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Organocatalytic Highly Enantioselective Synthesis of β-Formyl-α-hydroxyphosphonates

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Abstract: The cross-aldol reaction between enolizable aldehydes and α-ketophosphonates was achieved for the first time by using 9-amino-9-deoxy-*epi*-quinine as the catalyst. β-Formyl-α-hydroxyphosphonates were obtained in high to excellent enantioselectivities. The reaction works especially well with acetaldehyde, which is a tough substrate for organocatalyzed cross-aldol reactions. The products were demonstrated to have anticancer activities.

Keywords: aldehydes; hydroxyphosphonates; ketophosphonates; organocatalysis; primary amines

α-Hydroxyphosphonate derivatives are highly biologically active compounds.[1] Previous studies have demonstrated that these compounds have anti-cancer,[2] anti-virus,[3] anti-bacterial[4] and anti-fungal[4] activities. They are also proven inhibitors of such important enzymes as renin[5] and HIV (human immunodeficiency virus) protease and polymerase.[6] Due to their relevance to biomedical applications, there have been considerable interests in developing highly enantioselective methods for the synthesis of these compounds in recent years.[7–9] Our own interest[8] in this area led to the development of an organocatalyzed asymmetric synthesis of α-hydroxyphosphonates on the basis a proline derivative-catalyzed cross-aldol reaction.[8a,b] Nevertheless, although high enantioselectivities have been achieved in the cross-aldol reaction of ketones and α-ketophosphonates by others[9] and us,[8a,b] the cross-aldol reaction of enolizable aldehydes and α-ketophosphonates proves to be very difficult.[10] To the best of our knowledge, such a reaction has not been realized so far. Herein we wish to report the first organocatalyzed cross-aldol reaction of enolizable aldehydes and α-ketophosphonates for the highly enantioselective synthesis of tertiary β-formyl-α-hydroxyphosphonates,[11,12] using a quinine-derived primary amine as the catalyst and the preliminary biological study of these compounds.

Although L-proline and L-prolinamide (compounds **1** and **2**, Figure 2) are excellent catalysts for the cross-aldol reaction of acetone and α-ketophosphonates,[8a,b] they fail to catalyze the cross-aldol reaction between propanal and α-ketophosphonates.[10] After carefully comparing the proposed transition states[8b,e] of these two similar reactions (Figure 1), we believe the reaction failed in the case of propanal because of the unfavorable interactions between the enamine methyl group and the large phosphonate group in the transition state (Figure 1, right structure). Thus, we hypothesized that the reaction should proceed if such unfavorable interactions are alleviated.

One way to reduce the unfavorable interactions is to use acetaldehyde (**9a**) as the substrate,[13] since, with **9a**, the methyl group in the proposed transition state (Figure 1) will be replaced with a much smaller hydrogen atom (as in the acetone case). Acetaldehyde (**9a**) and diethyl benzoylphosphonate (**10a**) were then

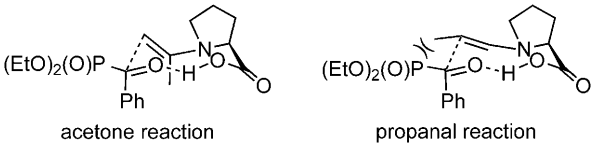


Figure 1. Proposed favoured transition states for the aldol reactions of α-ketophosphonate with acetone and propanal.

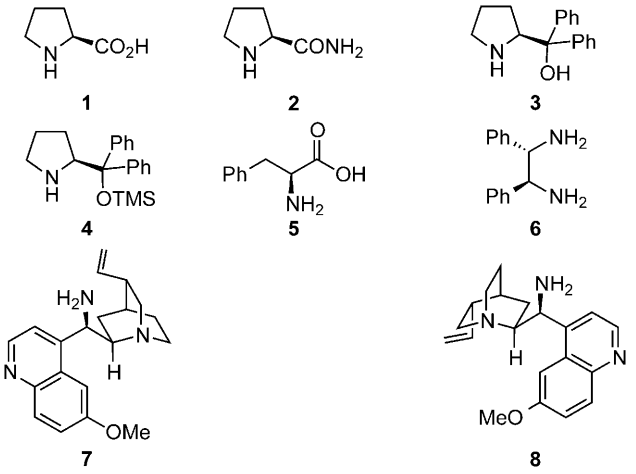
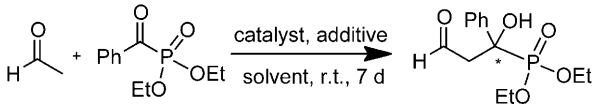


Figure 2. Catalysts screened for the cross-aldol reaction.

adopted as the substrates to test our hypothesis, using proline (**1**) and prolinamide (**2**) as the catalysts (Figure 2). As shown by the results collected in Table 1, indeed, after reacting in CH_2Cl_2 at room temperature for a week, the desired aldol product **11a** may be obtained in reasonable yields (50% and 59% with L-proline and L-prolinamide, respectively, entries 1 and 2). Diphenylprolinol catalysts **3** and **4** are known to catalyze highly enantioselective cross-aldol reactions of acetaldehydes;[13a,b,l] however, poorer results were obtained with these two catalysts (entries 3 and 4). Nevertheless, since acetaldehyde is a known tough substrate for organocatalyzed cross-aldol reactions,[13a,b,l] we were encouraged by these results even though the enantioselectivities obtained were impractical.

Another way to solve the aforementioned problem is to use a different catalyst, because the transition state is known to be dependent on the catalyst structure and the catalysis mechanism. In this regard, we were very interested in primary amine catalysts,[14] since primary amines would lead to less crowded transition states.[14a] Thus, we screened several primary amines as the catalyst for the cross-aldol reaction of **9a** and **10a** (compounds **5**–**8**, Figure 2). The results are also collected in Table 1. Among these catalysts, L-phenylalanine (**5**) is not effective at all as no desired product could be obtained after the reaction (entry 5). Nonetheless, in the presence of benzoic acid as the cocatalyst, (*S*,*S*)-1,2-diphenyl-1,2-ethanediamine (**6**) gave the expected product **11a** in 49% yield and 6% *ee* (entry 6). Catalysts **7** and **8**, derived from quinidine, and quinine, respectively, have been used by List and co-workers as the catalyst in an intramolecular aldol reaction;[14a] however, to the best of our knowledge, they have never been used in an intermolecular aldol reaction. When **7** was used as the catalyst with benzoic acid as the cocatalyst, the expected **11a** was obtained in 45% yield and 17% *ee* (entry 5).

Table 1. Catalyst screening and optimization of reaction conditions.[a]



Entry	Catalyst	Additive	Solvent	Yield [%][b]	*ee* [%][c]
1	**1**	none	CH_2Cl_2	50	9
2	**2**	none	CH_2Cl_2	59	13
3	**3**	$PhCO_2H$[d]	CH_2Cl_2	11	3
4	**4**	$PhCO_2H$[d]	CH_2Cl_2	9	10
5	**5**	none	CH_2Cl_2	0	–
6	**6**	$PhCO_2H$[e]	CH_2Cl_2	49	6
7	**7**	$PhCO_2H$	CH_2Cl_2	45	17
8	**8**	$PhCO_2H$	CH_2Cl_2	46	57[f]
9	**8**	CH_3CO_2H	CH_2Cl_2	30	71[f]
10	**8**	$EtCO_2H$	CH_2Cl_2	39	74[f]
11	**8**	CF_3CO_2H	CH_2Cl_2	23	41[f]
12	**8**	*p*-TsOH	CH_2Cl_2	0	–
13	**8**	MBA[g]	CH_2Cl_2	46	75[f]
14	**8**	MBA[g]	THF	51	86[f]
15	**8**	MBA[g]	CH_3CN	38	77[f]
16	**8**	MBA[g]	hexane	45	84[f]
17	**8**	MBA[g]	benzene	53	83[f]
18	**8**	MBA[g]	toluene	53	91[f]
19[g]	**8**	MBA[g]	toluene	75	93[f]

[a] Unless otherwise specified, all reactions were carried out with **10a** (0.30 mmol) and **9a** (1.5 mmol) in the specified solvent (2.0 mL) with the amine catalyst (10 mol%) and the acid cocatalyst (30 mol%) at room temperature for 7 days.
[b] Yield of isolated product after column chromatography.
[c] Determined by HPLC analysis on a ChiralCel OJ-H column.
[d] The loading of the acid cocatalyst was 10 mol%.
[e] The loading of the acid cocatalyst was 20 mol%.
[f] The opposite enantiomer was obtained.
[g] 4-Methoxybenzoic acid.
[h] Carried out at 0 °C.

The *ee* value was improved to 57% *ee* when compound **8** was applied (entry 6). Since catalyst **8** leads to highest *ee* value of the product, it was selected for further optimizations. Firstly, several acid cocatalysts were screened, and it was found that aliphatic acids, such as acetic acid and propoinic acid, led to improved *ee* values of the product (71% and 74%, respectively, entries 9 and 10); however, the yields of the product were lower. In contrast, stronger acids, such as trifluoroacetic acid and toluenesulfonic acid, are not effective (entries 11 and 12). Additional screening identified 4-methoxybenzoic acid as the best cocatalyst, as the highest *ee* value of 75% was obtained in a reasonable yield (46%, entry 13). Then the solvent effects were evaluated (entries 14–18), and toluene was identified as the best solvent for this reaction, because the product **11a** could be obtained in

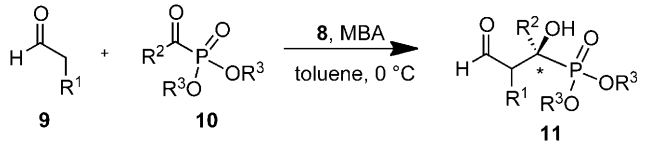
53% yield with a high *ee* value of 91% with this solvent (entry 16). Further optimization of the reaction temperature revealed that an improved yield of 75% of the desired product could be obtained at 0 °C, with also a slightly improved *ee* value of 93% (entry 17). The improved product yield at this temperature was probably due to reduced competing reactions. Further dropping the reaction temperature, however, leads to inferior reaction yield without improvement in the *ee* value (data not shown). It should be pointed out that the major enantiomer obtained with catalyst **8** is opposite to that obtained with the rest of the catalysts.

Next the scope of this reaction was evaluated with different α-ketophosphonate and aldehyde substrates. The results are presented in Table 2. As shown in Table 2, the size of the ester alkyl groups in the phosphonate has almost no influence on the enantioselectivity of this reaction, as similar *ee* values were obtained for the methyl, ethyl and isopropyl esters (entries 1–3). The same is true with the electronic nature of the substituents on the phenyl ring of the benzoylphosphonates: Excellent *ee* values were obtained for both electron-withdrawing and electron-donating substituents (entries 4–9).

Benzoylphosphonate with an *ortho*-chloro substituent is less reactive and the yield obtained was much lower (entry 10), which is most probably due to steric reasons. However, as shown in Table 2, the position of the substituent on the phenyl ring has almost no influence on the enantioselectivity (entries 5, 10–12). Propanal, which has failed with other catalysts, also participates in the reaction under these new conditions, and the reaction yielded the desired product in 44% yield as a diastereomeric mixture (*dr* 7:5), with *ee* values of 68% and 73% for the major and minor diastereomers, respectively (entry 13). The methyl and hydroxy groups in the major diastereomer were determined to be *anti* by NOE experiments.

The fact that all the products obtained in this study are liquid makes the direct determination of the absolute configuration of major enantiomer obtained in this reaction difficult. To determine the absolute configuration of the major enantiomer, compound **11f** was converted to its 2,4-dinitrophenylhydrazone derivative **12** (Figure 3), and its stereochemistry at the quaternary stereogenic center was successfully determined to be *R* by X-ray crystallography.[16] Thus, the absolute configuration of compound **11f** was assigned as *R*. On the basis of these results, a tentative mechanism is proposed to account for the formation of the major enantiomer in this reaction (Figure 4). The attack of the enamine on the *si* face of the hydrogen-bound α-ketophosphonate gives the expected *R*-enantiomer.

Table 2. Enantioselective synthesis of β-formyl-α-hydroxyphosphonates.[a]



9 10 11

Entry	R^1	R^2	R^3	*t* [d]	Product/ Yield [%][b]	*ee* [%][c]
1	H	Ph	Me	8	**11b**/67	96
2	H	Ph	Et	7	**11a**/75	93
3	H	Ph	*i*-Pr	5	**11c**/67	96
4	H	4-FC_6H_4	Et	7	**11d**/61	99
5	H	4-ClC_6H_4	Et	7	**11e**/62	94
6	H	4-BrC_6H_4	Et	7	**11f**/55	>99
7	H	4-IC_6H_4	Et	7	**11g**/54	95[d]
8	H	4-MeC_6H_4	Et	6	**11h**/67	96
9	H	4-$MeOC_6H_4$	Et	7	**11i**/66	92[d]
10	H	2-ClC_6H_4	Et	5	**11j**/35	96
11	H	3-ClC_6H_4	Et	7	**11k**/67	93[d]
12	H	3-ClC_6H_4	Me	7	**11l**/60	97
13	Me	Ph	Et	9	**11m**/44	68[e,f]

[a] All reactions were carried out with α-ketophosphonate **10** (0.30 mmol) and aldehyde **9** (1.50 mmol) in dry toluene (2.0 mL) with catalyst **8** (0.03 mmol, 10 mol%) and 4-methoxybenzoic acid (0.09 mmol, 30 mol%) at 0 °C.

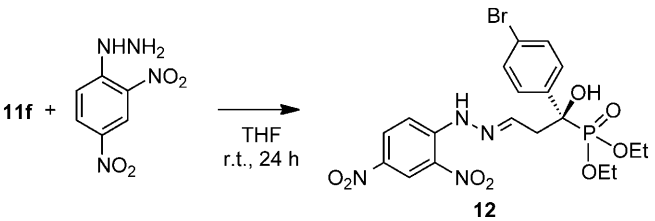
[b] Yield of isolated product after column chromatography.

[c] Unless otherwise specified, *ee* values were determined by chiral HPLC analyses on a ChiralCel OJ-H column.

[d] Determined by chiral HPLC analyses on a ChiralPak AD-H column.

[e] Value of the major diastereomer. The *ee* value of the minor enantiomer was 73%.

[f] The *dr* was 7:5 (^{1}H NMR analysis of the crude product); the Me and OH groups have the *anti* configuration in the major diastereomer as determined by NOE experiments.



12

Figure 3. Synthesis of 2,4-dinitrophenylhydrazone derivative **12**.

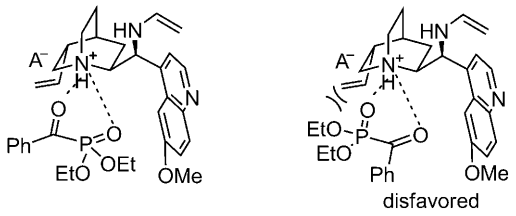


Figure 4. Proposed transition states for the formation of the major enantiomer (A^- = 4-methoxybenzoate).

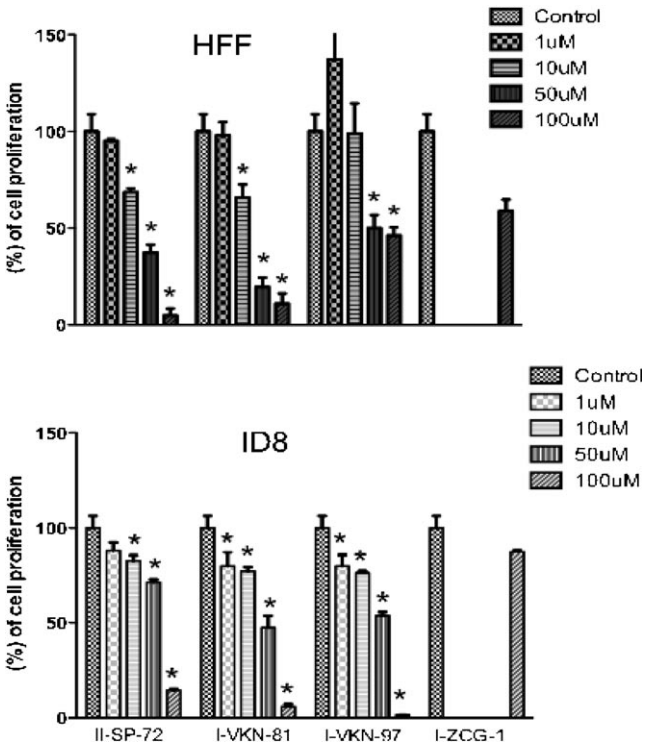


Figure 5. Inhibitory effect of the screened compounds on cell proliferation. [The results are expressed as percentage of the control (DMSO controls set at 100%). Data are given as means ± SEM, * $p < 0.05$ (Student's t-test)][15] (II-SP-72 is compound **11h**; I-VKN-81 is compound **11a**; I-VKN-97 is compound **11f**).

It is well known that α-hydroxyphosphonate derivatives are biologically active molecules. However, the biological activities of β-formyl-α-hydroxyphosphonates are still unknown. To assess their biological activities, we conducted some preliminary biological assays of these compounds. Thus, human immortalized foreskin fibroblasts (HFF) and ovarian cancer cells (ID8) were first incubated for 24 h, then the screened compounds were added in the indicated amounts and the cells were further incubated for another 48 h. Cell proliferation was assessed by the MTT assay as described previously and the results are presented in Figure 5.[15]

As shown in Figure 5, β-formyl-α-hydroxyphosphonate derivatives, II-SP-72 (**11h**), I-VKN-81 (**11a**) and I-VKN-97 (**11f**), significantly inhibited the proliferation of immortalized cell line HFF and ovarian cancer cell line ID8 in a dose-dependent manner (from 1 to 100 μM). In contrast, a similar α-hydroxyphosphonate derivative that does not contain an aldehyde group, I-ZCG-1 (Figure 6), displays only minor antiproliferative activity at a high concentration (100 μM). Interestingly, I-VKN-97 preferentially inhibited ID8 cancer cells rather than HFF immortalized cells. Moreover, antiproliferative effects of II-SP-72, I-VKN-81 and I-VKN-97 on other human (SKOV3 and K562) and murine tumour cells (B16F10) were also observed (data not shown).

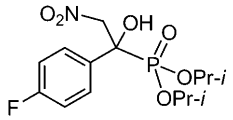


Figure 6. Structure of I-ZCG-1.

In summary, we have developed the first cross-aldol reaction of enolizable aldehydes and α-ketophosphonates for the highly enantioselective synthesis of tertiary β-formyl-α-hydroxyphosphonates. The reaction utilizes a quinine-derived primary amine as the catalyst, and excellent enantioselectivities were achieved for the cross-aldol products of acetaldehyde, which is unprecedented for such primary amine catalysts. A preliminary screen of some of the β-formyl-α-hydroxyphosphonate products indicates the products can suppress the proliferation of human and murine tumour cells, while are mild against immortalized cells (HFF).

Experimental Section

Typical Procedure for the Aldol Reaction

To a stirred solution of *p*-methoxybenzoic acid (13.7 mg, 0.09 mmol, 30 mol%) and quinine-derived amine **8** (9.7 mg, 0.03 mmol, 10 mol%) in toluene (2.0 mL) were added the α-ketophosphonate (0.30 mmol) and the aldehyde (1.5 mmol) at 0 °C. After completion of the reaction (monitored by TLC), the reaction mixture was concentrated under reduced pressure to yield the crude product, which was purified by column chromatography over silica gel (7:3 ethyl acetate/hexane) to furnish the desired β-formyl-α-hydroxyphosphonate as a pure compound.

Acknowledgements

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