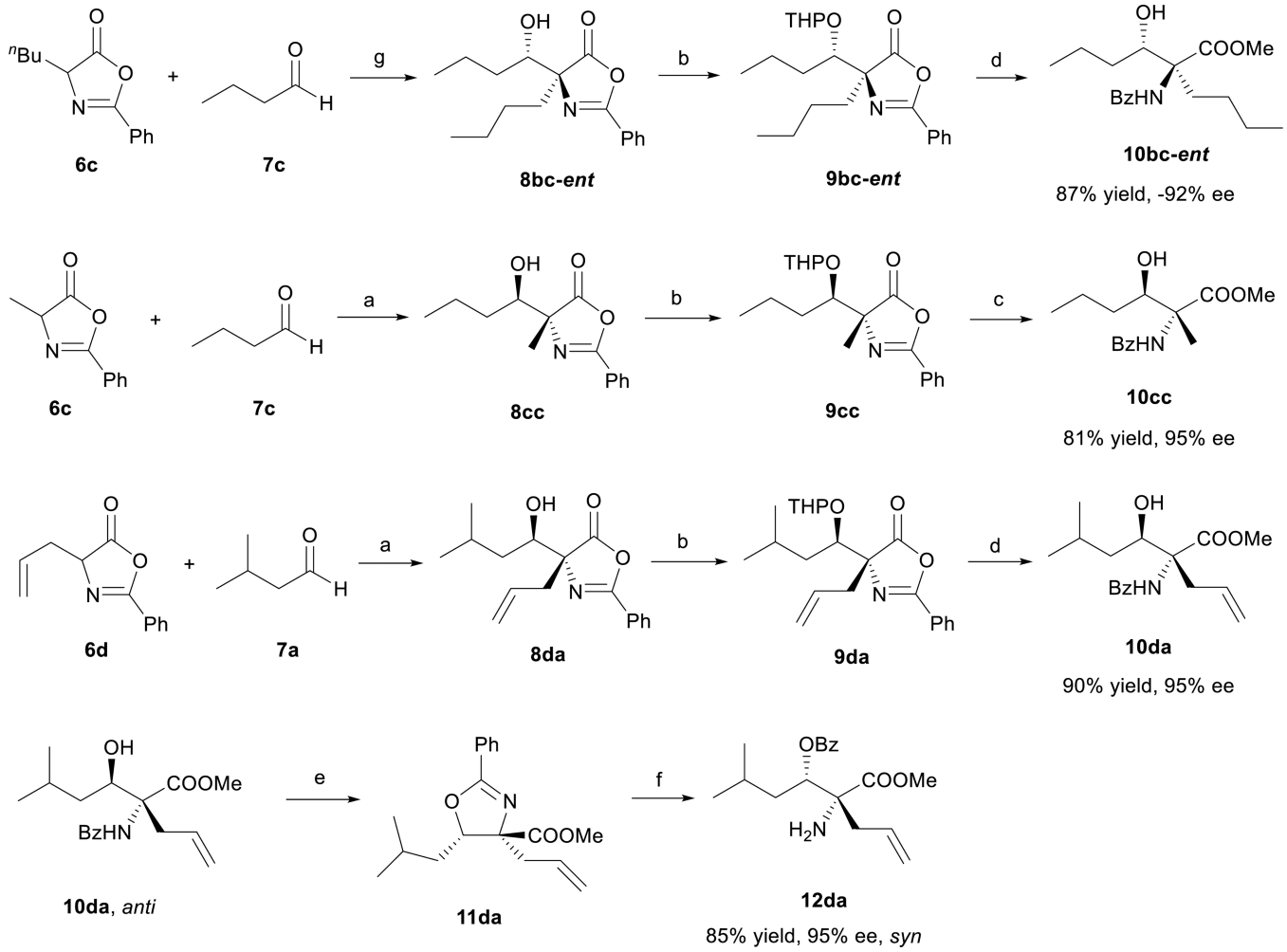


Figure 2.



Scheme 1.



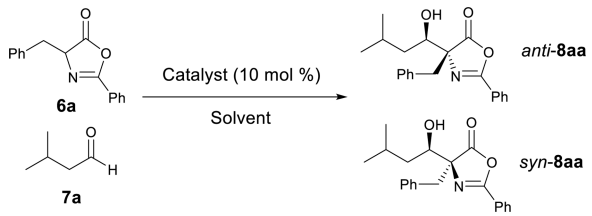
Scheme 2.

Transformation of aldol product **8**[a]

[a]Reagents and conditions: (a) **3d** (15 mol%), CH_2Cl_2, 4Å MS, −50°C; (b) PPTS, DHP, CH_2Cl_2, rt; then K_2CO_3, Na_2SO_4, MeOH, rt; (c) 2N HCl, MeOH, rt; (d) HCl in MeOH (~1.25 M), rt; (e) $SOCl_2$, THF, rt; (f) 2N HCl, THF, rt; (g) **3e** (15 mol%), CH_2Cl_2, 4Å MS, −50°. PPTS = pyridinium *p*-toluenesulfonate; DHP = 3,4-dihydro-2*H*-pyran

Table 1

Catalytic Asymmetric Aldol Reaction of Azlactone **6a** and aldehyde **7a**[a]



Entry	Catalyst	Solvent	Temp(°C)	Time	Conv. (%)[c]	ee (%)[c, d]	*antilsyn*[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 chiral HPLC analysis.

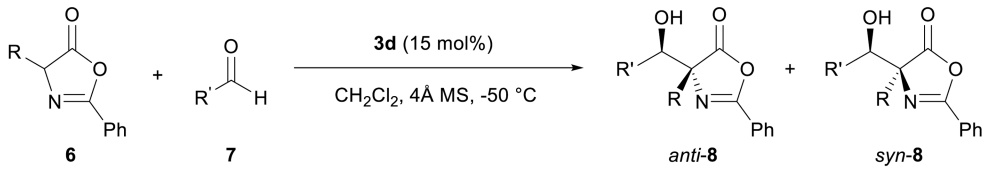
[d] ee (*antilsyn*).

[e] 10 mg of 4Å molecular sieves were added.

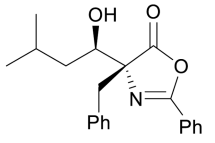
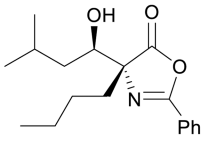
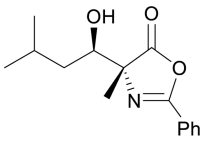
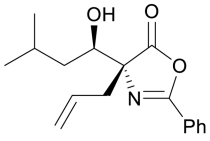
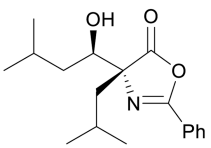
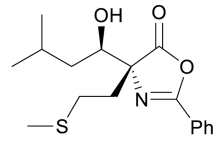
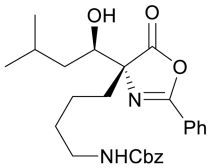
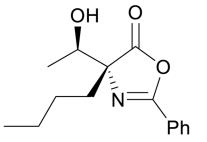
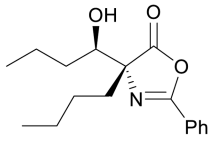
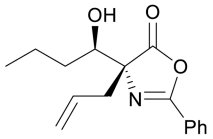
[f] 15 mol% **3d**

Table 2

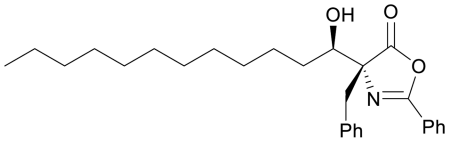
Scope of Reaction[a,b,e]



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	2[d]	3	4	5[c]	
					
8aa	**8ba**	**8ca**	**8da**	**8ea**	
92% yield, 94% ee, anti/syn = 97.5/2.5, 88 h	98% yield, 95% ee, *anti*/*syn* = 98/2, 102 h (97% yield, -90% ee, *anti*/*syn* = 97.5/2.5, 142 h)	92% yield, 95% ee, *anti*/*syn* = 98/2, 103 h	95% yield, 94% ee, *anti*/*syn* = 98/2, 109 h	89% yield, 93% ee, *anti*/*syn* = 97.5/2.5, 99 h	
6	7	8[c]	9[d]	10[d]	
					
8fa	**8ga**	**8bb**	**8bc**	**8dc**	
96% yield, 92% ee, *anti*/*syn* = 97/3, 120 h	95% yield, 94% ee, *anti*/*syn* = 97.5/2.5, 112 h	93% yield, 88% ee, *anti*/*syn* = 90.5/9.5, 114 h	95% yield, 94% ee, *anti*/*syn* = 97.5/2.5, 112 h (98% yield, -92% ee, *anti*/*syn* = 97/3,132 h)	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 4Å molecular sleves 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 Supporting Information for determination of relative and absolute configurations.