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Direct organocatalytic asymmetric α-hydroxymethylation of ketones and aldehydes

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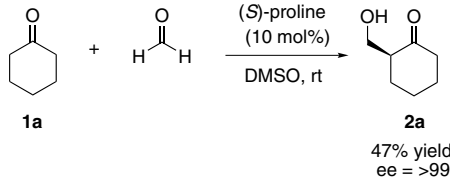
Abstract—Direct organocatalytic asymmetric α-hydroxymethylation of ketones and aldehydes with formaldehyde has been developed, which furnished the corresponding α-hydroxymethylated adducts with high chemo- and enantioselectivity. The reaction is catalyzed by proline derivatives and is a simple method for the enantioselective synthesis of α-hydroxymethylated ketones and aldehydes, and C-2 symmetric diols.

There are few reports on the asymmetric hydroxymethylation of carbonyl compounds using formaldehyde as the electrophile due to its small and symmetrical structure. One approach involved indirect aldol reactions with chiral Lewis acids as the catalyst.[1]

Organocatalysis has recently experienced a revitalization in catalytic asymmetric synthesis.[2] Asymmetric transformations mediated by amino acids and their derivatives have been particularly successful. In our endeavors to mimic direct aldol reactions that are catalyzed by 5-phospho-deoxyribose aldolase,[3] we have investigated the use of unmodified aldehydes and ketones as nucleophiles and amino acid derivatives as catalysts for asymmetric reactions.[4] Several groups have developed successful enantioselective direct aldol reactions.[5] Based on this work, we became interested in the potential of performing hydroxymethylations of ketones and aldehydes with formaldehyde.

Herein, we present direct catalytic asymmetric aldol and cross-aldol reactions with aqueous and gaseous formaldehyde furnishing α-hydroxymethylated ketones and aldehydes, respectively, with excellent enantioselectivity.

In an initial experiment, cyclohexanone **1a** (3.0 mmol), aqueous formaldehyde (1.5 mmol) and a catalytic amount of (*S*)-proline (10 mol %) were mixed in DMSO (4 mL) (Eq. 1). After stirring for 16 h at room temperature, the reaction mixture was quenched by the addition of brine and extracted with EtOAc (3 × 15 mL). The combined organic extracts were concentrated and the crude product purified by silica gel column chromatography to afford α-hydroxymethyl ketone **2a** in 47% yield with >99% ee.[6] We also performed the reaction by slowly bubbling gaseous formaldehyde into the reaction mixture for 1 h. This procedure furnished **2a** in 45% yield with >99% ee.



1a **2a**
47% yield
ee = >99%

(1)

Next, we performed the reaction with three other ketones (Table 1). The proline-catalyzed α-hydroxymethylations afforded ketones **2a–d** with excellent enantioselectivity. In fact, these are the highest ee's observed for a proline-catalyzed inter-molecular aldol reaction with unmodified ketones.[2] Furthermore, we observed high regioselectivity in the reaction with ketone **1d**. In this case, the products **2d** and **2d′** were formed in a 93/7 ratio. However, for the major regioisomer derived from (3*R*)-ketone **1d** there was a mismatch case with (*S*)-proline (entry 4). It is noteworthy

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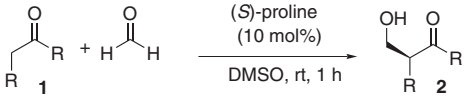
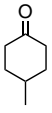
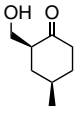
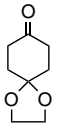
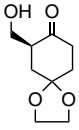
Table 1. Direct proline-catalyzed asymmetric α-hydroxymethylation of ketones

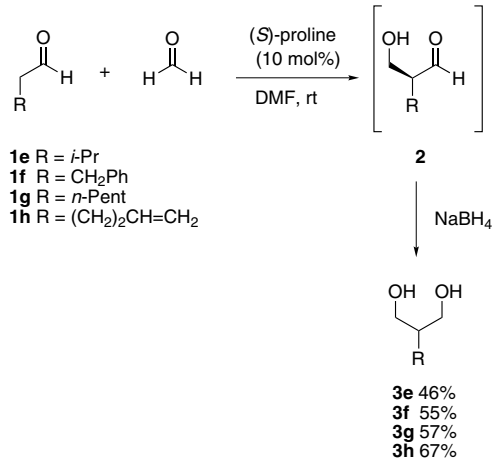


Entry	Ketone	Product	Yield[a] (%)	dr[b]	ee[c] (%)
1	 **1a**	 **2a**	45 (47)[d]		>99 (>99)[d]
2	 **1b**	 **2b**	41	3:1	96
3	 **1c**	 **2c**	40 (44)[d]		95 (96)[d]
4	 **1d**	 **2d**  **2d′**	25 (**2d′**/**2d** = 93/7)		95 57

[a] Isolated yield after silica gel column chromatography.
[b] Determined by NMR.
[c] Determined by chiral phase GC of the acylated α-hydroxymethyl adducts.
[d] Reaction performed with aqueous formaldehyde.

that the presence of water did not decrease the stereoselectivity of the transformation. The moderate yield of the products is compensated by the high enantioselectivity of the reaction and its simplicity.

To broaden the scope of this transformation, we investigated the organocatalytic enantioselective α-hydroxymethylation reaction of unmodified aldehydes. In an initial experiment, *i*-valeraldehyde (3 mmol) and aqueous formaldehyde (1.5 mmol) were mixed in DMF (4 mL) in the presence of a catalytic amount of (*S*)-proline (Scheme 1).[7] After 16 h of stirring the reaction was quenched by the addition of brine and then extracted with EtOAc (3×15 mL). The combined organic extracts were concentrated and the crude product purified by silica gel column chromatography to afford α-hydroxymethylaldehyde **2e** in 52% yield with >99% ee. The reaction was also performed by bubbling gaseous formaldehyde into the reaction mixture. After 1 h, the reaction mixture was quenched and the α-hydroxymethylaldehyde **2e** was isolated in 49% yield with >99% ee. Due to oligomerization of the product aldehyde, we decided to reduce it in situ with $NaBH_4$ to the corresponding C-2 symmetric diol **3e**.[8] In addition, we performed the proline-catalyzed α-hydroxymethylation reactions with other aldehydes. The reactions proceeded smoothly affording the corresponding diols **3f–h** upon reduction with $NaBH_4$. The reaction proceeded with excellent chemoselectivity and we did not observe self-aldolization of the donor aldehyde. In addition, the aldehydes provided the corresponding α-hydroxymethylated adducts in higher yields and enantioselectivities than the α-hydroxymethylation of ketones. The reaction was also readily scaled-up. In addition, aqueous formaldehyde was used as the acceptor for all substrates tested without affecting the enantioselectivity of the reaction.



Scheme 1. Direct proline-catalyzed α-hydroxymethylation of aldehydes.

A catalyst screen of the direct α-hydroxymethylation of cyclohexanone revealed that several hydroxy-proline derivatives and proline-dipeptides catalyzed the formation of **2a** with >99% ee. For example, 4-hydroxy-(*S*)-proline and 2-hydroxy-(*S*)-proline provided **2a** with 95% and 96% ee, respectively. Comparisons of the optical rotation of adduct **2a** with the literature revealed that (*S*)-proline and hydroxy-proline derivatives provided (2*S*)-hydroxymethyl ketones and aldehydes, respectively.[9] Hence, formaldehyde attacks the *si*-face of the proline-derived enamine providing the (2*S*)-carbonyl adducts (Fig. 1). This is in accordance with previously

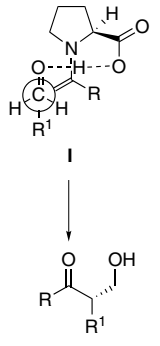


Figure 1. A plausible transition state.

reported proline-catalyzed aldol and cross-aldol reactions.[2,4a]

In conclusion, we have reported the novel direct catalytic asymmetric α-hydroxymethylation of unmodified ketones and aldehydes with aqueous or gaseous formaldehyde. The reactions proceed with excellent chemoselectivity and with enzyme-like enantioselectivity in 'wet' solvents. The reactions can be readily scaled-up and provide a low cost entry for either enantiomer of important building blocks for natural product synthesis.

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6. In a typical experiment, formaldehyde (1.5 mmol, 37% in aq solution) was added to a vial containing (*S*)-proline (10 mol%) and cyclohexanone (3 mmol) in DMSO (4.0 mL) at room temperature. After 16 h, the reaction mixture was quenched by the addition of brine and extracted with EtOAc (3×15 mL). The combined organic extracts were concentrated and the crude product purified by silica gel column chromatography (pentane/EtOAc 1:1) affording α-hydroxymethyl ketone **2a** in 47% yield with >99% ee. ^{1}H NMR, δ: 1.36–1.52 (m, 2H, CH_2); 1.57–1.75 (m, 2H, CH_2); 1.89–1.92 (m, 1H, OH); 1.97–2.12 (m, 2H, CH_2); 2.27–2.39 (m, 2H, CH_2); 2.42–2.54 (m, 1H, CH); 3.59 (dd, J = 11.5, 3.8, 1H, C*H*HOH); 3.72 (dd, J = 11.5, 7.5, 1H, CH*H*OH). ^{13}C NMR, δ: 24.9, 27.7, 30.2 (3×CH_2); 42.4 (*C*H_2CO); 52.5 (CH), 63.0 (CH_2OH); 215.0 (C=O). GC: (CP-Chirasil-Dex CB); T_{inj} = 250 °C, T_{det} = 275 °C, flow = 1.8 mL/min, t_i = 90 °C (2 min), t_f = 110 °C, rate = 0.3 °C/min; retention times of acetylated compound: t_{maj} = 41.6, t_{min} = 41.1.
7. The reaction also proceeds in other solvents, however, the highest chemoselectivity was observed in DMF.
8. In a typical experiment, gaseous formaldehyde was slowly bubbled into a vial containing (*S*)-proline (10 mol%) and *i*-valeraldehyde (1 mmol) in DMF (4.0 mL) at room temperature. After 1 h, the reaction was quenched by the addition of MeOH (2 mmol) and excess $NaBH_4$ (0.2 g) was added at 0 °C. The reaction mixture was quenched by pouring into a vigorously stirred mixture of 1 N HCl and EtOAc. The aqueous layer was extracted with EtOAc (3×15 mL). The combined organic extracts were concentrated and the crude product purified by silica gel column chromatography (pentane/EtOAc 1:1) furnishing the C-2 symmetric diol **3e** in 46% yield. ^{1}H NMR, δ: 0.88 (d, J = 6.8, 6H, 2×CH_3); 1.46–1.54 (m, 1H, CH_2C*H*); 1.67 (h, J = 6.8, 1H, C*H*(CH_3)$_2$); 3.15 (br s, 2H, 2×OH); 3.71 (dd, J = 10.4, 7.8, 2H, 2×C*H*HOH); 3.81 (dd, J = 10.4, 3.4, 2H, 2×CH*H*OH). ^{13}C NMR, δ: 20.5 (2×CH_3); 26.6 (*C*H(CH_3)$_2$); 48.0 (*C*HCH_2), 65.1 (2×CH_2). The ee of the α-hydroxymethyl aldehyde **2e** was determined by chiral GC: (CP-Chirasil-Dex CB); T_{inj} = 250 °C, T_{det} = 275 °C, flow = 1.8 mL/min, t_i = 90 °C (5 min), t_f = 170 °C, rate = 5 °C/min; retention times: t_{maj} = 10.6, t_{min} = 10.3.
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