Organocatalytic Enantioselective Synthesis of Secondary α-Hydroxycarboxylates

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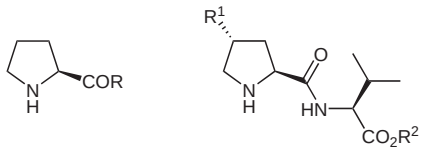
Abstract: Enantioenriched secondary α-hydroxycarboxylates have been synthesized in good yields and enantioselectivities by using the cross-aldol reaction of ketones and ethyl glyoxylate with a proline-derived dipeptide as the catalyst.

Key words: aldol reaction, enantioselectivity, organocatalysis, ethyl glyoxylate, ketones, α-hydroxycarboxylate

Secondary α-hydroxycarboxylic acids and their alkyl esters are very useful intermediates in the synthesis of many bioactive natural products.[1] Owing to their synthetic relevance, several asymmetric methods have been developed for the synthesis of these compounds in enantioenriched forms. For example, enantioenriched secondary α-hydroxycarboxylates have been synthesized through the asymmetric reduction of α-ketoesters, with either chiral metal complexes,[2] or chiral auxilaries,[3] or enzymes.[4] These compounds have also been synthesized through the addition of a nucleophilic reagent to glyoxylates in the presence of chiral metal complexes.[5] Alternatively, they may be obtained through the enzymatic resolution of racemic α-hydroxycarboxylates.[6]

Since List and Barbas III published their seminal work on the L-proline-catalyzed asymmetric cross-aldol reaction of aldehydes and ketones,[7] many new L-proline derivatives have been prepared and extensively studied as organocatalysts in the asymmetric cross-aldol reactions.[8] There are also a few examples where these organocatalysts are used for the enantioselective synthesis of α-hydroxycarboxylic acid derivatives.[9,10] For example, Gong and co-worker reported that a bifunctional prolinamide derivative is a good catalyst for the asymmetric synthesis of α-hydroxycarboxylic acids.[9] Nevertheless, all the reported methods can only produce tertiary α-hydroxycarboxylates.[9,10] To the best of our knowledge, there is no general organocatalyzed aldol approach for the enantioselective synthesis of secondary α-hydroxycarboxylates. Recently, we and others have demonstrated[9–11] that L-proline derivatives are very efficient catalysts for the cross aldol reaction of ketones and activated carbonyl compounds, such as, 1,2-diketones,[11a] α-ketophosphonates,[11b] and α-formylphosphonate hydrates.[11c] During the research on the enantioselective synthesis of secondary α-hydroxyphosphonates from α-formylphosphonate hydrates,[11c] we envisioned that enantioenriched secondary α-hydroxycarboxylates should be accessible from the direct aldol reaction of glyoxylates (α-formylcarboxylates) and ketones. Herein we wish to report our preliminary results on the enantioselective synthesis of secondary α-hydroxycarboxylates from a direct aldol reaction of ketones and ethyl glyoxylate by using an L-proline-derived dipeptide as the catalyst.

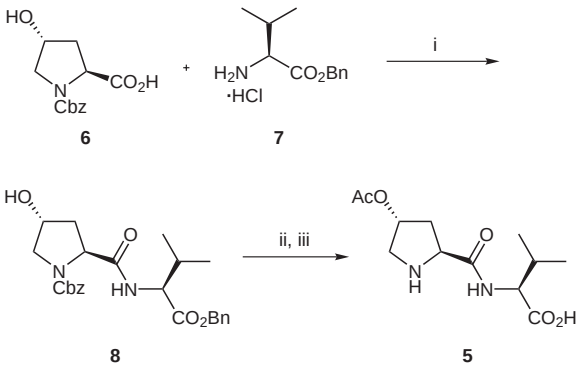
On account of our earlier study,[11a–c] some readily available L-proline derivatives (Figure 1) were chosen as the catalysts. With the exception of catalyst **5**, these catalysts are either commercially available products (**1**, **2**) or known compounds (**3**, **4**); the latter were synthesized according to the reported methods.[7f,12] The synthesis of the new catalyst **5** is shown in Scheme 1. The coupling of Cbz-protected (*R*)-4-hydroxy-L-proline (**6**)[13] and L-valine benzyl ester·HCl (**7**) in the presence of EDCI/HOBt led to the protected dipeptide derivative **8** in 86% yield. Acetylation of **8** with acetyl chloride in the presence of pyridine followed by hydrogenation under standard conditions gave the desired catalyst **5** in almost quantitative yield.



1 R = NH_2
2 R = OH

3 $R^1 = R^2 = H$
4 $R^1 = H$; $R^2 = Me$
5 $R^1 = OAc$; $R^2 = H$

Figure 1 Catalysts screened for the cross-aldol reaction



6 **7** **8** **5**

Scheme 1 Synthesis of catalyst **5**. *Reagents and conditions*: (i) EDCI, HOBt, NMP, CH_2Cl_2, 86%; (ii) AcCl, pyridine, CH_2Cl_2,

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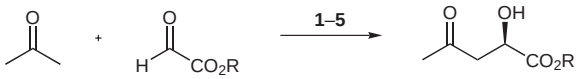
Table 1 Catalyst Screening and Reaction Conditions Optimization[a]



9a **10a** (R = Et), **10a'** (R = Me), **10a''** (R = *t*-Bu) **11a** (R = Et), **11a'** (R = Me), **11a''** (R = *t*-Bu)

Entry	Catalyst	**10**	Solvent	Temp (°C)	Yield (%)[b]	ee (%)[c]
1	**1**	**10a**	Acetone	r.t.	94	20
2	**2**	**10a**	Acetone	r.t.	72	20
3	**3**	**10a**	Acetone	r.t.	31	50
4	**4**	**10a**	Acetone	r.t.	60	42
5	**5**	**10a**	Acetone	r.t.	89	60
6	**5**	**10a′**	Acetone	r.t.	86	52
7	**5**	**10a″**	Acetone	r.t.	62	25
8	**5**	**10a**	MeCN	r.t.	78	56
9	**5**	**10a**	THF	r.t.	65	54
10	**5**	**10a**	$CHCl_3$	r.t.	91	65
11[d]	**5**	**10a**	$CHCl_3$	0	85	80
12[e]	**5**	**10a**	**$CHCl_3$**	**–10**	**90**	**91**
13[e]	**5**	**10a**	$CHCl_3$	–20	52	91

[a] Unless otherwise specified, all reactions were carried out with acetone (0.25 mL), glyoxylate (0.5 mmol), and the catalyst (0.05 mmol, 10 mol%) in the specified solvent (0.25 mL) for 10 h.
[b] Yield of isolated products after flash chromatography.
[c] Determined by chiral GC analysis with a Chiraldex GTA column. The absolute configuration was determined through the comparison of the observed optical rotation with the reported data (ref. 14).
[d] Reaction time: 24 h.
[e] Reaction time: 48 h.

99%, (iii) H_2/Pd-C (10%), MeOH, 98%.

By using acetone (**9a**) and ethyl glyoxylate (**10a**) as the model compounds, the reactivity and asymmetric induction of the above catalysts (**1**–**5**, Figure 1) were screened and the results are summarized in Table 1.

When 10 mol% of L-prolinamide (**1**) was used as the catalyst, the reaction in excessive acetone as the solvent gave the desired secondary α-hydroxy carboxylate product **11a** in 94% yield after 10 hours at room temperature, albeit with a very low ee value of only 20% (entry 1). Under similar conditions, L-proline also led to 20% ee of the product (entry 2). These results are in striking contrast to those of α-ketophosphonates, where these catalysts lead to excellent enantioselectivities.[11b,c]

Dipeptide catalysts such as **3**[7f] and **4**[12b] have been successfully applied in asymmetric aldol reactions and, therefore, they were also screened in the current study. The dipeptide catalyst **3**[7f] produced the desired product **11a** in a much improved enantioselectivity (50%); nevertheless, the yield was much lower (31%, entry 3). This low reactivity of catalyst **3** was presumably caused by its poor solubility in acetone. Indeed, protecting the terminal carboxylic group of catalyst **3** as its methyl ester, which gives catalyst **4**,[12b] results in much a better yield (60%) of **11a** (entry 4). Unfortunately, the ee value of the product dropped to 42% (entry 4). These results indicate that the terminal carboxylic acid proton is beneficial for the enantioselectivity, whereas the solubility of the catalyst in the reaction system is important for its reactivity. Therefore, the new catalyst **5**, possessing an acetyloxy group at the C-4 position of the proline backbone, was designed and synthesized (Scheme 1). This design is to keep the enantioselectivity of **3** but to increase the reactivity through enhanced solubility. To our pleasure, under similar conditions, catalyst **5** gave the aldol product **11a** in 89% yield with an ee value of 60% (entry 5).

The size of the ester group of the gyloxylate substrate was also probed. Both the smaller methyl ester (**10a′**, entry 6) and the larger *tert*-butyl ester (**10a″**, entry 7) were found to give inferior enantioselectivities under similar conditions than the ethyl ester (entry 5). Thus, the size of the ester group plays an important role on the enantioselec-

tivity, and ethyl gyloxylate (**10a**) was identified as the best substrate for catalyst **5**.

The reaction conditions were further optimized in order to obtain the highest enantioselectivity in this reaction. As shown in Table 1, at room temperature, the best enantioselectivity (65% ee) was obtained when $CHCl_3$ was used as the solvent (entry 10), whereas MeCN (entry 8) and THF (entry 9) proved to be worse solvents. Further optimization of the reaction temperature led to an increase of the enantioselectivity. When the temperature was lowered to 0 °C, an ee value of 80% was obtained (entry 11). Similar reaction at –10 °C resulted in the highest enantioselectivity of 91% (entry 12). Nonetheless, further dropping the reaction temperature to –20 °C did not improve the enantioselectivity, but instead had an adverse effect on the reactivity of the catalyst (entry 13).

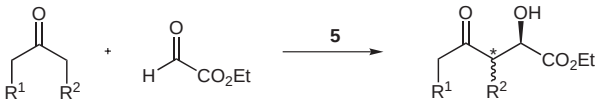
The absolute configuration of the newly formed chiral center in **11a** was determined to be *R* by comparing the observed optical rotation with the reported data.[14]

To study the scope of this reaction, a series of ketone substrates was subjected to the optimized conditions (–10 °C, 10 mol% catalyst loading, and $CHCl_3$ as the solvent).[15] The results are summarized in Table 2.

Besides acetone (entry 1), other aliphatic ketones, such as 2-butanone (**9b**, entry 2), 2-pentanone (**9c**, entry 3) and 4-methyl-2-pentanone (**9d**, entry 4), also participate in this reaction. The aldol reaction of 2-butanone leads to the formation of two regioisomers in a 1.5:1 ratio with a combined yield of 70%. The major regioisomer **11b** is a thermodynamic product, which was obtained in 90% de for the *anti* product; and the ee value for this diastereoisomer is 98% (entry 2). The minor regioisomer **11b′** is a kinetic product, which was obtained in 84% ee. The reaction of 2-pentanone (**9c**, entry 3) and 4-methyl-2-pentanone (**9d**, entry 4) with ethyl glyoxylate, however, produces only the kinetic regioisomers **11c** and **11d** in 62% and 35% yields, respectively. The ee values of these two products were 74% and 86%, respectively. In contrast, the aldol reaction of α-methoxyacetone (**9e**) yielded only the thermodynamic product **11e** in a 70:30 diastereomeric ratio with 89% and 57% ee for the major and minor diastereomers, respectively (entry 5).

Cyclic ketones (**9f–i**) are also good substrates for this reaction. Cyclopentanone (**9f**) led to the desired aldol prod-

Table 2 Enantioselective Cross-Aldol Reaction of Ethyl Glyoxylate (**7a**) and Various Ketones[a]



9 **10a** **11**

Entry	R^1	R^2	Product	Yield (%)[b]	dr	ee (%)[c]
1	H	H	**11a**	90		91
2	H	Me	**11b**	42[d]	95:5[e]	98
	Me	H	**11b′**	28[d]		84
3[f,g]	Et	H	**11c**	62		74
4[f,g]	*i*-Pr	H	**11d**	35		86
5[f,g]	OMe	H	**11e**	56	70:30[e]	89 (57)
6	$–(CH_2)_2–$		**11f**	72	60:40[h]	95 (85)
7	$–(CH_2)_3–$		**11g**	70	90:10[i]	88
8[f]	$–CH_2OCH_2–$		**11h**	74	80:20[i]	80 (26)
9[f]	$–CH_2SCH_2–$		**11i**	75	90:10[i]	81[j]

[a] Unless otherwise specified, all reactions were carried out with the ketone (0.25 mL), ethyl glyoxylate (0.5 mmol), and the catalyst (0.05 mmol, 10 mol%) in $CHCl_3$ (0.25 mL) at –10 °C for 48 h.
[b] Yields of isolated products after flash chromatography.
[c] The ee was determined by chiral GC analysis with a Chiraldex GTA column. The stereochemistry of the α-carbon was assigned on the basis of the reaction mechanism.
[d] Yields of the individual regioisomer as determined by GC analysis.
[e] The *anti*/*syn* ratio was determined by GC analysis of the crude mixture.
[f] Reaction time: 72 h.
[g] 20 mol% of catalyst was used.
[h] The *syn*/*anti* ratio was determined by NMR.
[i] The *anti*/*syn* ratio was determined by NMR.
[j] The ee was determined by chiral HPLC analysis with a Chiralpak AD-H column.

uct **11f** in 72% yield with a diastereomeric ratio of 60:40 (entry 6). The major diastereoisomer, which was determined to be *syn*,[16] was obtained in 95% ee. The minor *anti* diastereoisomer was obtained in 85% ee. Under these conditions, cyclohexanone resulted in a 70% yield of the aldol product **11g**[17] in an excellent diastereoselectivity (90:10, entry 7). The major diastereoisomer, which was determined to be *anti*,[17] was obtained in 88% ee. Similar results were also obtained for 4-oxacyclohexanone (**9h**, entry 8) and 4-thiacyclohexanone (**9i**, entry 9), except the ee values are slightly inferior for the products of these two substrates **(**80% and 81% ee, respectively).

In conclusion, the direct aldol reaction of ethyl glyoxylate and various ketones has been realized by using the novel L-proline-derived dipeptide **5** as the organocatalyst. This catalyst displays good to high enantioselectivities (up to 98% ee) and diastereoselectivities (up to 90% de), especially when six-membered cyclic ketones are used as the substrates.

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(15) **General Experimental Procedure**
To a stirred solution of ethyl glyoxylate (51.0 mg, 0.5 mmol) and the ketone (0.25 mL) in $CHCl_3$ (0.25 mL) was added catalyst **5** (13.6 mg, 0.05 mmol) at –10 °C. The reaction mixture was stirred at this temperature for 24–72 h. The solvent was then evaporated under vacuum and the residue was purified by flash chromatography (EtOAc–hexane, 1:2) over silica gel to furnish the desired secondary α-hydroxycarboxylate as a pure compound. ^{1}H NMR and ^{13}C NMR data of new compounds are collected below.
Compound **5**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.83 (t, *J* = 7.5 Hz, 6 H), 1.90–1.92 (m, 1 H), 1.99 (s, 3 H), 2.06–2.11 (m, 2 H), 2.96 (d, *J* = 3.0 Hz, 2 H), 3.79 (t, *J* = 8.0 Hz, 1 H), 4.12 (q, *J* = 4.5 Hz, 1 H), 5.08 (d, *J* = 2.5 Hz, 1 H), 8.10 (d, *J* = 9.5 Hz, 1 H, CONH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.3, 19.8, 21.7, 31.1, 37.6, 53.0, 57.2, 59.9, 76.6, 170.8, 173.5, 173.7 ppm.
Compound **8**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.72–0.98 (m, 6 H), 2.00–2.40 (m, 3 H), 3.42–3.79 (m, 3 H), 4.38–4.61 (m, 3 H), 5.00–5.33 (m, 4 H), 7.20–7.52 (m, 11 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.8, 19.2, 31.4, 37.3 (40.0), 54.8 (56.0), 57.7 (57.3), 59.3 (59.7), 67.2, 67.7, 70.1 (69.5), 128.1 (2 C), 128.3 (2 C), 128.6 (2 C), 128.7 (2 C), 128.8 (2 C), 135.7, 136.6, 156.4 (155.6), 171.9, 172.7 (171.6) ppm.
Compound **11c**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.91 (t, *J* = 8.3 Hz, 3 H), 1.28 (t, *J* = 7.0 Hz, 3 H), 1.20 (q, *J* = 7.3 Hz, 2 H), 2.43 (t, *J* = 7.5 Hz, 2 H), 2.87 (dd, *J* = 17.5, 6.5 Hz, 1 H), 2.94 (dd, *J* = 17.5, 4.0 Hz, 1 H), 4.21–4.30 (m, 2 H),

4.68 (dd, *J* = 6.5, 4.0 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.8, 14.3, 17.2, 45.5, 46.1, 62.1, 67.3, 174.0, 208.8 ppm.

Compound **11d**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.88 (d, *J* = 7.0 Hz, 6 H), 1.24 (t, *J* = 7.3 Hz, 3 H), 2.09–2.13 (m, 1 H), 2.28 (d, *J* = 7.0 Hz, 2 H), 2.83 (dd, *J* = 17.5, 6.0 Hz, 1 H), 2.86 (dd, *J* = 17.5, 4.0 Hz, 1 H), 3.19 (br s, 1 H), 4.18–4.22 (m, 2 H), 4.42 (m, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.3, 22.7 (2 C), 24.8, 46.6, 52.5, 62.1, 67.2, 174.0, 208.5 ppm.

Compound **11e** (diastereomeric mixture), major isomer: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.30 (t, *J* = 7.5 Hz, 3 H), 2.25, (s, 3 H), 3.56 (s, 3 H), 3.94 (d, *J* = 2.5 Hz, 1 H), 4.20–4.4.28 (m, 2 H), 4.58 (d, *J* = 2.5 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.3, 27.4, 60.2, 62.6, 72.3, 89.0, 171.6, 208.5 ppm.

Compound **11e** (diastereomeric mixture), minor isomer: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.33 (t, *J* = 7.5 Hz, 3 H), 2.29 (s, 3 H), 3.44 (s, 3 H), 3.95 (d, *J* = 2.5 Hz, 1 H), 4.28–4.30 (m, 2 H), 4.50 (d, *J* = 2.0 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.5, 27.5, 59.9, 62.4, 72.1, 87.7, 171.9, 209.9 ppm.

Compound **11h** (diastereomeric mixture), major isomer: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.26 (t, *J* = 7.0 Hz, 3H), 2.37 (dt, *J* = 15.0, 2.0 Hz, 1 H), 2.56–2.63 (m, 1 H), 3.10–3.16 (m, 2 H), 3.70 (td, *J* = 11.5, 3.0 Hz, 1 H), 3.83 (t, *J* = 11.0 Hz, 1 H), 4.02 (m, 1 H), 4.18–4.30 (m, 4 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.3, 42.5, 54.0, 62.3, 68.0, 68.1, 70.0, 173.1, 205.9 ppm.

Compound **11h** (diastereomeric mixture), minor isomer: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.27 (t, *J* = 7.0 Hz, 3 H), 2.47 (dt, *J* = 15.0, 3.5 Hz, 1 H), 2.56–2.63 (m, 1 H), 2.85–2.98 (m, 2 H), 3.77 (td, *J* = 10.5, 4.0 Hz, 1 H), 3.89 (t, *J* = 9.5 Hz, 1 H), 4.03–4.18 (m, 1 H), 4.12–4.30 (m, 3 H), 4.65 (d, *J* = 3.5 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.4, 42.5, 54.7, 62.4, 67.5, 68.2, 68.3, 173.4, 205.5 ppm.

Compound **11i**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.28 (t, *J* = 7.0 Hz, 3 H), 2.64–2.78 (m, 2 H), 2.89–3.10 (m, 3 H), 3.13 (br s, 1 H), 3.18–3.30 (m, 2 H), 4.13 (m, 1 H), 4.25 (q, *J* = 7.2 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.3, 29.9, 32.6, 44.4, 56.0, 62.2, 71.0, 172.9, 208.0 ppm.

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