Aminophosphonates as organocatalysts in the direct asymmetric aldol reaction: towards *syn* selectivity in the presence of Lewis bases

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Chiral α-aminophosphonates have been synthesized and their performance was evaluated as organocatalysts in the direct asymmetric aldol reaction. High enantioselectivities (up to 99% ee) were achieved for a range of substituted cyclohexanones and benzaldehydes. Several organic bases, such as DBU, DBN, and TMG, were used together with the α-aminophosphonates in the aldol reactions and were found to favor *syn*-selectivity.

α-Aminophosphonates and their derivatives are important compounds possessing diverse and useful biological activities.[1] α-Aminophosphonates are analogous to amino acids and have found applications ranging from medicine to agriculture, *e.g.* as antibiotics,[2] enzyme inhibitors,[3] anti-cancer agents,[4] and herbicides.[5] These biological properties are mostly associated with the tetrahedral structure of the phosphonyl group acting as a "transition-state analogue".[6] Cyclic α-aminophosphonates have found promising applications as surrogates of proline, increasing the need for their syntheses in enantiomerically pure form.[7] However, despite the similarities with proline, to our knowledge there is only one report of their use as a ligand for catalysis.[8]

Proline has recently re-emerged as a highly enantioselective catalyst for the direct asymmetric aldol reaction as one of the most powerful methods for the construction of complex chiral polyol architectures. Early developments for the intramolecular aldol cyclisations were independently reported by Hajos and Parrish[9] and by Wiechert and co-workers[10] in 1971, and paved the way for the development of the concept of small organic molecules as catalysts. Barbas, List and co-workers demonstrated that L-proline was a powerful catalyst in the asymmetric intermolecular direct aldol reaction.[11] However, a rather high catalyst loading (around 20 mol%) is usually required to effect the reaction in a reasonable timescale. Other proline-based compounds including diamines, small peptides, tetrazole and sulfonamides were found to catalyze the aldol reaction. Sulfonamides are modular catalysts, which allowed for an enantioselectivity of up to 98% ee while maintaining high activity at low catalyst loadings.[12]

Cyclic (2*S*)-pyrrolidin-2-ylphosphonic acid **1** shown below (Fig. 1) is an analog of D-proline, and could be readily prepared from diethyl (2*S*)-pyrrolidin-2-ylphosphonate **2**. It was thought that the replacement of the carboxyl group in proline by a phosphonate would result in a functional group of sufficient acidity to catalyze the aldol reaction.

Therefore, we found it interesting to computationally investigate the enantioselectivity of the aldol reaction between acetone and 4-nitrobenzaldehyde, using the α-aminophosphonate **1** as a catalyst at the B3LYP/6-31G(d) level of theory, in order to explore the potential of the α-aminophosphonates.

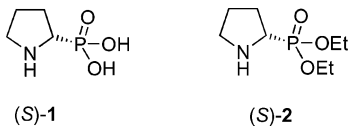
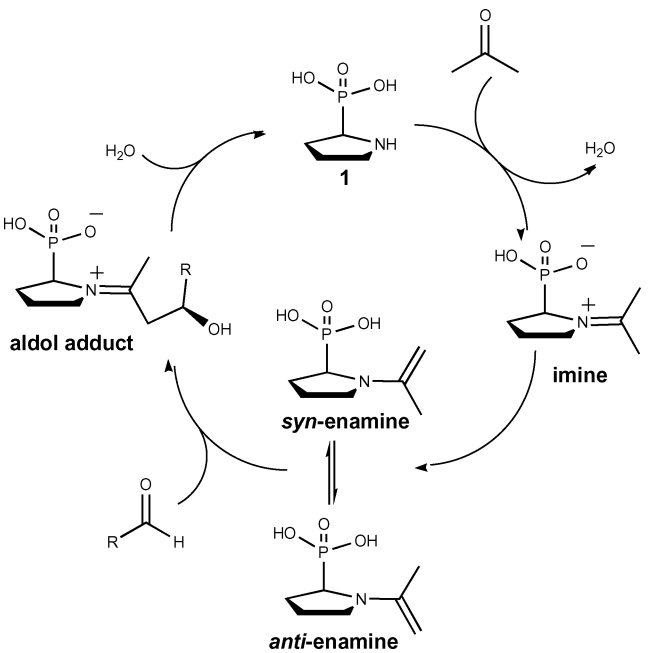


Fig. 1

We report herein that α-aminophosphonates catalyze the enantioselective aldol reaction between unmodified ketones and aldehydes to provide aldol adducts with up to 99% ee.

Computational investigation of enantioselectivity

Several computational investigations of the potential energy surface of the aldol reactions between L-proline and aldehydes have been performed and the reaction is suggested to go *via* the enamine mechanism.[13] Therefore, we have investigated possible activated complexes in the addition of 4-nitrobenzaldehyde to the *syn*- and *anti*-enamine of aminophosphonate **1** and acetone involving the enamine mechanism (Scheme 1).



Scheme 1

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Both the *syn*- and *anti*-enamine derived from aminophosphonate **1** and acetone have been calculated at the B3LYP/6-31G(d) level of theory and the difference in enthalpy was found to be only 0.3 kcal mol^{-1} in favor of the *anti*-enamine. This shows that the aldehyde possibly could react with both the *syn*- and *anti*-enamine of the aminophosphonate **1** and acetone. Initially, 4-nitrobenzaldehyde forms a complex with either the *syn*- or *anti*-enamine in which the phosphate hydroxyl group is hydrogen bonded to the carbonyl group in 4-nitrobenzaldehyde. These enamine-aldehyde complexes are 12.5 kcal mol^{-1} (*anti*) and 11.0 kcal mol^{-1} (*syn*) more stable than free enamine and 4-nitrobenzaldehyde.

In order to investigate the enantioselectivity of the catalyst, the activated complexes for the reaction between 4-nitrobenzaldehyde and the *syn*- and *anti*-enamine of aminophosphonate **1** and acetone were calculated. Different activated complexes leading to (*S*)- and (*R*)-aldol products have been considered. For example, different hydrogen bonding from the two acid functions to the carbonyl oxygen in the aldehyde with aminophosphonate **1** and different conformations around the forming C–C bond have been considered (Fig. 2).

In the transition states for the reaction between the enamine and aldehyde, the hydrogen of the hydroxyl group is simultaneously transferred to the carbonyl oxygen along with carbon–carbon bond formation. The calculations show that the activation enthalpy for the most stable transition state (**R-TSc**) for the addition of 4-nitrobenzaldehyde to the *anti*-enamine is 9.3 kcal mol^{-1} relative to the *anti*-enamine–4-nitrobenzaldehyde complex.

The major geometrical differences between the two most stable transitions states in the addition of 4-nitrobenzaldehyde to the *anti*-enamine, **R-TSc** and **S-TSc**, originates from the different orientation of the phenyl ring, which leads to a tilt in the aldehyde

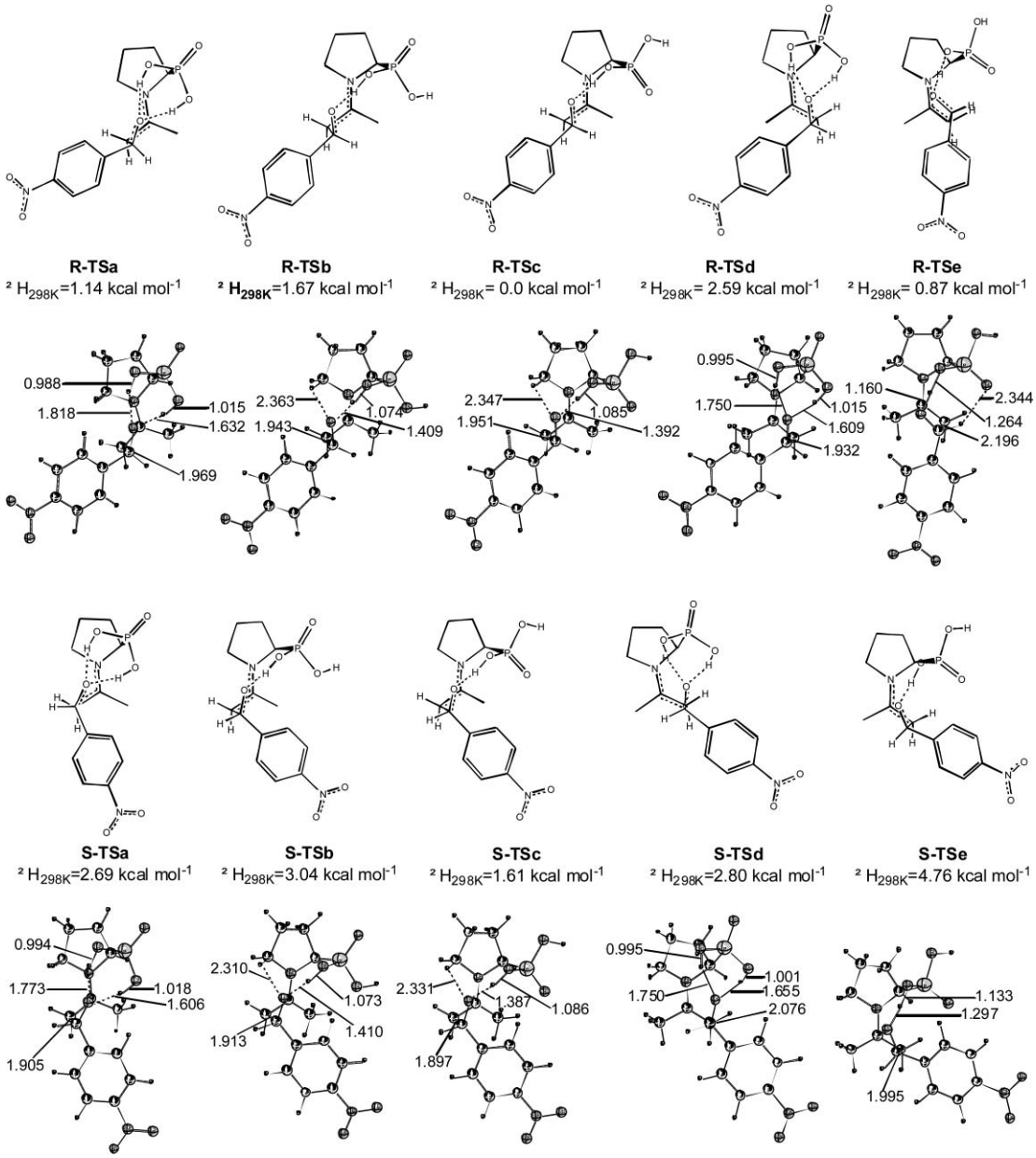


Fig. 2

in the **S-TSc** due to the interaction between the phenyl and the methyl group in the enamine part of the catalyst. The second difference is seen in the distance of the carbon–carbon bond formation. In all the calculated transition states leading to (*R*)-product, the C–C distances are longer than those found in the transition states leading to (*S*)-product (**R-TSc**: 1.95 Å, **S-TSc**: 1.90 Å). All the computed transition states for the addition of aldehyde to *anti*-enamine are arranged to form a six-membered chair-like ring similar to Zimmerman–Traxler.

At the B3LYP/6-31G(d) level of theory, the difference in enthalpy of activation between the two most stable activated complexes, **R-TSc** and **S-TSc**, is 1.64 kcal mol^{-1}, favoring the formation of (*R*)-products. Thus, the calculations predict (*R*)-aldol adduct in 88% ee for addition of aldehyde to the *anti*-enamine.

The transition states for the addition of 4-nitrobenzaldehyde to the *syn*-enamine are generally one to a few kcal mol^{-1} higher in energy than for the transition states for the addition to the *anti*-enamine. However, the most stable transition state for addition to the *syn*-enamine, **R-TSe**, is merely 0.87 kcal mol^{-1} higher in energy than **R-TSc**. This shows that both the *syn*- and *anti*-enamine could play a role in the aminophosphonate catalyzed aldol reaction. In **R-TSe**, the C–C distance of the forming C–C bond is significantly longer (2.19 Å) than in all other transition states. Another feature present in the **R-TSe** transition state is the short distance between the aldehyde proton and the non-hydroxy oxygen in the phosphonate group (2.344 Å), which could contribute to electrostatic stabilization of **R-TSe**. In contrast to the *anti*-enamine transition states, **R-TSe** can be viewed as a transition state with the conformation of a boat-like six-membered ring and cannot be rationalized to a chair-like transition state similar to Zimmerman–Traxler.

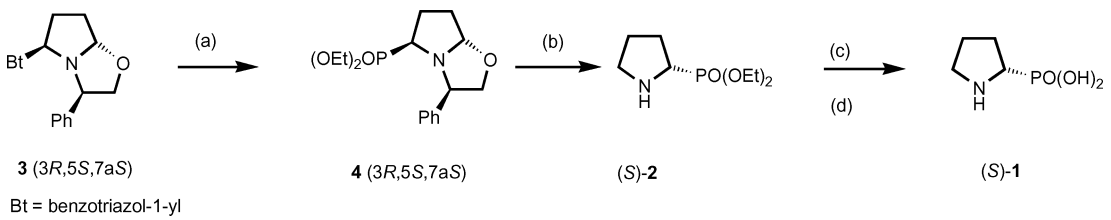
The enthalpy difference between the most stable activated complexes leading to (*R*)- and (*S*)-product, **R-TSe** and **S-TSd**, is 1.93 kcal mol^{-1}, favoring the (*R*)-product. Thus, the calculations predict (*R*)-aldol adduct in 97% ee for addition of aldehyde to the *syn*-enamine.

Most of the calculations of the transition states were performed as a predicted tool for the enantioselectivity for aminophosphonate **1**, and thus, the calculation of the transition states were performed by analogy to L-proline. However, the aminophosphonate **1** is the analogue of D-proline, and this explains the difference in stereochemistry between the calculated and synthesized aminophosphonate.

Evaluation of aminophosphonates

Aminophosphonate **2** was prepared according to the method described by Katritzky *et al*.[14] Starting from oxazolopyrrolidine **3** and subsequent Arbuzov reaction in the presence of the Lewis acid, $ZnBr_2$ (10 mol%), converted **3** into the desired oxazolopyrrolidine phosphonate **4** as single diastereoisomer. Aminophosphonic acid **1** was finally obtained in 88% yield, as a white powder, by cleavage of the ester functions in acidic medium (6 M HCl) followed by treatment with propylene oxide (Scheme 2).[15]

The efficiency of the novel aminophopshonates **1** and **2** as organocatalysts was evaluated in the direct aldol reaction of 4-nitrobenzaldehyde and acetone using DMSO as solvent. In the initial experiments, the catalyst was employed at 20 mol% with respect to the aldehyde and an excess of acetone 20 vol% (27 mol equiv.) (Scheme 3).[16] The results for different reaction conditions are summarized in Table 1.

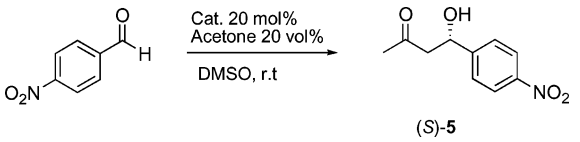


Scheme 2 *Reagents and conditions*: a) $P(OEt)_3$ (2 eq.), $ZnBr_2$ (0.3 eq.), CH_2Cl_2, 0 °C, overnight. b) H_2, Pd/C, HCl–EtOH, overnight. c) 6 M HCl, reflux 12 h. d) Propylene oxide EtOH, reflux, 3 h.

Table 1 Aminophosphonate-catalyzed aldol reaction of acetone and 4-nitrobenzaldehyde[a]

Entry	Cat.	Conditions	Time/h	Conv. (%)[b]	Ee (%)[c]
1	**1**	—	43	63	82
2	**1**	1% H_2O	24	21	76
3	**1**	1% PBS[d]	24	66	52
4	**1**	0.1% PBS[d]	19	40	62
5	**1**	20% DBU	(15 min)	83	44
6	**1**	0.2% DBU	2.5	30	52
7	**1**	5% DBU–Tol : IPA (9 : 1)	1	68	52
8	**2**[e]	—	24	69	82
9	**2**	1% H_2O[d]	24	35	72
10	**2**	0.1% PBS[d]	19	35	76

[a] Unless otherwise stated, all reactions were carried out using 0.1 M aldehyde and 20 mol% catalyst in 1 mL DMSO : acetone (4 : 1). [b] The yields were determined by ^1H NMR spectroscopy. [c] The ee was determined by chiral HPLC analysis using a Kromasil CHI-TBB. The major enantiomer was assigned to be (*S*) by comparison with literature. [d] Phosphate buffer at pH 7.1. [e] The reaction was performed using 5 mol% catalyst **2**.



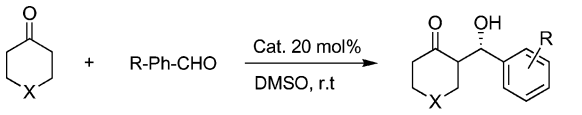
Scheme 3

Thus, aminophosphonic acid **1** catalyzed the asymmetric formation of aldol adduct (*S*)-**5** in 82% ee with good yield and practical reaction time. Catalyst **2** was found to be more reactive and typical catalyst loading of 5 mol% provided the aldol product in 69% yield with a 82% ee after 24 h (entry 8).

Recently, we and others have found that addition of water at low concentration (1–2 vol%) resulted in an increase of the reaction rates of the aldol reaction.[17] Water is thought to participate in a proton relay that could allow for enamine formation in organic solvents. We reported remarkable effects on enantioselectivity and reactivity under aqueous reaction conditions. However, addition of water (1 mol%) to catalyst **1** resulted in lower reactivity providing (*S*)-**5** in only 76% ee (entry 2). Furthermore, while there was an increase in reactivity in the presence of 1 vol% PBS in DMSO with aminophosphonic acid catalyst **1**, it had a deleterious effect on the enantioselectivity, which decreased from 82% to 52% ee. In addition, using 0.1 vol% PBS resulted in an improved ee of 62%, while keeping a high reactivity (entries 3, 4). The same trend in enantioselectivity could be observed with the aminophosphonate ester catalyst **2** under similar conditions as shown in entries 9 and 10.

Next we studied the influence of organic bases on the aldol reaction between acetone and 4-nitrobenzaldehyde and using exclusively catalyst **1** (20 mol%). We presumed that addition of organic base would facilitate enamine formation and thus accelerate the reaction. The organic base could also solvate the acidic proton in the Zimmerman–Traxler transition state. Differences in reaction rates became clearly visible: in the presence of 20 mol% DBU with respect to aldehyde in DMSO, the reaction was driven to 83% conversion after only 15 min. Even at 0.2 mol% DBU, the conversion was at 30% after 2.5 h (entries 5,6). Similarly, 5 mol% DBU in toluene: isopropanol (IPA) (9 : 1) resulted in 68% conversion after 1 h (entry 7). However this observed base-accelerating effect was at the expense of the enantioselectivity. This observation suggests that DBU could participate in the transition state.

The cyclic ketones (Scheme 4, Table 2) were found to be suitable substrates for this aldol reaction with both catalysts, **1** and **2**, giving aldol products in good yield after 24 h, although with moderate diastereocontrol. Excellent enantioselectivities up to 99% were observed for both *syn* and *anti* isomers in the reaction of cyclohexanone derivatives. Typically, aminophosphonic acid **1** (20 mol%) catalyzed the reaction of cyclohexanone with 4-nitrobenzaldehyde to produce adducts *syn*-**11** and *anti*-**11** in up to 97% ee (entry 3). This also represents a significant improvement of enantioselectivity relative to reactions catalyzed with proline and its derived compounds with a maximum of 90% ee for *anti* and 74% ee for *syn* products.[11,12] Catalyst **2** (20 mol%) promoted the reaction with a higher reaction rate than **1** and with up to 97% ee (entry 4).



6 X = -
7 X = CH_2
8 X = CHMe
9 X = *t*BuCH

10 R = 4-NO_2; X = -
11 R = 4-NO_2; X = CH_2
12 R = 4-NO_2; X = O
13 R = 4-NO_2; X = S
14 R = 4-NO_2; X = *t*BuCH
15 R = 4-CN; X = CH_2
16 R = 2-Cl; X = CH_2

Scheme 4

Aminophosphonate **2** was found to be very efficient and could be used with only 2 mol% catalyst loadings with respect to the aldehyde acceptor without deleterious effect on enantioselectivity. Additionally, **2** was still very efficient even with only 2 mol equivalents of the corresponding ketone donor. Thus, under these conditions, *i.e.* **2** (5 mol%) and ketone (2 mol equiv.), a range of cyclohexanones were explored, although a longer reaction time is needed (entries 5–11). Equally high enantioselectivities (up to 99%) were observed (entries 3–9), with a slightly lower 89% ee for *anti*-**12** (entry 7).

It also appears that catalyst **2** favors the formation of the *anti* isomer. Noteworthy examples include *anti*-**12** and *anti*-**13** (entries 7–8). In the case of 4-*tert*-butylcyclohexanone, the aldol reaction produced only two diastereoisomers, *anti-trans*-**14** and *syn-trans*-**14**, out of four possible in a 1 : 1 ratio.[18] Thus, after 44 h the aldol product was obtained in 52% yield and with 96% ee for

Table 2 Aminophosphonate-catalyzed aldol reaction of cyclic ketones and 4-nitrobenzaldehyde[a]

Entry	Aldol product	Cat (mol%)	Time/h	Yield (%)[b] (*syn* : *anti*)	Ee (%)[c] *syn* : *anti*
1	**10**	**1** (20)	23	51 (1 : 1)	46 : nd
2	**10**	**2** (20)	27	51 (3 : 2)	rac : nd
3	**11**	**1** (20)	21	47 (1 : 1)	97 : 97
4	**11**	**2** (20)	21	91 (1 : 2)	97 : 96
5	**11**	**2** (5)	96	73 (1: 2)	96 : 96
6	**11**	**2** (2)	144	68 (2 : 3)	96 : 94
7	**12**	**2** (5)	120	79 (1 : 4)	nd : 89
8	**13**	**2** (5)	120	36 (1 : 9)	nd : 99
9	**14**	**2** (5)	44	52 (1 : 1)	nd : 96
10	**15**	**2** (5)	96	51 (2 : 3)	97 : 97
11	**16**	**2** (5)	96	68 (1 : 1)	nd : 98

[a] Unless otherwise stated, all reactions were carried out using 0.2 M aldehyde, 0.4 M ketone and corresponding amount catalyst (see the table) in 1 mL DMSO. [b] The yields are based on isolated product. [c] The ee was determined by chiral HPLC analysis using a Chiralcel-OD column or a Kromasil CHI-TBB. [d] Reactions were carried out at 0.05 M.

Table 3 Effect of additives on the aminophosphonate-catalyzed aldol reaction of cyclohexanone with 4-nitrobenzaldehyde[a]

Entry	Aldol product	Cat. (mol%)	Additives (mol%)	Time/h	Conv. (%)[b] (*syn* : *anti*)	ee (%)[c] *syn* : *anti*
1	**11**	**1** (5)	DBU (5)	72	60 (2 : 1)	91 : 45
2	**11**	**Pro** (5)	DBU (5)	24	82 (1 : 1)	rac
3	**11**	**1** (5)	DBN (5)	72	56 (2 : 1)	90 : 45
4	**11**	**Pro** (5)	DBN (5)	24	quant.	rac
5	**11**	**1** (5)	TMG (5)	72	47 (2 : 1)	90 : 45
6	**11**	**Pro** (5)	TMG (5)	24	quant.	rac
7	**11**	**1** (5)	H_2O (200)	24	no reaction	—
8	**11**	**2** (5)	PNP (20)	24	35 (1 : 2)	96 : 97
9	**11**	**2** (5)	H_2O (200)	24	40 (1 : 2)	96 : 98

[a] Unless otherwise stated, all reactions were carried out using 0.2 M aldehyde, 0.4 M ketone and the corresponding amount of catalyst (see the table) in 1 mL DMSO. [b] Conversion as determined by ^{1}H NMR. [c] The ee was determined by chiral HPLC analysis using a Chiralcel-OD column or a Kromasil CHI-TBB, after flash chromatography.

the isomer *anti-trans*-**14** (entries 9).[19] This high enantioselectivity is also observed for other aromatic aldehydes to produce aldol adducts **15** with 97% ee for both diastereomers, and **16** with 98% ee for the *anti* isomer (entries 10–11).[20]

The effectiveness of catalyst **2** over catalyst **1** may be attributed to a higher solubility of **2** in organic solvents. Moreover, it is not yet clear whether catalyst **2** is involved as a dimer in a dual catalyst–enaminium transition-state, suggesting a second order reaction with respect to catalyst **2**. Such a transition-state model has been previously discussed.[21]

Perhaps most importantly, we have found that organic bases can be employed as co-catalysts to enforce *syn*-selectivity. From the above-mentioned results in Table 1, we envisioned that a transition state stabilized with an organic base, in a boat conformation, would favor the *syn* product. As shown in Table 3, a combination of aminophosphonic acid **1** and one of the organic bases (DBU, DBN or TMG) in 5 mol% of each allows the addition of cyclohexanone to 4-nitrobenzaldehyde with 2 : 1 *syn*-selectivity. Remarkably, *syn*-**11** and *anti*-**11** aldol products are isolated with 91 and 45% ee, respectively—while still using only 2 mol equivalents of ketone donor (entries 1, 3, 5). In a stark contrast, a similar catalyst combination incorporating proline (as the catalyst) and one organic base produced a 1 : 1 mixture of *anti*-**11** and *syn*-**11** aldol adducts. Although a remarkable increase of the reaction rate was observed, the aldol products are obtained in racemic form for both diastereomers (entries 2, 4, 6). We also examined the impact of the protic additives. However, with added water aminophosphonic acid **1** did not promote the reaction (entry 7). On the other hand, addition of 4-nitrophenol (PNP) did not influence significantly the selectivity of the reaction with aminophosphonate **2** as the catalyst (entry 8). Interestingly, the asymmetric aldol reaction proceeded efficiently in aqueous organic solvent (200 mol% water), keeping excellent level of enantioselectivity.

Conceptually, these results demonstrate that *anti–syn* selectivity can be easily modulated by the appropriate combination of an organocatalyst together with an organic base as co-catalyst. Moreover, the high enantioselectivity in aqueous media alludes to a possible reactivity in water.

In summary, we have introduced chiral α-aminophosphonates as a new class of efficient organocatalysts for the asymmetric direct aldol reaction.

Both enantiomers of catalysts **1** and **2** can be easily prepared on a large scale from commercially available compounds. For the first time, excellent enantioselectivity is achieved for both *anti* and *syn* isomers of aldol adducts derived from cyclohexanone, while maintaining low catalyst loadings (2 mol%). Furthermore, organic bases can be employed as co-catalysts to enforce *syn*-selectivity while keeping a high level of enantioselectivity.

B3LYP/6-31G(d) calculations of structures and energies of possible, diastereoisomeric activated complexes showed the decisive role of the tetrahedral phosphonate group in catalyst **1** on the enantioselectivity. The predicted enantioselectivities were in agreement with the experimental values, although the present model does not account for reactivity of **2** or the influence of organic bases.

The *syn*-directing effects of organic bases together with the possibility of substituent variation on the phosphonyl part are expected to allow for appropriate tuning of the aminophosphonate catalysts. A study aimed at the understanding of the mechanism is currently under way.

Acknowledgements

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16 Typical procedure for aldol reaction: Aminophosphonate catalyst **1** or **2** (0.2 mmol) and aldehyde (1.0 mmol) were added to a solution of acetone (0.2 mL) and DMSO (0.8 mL). The mixture was stirred at rt for the given time. The reaction was then quenched with saturated aqueous NH_4Cl (1 mL) and then extracted with EtOAc (3 × 1 mL). The organic layers were dried over Na_2SO_4 and concentrated under vacuum. Analytical samples were obtained by flash chromatography (silica gel, hexane–EtOAc). Enantiomeric excess was determined by chiral HPLC using a Kromasil TBB-CHI chiral column (Table 1 and 2) and a Chiralcel-OD column (Table 2). For comparison and in all cases, pure racemic and chiral aldol adducts were prepared by using D,L-proline and L-proline respectively.
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19 The same reaction in presence of L-proline, under previously reported conditions,[18] provided a 1 : 1 mixture of *anti*- and *syn*-*trans* aldol products (with 68% ee for the *anti*-isomer).
20 All new compounds gave satisfactory analytical and spectral data. Characterization data for selected examples are given below: (2*R*,1′*R*)-[Hydroxy-(4-nitrophenyl)-methyl]-cyclohexanone and (2*S*,1*R*)-2-[1 -hydroxy-(4-nitrophenyl)-methyl]-cyclohexanone. *syn* and *anti* Diastereomers were separated by flash column chromatography (EtOAc–hexane, 1 : 5) to yield the *title compounds* as white solids. *anti* ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 8.20$ (2H, d, $J = 8.7$ Hz, Ar*H*), 7.49 (2H, d, $J = 8.7$ Hz, Ar*H*), 4.98 (1H, d, CHC*H*OH), 2.59 (1H, m, C*H*CHOH), 2.50–2.37 (2H,m, CH_2C(O), 2.16–1.55 (6H, m, c-hex-*H*). HPLC: Chiralcel-OD. Hexane–*i*-PrOH, 95 : 5, 1.5 mL min^{-1}, 254 nm: t_R (major) = 16.4 min; t_R (minor) = 12.8 min. *syn* ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 8.20$ (2H, d, $J = 8.7$ Hz, ArH), 7.51 (2H, d, $J = 8.7$ Hz, ArH), 5.49 (1H, m, CHC*H*OH), 2.63 (1H, m, C*H*CHOH), 2.47–2.30 (2H, m, CH_2C(O), 2.13–1.36 (6H, m, c-hex-*H*). HPLC: Chiralcel-OD. Hexane–*i*-PrOH, 95 : 5, 1.5 mL min^{-1}, 254 nm: t_R (major) = 11.5 min; t_R (minor) = 12.4 min. (2*R*,1′***R***)-[Hydroxy-(4-nitrophenyl)-methyl]-tetrahydrothiopyran-4-one. *anti* ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 8.23$ (2H, d, $J = 8.7$ Hz, Ar*H*), 7.52 (2H, d, $J = 8.7$ Hz, Ar*H*), 4.99 (1H, d, CHC*H*OH), 3.36 (1H, m, CHCHO*H*), 2.93–2.88 (3H, m), 2.73–2.68 (2H, m), 2.55–2.48 (2H, m). HPLC: Chiralcel-OD. Hexane–*i*-PrOH, 90 : 10, 1.5 mL min^{-1}, 254 nm: t_R (major) = 31.6 min; t_R (minor) = 20.8 min.
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