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Organocatalytic Highly Enantioselective Synthesis of Secondary α-Hydroxyphosphonates†

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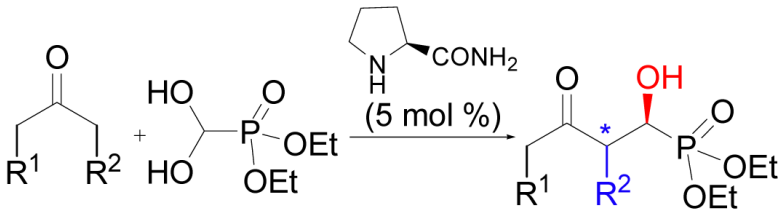
Abstract



dr up to >95:5
ee up to >99%

The first organocatalytic cross aldol reaction of ketones and diethyl formylphosphonate hydrate has been realized by using readily available L-prolinamide as the catalyst. Secondary α-hydroxyphosphonates have been synthesized in high enantioselective (up to >99% ee) and good diastereoselectivity.

As close analogs of α-amino acids, αhydroxyphosphonate derivatives have been shown to be very important enzyme inhibitors.[1] For example, they are inhibitors of renin[2] or human immunodeficiency virus (HIV) protease and polymerase.[3] They also show anti-virus[4] and anti-cancer activities.[5] Because of their important biological activities, achieving high enantioselectivity in the synthesis of α-hydroxyphosphonates has been the goal of organic chemists.[6] Recently, we reported the first prolinecatalyzed asymmetric aldol reaction of α-ketophosphonates for the highly enantioselective synthesis of tertiary α-hydroxyphosphonates (Eq 1).[7] However, from a biological point of view, secondary α-hydroxyphosphonates seem more significant, as all chiral natural amino acids are secondary amines. The optically enriched forms of secondary α-hydroxyphosphonates are mainly obtained through enzymatic methods,[6a] such as kinetic resolution of racemic mixture by bacteria, fungi or

Affectionately dedicated to Professor Waldemar Adam on the occasion of his 69th birthday.

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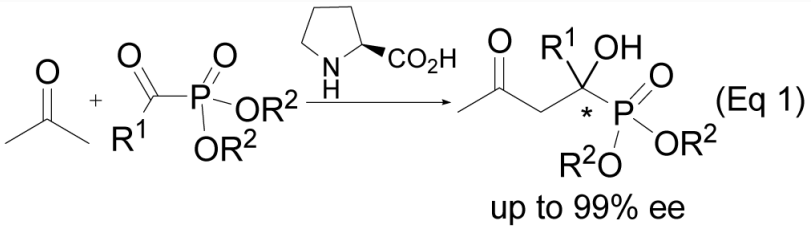
Supporting Information Available Experimental procedures, NMR spectra for new compounds, and HPLC analysis data. This material is available free of charge via the Internet at http://pubs.acs.org.



lipases[8] or through asymmetric reduction of α-ketophosphonate with baker's yeast or fungi.[6a,9] Only a few chemical methods are available,[6b,c] which include the asymmetric reduction of α-ketophosphonates,[10] asymmetric oxidation of benzylphosphonates[11] and diastereoselective addition of dialkyl phosphites to aldehydes (phosphoaldol reaction).[12a,b] These methods are either not catalytic, use special reagents that are difficult to handle, or have very limited substrate scope. A catalytic method based on the phosphoaldol reaction was also reported,[12c-g] but the enantioselectivities obtained were dependent on the substrates. Most recently, Chen and co-workers reoported a vanadium-catalyzed oxidative kinetic resolution for the high enantioselective synthesis of secondary α-hydroxyhosphonates;[13] nonetheless, the disadvantage of this method is the sacrifice of 50% of the starting material.[13] Thus, the development of a catalytic highly enantioselective method for the synthesis of secondary α-hydroxyphosphonates is warranted. Herein, we wish to report our preliminary results of a highly enantioselective synthesis of secondary α-hydroxyphosphonates via a prolinamide-catalyzed asymmetric aldol reaction.[14]

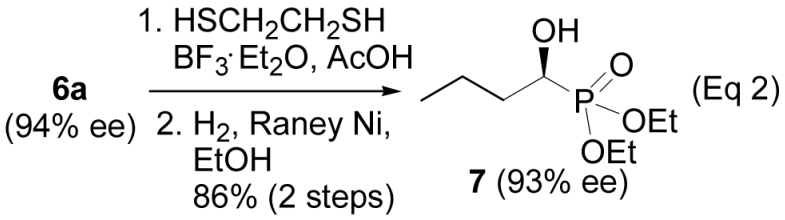
Synthesizing secondary α-hydroxyphosphonates by using our reported protocol[7] would require formylphosphonate as the starting material (Eq 1, R^1 = H). However, although diethyl formylphosphonate is a known compound,[15] it is unstable, and all our attempts to react this substance with acetone failed. Then we turned our attentions to its hydrate (**4**), because it was reported to be more stable and in equilibrium with its formyl form.[16]

By using acetone (**5a**) as the model compound, we screened some readily available L-proline-derivatives (Figure 1) as the catalyst for the cross aldol reaction of diethyl formylphosphonate hydrate (**4**). The results are summarized in Table 1.

As shown in Table 1, although L-proline is a good catalyst for the cross aldol reaction of α-ketophosphonates,[7] it failed to catalyze the aldol reaction of **4** (entry 1), presumably because **4** is incompatible with its acidity. In contrast, less acidic L-proline tetrazole (**2**) and L-prolinamide (**3**) proved to be good catalysts for the desired reaction. At 10 mol % catalyst loading and room temperature, the aldol product **6a** was obtained in 72% (entry 2) and 84% ee (entry 3), respectively. The reaction conditions were further optimized for **3**, as it is more reactive and enantioselective. Catalyst **3** is slightly less reactive in CH_2Cl_2 (entry 4), but the enantioselectivity maintains at the same level as in acetone. Other common solvents used for aldol reactions, such as DMSO (entry 5) and DMF (entry 6), proved to be less effective than excessive acetone (entry 3). Nevertheless, lowering the reaction temperature to 0 °C resulted in an increase of the enantioselectivity (to 92% ee, entry 7). It is interesting to note that the catalyst loading can be further reduced to 5 mol %, without affecting the enantioselectivity, although the reaction is a little bit slower (entry 8). Further dropping of the reaction temperature to -20 °C did not improve the enantioselectivity, instead has an adverse effect on the reactivity of the catalyst (entry 9). Similar reaction with D-prolinamide (*ent*-**3**) as the catalyst produced comparable results as those of L-prolinamide, except that the opposite enantiomer of the product was obtained as the major one (entry 10).

In order to determine the absolute configuration of the product, the carbonyl group in product **6a** was reduced to the methylene group in two steps (Eq 2) to give compound **7**, for which the

absolute configuration is known.[17] Compound **7** is dextrorotary, which indicates that the newly formed chiral center is *S*-configured.[17]

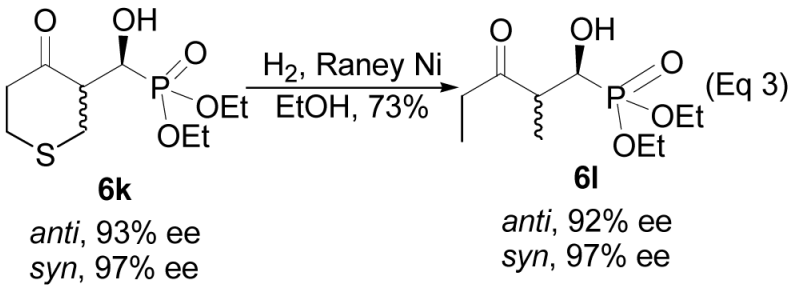


Further studies were carried out under the optimized conditions (0 °C, 5 mol % catalyst loading, and excessive ketone as solvent if possible) to understand the scope of this new reaction, and the results are summarized in Table 2.

Besides acetone (entry 1), other unsubstituted aliphatic ketones, such as 2-butanone (**5b**, entry 2) and 2-pentanone (**5c**, entry 3), also participate in this reaction. The reaction of **5b** and **4** gives rise to a mixture of two inseparable regioisomers (**6b** and **6b'**) in a ratio of 3:1. The major regioisomer (**6b**) is a kinetic product, which was obtained in 93% ee. The thermodynamic product (**6b'**) was obtained in a 90% de for *anti* product and the ee value for this diastereomer is 99% (entry 2). Similarly, the reaction **5c** and **4** yielded these two products in about 12:1 ratio, with a 97% ee for the major kinetic product (**6c**), and a single *anti* diastereomer for the minor product (**6c'**) in high enantioselectivity (99% ee, entry 3). However, 3-pentanone reacts very slowly and leads to the decomposition of **4** (data not shown).

Substituted ketones may also be used in this reaction. For example, the aldol reaction of α-chloroacetone (**5d**) produces only the kinetic regioisomer in 65% yield and 90% ee (entry 4). In contrast, acetol (**5e**) generates very poor enantioselectivity (43% ee) of the product (entry 5), presumably due to the interference of the free hydroxy group. Once the hydroxy group is methylated, compound**5f** again generates excellent enantioselectivity for the product (**6f**, 85% ee, entry 6). Similar enantioselectivity (86% ee) was also obtained for the aldol product (**6g**) of 2,5-hexanedione.

Some cyclic ketones were also studied. Cyclopentanone yielded the aldol product (**6h**) in excellent yield (94%) and diastereoselectivity (95:5, entry 8). The major diastereomer, which was determined to be *syn* by NOE, was obtained essentially as a pure enantiomer (>99% ee). The reaction of cyclohexanone generates a 65:35 *anti/syn* mixture (**6i**) in excessive cyclohexanone with 93% and 86% ee for these two diastereomers, respectively (entry 9). Similar reaction using CH_2Cl_2 as solvent with 10 mol % of the catalyst (entry 10) led to improved enantioselectivities of these two diastereomers (96% and 95% ee, respectively). Under these conditions, 4-oxacyclohexanone (**5j**) and 4-thiacyclohexanone (**5k**) also perform better. A 70:30 *anti/syn* mixture was obtained for **6j**, with 97% and 99% ee for the major and minor diastereomers, respectively (entry 11). The same *anti/syn* diastereoselectivity was also obtained for the product of **5k**, with 93% and 97% ee, respectively (entry 12). As a potential application of this product, **6k** may be readily desulfurized to give product **6l** in good yield (Eq 3), with total retention of the stereochemistry. Product **6l** can be viewed as the aldol product of 3-pentanone and **4**; however, as aforementioned, such a direct aldol reaction is not feasible with the L-prolinamide catalysis at this moment.



6k

anti, 93% ee
syn, 97% ee

6l

anti, 92% ee
syn, 97% ee

To account for the formation of the *S*-configured α-hydroxyphosphonate as the major enantiomer, we propose a reaction mechanism as shown in Scheme 1, which is similar to other proline derivative-catalyzed cross aldol reactions.[18] The *re* face attack is disfavored due to the unfavorable steric interaction between the large axial phosphonate group and the axial methyl group (Scheme 1, right). Thus, the *si* face attack is favored, which leads to the observed product (Scheme 1, left).

In summary, we have developed the first organocatalytic cross aldol reaction of ketones and diethyl formylphosphonate hydrate by using readily available L-prolinamide as the catalyst. Secondary α-hydroxyphosphonates have been synthesized in high enantioselectivity (up to >99% ee) and good diastereoselectivity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

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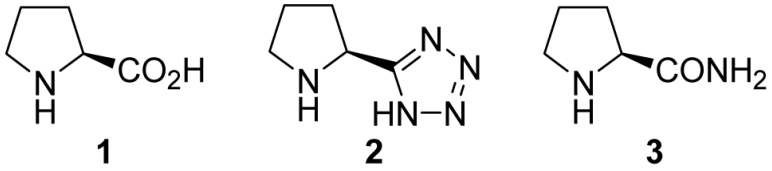
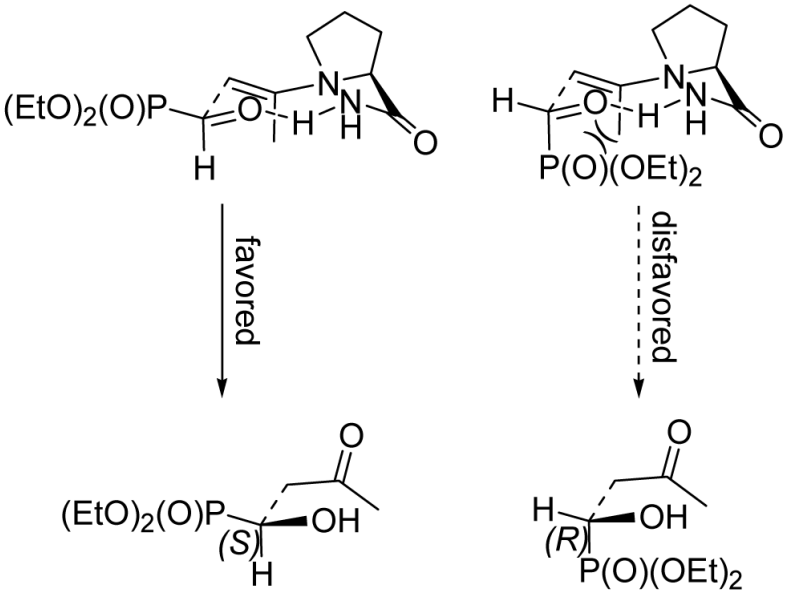


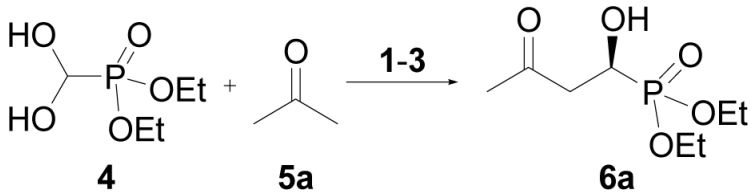
Figure 1.
Catalysts screened for the cross aldol reaction.



Scheme 1.
Proposed Transition State Structures

Table 1

Catalyst Screening and Reaction Condition Optimizations[a]



4 **5a** **6a**

entry	catalyst	solvent	temp (°C)	time (h)	yield (%)[b]	ee (%)[c]
1	**1**	acetone	rt	24	—	—
2	**2**	acetone	rt	24	46	72
3	**3**	acetone	rt	3	93	84
4	**3**	CH_2Cl_2	rt	10	76	84
5	**3**	DMSO	rt	10	45	79
6	**3**	DMF	rt	10	55	60
7	**3**	acetone	0	10	95	92
8[d]	**3**	acetone	**0**	**24**	**95**	**94**
9[d]	**3**	acetone	-20	24	62	94
10	***ent*-3**	acetone	0	24	91	92[e]

[a] Unless otherwise indicated, all reactions were performed with freshly prepared diethyl formylphosphonate hydrate (**4**, 0.5 mmol), acetone (0.2 mL), solvent (0.4 mL) and catalyst (10 mol %) at 0 ° C.

[b] Yield of isolated product after column chromatography.

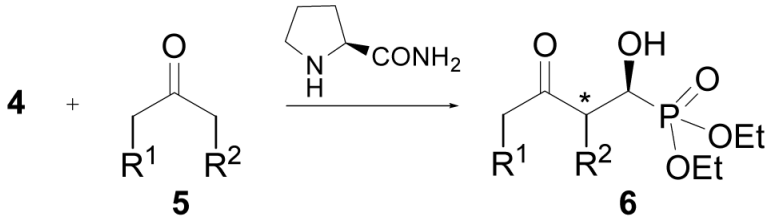
[c] The enantiomeric excess was determined by chiral GC analysis with a Chiraldex GTA column.

[d] With 5 mol % of catalyst loading.

[e] (*R*)-**6a** was obtained as the major enantiomer.

Table 2

Enantioselective Cross Aldol Reaction of Diethyl Formylphosphonate Hydrate (**4**) and Various Ketones.[a]



entry	R^1	R^2	product/ yield (%)[b]	dr[c]	ee (%)[d]
1	H	H	**6a**/95	—	94[e]
2	Me	H	**6b**/62[f]	—	93[e]
	H	Me	**6b'** /20[f]	95:5[g]	99[e]
3	Et	H	**6c**/58[f]	—	97[e]
	H	Et	**6c'**/5[f]	>95:5[g]	99[e]
4	Cl	H	**6d**/65	—	90[e]
5	OH	H	**6e**/75	—	43[h]
6	OMe	H	**6f**/77	—	85
7	$AcCH_2$	H	**6g**/60	—	86
8	$—(CH_2)_2—$		**6h**/ 94	95:5[i]	>99
9	$—(CH_2)_3—$		**6i**/82	65:35[g]	93(86)
10[j]	$—(CH_2)_3—$		**6i**/90[k]	65:35[g]	96(95)
11[j]	$—CH_2OCH_2—$		**6j**/85[k]	70:30[g]	97(99)
12[j]	$—CH_2SCH_2—$		**6k**/88[k]	70:30[g]	93(97)[l]

[a] Unless otherwise indicated, all reactions were performed with freshly prepared diethyl formylphosphonate hydrate (**4**, 0.5 mmol), ketone (0.6 mL) and L-prolinamide (5 mol %) at 0 °C; the absolute configuration is tentatively assigned for **6b-k** on the basis of the reaction mechanism.

[b] Yield of isolated product after column chromatography.

[c] Determined by ^{1}H NMR.

[d] Unless otherwise noted, enantiomeric excess was determined by HPLC analyses with a Chiralpak AD-H column; values in parentheses are for the minor diastereomer.

[e] The enantiomeric excess was determined by chiral GC analysis with a Chiraldex GTA column.

[f] Yields of individual regioisomer as determined by ^{1}H NMR.

[g] *anti/syn* ratio as determined by NMR.

[h] With a Chiralcel OJ-H column.

[i] *syn/anti* ratio as determined by NMR.

[j] The reaction was performed with **4** (0.5 mmol), ketone (0.2 mL), CH_2Cl_2 (0.5 mL) and L-prolinamide (10mol %) at -20 °C for 24 h.

[k] Combined yield of two inseparable diastereomers.

[l] With a Chiralcel OD-H column.