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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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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°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_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 (*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%), CH₂Cl₂, 4 Å MS, −50 °C; (b) PPTS, DHP, CH₂Cl₂, rt; then K₂CO₃, Na₂SO₄, MeOH, rt; (c) 2 N HCl, MeOH, rt; (d) HCl in MeOH (~1.25 M), rt; (e) SOCl₂, THF, rt; (f) 2 N HCl, THF, rt; (g) **3e** (15 mol%), CH₂Cl₂, 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

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Notes and references

- (a) D. H. Williams, *Acc. Chem. Res.*, 1984, **17**, 364; (b) C. M. Harris, H. Kopecka and T. M. Harris, *J. Am. Chem.*

- Soc.*, 1983, **105**, 6915; (c) R. Nagarajan, A. A. Schabel, J. L. Occolowitz, F. T. Counter and J. L. Ott, *J. Antibiot.*, 1988, **41**, 1431.
- 2 (a) T. Kato, H. Hinoo, Y. Terui, J. Kikuchi and J. Shoji, *J. Antibiot.*, 1988, **41**, 719; (b) J. Shoji, H. Hinoo, K. Matsumoto, T. Hattori, T. Yoshida, S. Matsuura and E. Kondo, *J. Antibiot.*, 1988, **41**, 713; (c) S. A. Carr, E. Block and C. E. Costello, *J. Org. Chem.*, 1985, **50**, 2854.
- 3 (a) S. L. Schreiber, *Science*, 1991, **251**, 283; (b) D. A. Evans and A. E. Weber, *J. Am. Chem. Soc.*, 1986, **108**, 6757.
- 4 (a) T. Fujita, K. Inoue, S. Yamamoto, T. Ikumoto, S. Sasaki, R. Toyama, K. Chiba, Y. Hoshino and T. Okumoto, *J. Antibiot.*, 1994, **47**, 208; (b) T. Fujita, K. Inoue, S. Yamamoto, T. Ikumoto, S. Sasaki, R. Toyama, K. Chiba, Y. Hoshino and T. Okumoto, *J. Antibiot.*, 1994, **47**, 216; (c) S. Sasaki, R. Hashimoto, M. Kiuchi, K. Inoue, T. Ikumoto, R. Hirose, K. Chiba, Y. Hoshino, T. Okumoto and T. Fujita, *J. Antibiot.*, 1994, **47**, 420; (d) T. Fujita, N. Hamamichi, M. Kiuchi, T. Matsuzaki, Y. Kitao, K. Inoue, R. Hirose, M. Yoneta, S. Sasaki and K. Chiba, *J. Antibiot.*, 1996, **49**, 846.
- 5 (a) B. T. Lotz and J. Miller, *J. Org. Chem.*, 1993, **58**, 618; (b) M. J. Miller, *Acc. Chem. Res.*, 1986, **19**, 49.
- 6 S. V. Pansare and J. C. Vederas, *J. Org. Chem.*, 1987, **52**, 4804.
- 7 D. Tanner, *Angew. Chem., Int. Ed.*, 1994, **33**, 599.
- 8 For selected examples, see: (a) Y. Ito, M. Sawamura and T. Hayashi, *J. Am. Chem. Soc.*, 1986, **108**, 6405; (b) Y. Ito, M. Sawamura, E. Shirakawa, K. Hayashizaki and T. Hayashi, *Tetrahedron*, 1988, **44**, 5253; (c) D. A. Evans, J. M. Janey, N. Magomedov and J. S. Tedrow, *Angew. Chem., Int. Ed.*, 2001, **40**, 1884; (d) J. Kobayashi, M. Nakamura, Y. Mori, Y. Yamashita and S. Kobayashi, *J. Am. Chem. Soc.*, 2004, **126**, 9192; (e) M. C. Willis, G. A. Cutting, V. J.-D. Piccio, M. J. Durbin and M. P. John, *Angew. Chem., Int. Ed.*, 2005, **44**, 1543; (f) F. Sladojevich, A. Trabocchi, A. Guarna and D. J. Dixon, *J. Am. Chem. Soc.*, 2011, **133**, 1710; (g) T. Yoshino, H. Morimoto, G. Lu, S. Matsunaga and M. Shibasaki, *J. Am. Chem. Soc.*, 2009, **131**, 17082; (h) B. M. Trost and F. Miede, *J. Am. Chem. Soc.*, 2014, **136**, 3016.
- 9 For selected examples, see: (a) M. Horikawa, J. Busch-Peterson and E. J. Corey, *Tetrahedron Lett.*, 1999, **40**, 3843; (b) T. Ooi, M. Taniguchi, M. Kameda and K. Maruoka, *Angew. Chem., Int. Ed.*, 2002, **41**, 4542; (c) T. Ooi, M. Kameda, M. Taniguchi and K. Maruoka, *J. Am. Chem. Soc.*, 2004, **126**, 9685; (d) R. Thayumanavan, F. Tanaka and C. F. Barbas III, *Org. Lett.*, 2004, **6**, 3541; (e) L. Li, K. G. Klauber and D. Seidel, *J. Am. Chem. Soc.*, 2008, **130**, 12248; (f) W.-B. Chen, Z.-J. Wu, J. Hu, L.-F. Cun, X.-M. Zhang and W.-C. Yuan, *Org. Lett.*, 2011, **13**, 2472.
- 10 For selected examples, see: (a) V. P. Vassilev, T. Uchiyama, T. Kajimoto and C.-H. Wong, *Tetrahedron Lett.*, 1995, **36**, 4081; (b) T. Kimura, V. P. Vassilev, G.-J. Shen and C.-H. Wong, *J. Am. Chem. Soc.*, 1997, **119**, 11734; (c) M. L. Gutierrez, X. Garrabou, E. Agosta, S. Servi, T. Parella, J. Joglar and P. Clapés, *Chem.-Eur. J.*, 2008, **14**, 4647; (d) K. Hernandez, I. Zelen, G. Petrillo, I. Usón, C. M. Wandtke, J. Bujons, J. Joglar, T. Parella and P. Clapés, *Angew. Chem., Int. Ed.*, 2015, **54**, 3013–3017.
- 11 For selected examples, see: (a) B. Tao, G. Schlingloff and K. B. Sharpless, *Tetrahedron Lett.*, 1998, **39**, 2507; (b) A. Morgan, C. E. Masse and J. S. Panek, *Org. Lett.*, 1999, **1**, 1949; (c) H. Park, B. Cao and M. M. Joullie, *J. Org. Chem.*, 2001, **66**, 7223.
- 12 For selected examples, see: (a) R. Noyori, T. Ikeda, T. Ohkuma, M. Widhalm, M. Kitamura, H. Takaya, S. Akutagawa, N. Sayo, T. Saito, T. Taketomi and H. Kumobayashi, *J. Am. Chem. Soc.*, 1989, **111**, 9134; (b) R. Kuwano, S. Okuda and Y. Ito, *J. Org. Chem.*, 1998, **63**, 3499; (c) C. Mordant, P. Dünkermann, V. Ratovelomanana-Vidal and J. P. Genet, *Eur. J. Org. Chem.*, 2004, 3017; (d) C. Mordant, P. Dünkermann, V. Ratovelomanana-Vidal and J. P. Genet, *Chem. Commun.*, 2004, 1296; (e) K. Makino, T. Goto, Y. Hiroki and Y. Hamada, *Angew. Chem., Int. Ed.*, 2004, **43**, 882; (f) K. Makino, Y. Hiroki and Y. Hamada, *J. Am. Chem. Soc.*, 2005, **127**, 5784.
- 13 (a) B. M. Trost and X. Ariza, *Angew. Chem., Int. Ed.*, 1997, **36**, 2635; (b) B. M. Trost and C. B. Lee, *J. Am. Chem. Soc.*, 1998, **120**, 6818; (c) B. M. Trost and C. B. Lee, *J. Am. Chem. Soc.*, 2001, **123**, 12191.
- 14 M. Terada, H. Tanaka and K. Sorimachi, *J. Am. Chem. Soc.*, 2009, **131**, 3430.
- 15 For total synthesis of Mycestericin D, E, F and G, see: (a) K. Shibata, K. Shingu, V. P. Vassilev, K. Nishide, T. Fujita, M. Node, T. Kajimoto and C.-H. Wong, *Tetrahedron Lett.*, 1996, **37**, 2791; (b) T. Fujita, N. Hamamichi, T. Matsuzaki, Y. Kitao, M. Kiuchi, M. Node and R. Hirose, *Tetrahedron Lett.*, 1995, **36**, 8599; (c) K. Nishide, K. Shibata, T. Fujita, T. Kajimoto, C.-H. Wong and M. Node, *Heterocycles*, 2000, **52**, 1191; (d) Y. Iwabuchi, M. Furukawa, T. Esumi and S. Hatakeyama, *Chem. Commun.*, 2001, 2030; (e) L. Berhal, S. Takechi, N. Kumagai and M. Shibasaki, *Chem.-Eur. J.*, 2011, **17**, 1915; (f) N. W. G. Fairhurst, M. F. Mahon, R. H. Munday and D. R. Carbery, *Org. Lett.*, 2012, **14**, 756.
- 16 Please see ESI† for details.
- 17 M. Miyashita, A. Yoshikoshi and P. A. Grieco, *J. Org. Chem.*, 1977, **42**, 3772.
- 18 C. R. Strader, C. J. Pearce and N. H. Oberlies, *J. Nat. Prod.*, 2011, **74**, 900.