Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 5681–5684
Tetrahedron Letters

Amino alcohol catalyzed direct asymmetric aldol reactions: enantioselective synthesis of *anti*-α-fluoro-β-hydroxy ketones ☆

Guofu Zhong,[c,*] Junhua Fan[a,b,c] and Carlos F. Barbas, III[a,b,c,*]

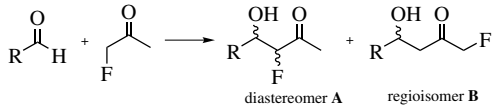
[a]*The Skaggs Institute for Chemical Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA*
[b]*The Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA*
[c]*The Department of Molecular Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA*

Received 16 April 2004; revised 19 May 2004; accepted 19 May 2004

Abstract—Prolinol but not proline-(a recently established catalyst of simple intermolecular aldol reactions) was found to be an efficient catalyst for fluoroaldol reactions providing *anti*-α-fluoro-β-hydroxy ketones with good regio-, diasterio-, and enantioselectivities.

The replacement of hydroxy groups or hydrogen atoms in drug molecules with fluorine has long been a strategy for modifying their pharmacological activity.[1] Due to fluorine's strongly electron withdrawing nature, incorporation of fluorine into organic molecules alters their chemical and physiological properties often leading to unpredictable yet interesting products.[2] From this point of view, α-hydroxyaldol (α,β-dihydroxy ketone) moiety, which is widely found in the important naturally occurring bioactive substances, would be one of the most intriguing targets for the fluorine modification. In particular α-fluoro carbonyl compounds are of significant utility in glycobiology research.[2c,d] Provided this unique potential of fluorine in pharmaceutical chemistry, there is an unmet demand for catalytic synthetic methodologies that provide for the synthesis of fluorinated stereogenic centers. Despite recent advances[3] in the area of catalytic asymmetric aldol reactions, enantioselective synthesis of α-fluoroaldols (α-fluoro-β-hydroxy ketones) remains a major challenge. To address this problem, we have studied the aldol reaction of fluoroacetone. The aldol reaction of fluoroacetone with an aldehyde acceptor presents significant demands on the catalyst since the reaction can lead to the formation of three different regio- and diastereomeric products and their enantiomers (Scheme 1). Indeed, indirect regioselective routes to the synthesis of racemic fluoroadols have only recently been reported.[4a] In this communication, we report the first amino alcohol catalyzed direct asymmetric aldol reactions[5] of unmodified fluoroacetone with aldehydes using chiral prolinol as catalyst, providing *anti*-α-fluoro-β-hydroxy ketones with good regio-, diasterio-, and enantioselectivities.

Encouraged by our studies concerning amino acid and amino acid derived catalysts of aldol, Mannich, and Michael reactions[5a] we sought to extend this strategy to the asymmetric synthesis of α-fluoro-β-hydroxy ketones **A**. The fluoroaldol product **B** can be synthesized in racemic form via a tributylboron enolate strategy and one of its enantiomers may be addressed by enzymatic catalysis.[4b] However, the *syn*/*anti* **A** product has only been obtained via antibody catalysis.[6e,7] Provided the amine-based catalysis of the antibody approach[6,8] we anticipated that organocatalysis might also provide a

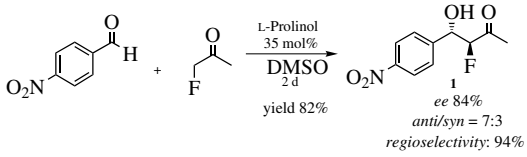


Scheme 1. Aldol reaction of an aldehyde and fluoroacetone.

Keywords: Organocatalysis; Fluoroaldol; Asymmetric synthesis; Aminocatalysis.
☆ Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.05.107
* Corresponding authors. Tel.: +1-858-784-9098; fax: +1-858-784-2583; e-mail addresses: gzhong@scripps.edu; carlos@scripps.edu

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.05.107

solution to this synthetic challenge. Initial studies of the aldol reaction of 4-nitrobenzaldhyde and fluoroacetone mediated by L-proline or 5,5-dimethyl thiazolidinium-4-carboxylate (DMTC) catalyst, the most promising amino acids described for the aldol reaction, were disappointing and yielded a complex mixture of products. Catalyst screening was then performed. Following the screening method used in the search for class I aldolase antibodies,[6,8] a mechanism-based simple β-diketone (2,4-pentanedione) was employed to report on a catalysts ability to form enamines via an enaminone reporter group. Of the amines tested, those that produced the characteristic enaminone absorption maximum at 316 nm after incubation with 2,4-pentanedione in DMSO, were shown to possess aldolase activity. Among the catalysts identified was L-prolinol, which demonstrated strong enaminone absorption after mixing with 2,4-pentanedione in DMSO. Catalysts were then studied for their ability to catalyze the fluoroaldol addition reaction. When a solution of 4-nitrobenzaldhyde (1.0 mmol) and L-prolinol (35 mol%) in fluoroacetone/DMSO (2.0 mL/10 mL) was maintained at room temperature for 2 days, the three-fluoroaldol products, *anti*-**1**, *syn*-**1**, and *regioisomer*-**1** (**B**, when R = 4-nitrophenyl in Scheme 1), were cleanly formed in 82% yield. The products were formed with promising diastereoselectivity dr (*anti*-**1**/*syn*-**1**) 7:3[9] and excellent regioselectivity, 94%. Significantly the ee of the major product *anti*-**1** was determined by chiral-phase HPLC to be 84% (Eq. 1). Solvent screening showed that DMSO and 1,4-dioxane were optimal solvents with respect to the enantioselectivity of the reaction.



(1)

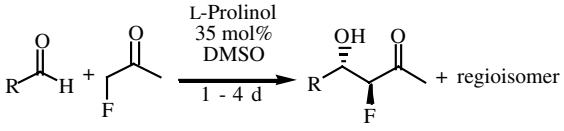
This result prompted us to study the generality of the prolinol catalyzed fluoroaldol reaction. As shown in Table 1, α-fluoroaldols could be prepared using aliphatic aldehydes as acceptors in moderate yields (entry 5 and 6: 34% and 29%) and with increased yields in cases involving aromatic aldehydes (entries 1–4: 50–72%). The diastereoselectivity of the reactions were typically good, dr (*anti*/*syn*) from 7:3 to 10:1. In most cases, the products were formed with very high regioselectivities (over 20:1) and with the *anti*-α-fluoro-β-hydroxy ketones as the major products. An exception is entry 3 were *regioisomer*-**B** was obtained as main product (**A**/**B** = 1:4). Most significantly the *anti*-α-fluoroaldols (**1**–**6**) were consistently obtained with good enantioselectivities (79–87% ee).

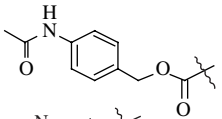
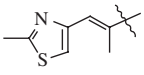
The absolute configurations of *anti*-α-fluoroaldols **3**–**6** were assigned based on the X-ray crystal structure of *anti*-α-fluoroaldol **1** (Fig. 1) and assignment of *anti*-α-fluoroaldol **2**.[10] The observed enantioselectivities of the reactions can be rationalized by invoking an enamine mechanism operating through a chair transition state where the *si*-face of an *E*-enamine of fluoroacetone and L-prolinol attacks the *re*-face of the aldehyde to provide the *anti*-α-fluoroaldol product (Fig. 2).

The availability of both L- and D-prolinol provides for the enantioselective synthesis of both enantiomers of *anti*-α-fluoroaldols with good ee. Further, the β-diketone 2,4-pentanedione can be used for screening small molecule aldol catalysts that use an enamine mechanism. Studies addressing the synthetic scope of prolinol catalysis in asymmetric reactions are ongoing.[11]

Typical experimental procedure: To a solution of the aldehyde (1.0 mmol) and fluoroacetone (2.0 mL) in anhydrous DMSO (10 mL), L-prolinol (35 mol%) or D-prolinol was added. The resulting homogeneous reaction mixture was kept at room temperature for 1–4 days.

Table 1. *anti*-α-Fluoroaldols prepared from prolinol catalyzed aldol reactions of aldehydes and fluoroacetone



Entry	R	Dr[a] (*anti*/*syn*)	Yield (%)[b]	Regioselectivity[c] (**A**/**B**)	ee (%)[d] (*anti*)
1	*p*-O_2N-Phenyl	7:3	82	47:3	84
2	Phenyl	9:1	72	>20:1	87
3		9:1	51	1:4	83
4		10:1	50	>20:1	85
5	Cyclohexyl	5:1	34	>20:1	80
6	*iso*-Butyl	3:1	29	>20:1	79

[a] Determined by ^1H NMR spectroscopy.
[b] Overall yield.
[c] The ratio (**A**/**B**) is that of the diastereomers/regioisomer (see Scheme 1).
[d] The ee of the *anti*-isomer was determined by chiral phase HPLC.

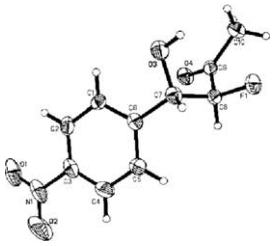


Figure 1. The ORTEP plot of X-ray structure of *anti*-α-fluoroaldol **1**.

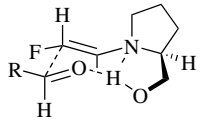


Figure 2. Proposed transition state of the L-prolinol catalyzed fluoroaldol reaction.

Then saturated NH_4Cl was added. The reaction mixture was extracted with ethyl acetate. The extracts were dried over $MgSO_4$. Evaporation of solvent followed by flash column chromatography on silica gel to give regio- and diastereo-products separately. Enantiomeric excesses and diastereoselectivities of the *anti*-fluoroaldols were measured by chiral phase HPLC and ^1H NMR analysis. Racemic fluoroaldol products were prepared similarly using DL-prolinol as catalyst. The ee was determined by chiral-phase HPLC with hexane/*iso*-propanol.

*(3S,4S)-3-Fluoro-4-hydroxy-4-(4′-nitrophenyl)-butan-2-one (anti-***1***) from L-prolinol catalysis*: ^1H NMR (300 MHz, $CDCl_3$): δ 8.23 (2H, d, J 8.8), 7.57 (2H, d, J 8.8), 5.19 (1H, dd, J 14.3, 5.7), 4.84 (1H, dd, J 48.8, 5.7), 2.22 (3H, d, J 5.3); ^{13}C NMR (400 MHz, $CDCl_3$): δ 207.3, 148.0, 144.7, 127.9, 123.7, 94.8, 72.7, 27.4; HPLC (Daicel Chiralpak AS, *i*-propanol/hexane = 15:85, flow rate 1.0 mL/min, $\lambda = 254$ nm): $t_{minor} = 12.7$ min, $t_{major} = 15.4$ min, ee 84%; HR-MS (MALDI-FTMS): 250.0489; $C_{10}H_{10}FNO_4Na^+$ (calcd 250.0486).

Supplementary material

Complete analytical data for all new compounds, data from solvent screen, and X-ray structure data. The supplementary data is available online in ScienceDirect.

Acknowledgements

This study was supported by the NIH (CA27489) and The Skaggs Institute for Chemical Biology. We thank Raj K. Chadha for X-ray crystal structure determination of *anti*-α-fluoroaldol **1**.

References and notes

1. (a) *Asymmetric Fluoroorganic Chemistry: Synthesis, Applications and Future Directions*; Ramachandran, P. V., Ed.; American Chemical Society: Washington, DC, 2000; (b) *Biomedical Frontiers of Fluorine Chemistry*; Ojima, I., McCarthy, J. R., Welch, J. T., Eds.; American Chemical Society: Washington, DC, 1996; (c) Welch, J. T.; Eswarakrishnan, S. In *Fluorine in Bioorganic Chemistry*; John Wiley & Sons: New York, 1990; (d) Resnati, G. *Tetrahedron* **1993**, *49*, 9385.
2. (a) Greedy, B.; Paris, J.-M.; Vidal, T.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2003**, *42*, 3291; (b) Muñiz, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 1653; (c) Burkart, M. D.; Zhang, Z.; Hung, S.-C.; Wong, C.-H. *J. Am. Chem. Soc.* **1997**, *119*, 11743; (d) Davis, F. A.; Zhou, P.; Murphy, C. K.; Sundarababu, G.; Qi, H.; Han, W.; Przeslawski, R. M.; Chen, B.-C.; Carroll, P. J. *J. Org. Chem.* **1998**, *63*, 2273.
3. For reviews of the enantioselective aldol reaction, see: (a) Carreira, E. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Heidelberg, 1999; Vol. 3, Chapter 29.1; (b) Machajewski, T. D.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1352; (c) Nelson, S. G. *Tetrahedron: Asymmetry* **1998**, *9*, 357; (d) Gröger, H.; Vogel, E. M.; Shibasaki, M. *Chem. Eur. J.* **1998**, *4*, 1137.
4. For chemical synthesis of α-fluoro-β-hydroxy ketones, see: (a) Sinha, S. C.; Dutta, S.; Sun, J. *Tetrahedron Lett.* **1999**, *41*, 2000; For enzymatic synthesis, see: (b) Barbas, C. F., III; Wang, Y.-F.; Wong, C.-H. *J. Am. Chem. Soc.* **1990**, *112*, 2013.
5. For direct catalytic asymmetric aldol reactions, see: (a) Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2001**, *123*, 5260; (b) Mase, N.; Tanaka, F.; Barbas, C. F., III. *Org. Lett.* **2003**, *5*, 4369; (c) Mase, N.; Tanaka, F.; Barbas, C. F., III. *Angew. Chem., Int. Ed.* **2004**, *43*, 2420; (d) Yoshikawa, N.; Yamada, Y. M. A.; Das, J.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 4168; For organocatalytic Mannich reactions see: (e) Notz, W.; Tanaka, F.; Watanabe, S.; Chowdari, N. S.; Turner, J. M.; Thayumanavan, R.; Barbas, C. F., III. *J. Org. Chem.* **2003**, *68*, 9624; For organocatalytic Michael reactions see: (f) Betancort, J. M.; Barbas, C. F., III. *Org. Lett.* **2001**, *3*, 3737.
6. (a) Wagner, J.; Lerner, R. A.; Barbas, C. F., III. *Science* **1995**, *270*, 1797; (b) Björnestedt, R.; Zhong, G.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **1996**, *118*, 11720; (c) Zhong, G.; Hoffmann, T.; Lerner, R. A.; Danishefsky, S.; Barbas, C. F., III. *J. Am. Chem. Soc.* **1997**, *119*, 8131; (d) Barbas, C. F., III; Heine, A.; Zhong, G.; Hoffmann, T.; Gramatikova, S.; Björnestedt, R.; List, B.; Anderson, J.; Stura, E. A.; Wilson, E. A.; Lerner, R. A. *Science* **1997**, *278*, 2085; (e) Hoffmann, T.; Zhong, G.; List, B.; Shabat, D.; Anderson, J.; Gramatikova, S.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **1998**, *120*, 2768; (f) Zhong, G.; Shabat, D.; List, B.; Anderson, J.; Sinha, S. C.; Lerner, R. A.; Barbas, C. F., III. *Angew. Chem., Int. Ed.* **1998**, *37*, 2481.
7. One report utilizing 1-fluoro-3,3-dimethylbutanone as a donor provides a α-fluoro-β-hydroxy ketone **A** product, where the formation of **B** is not possible, see: Welch, J. T.; Seper, K. W. *Tetrahedron Lett.* **1984**, *25*, 5247.
8. Zhong, G.; Lerner, R. A.; Barbas, C. F., III. *Angew. Chem., Int. Ed.* **1999**, *38*, 3738.
9. *anti*/*syn* Ratio was determined by ^1H NMR (the coupling constants: $J_{HH(anti\ HO–CH–CH–F)} = 5.7$ Hz, $J_{HH(syn\ HO–CH–CH–F)} = 2.6$ Hz).
10. The absolute configuration of *anti*-α-fluoroaldol **2** was assigned by conversion of it to known 4-phenyl-3(*R*),4(*S*)-epoxybutanone, $[\alpha]_D$ −81 (*c* 1.0, $CHCl_3$) (see: lit. −87.7, *c* 1.32 in $CHCl_3$, 93% ee in *Tetrahedron Lett.* **1999**, *40*, 6069).
11. For methoxymethyl pyrrolidine (O-protected prolinol) used as a chiral auxiliary in asymmetric syntheses, see excellent review: (a) Enders, D.; Klatt, M. *Synthesis* **1996**,

1403; (b) L-Prolinol has been used as catalyst in the asymmetric reduction of ketones with borane, see: Brunel, J. M.; Maffei, M.; Buono, G. *Tetrahedron: Asymmetry* **1993**, *4*, 2255; and as a catalyst in the Robinson annulation reaction, see: (c) Bui, T.; Barbas, C. F., III. *Tetrahedron Lett.* **2000**, *41*, 6951.