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Organocatalytic Enantioselective Synthesis of α-Hydroxy Phosphonates

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Although their biological activities have not been extensively explored,[1] α-hydroxy phosphonic acid derivatives have been shown to be very important enzyme inhibitors. For example, they are inhibitors of such important medicinal enzymes as renin[2] or human immunodeficiency virus (HIV) protease and polymerase.[3] They also show anti-virus[4] and anti-cancer activities.[5] It is well-known that, in a racemic mixture, normally only one enantiomer shows the observed activities, and therefore, an enantioselective method for the synthesis of these compounds is highly desirable. Optically active α-hydroxy phosphonates are very useful precursors to other optically active α-hydroxy phosphonic acid derivatives. However, achieving high enantioselectivity in the synthesis of α-hydroxy phosphonates is a still a challenging task for organic chemists. The optically enriched forms of these compounds are mainly obtained through enzymatic methods,[6] such as kinetic resolution of racemic mixture by bacteria, fungi, or lapses[7] or through asymmetric reduction of α-keto phosphonate with baker's yeast or fungi.[6,8] A few available chemical methods[9] include asymmetric reduction of α-keto phosphonates,[10] asymmetric oxidation of benzyl phosphonates,[11] and diastereoselective addition of dialkyl phosphites to aldehydes (phosphoaldol reaction).[12a,b] These methods are either not catalytic, using 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,d] but the enantioselectivities obtained were dependent on the substrates. Furthermore, all of the reported methods are only suitable for the synthesis of secondary α-hydroxy phosphonates. To the best of our knowledge, there is no general method for the synthesis of optically active tertiary α-hydroxy phosphonates.[13]

Recent progresses[14] in the proline-catalyzed asymmetric cross aldol reaction of activated ketones have revealed that a compound, such as glyoxylate, is a good substrate for asymmetric aldol reaction.[14d,e] These results prompted us to study the possibility of using such a cross aldol reaction for the asymmetric synthesis of optically active α-hydroxy phosphonates. Due to the susceptibility of α-keto phosphonate toward nucleophilic attack and the leaving group ability of the phosphonate group, it can be considered as a synthetic equivalent of acid chloride.[15] It is, therefore, not surprising that the cross aldol reaction of α-keto phosphonate and ketone has never been studied in the literature, even with nonchiral reagents. However, when we carefully examined the proposed aldol reaction of enamine with α-keto phosphonate, it appeared the reaction intermediate can lead to either the desired α-hydroxy phosphonate or a 1,3-diketone product through the elimination of the phosphonate group.[14c,15] Wiemer and co-workers have shown that tertiary α-hydroxy phosphonates are reasonably stable.[13] On the basis of their results, we hypothesized that formation of α-hydroxy phosphonate should be feasible if the reaction conditions are appropriate. Herein we wish to report our preliminary results of the first highly enantioselective synthesis of tertiary α-hydroxy phosphonates based on a novel cross aldol reaction of α-keto phosphonates and ketones.

By using diethyl benzoylphosphonate and acetone as the model compounds, we first screened some readily available proline derivatives (Figure 1) as the catalyst. The cross aldol reaction went smoothly at room temperature in acetone[16] with all these catalysts, and excellent yields of the aldol product were obtained. Although L-prolinamide is a more reactive catalyst, only a moderate enantioselectivity was obtained (54% ee).[17] L-Proline tetrazole induced a poor 34% ee for the same reaction.[17] Nevertheless, the results of L-proline were promising, which are collected in Table 1.

With 20 mol % of L-proline as the catalyst, a good enantiomeric excess value of 71% of the desired aldol product was obtained in a yield of 85% at room temperature (entry 1). When the reaction was carried out at −30 °C, a much better enantiomeric excess value of 87% was obtained (entry 2). The corresponding methyl ester is even more temperature sensitive. While at room temperature a poor enantiomeric excess value of 35% was obtained,[17] an excellent enantioselectivity of 95% was obtained at −30 °C (entry 3). The *iso*-propyl ester also yields an excellent enantioselectivity of 96% at this subambient temperature (entry 4). Some 4-substituted benzoyl substrates were also studied for this reaction (entries 5−12). It appears that the enantioselectivity is dependent on both the R^1 and R^2 groups. When the R^2 group is the same (e.g., Et), the electronic nature of the *para* substituents plays some role on the enantioselectivity. With the exception of the fluoro substituent, electron-withdrawing groups generally perform better in enantioselectivity than do electron-donating groups. Also they are more reactive. The effects of the size of the R^2 group are also evident. For example, with benzoylphosphonate, the methyl and *iso*-propyl esters perform the best (95 and 96% ee, respectively); while for 4-fluorobenzoylphosphonate, the *iso*-propyl ester produces the best enantioselectivity (96% ee). Catalyst loading was found to be critical to high enantioselectivity. With a larger 50 mol % loading, although the reaction is slightly faster, worse enantioselectivities of the products were obtained in most cases. For example, with a 20 mol % loading, an enantiomeric excess of 99% was obtained for the *para*-bromo derivative (entry 9); similar reaction with 50 mol % loading produced a product of only 74% ee.[17] Control experiments showed this was due to slow racemization of the product caused by the excessive catalyst.

Alkyl-substituted ketophosphonates are also good substrates for this reaction. Diethyl acetylphosphonate yields the aldol product in excellent yield with a high enantiomeric excess of 92% (entry 13) at room temperature. The enantiomeric excess improved to 97% when the temperature was lowered to 0 °C (entry 14). Similarly, phenylacetylphosphonate also produces excellent enantiomeric excess of the product (92% ee, entry 15). However, when the chain length was further extended to benzylacetyl, a significant drop of the enantioselectivity (to 81%) was observed (entry 16).

α-Hydroxy phosphonates with unsaturated side chains are very useful,[13] as the side chain can be readily elaborated to introduce other functional groups. Thus, we also briefly studied the aldol

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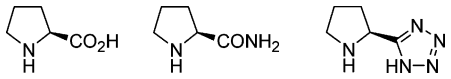
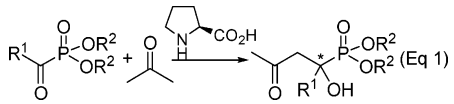


Figure 1. Catalysts screened for the cross aldol reaction.

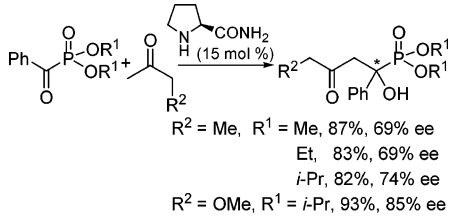
Table 1. Enantioselective Synthesis of α-Hydroxy Phosphonates[a]



entry	R^1	R^2	T (°C)	time (h)	yield (%)[b]	ee (%)[c]
1	Ph	Et	rt	24	85	71
2	Ph	Et	−30	96	65	87
3	Ph	Me	−30	96	66	95
4	Ph	*i*-Pr	−30	120	60	96
5	*p*-Cl−C_6H_4	Et	−30	96	68	91
6	*p*-Cl−C_6H_4	*i*-Pr	−30	96	63	95
7	*p*-F−C_6H_4	Et	−30	120	47	80
8	*p*-F−C_6H_4	*i*-Pr	−30	120	68[d]	96
9	*p*-Br−C_6H_4	Et	−30	96	66	>99
10	*p*-I−C_6H_4	Et	−30	96	67	94
11	*p*-Me-C_6H_4	Et	−30	96	63[d]	85
12	*p*-MeO−C_6H_4	Et	−30	96	32[d]	86
13	Me	Et	rt	24	94	92
14	Me	Et	0	72	91	97
15	$PhCH_2$	Et	rt	24	86[d]	92
16	$PhCH_2CH_2$	Et	0	48	76	81
17	*trans*-CH_3CH═CH	Et	−30	108	67	98

[a] All reactions were carried out with the keto phosphonate (0.50 mmol) in dry acetone (2.0 mL), with L-proline (0.10 mmol, 20 mol %) as the catalyst for the specified reaction time and temperature, unless otherwise specified. [b] Yield of isolated product after column chromatography. [c] Enantioselectivity was determined by HPLC analyses; the absolute configuration of the major enantiomer was not determined. [d] With L-proline (0.25 mmol, 50 mol %) as the catalyst.

Scheme 1



reaction of diethyl *trans*-2-butenoylphosphonate. The reaction proceeded smoothly at −30 °C, and the desired aldol product was obtained in 67% yield and 98% ee (entry 17). Although for this specific substrate Michael addition is possible, no such product was observed in the crude reaction mixture.

Ketones, such as 2-butanone and methoxyacetone, also participate in this reaction if L-prolinamide is used as the catalyst. Such a cross aldol reaction with benzoylphosphonates produced only one regioselective product in good enantioselectivities (Scheme 1).

In summary, we have developed an organocatalytic highly enantioselective cross aldol reaction of α-ketophosphonates and ketones for the highly enantioselective synthesis of optically active tertiary α-hydroxyphosphonates. This method can be applied to α-ketophosphonates with alkyl, aryl, and alkenyl substituents.

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

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(16) DMF, DMSO, and CH_2Cl_2 are worse solvents for this reaction.
(17) See Supporting Information for details.

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