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

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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 glycochemistry research.2,3,4 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 advances3 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 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 reactions5a 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 approach6e,7 we anticipated that organocatalysis might also provide a
solution to this synthetic challenge. Initial studies of the aldol reaction of 4-nitrobenzaldehyde 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, a mechanism-based simple β-diketone (2,4-pentanenedione) was employed to report on a catalysts ability to form enamines via an enamine reporter group. Of the amines tested, those that produced the characteristic enamine absorption maximum at 316 nm after incubation with 2,4-pentanenedione in DMSO, were shown to possess aldolase activity. Among the catalysts identified was L-prolinol, which demonstrated strong enamine absorption after mixing with 2,4-pentanenedione in DMSO. Catalysts were then studied for their ability to catalyze the fluoroaldol addition reaction. When a solution of 4-nitrobenzaldehyde (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-syn-1) 7.39 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.

The availability of both L- and D-prolinol provides for the enantioselective synthesis of both enantiomers of anti-α-fluoroaldol catalysts that use 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 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. 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).

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Dr+ (anti/syn)</th>
<th>Yield (%)b</th>
<th>Regioselectivityc (A/B)</th>
<th>ee (%)d (anti)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>p-O2N-Phenyl</td>
<td>7:3</td>
<td>82</td>
<td>47:3 (A/B)</td>
<td>84</td>
</tr>
<tr>
<td>2</td>
<td>Phenyl</td>
<td>9:1</td>
<td>72</td>
<td>&gt;20:1</td>
<td>87</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>9:1</td>
<td>51</td>
<td>1:4</td>
<td>83</td>
</tr>
<tr>
<td>4</td>
<td>Cyclohexyl</td>
<td>10:1</td>
<td>50</td>
<td>&gt;20:1</td>
<td>85</td>
</tr>
<tr>
<td>5</td>
<td>iso-Butyl</td>
<td>5:1</td>
<td>34</td>
<td>&gt;20:1</td>
<td>80</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>3:1</td>
<td>29</td>
<td>&gt;20:1</td>
<td>79</td>
</tr>
</tbody>
</table>

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.
Then saturated NH₄Cl was added. The reaction mixture was extracted with ethyl acetate. The extracts were dried over MgSO₄. Evaporation of solvent followed by flash column chromatography on silica gel to give regio- and diastereoproducts separately. Enantiomeric excesses were measured by chiral phase HPLC and $^1$H NMR analysis.

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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.

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References and notes
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9. antisyln Ratio was determined by $^1$H NMR (the coupling constants: $J_{}\text{HH}($anti-$\text{HO-CH-CH-F}) = 5.7$ Hz, $J_{}\text{HH}($syn-$\text{HO-CH-CH-F}) = 2.6$ Hz).
10. The absolute configuration of anti-$\alpha$-fluoroaldol 2 was assigned by conversion of it to known 4-phenyl-3($\beta$)-4(S)-epoxybutanone, [$\alpha]_{D}^{25} -$81 (c 1.0, CHCl₃) (see: lit. $-87.7, c 1.32$, in CHCl₃, 93% ee in Tetrahedron Lett. 1999, 40, 6069).
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(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 annihilation reaction, see: (c) Bui, T.; Barbas, C. F., III. *Tetrahedron Lett.* 2000, 41, 6951.