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Organocatalytic Enantioselective Synthesis of Both Diastereomers of α -Hydroxyphosphinates

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Abstract

Racemic α -acylphosphinates and formylphosphate hydrate were used directly as the substrates in a proline derivative-catalyzed cross aldol reaction with ketones. Because of the preexisting the phosphorus stereogenic center, a mixture of two diastereomers of the corresponding α -hydroxyphosphinates were obtained in this reaction. Good to high enantioselectivities (up to 99% ee) were obtained simultaneously for both of these two diastereomers in good yields. Good diastereoselectivities were also obtained when the reaction generates an additional carbon stereogenic center.

Introduction

α -Hydroxyphosphinic acid derivatives, such as α -hydroxyphosphinates, have been shown to be very important enzyme inhibitors.¹ For example, α -hydroxyphosphinate-derived peptides have been used as the inhibitors of human immunodeficiency virus (HIV) protease² and renin.³ Also these compounds have found use as GABA antagonists⁴ or herbicides.^{5,6} With the exception of phosphinic acids, the phosphoryl group in other phosphinic acid derivatives, such as phosphinates, generally are chiral because the pentavalent phosphorus atom has a tetrahedral structure. Recent study⁶ also revealed that phosphinate enantiomers due to such phosphorus chirality may have totally different biological activities: One enantiomer was found significantly more herbicidal than the other enantiomer or the racemic mixture.⁶ This finding evinces the importance of the phosphorus chirality in the biological activity of the phosphinate compounds. Thus, developing an asymmetric synthesis for α -hydroxyphosphinates that can fix both the stereochemistry of the α -hydroxy-substituted carbon and the phosphorus stereogenic centers during the synthesis is very important. Such a method is expected to have the potential of lowering production costs and use rates, reducing the side effects, and lessening the environmental burden during the manufacture and application of these materials.

Besides the enzymatic resolution of racemic α -hydroxyphosphinates⁷ and the synthesis starting with optically active α -hydroxyphosphonates⁸ or α -hydroxy-*H*-phosphinates,⁷ only a handful of chemical methods are available for the synthesis of optically active α -hydroxyphosphinates.⁸ Shibuya and coworkers have reported a synthesis via the diastereoselective reaction of chiral aldehydes and achiral phosphites (a phosphoaldol reaction).^{9a} Alternatively, the phosphoaldol reaction may be carried out with achiral aldehydes and chiral phosphites.^{9b} An enantioselective

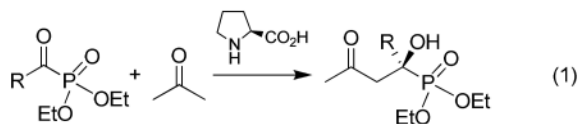
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Supporting Information **Available**. Full citation of references 4a and 4b, HPLC conditions, characterization data and NMR spectra for all new compounds, HPLC analysis spectra, and CIF data for compound *ent-7d*. This material is available free of charge via Internet at <http://pubs.acs.org>.

method based on the phosphoaldol reaction was as also reported;^{8c} however, due to the intrinsic chirality of the phosphinate group, this method actually generates a mixture of diastereomers, which has not been analyzed for its ee values.^{9c} While the above chemical methods produce useful degrees of stereocontrol at the hydroxy-substituted α -carbon center, none of them has addressed the stereochemistry of the phosphinate group. Simultaneously fixing the stereochemistry of both the α -carbon and phosphorus stereogenic centers during the synthesis of α -hydroxyphosphonates is still a great challenge for organic chemists.

Recently we reported the first organocatalytic cross aldol reaction¹⁰ of α -ketophosphonates and ketones for the synthesis of α -hydroxyphosphonates (Eq 1).^{11a,b} In principle, this reaction may be used for the preparation of α -hydroxyphosphinates, since the structure of α -ketophosphinates and α -ketophosphonates are very similar. Nonetheless, unlike α -ketophosphonates, α -ketophosphinates are chiral due to the chirality of the phosphorus atom. To use a racemic starting material (**A**) in a catalytic enantioselective synthesis (Scheme 1) to get both diastereomeric products (**B** and **C**) in high ee values is highly challenging because 1) the preexisting stereogenic center in substrate **A** may interfere with the enantiofacial selectivity of the catalyst so that matched reactants generate diastereomers with higher enantiomeric excesses.¹² 2) the preexisting stereogenic center in substrate **A** may affect the reaction rates of the individual enantiomeric substrates and lead to a kinetic resolution.¹³ If the reaction rates k_+ and k_- is equal, a kinetic resolution is avoidable, and the reaction may be carried out with 100% conversion of the racemic substrate, which is the major advantage of this approach as compared with the normal kinetic resolution where the maximum conversion of the substrate is only 50%. Because it is difficult to meet both requirements at the same time, it is not surprising that only a few of such chemical reactions are known in the literature.¹⁴ Gotor and coworkers have classified this type of reactions into the stereodivergent parallel kinetic resolution.¹⁵ Nevertheless, it should be pointed out that this type of reactions does not always fulfill one of the guidelines laid down for parallel kinetic resolution by Eames:¹⁶ the reactions must afford distinct and *easily separable* products. While the diastereomers obtained in this type of reactions are distinct, they are not always easy to separate, as with our α -hydroxyphosphinate products (see below).



It is our contention that the enantiofacial selectivity of the aldol reaction of α -ketophosphonates is mainly determined by the size difference between the phosphonate and the alkyl group of the α -ketophosphonate,^{11b} while the actual stereochemistry of the phosphorus atom should have minimum influence on the enantiofacial selectivity (Scheme 2). Furthermore, the phosphonate group is pointing away from the reaction center in the favored transition state¹¹ and, therefore, its stereochemistry should not have a major influence on the reaction rate. Thus, we hypothesized that such a cross aldol reaction may be used for the high enantioselective synthesis of both diastereomers of the α -hydroxyphosphinates from racemic α -ketophosphinates. Herein, we wish to report a catalytic and highly enantioselective synthesis of both diastereomers of α -hydroxyphosphinates with simultaneous fixing of both the hydroxy-substituted α -carbon and the phosphorus stereogenic centers in the products through a proline derivative-catalyzed cross aldol reaction of racemic acylphosphinates and ketones.

Results and Discussion

Ethyl benzoylphenylphosphinate (**5a**) and acetone (**6a**) were used as the model compounds to study the reaction conditions. We screened several readily available proline-derivatives as the

catalyst (Figure 1). The results are summarized in Table 1. The cross aldol reaction went smoothly at room temperature with all these catalysts and excellent yields of the aldol product were obtained. Although L-prolinamide (**1**), (S)-N-tosylprolinamide (**2**), and L-proline tetrazole (**3**) are very reactive catalysts, only moderate enantioselectivities were obtained for the two diastereomeric products **7a** and **8a** (entries 1-3). Nevertheless, the results of L-proline (**4**) were promising: Using a 20 mol % loading of **4** and acetone as the solvent at room temperature, **7a** and **8a** were obtained in a total yield of 89% in a ratio of 53:47. The ee values of these two diastereomeric products were determined to be 95% and 74%, respectively (entry 4). Other solvents, such as THF, CH₂Cl₂, DMF, DMSO, and an ionic liquid, proved to be inferior to acetone (entries 5-9). To our pleasure, by lowering the reaction temperature to -30 °C, the enantioselectivities of these two products were further improved to 99% and 91% ee, respectively, although the reaction was slower at this temperature and the total yield was lower (entry 10). It should be pointed out that, under all these conditions, diastereomeric products **7a** and **8a** were obtained in a ratio of roughly 50:50 with different degree of conversions of the substrate (from around 60% to over 90%), which hints that the reaction rates of both enantiomeric substrates of **5a** are almost equal.

The scope of this reaction was then evaluated, and the results are collected in Table 2. It was found that, besides ethyl benzoylphenylphosphinate (entry 1), substituted benzoylphosphinates were also good substrates for this reaction. For example, 98% and 91% ee were obtained for the two diastereomeric products of 4-fluorobenzoylphosphinate (**5b**) in 67% total yield under the optimized reaction conditions (entry 2). Also good ee values (98% and 80% ee, respectively) were obtained for the product of 3-fluorobenzoylphosphinate (**5c**, entry 3). Similarly, 4-bromo- (**5d**), 4-chloro- (**5e**) and 3-chloro- (**5f**) substituted derivatives also produce excellent results (entries 4-6). Substrates substituted with electron-donating groups (i.e., Me, OMe, **5g** and **5h**) react more slowly, but the enantioselectivities obtained for the products are very good (entries 7-8). A heteroarene-substituted (thiophen-2-yl) α -ketophosphinate (**5i**) also leads to good enantioselectivity for one of the diastereomer (84% ee), whereas the enantioselectivity for the other diastereomer is slightly lower (62% ee, entry 9). Alkyl-substituted α -ketophosphinates react in a similar manner. For example, ethyl acetylphenylphosphinate (**5j**) gives 95% and 87% ee of the two diastereomeric products, respectively (entry 10). Similar results were also obtained for ethyl phenylpropionylphosphinate (**5k**, entry 11). From the results in Table 2, it is evident that the stereochemistry of the phosphinate group does have some influence on the enantioselectivity of this reaction: The ee value of one of the two diastereomers is always slightly higher than the other. Nevertheless, the reactivity of the two enantiomers of the racemic starting acylphosphinates are almost the same since the ratio of the two diastereomeric products **7** and **8** maintained around 50:50 in all cases.

Methyl α -ketophosphinates also participate in this reaction. However, determining the enantiomeric excess values of the products is highly challenging, as the enantiomers cannot be separated by the columns we have (data not shown).

To determine the absolute configuration of the major enantiomers formed in this reaction, the two diastereomeric products **7** and **8** have to be separated. While compounds **7** and **8** obtained in this reaction cannot be separated by column chromatography, we did achieve separation through recrystallization in a few cases, and suitable crystals for the X-ray crystallographic analysis were obtained for the enantiomer of products **7d** (*ent-7d*) with D-proline as the catalyst. As shown in Scheme 3, ethyl (4-bromobenzoyl)phenylphosphinate (**5d**) was allowed to react with acetone using D-proline as the catalyst under the optimized conditions identified for L-proline. The diastereomeric mixture of *ent-7d* and *ent-8d* obtained this way was separated by careful recrystallization from a mixture solvent of EtOAc and hexane (The diastereomeric products were dissolved in a minimum amount of EtOAc and then diluted with hexane. The

solution was kept at an open system in such a way that the solvents evaporated very slowly. After 24 h at rt, about 70% of compound *ent-7d* crystallized out.). The crystalline compound obtained was identified to be *ent-7d*, whereas the mother liquor contains mainly the remaining *ent-8d*. The absolute configuration of *ent-7d* was determined to be *S* for both the α -carbon and the phosphorus stereogenic centers (S_C, S_P) by X-ray crystallography.¹⁷ To determine the absolute configuration of the other diastereomers, separate HPLC analyses of the racemic product, the product obtained from L-proline (Table 2, entry 1) and D-proline (Scheme 3), and pure *ent-7d* were undertaken.¹⁸ From the results of the racemic sample, it is clear that the stereoisomers with retention times of 48.1 min and 113.8 min are a pair of enantiomers, and those with retention times 27.2 min and 117.1 min of are the other pair of enantiomers (please see page S-61 of the Supporting Information¹⁸). Pure *ent-7d*, which has been determined to be $S_C S_P$ by X-ray crystallography, shows a retention time of 48.1 min (page S-62). Thus, the stereoisomer with the retention time of 113.8 min should have the stereochemistry of $R_C R_P$ since it is the enantiomer of *ent-7d* (that is, it is **7d**). With these results at hand, it is relatively easy to determine the stereochemistry of the other two enantiomers by using the HPLC analysis of the compounds **7d/8d** obtained in Table 2, entry 1. In this HPLC spectrum (page S-64), one major peak is at 111.2 min, which was assigned to $R_C R_P$ as described above. The other major peak is at 115.1 min, which must be $R_C S_P$, because most of the *R*-configured phosphinate group has been already fixed in compound **7d** (retention time 111.2 min). Thus, the peak at 27.2 min must be $S_C R_P$. On the basis of the above analysis, compound **8d** should have a stereochemistry of R_C, S_P (retention time 117.1 min in S-60), which is also consistent with the reaction mechanism.

On the basis of the aforementioned results, a mechanism is proposed to account for the enantioselectivity outcome (Scheme 4). Just as we expected, it does not matter whether the stereochemistry of the phosphorus atom in acylphosphinate **5a** is *R* (TS-I and II) or *S* (TS-III and IV), the attack of the enamine onto the *si*-face of this substrate is always favored (TS-I and TS-III in Scheme 4), because the unfavorable steric interactions between the large axial phosphinate group and the axial enamine methyl group (see TS-II and TS-IV) are avoided in these two transition states. These favored transition states lead to the formation of $R_C R_P$ -**7a** and $R_C S_P$ -**8a** diastereomers as the major products, as observed in the experiment. These results are also in accord with those of the aldol reaction of acylphosphonate derivatives catalyzed by similar catalysts (Scheme 2).¹¹

Next the aldol reaction of the hydrate of ethyl formylphosphinate (**9**) was studied. This reaction is expected to generate secondary α -hydroxyphosphinates, which are closer analogues of proteinogenic α -amino acids. The results of this reaction are summarized in Table 3. When acetone was used as the substrate at room temperature, L-proline (**4**) failed to generate any desired product (entry 1), probably because compound **9** is not compatible with the acidity of **4**. These results are not surprising, since previously we obtained similar results with formylphosphonate hydrate.^{11b} When less acidic L-prolinamide (**1**) was used as the catalyst under the above conditions (entry 2), the desired product was obtained in 89% yield with ee values of 90% and 79% for $S_C R_P$ (**10a**) and $S_C S_P$ (**11a**) products, respectively, in a ratio of 50:50. (The absolute configuration of products was assigned on the basis of the proposed mechanism in Scheme 4). When the reaction was carried out at 0 °C, the ee values of these two products were further improved to 93% and 87%, respectively (entry 3). Cyclopentanone may also be used in this reaction (entry 4). Although this reaction potentially can generate 8 diastereomers, it was found that only the *syn* diastereomers (referring to the newly formed carbon stereogenic centers)¹⁹ was formed during the reaction (>99:1 dr), and the ee value of the two diastereomers *syn-10b* (configuration: S_C, S_C, R_P) and *syn-11b* (configuration: S_C, S_C, S_P) obtained at room temperature are 97% and 62%, respectively. When the reaction was carried out at 0 °C, the ee value of *syn-11b* was further improved to 87% (entry 5). Cyclohexanone and 4-oxocyclohexanone are also suitable substrates for this reaction;

nevertheless, the reactions are less diastereoselective (entries 6 and 7). For cyclohexanone an *anti/syn* ratio of 65:35 were obtained, and the four diastereomers **10c** and **11c** were obtained in 98%, 95%, 89%, and 93% ee, respectively (entry 6). Similarly, 4-oxacyclohexanone yielded an *anti/syn* ratio of 60:40, and the ee values for the four diastereomers **10d** and **11d** are 99%, 94%, 26%, and 99% ee, respectively (entry 7). The low diastereoselectivities observed for six-membered cyclic ketones versus cyclopentanone are in-line with our previous report on cross-aldol reaction of the α -formylphosphonate hydrate derivative^{11b} and are probably due to steric reasons, although the exact reason is not clear at this moment. Since these products are inseparable liquid compounds by column chromatography, it is impossible to assign the ee values to the corresponding structures without ambiguity. Nevertheless, it is clear from Table 3 that the ratio of 50:50 were achieved in each entry for compound containing R_P and S_P stereogenic centers, which indicates that both enantiomers of the racemic substrate **9** react efficiently under the reaction conditions.

Conclusions

In summary, a novel method for the highly enantioselective synthesis of the biologically significant α -hydroxyphosphinates was developed on the basis of a proline derivative-catalyzed asymmetric aldol reaction of ketones and α -ketophosphinates or α -formylphosphinate hydrate. Both the newly formed carbon stereogenic centers and the phosphorus stereogenic center were fixed during the aldol reaction.

Experimental Section

General experimental procedure for the synthesis of tertiary α -hydroxyphosphinate via aldol reaction of racemic α -ketophosphinate

To a stirred solution of the α -ketophosphinate (0.5 mmol) and dry acetone (2.0 mL) was added L-proline (0.10 mmol, 20 mol %) at -30 °C. The reaction mixture was stirred at this temperature for the time as specified in Table 1 (monitored by TLC) and then quenched by few drops of water. The mixture was extracted with ethyl acetate (3 \times 10 mL), and the combined extracts were washed with brine solution (2 mL), dried over MgSO₄, and then evaporated to give the crude product, which was purified by column chromatography over silica gel (4:1 ethyl acetate/hexane) to furnish the desired α -hydroxyphosphinate as a pure compound (a mixture of two inseparable diastereomers).

Ethyl (1-hydroxy-3-oxo-1-phenylbutyl)(phenyl)phosphinate (**7a/8a**)

white solid, mp 91-92 °C; ¹H NMR (500 MHz, CDCl₃) δ (mixture of two diastereomers) 1.13 and 1.36 (t, J = 7.0 Hz, 3 H), 2.05 and 2.17 (s, 3 H), 3.05 and 3.08 (d, J = 8.0 Hz, 0.5 H), 3.75-4.15 (m, 2 H), 4.88 and 5.06 (br s, 1 H), 7.15-7.66 (m, 10 H); ¹³C NMR (125 MHz, CDCl₃) δ (mixture of two diastereomers) 16.6 (q), 32.5 (q), 46.7 (q), 62.2 (q), 76.2 and 76.4 (d), 126.2 and 126.6 (d), 126.8 (q), 127.6 and 127.8 (d), 127.9 and 128.0 (d), 128.1 (q), 132.6 and 132.7 (d), 133.4 and 133.7 (d), 139.2 (q), 210.1 (q); ³¹P NMR (CDCl₃) δ (mixture of two diastereomers) 36.3, 37.4; ν_{\max} (neat, cm⁻¹): 3212, 1710, 1598, 1510, 1475, 1439, 1411; Anal. Calcd. for C₁₈H₂₁O₄P: C, 65.05; H, 6.37; Found: C, 64.75; H, 6.45.

General procedure for the synthesis of secondary α -hydroxyphosphinate via aldol reaction of racemic α -formylphosphinate hydrate

To a stirred solution of the formylphosphinate hydrate (108 mg, 0.5 mmol) in the ketone (0.5 mL) in dry CH₂Cl₂ at 0 °C was added L-prolinamide (2.9 mg, 0.025 mmol, 5 mol %). The reaction mixture was stirred at this temperature for 24-32 h (depending on the substrate). The solvent was evaporated under vacuum and the residue was purified by flash chromatography

(EtOAc) over silica gel to furnish the desired secondary α -hydroxyphosphinate as a pure compound (a mixture of inseparable diastereomers).

Ethyl (1-hydroxy-3-oxobutyl)(phenyl)phosphinate (10a/11a)

Colorless oil; ^1H NMR (500 MHz, CDCl_3) δ (mixture of two diastereomers) 1.28 (2 t, $J = 7.0$ Hz, 3 H), 2.14 (s, 3H), 2.68–2.84 (m, 2 H), 3.91–3.99 (m, 1 H), 4.07–4.14 (m, 1 H), 4.47–4.58 (m, 1 H); ^{13}C NMR (125 MHz, CDCl_3) δ (mixture of two diastereomers) 16.7(q), 30.9 (d), 44.1 (q), 61.9 (q), 65.8 and 66.5 (d, $J_{\text{CP}} = 121.6$ and 120.1 Hz), 127.4 and 128.4 (d, $J_{\text{CP}} = 25.8$ and 25.3 Hz), 128.8 (q), 132.8 (q), 133.0 (d), 207.2 (q); ^{31}P NMR (CDCl_3) δ (mixture of two diastereomers) 39.6, 40.1; ν_{max} (neat, cm^{-1}): 3251, 1715, 1592, 1479, 1439, 1394 1362; Anal. Calcd. for $\text{C}_{12}\text{H}_{17}\text{O}_4\text{P}$: C, 56.25; H, 6.69; Found: C, 56.11; H, 6.88.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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 17. For the ORTEP drawing of compound *ent-7d*, please see the Supporting Information.
 18. For details, please see the Supporting Information.
 19. The *syn/anti* stereochemistry was determined by the NOE experiments on the products *syn-10b/syn-11b* and *anti-10c/anti-11c* (for details, please see Pages S-59 and S-60 of the Supporting Information). The results are also in-line with those of the corresponding α -hydroxyphosphonates (please see reference 11b).

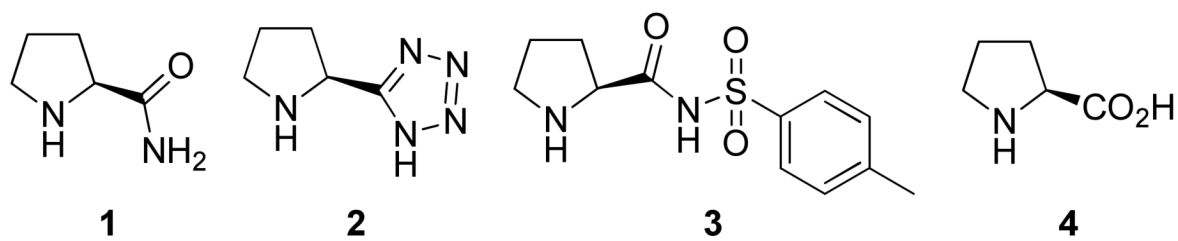
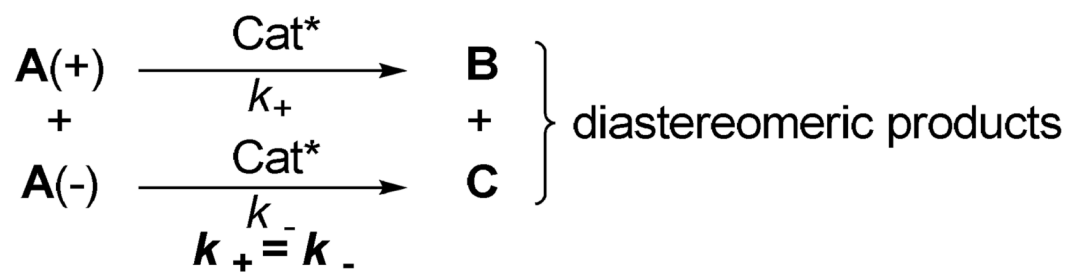
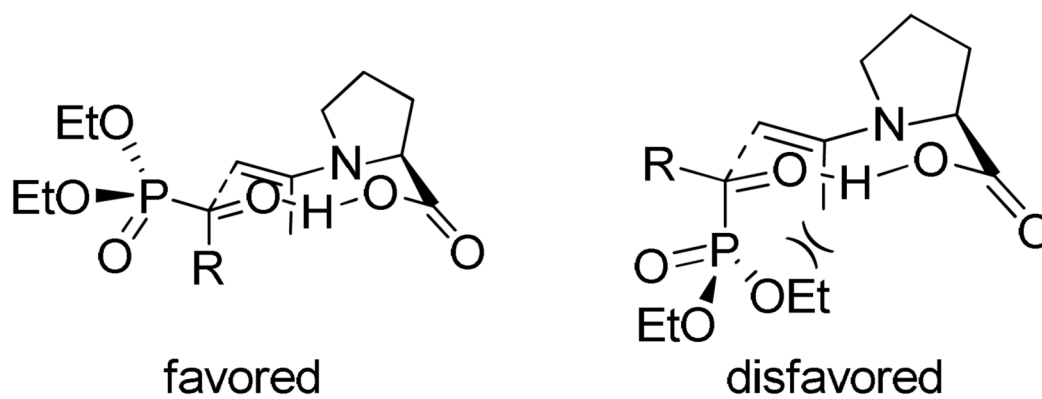


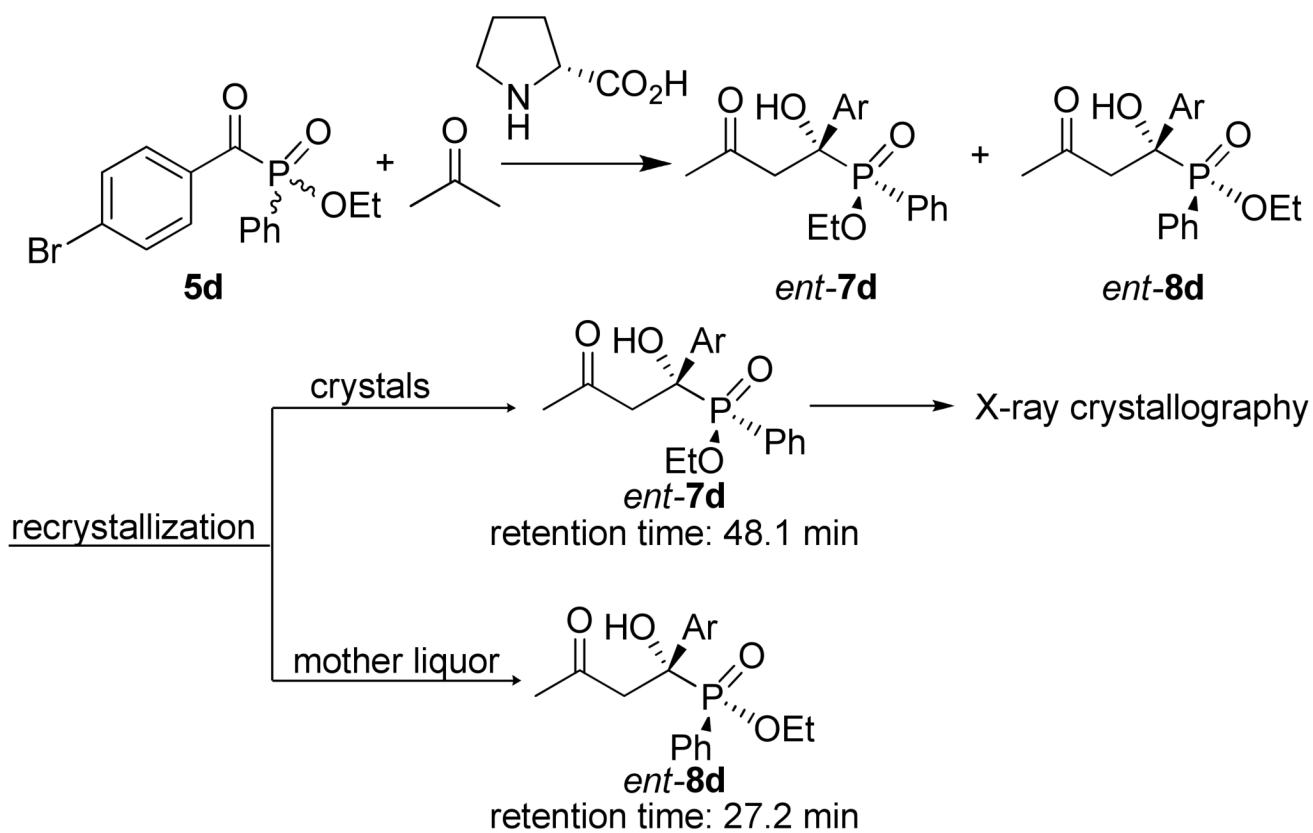
Figure 1.
Catalysts Screened for the Cross Aldol Reaction

**Scheme 1.**

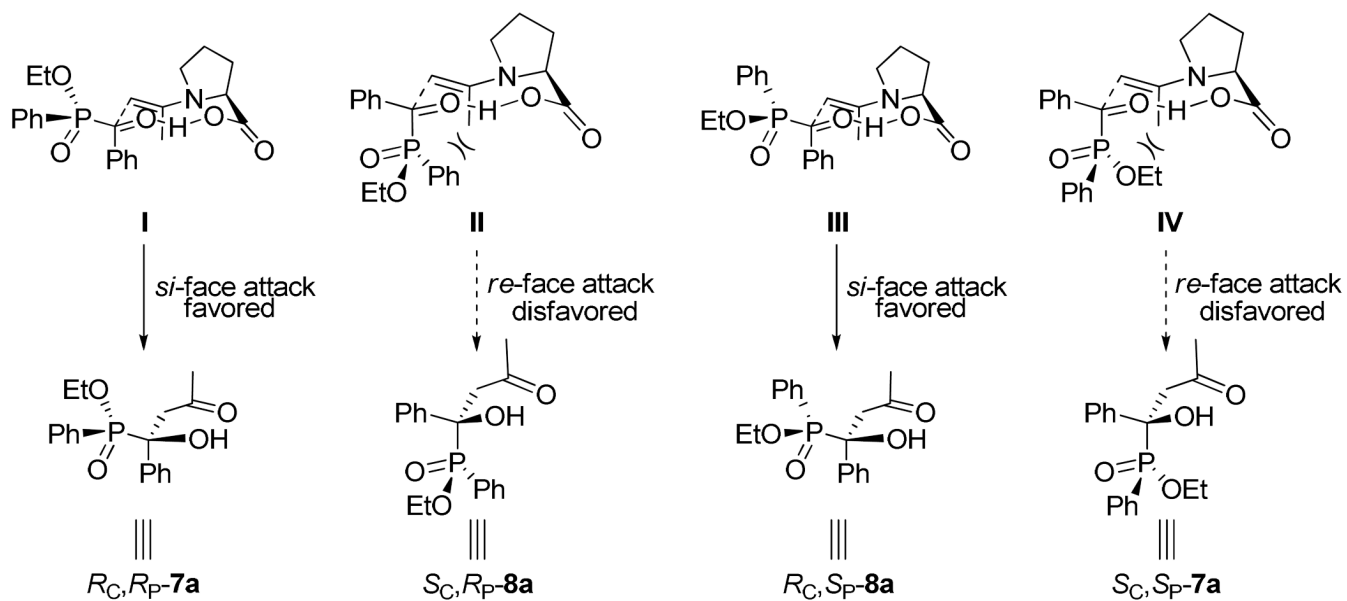
Catalytic Enantioselective Reaction with a Racemic Substrate



Scheme 2.
Proposed Transition States for the Cross Aldol Reaction of α -Ketophosphonates



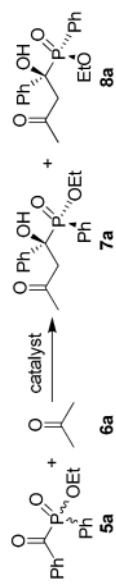
Scheme 3.
Determination of the Absolute Configuration of the Reaction Products



Scheme 4.
Proposed Mechanism for the Cross Aldol Reaction of Acylphosphinates

Table 1

Cross aldol reaction of ethyl (benzoylphenyl)phosphinate (**5a**) and acetone (**6a**) catalyzed by L-proline derivatives^a



entry	catalyst	loading ^b	solvent	yield (%) ^c	ee (%) ^d	7a	8a	7a/8a ^e
1 ^f	1	10	acetone	93		72	47	55:45
2 ^f	2	10	acetone	63		45	28	58:42
3 ^f	3	10	acetone	83		82	62	54:46
4 ^f	4	20	acetone	89		95	74	53:47
5	4	20	THF	90		95	67	52:48
6	4	20	CH ₂ Cl ₂	79		94	65	50:50
7	4	20	DMSO	81		52	32	48:52
8	4	20	DMF	81		69	39	58:42
9 ^g	4	20	acetone	87		91	59	59:41
10 ^{f/h}	4	20	acetone	58		99	91	52:48

^aUnless otherwise indicated, all reactions were carried out with the ketophosphinate **5a** (0.50 mmol), acetone (0.5 mL), and the catalyst in the specified solvent (1.0 mL) at rt for 24 h.

^bmol %.

^cTotal yield of the inseparable diastereomers (**7a** and **8a**) isolated after column chromatography.

^dDetermined by HPLC analyses.

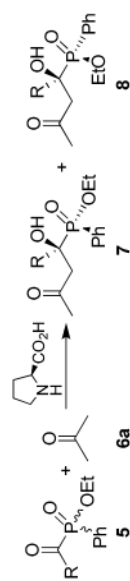
^eThe ratio of **7a**/**8a**; determined by ¹H NMR analyses.

^f2.0 mL of acetone was used.

^gIonic liquid 1-butyl-3-methylimidazolium tetrafluoroborate (300 mg) was added.

^hCarried out at -30 °C for 96 h.

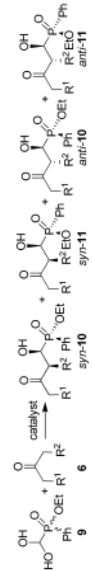
Table 2

L-Proline-Catalyzed Aldol Reaction of Racemic α -Ketophosphinates and Acetone^a

entry	R	T (°C)	time (h)	yield (%) ^b	ee (%) ^c		dr ^d
					7	8	
1	Ph(a)	-30	96	58	99	91	52:48
2	4-F-C ₆ H ₄ (b)	-30	120	67	98	91	50:50
3	3-FC ₆ H ₄ (c)	0	36	89	96	80	52:48
4	4-BrC ₆ H ₄ (d)	-30	120	70	97	87	54:46
5	4-ClC ₆ H ₄ (e)	-30	120	65	94	73	52:48
6	3-ClC ₆ H ₄ (f)	0	36	92	99	89	53:47
7	4-MeC ₆ H ₄ (g)	-30	120	45	90	80	54:46
8	4-MeOC ₆ H ₄ (h)	rt	40	87	93	71	56:44

^dThe ratio of 7:8 or vice versa; determined by ¹H NMR analyses.

Table 3

Aldol Reaction of Racemic Formylphosphinate Hydrate and Ketones^a


entry	R ¹	R ²	catalyst	10 and 11	time (h)	yield (%) ^b	10/11 ^c	syn/anti ^d	syn-10	syn-11	anti-10	anti-11
1 ^f	H	H	4	a	24	0	---	---	---	---	---	---
2 ^f	H	H	1	a	1.5	89	50:50	---	90 ^g	79 ^g	---	---
3	H	H	1	a	7	91	50:50	---	93 ^g	87 ^g	---	---
4 ^f	-(CH ₂) ₂ -		1	b	24	79	50:50	>99:1	97	62	---	---
5	-(CH ₂) ₂ -		1	b	30	83	50:50	99:1	96	87	---	---
6	-(CH ₂) ₃ -		1	c	32	88	50:50	35:65	98 ^h	95 ^h	89 ^h	93 ^h
7	-(CH ₂ OCH ₂)-		1	d	30	91	50:50	40:60	99 ^h	94 ^h	26 ^h	99 ^h

^aUnless otherwise indicated, all reactions were carried out with the racemic formylphosphinate hydrate (0.50 mmol) in dry ketone (0.5 mL) with the catalyst (0.10 mmol, 5 mol %) for the specified reaction time at 0 °C.

^bTotal yield of the inseparable diastereomers (**10** and **11**) isolated after column chromatography.

^cDetermined by ¹H NMR analyses; the value refers to the ratio of the products containing *RP* and *SP* stereochemistry.

^dDetermined by ¹H NMR analyses, *syn* and *anti* refer to the stereochemistry of the two newly generated carbon stereogenic centers.

^eEnantioselectivity was determined by HPLC analyses.

^fThe reaction was carried out at room temperature.

^gThis compound does not have *syn* or *anti* stereochemistry.

^hThe assignments of the ee values to the structures are arbitrary in these cases. Due to partial overlaps of some of the peaks, the error limit of the ee values is considerably larger than normal.