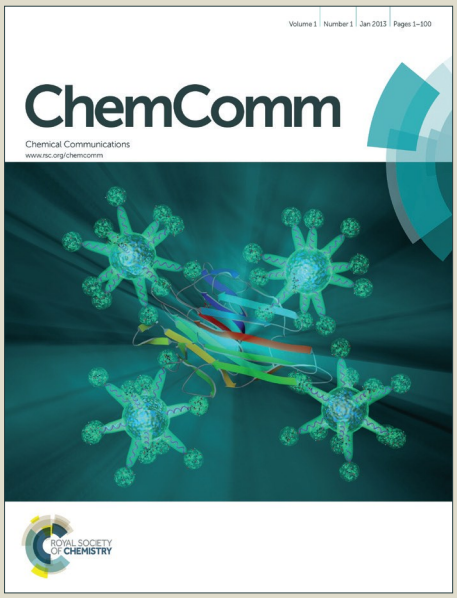
ChemComm

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: D. Kowalczyk and L. Albrecht, *Chem. Commun.*, 2015, DOI: 10.1039/C4CC09477H.



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemcomm

View Article Online
DOI: 10.1039/C4CC09477H

Chemical Communications

RSCPublishing

COMMUNICATION

Organocatalytic Biomimetic Approach to α-Aminophosphonates

Cite this: DOI: 10.1039/xoxxoooooox

Dorota Kowalczyk,[a] and Łukasz Albrecht[a,*]

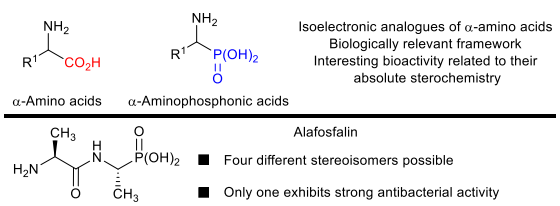
Received ooth January 2012,
Accepted ooth January 2012

DOI: 10.1039/xoxxoooooox

www.rsc.org/

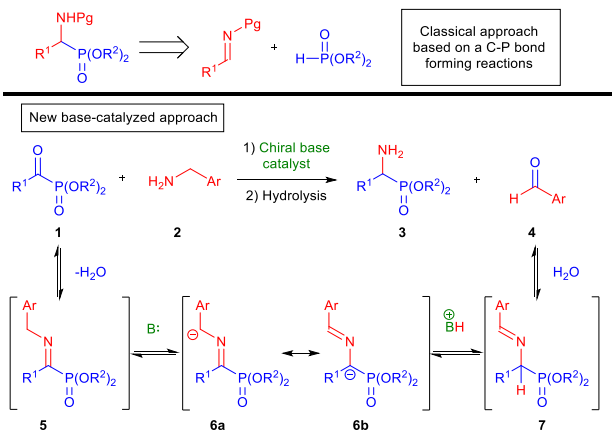
A novel biomimetic approach to optically active α-aminophosphonates utilizing readily available acylphosphonates and 2-chlorobenzylamine as starting materials has been described. The enantioselective protonation constitutes the main enantiodifferentiating step in the developed strategy. This nature-inspired approach proceeds efficiently and in a highly stereoselective manner.

α-Aminophosphonates and α-aminophosphonic acids constitute an important group of naturally occurring compounds that can be considered as isoelectronic analogues of the natural α-amino acids (Scheme 1). As such they have received a considerable interest over the years.[1] Their biological activity including antiviral,[2] antibacterial,[3] antifungal[4] and anticancer[5] activity is well recognized. Furthermore, they inhibit activity of various proteolytic enzymes including HIV protease,[6] renin,[7] synthase,[8] or PTPases.[9] Importantly, the absolute configuration of α-aminophosphonic acids and their derivatives determines the biological activity of this group of compounds.[10] This can be exemplified by the Alafosfalin, a dipeptide consisting of an alanine and a phosphaalanine residues.[11] Due to the presence of two stereogenic centers in the molecule, it can exists as four different stereoisomers. However, only one exhibits strong antibacterial activity. Consequently, the development of methods for the enantioselective preparation of α-aminophosphonic acid derivatives is of significant interest to the chemical community.



Scheme 1. α-Aminophosphonic acids as isosters of α-amino acids.

Most enantioselective methods for the synthesis of optically active α-aminophosphonates rely on the construction of the C-P bond via a Pudovik reaction of H-phosphonates with imines (Scheme 2, top).[12,13] Various organocatalytic activation strategies including H-bonding[13a] or bifunctional[13b,c] catalysis and Brønsted acid[13d,e] or base[13f,g] activation, have been successfully employed to accomplish this reaction. To our surprise, alternative, enantioselective methods for the synthesis of α-aminophosphonates are scarcer and usually provide more elaborated derivatives.[14] Furthermore, no method based on an enantioselective protonation exists in the literature.



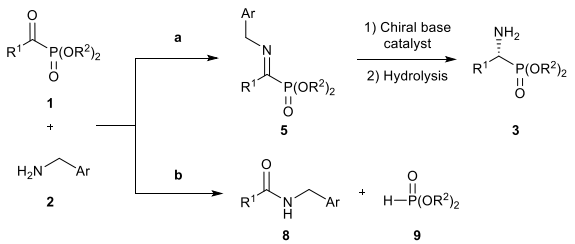
Scheme 2. Enantioselective, biomimetic synthesis of α-aminophosphonates via a Brønsted base catalysis.

Herein, we report a novel and biomimetic approach to biologically relevant α-aminophosphonates **3** (Scheme 2, bottom). It utilizes a base-catalyzed isomerization of a double bond in the corresponding *N*-benzylimines **5** followed by a hydrolytic deprotection of the amine moiety. Such a synthetic strategy is nature-inspired as it mimics an enzyme promoted transamination process that converts α-keto acids into α-amino acids in the biological systems.[15] Notably, a biomimetic

Brønsted base catalyzed synthesis of α-amino acids from α-keto esters has been recently described in the literature.[16]

In the designed biomimetic synthetic strategy, a chiral Brønsted base catalyst serves a dual purpose. Firstly, it deprotonates the corresponding *N*-benzylimines **5** in the benzylic position to afford an allylic-type carbanion that can be described by two mesomeric structures **6a** and **6b**. Secondly, it protonates the anion **6b** in the α-position to the phosphoryl group to give after hydrolysis the desired α-aminophosphonate **3**. At this stage the stereochemistry of the product is established. For this reason the chiral catalyst has to provide an efficient discrimination of the two enantiotopic faces of an anion **6b** in order to achieve stereodifferentiating transformation. Due to the size of a proton this task is particularly difficult and enantioselective strategies based on the protonation reaction are receiving increasing attention of the chemical community in recent years.[17]

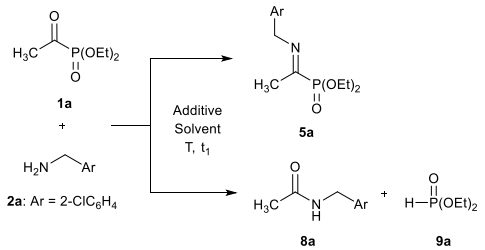
However, at the outset of our studies the synthesis of the *N*-benzylimines **5** derived from acylphosphonates **1** seemed particularly challenging (Scheme 3). The literature search showed that the availability of such a system is quite limited presumably due to the liability of the C-P bond in acylphosphonates **1** that manifests during the formation of the imine **5**. Initial addition of the amine **2** to phosphonate **1** yields tetrahedral intermediate that can further react according to two different reaction pathways. Elimination of the water molecule yields desired imine **5** (Scheme 3, route a). However, at this stage the cleavage of the C-P bond can also occur to give the corresponding amide **8** and H-phosphonate **9** as products (Scheme 3, route b). Therefore, in order to develop an efficient and biomimetic approach to α-aminophosphonates **3** studies on the condensation reaction between **1** and **2** were undertaken.



Scheme 3. Asymmetric, biomimetic synthesis of α-aminophosphonates via a Brønsted base catalysis – main challenges.

Optimization studies were performed using diethyl acetylphosphonate **1a** as a model substrate (Table 1). Preliminary studies identified 2-chlorobenzylamine **2a** as the most suitable amine for the devised synthetic strategy (see Electronic Supplementary Information for the amine screening details). Initially the temperature of the condensation reaction was optimized. Disappointingly, it was found that at lower temperatures the reaction proceeded according to the undesired reaction pathway (Table 1, entry 1). Delightfully, elevation of the temperature made the formation of the anticipated imine **5a** possible (Table 1, entries 2-5). However, the C-P bond cleavage turned out to be a dominant reaction pathway. The best conversion into the desired product **5a** was obtained at 50 °C (Table 1, entry 4) and at this temperature the solvent screening was performed (Table 1, entries 6-8). Among solvent tested, chlorinated solvents proved optimal with chloroform being the best suited solvent (Table 1, entry 7). With the optimal solvent identified, the optimization studies were directed towards the influence of the additive on the reaction outcome (Table 1, entries 9,10). As the expulsion of the water molecule is required for the reaction to occur via the desired reaction pathway, the influence of various drying agents was evaluated. It was found that the use of both molecular sieves and magnesium sulphate resulted in an increased conversion into **5a**. As molecular sieves gave better results the condensation time was evaluated using MS 4Å as an additive. Running the condensation for 30 minutes proved optimal (Table 1, entry 9). Shorter reaction time resulted in only partial conversion of **1a** (Table 1, entry 11) and prolongation of the condensation step led to the undesired H-phosphonate **9a** (Table 1, entry 12).

Table 1. Synthesis of imines **5** – optimization studies. [a]



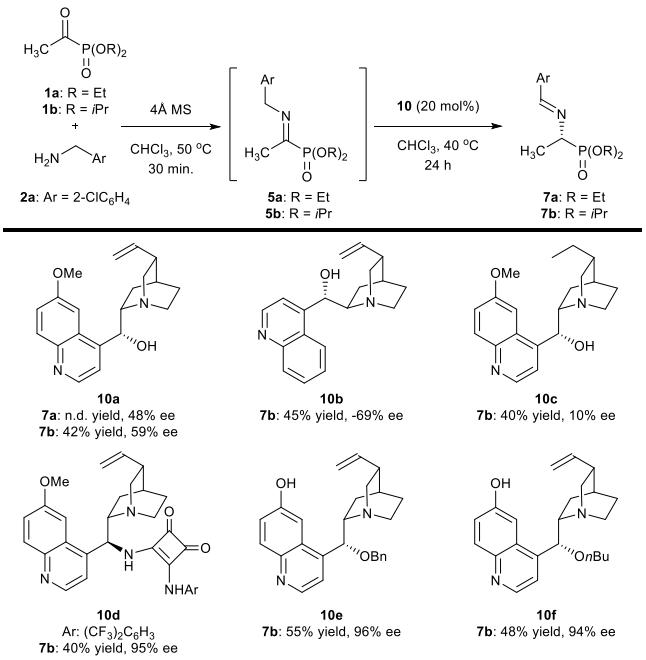
	Solvent	T [°C]	Additive	t_1 [min]	**1a**:**5a**:**9a** ratio[b]	Conv. [%][c]
1	DCE	0	-	30	0:0:1	0
2	DCE	rt	-	30	0:1:5	20
3	DCE	40	-	30	0:1:3	25
4	DCE	50	-	30	0:1:2	33
5	DCE	60	-	30	0:1:3	25
6	CH_2Cl_2	50	-	30	0:2:3	40
7	$CHCl_3$	50	-	30	0:1:1	50
8	Toluene	50	-	30	0:1:3	25
9	$CHCl_3$	50	MS 4Å	30	0:3:1	75
10	$CHCl_3$	50	$MgSO_4$	30	0:2:1	67
11	$CHCl_3$	50	MS 4Å	10	5:4:1	40
12	$CHCl_3$	50	MS 4Å	60	0:2:8	18

[a] Reactions performed on a 0.1 mmol scale (see Electronic Supplementary Information for detailed reaction conditions). [b] As determined by a ^{31}P NMR of a crude reaction mixture. [c] Conversion into the desired product **5a** is given.

With the condensation reaction conditions in hand, the base-catalyzed isomerisation reaction was studied (Scheme 4, for a full screening results, see Electronic Supplementary Information). Therefore, when the condensation reaction was accomplished different chiral catalysts **10a-f** derived from cinchona alkaloids were added to the crude reaction mixture. Gratifyingly, it turned out that the devised synthetic strategy based on an isomerization reaction of imine **5a** proceeding via the deprotonation/enantioselective protonation mechanism was possible to perform under basic conditions. Furthermore, the use of a simple cinchona alkaloid quinine **10a** as a catalyst afforded the target product **7a** in 48% ee confirming the viability of the proposed method for the preparation of optically active products. However, the ethyl phosphonate **7a** thus obtained proved difficult to isolate in a pure form under flash chromatography conditions. For this reason diisopropyl acetylphosphonate **1b** was employed in the devised reaction sequence. Delightfully, the reaction sequence involving condensation/isomerization reactions with **1b** proceeded also smoothly to afford imine **5b** which was possible to isolate in a pure form by means of a flash chromatography with even higher enantiomeric excess (59% ee),

View Article Online
DOI: 10.1039/C4CC09477H
COMMUNICATION

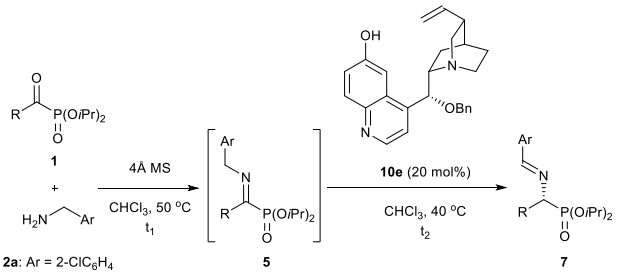
albeit in moderate yield. Further studies were focused on the identification of the optimal catalytic system for the studied transformation. Cinchonine **10b** gave comparable, but opposite enantioselectivity. The use of dihydroquinine **10c** with the ethyl substituent instead of the vinyl moiety led to deteriorated result (10% ee). Gratifyingly, the employment of bifunctional catalysts **10d-f** bearing an additional H-bonding functionality allowed for the significant improvement of the enantioselectivity of the reaction. Among different H-bonding units evaluated, namely the squaramide moiety (catalyst **10d**) and phenolic hydroxyl group (cupreine-derived-catalysts **10e** and **10f**), the latter proved more efficient in terms of reaction yields with catalyst **10e** being the most optimal.



Scheme 4. Biomimetic asymmetric synthesis of α-aminophosphonates **7** – isomerization reaction optimization.

Having established the best reaction conditions both for the condensation and isomerization step, the scope of the methodology was studied (Table 2). In some of the cases longer reaction times for both of the reactions were required in order to achieve full conversion. Application of acylphosphonates **1c**,**d** with longer alkyl chains afforded the desired products **7c**,**d** with no significant influence neither on the yield nor on the enantioselectivity of the reaction (Table 2, entries 2,3). Interestingly, the incorporation of more sterically demanding alkyl group (*i*Pr) resulted in the formation of the product **7d** in lower yield and with the decreased enantiomeric excess (Table 2, entry 4). However, when the branching of the alkyl chain was moved from the α- into the β-position of the starting acylphosphonate **1** very good results were again obtained (Table 2, entry 5). Importantly, the incorporation of different functional groups in the side-chain of target α-aminophosphonates **7** proved possible. Both olefinic moiety and the phenyl group were successfully introduced into the target products employing a devised synthetic strategy. α-Aminophosphonates **7e** and **7f** were obtained with good overall yields and with excellent stereocontrol.

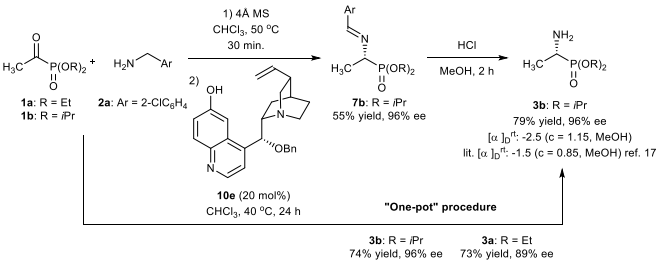
Table 2. Biomimetic asymmetric synthesis of α-aminophosphonates **7** – reaction scope.[a]



	R	7	t_1 [min][b]	t_2 [h][c]	Yield [%][d]	ee [%][e]
1	Me	**7b**	30	24	55	96
2	Pr	**7c**	120	30	59	92
3	Bu	**7d**	120	30	56	90
4	*i*Pr	**7e**	120	30	20	72
5	*i*Bu	**7f**	180	24	62	91
6	3-Butenyl	**7g**	180	24	63	95
7	$PhCH_2CH_2$	**7h**	30	30	40	94

[a] Reactions performed on a 0.1 mmol scale (see Electronic Supplementary Information for detailed reaction conditions). [b] Reaction time for the condensation step. [c] Reaction time for the isomerization step. [d] Isolated yield over two steps. [e] Determined by a chiral stationary phase HPLC.

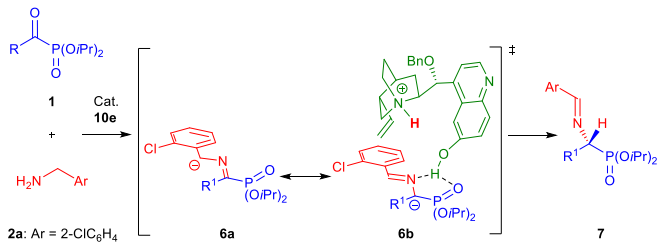
In the final part of the studies a possibility to deprotect the amine moiety in **7** was demonstrated (Scheme 5). It was found that under acidic conditions the imine **7b** could be efficiently hydrolysed to the corresponding free amine **3b**. Importantly, hydrolysis occurred with essentially preserved enantioselectivity. Interestingly, the synthesis of **3b** could be performed directly from **1b** employing a "one-pot" protocol without the isolation and purification of **7b** with high overall yield and enantioselectivity. Furthermore, such a synthetic approach proved viable for the preparation of diethyl phosphonate yielding **3a** in 73% overall yield and 89% ee.



Scheme 5. Enantioselective synthesis of α-aminophosphonates **3** with a free amine moiety.

This result allowed us to assign the absolute stereochemistry of the α-aminophosphonate **3b** and in turn of **7b** as *R* by the chemical correlation.[18] The absolute configuration of all remaining products **3b**,**7b-h** was assigned by analogy. Based on the assignments of the absolute configuration a plausible reaction mechanism was proposed (Scheme 6). The reaction was initiated by a condensation of the acylphosphonate **1** with the 2-chlorobenzylamine **2a**. Subsequent deprotonation with the catalyst **10e** afforded the protonated catalyst and carbanion **6** which was in turn protonated in an enantioselective fashion. It is

postulated that the H-bonding interactions between the free hydroxyl group of the catalyst **10e** present in the quinoline ring with the nitrogen atom and the oxygen atom was crucial for the stereochemical reaction outcome. Therefore, the proton from the quinuclidine nitrogen atom of the protonated catalyst **10e** was delivered to the carbon atom adjacent to the phosphoryl group of carbanion **6b** from the top face giving *R*-configured product **7**.



Scheme 6. Enantioselective synthesis of α-aminophosphonates **7** – mechanistic considerations.

Conclusions

In conclusion, we have developed a novel biomimetic approach to the highly enantiomerically enriched α-aminophosphonates. The strategy is based on a Brønsted base catalyzed isomerization of the double bond in the corresponding *N*-benzylimines derived from acylphosphonates. Interestingly, enantioselective protonation of the carbanion constitute the main enantiodifferentiating step in the developed methodology.

Acknowledgements

This work was realized within Lider programme from the National Center for Research and Development (NCBR, grant number LIDER/01/87/L3/11/NCBR/2012).

Notes and references

[a] Institute of Organic Chemistry, Chemistry Department, Lodz University of Technology, Żeromskiego 116, 90-924 Łódź, Poland, e-mail: lukasz.albrecht@p.lodz.pl.

Electronic Supplementary Information (ESI) available: [screening details, experimental procedures, and characterization of the products, HPLC traces]. See DOI: 10.1039/c000000x/

1 (a) P. Kafarski and B. Lejczak, *Phosphorous, Sulfur Silicon Relat. Elem.* 1991, **63**, 193; (b) D. A. McLeod, R. I. Brinkworth, J. A. Ashley, K. D. Janda and P. Wirsching, *Bioorg. Med. Chem. Lett.* 1991, **1**, 653; (c) V. P. Kukhar and H. R. Hudson, *Aminophosphonic and Aminophosphinic Acids*, JohnWiley & Sons: Chichester, UK, 2000; (d) J.-A. Ma, *Chem. Soc. Rev.* 2006, **35**, 630; (e) M. Ordóñez, H. Rojas-Cabrera and C. Cativiela, *Tetrahedron* 2009, **65**, 17.

2 J. Huang and R. Chen, *Heteroat. Chem.* 2000, **11**, 480.

3 For selected examples, see: (a) K. S. Kim, E. Y. Hurh, J. N. Youn and J. I. Park, *J. Org. Chem.* 1999, **64**, 9272; (b) S. N. Osipov, O. I. Artyushin, A. F. Kolomiets, C. Bruneau and P. H. Dixneuf, *Synlett* 2000, 1031; (c) B. C. Ranu, A. Hajra and U. Jana, *Org. Lett.* 1999, **1**, 1141; (d) W. Liu, C. J. Rogers, A. J. Fisher and M. D. Toney, *Biochemistry* 2002, **41**, 12320; (e) J. D. Moore, K. T. Sprott and P. R. Hanson, *J. Org. Chem.* 2002, **67**, 8123; (f) J. Grembecka, A. Mucha, T. Cierpicki and P. Kafarski, *J. Med. Chem.* 2003, **46**, 2641.

4 (a) L. Maier and P. J. Diel, *Phosphorous, Sulfur Silicon Relat. Elem.* 1991, **57**, 57; (b) L. Maier and P. J. Diel, *Phosphorous, Sulfur Silicon Relat. Elem.* 1994, **90**, 259.

5 G. Lavielle, P. Hautefaye, C. Schaeffer, J. A. Boutin, C. A. Cudennec and A. Pierré, *J. Med. Chem.* 1991, **34**, 1998.

6 (a) B. Stowasser, K.-H. Budt, J.-Q. Li, A. Peyman and D. Ruppert, *Tetrahedron Lett.* 1992, **33**, 6625; (b) K. Senten, L. Daniëls, P. Var der Veken, I. De Meester, A.-M. Lambeir, S. Scharpé, A. Haemers and K. Augustyns, *J. Comb. Chem.* 2003, **5**, 336.

7 D. V. Patel, K. Rielly-Gauvin and D. E. Ryono, *Tetrahedron Lett.* 1990, **31**, 5587.

8 M. Emgenbroich and G. Wulff, *Chem. Eur. J.* 2003, **9**, 4106.

9 (a) T. R. Jr. Burke, J. J. Jr. Barchi, C. George, G. Wolf, S. E. Shoelson and X. Yan, *J. Med. Chem.* 1995, **38**, 1386; (b) T. R. Jr. Bruke, H. K. Kole and P. P. Roller, *Biochem. Biophys. Res. Commun.* 1994, **204**, 129.

10 M. Drąg, M. Pawelczak and P. Kafarski, *Chirality* 2003, **15**, S104.

11 (a) J. G. Allen, F. R. Atherton, M. J. Hall, C. H. Hassall, S. W. Holmes, R. W. Lambert, L. J. Nisbet and P. S. Ringrose, *Nature* 1978, **272**, 56; (b) F. R. Atherton, M. J. Hall, C. H. Hassall, R. W. Lambert and P. S. Ringrose, *Antimicrob. Agents Chemother.* 1979, **15**, 677; (c) M. Yager, C. Taylor and A. B. III Smith, *J. Am. Chem. Soc.* 1994, **116**, 9377; (d) V. Coeffard, I. Beaudet, M. Evain, E. Le Grognec and J.-P. Quintard, *Eur. J. Org. Chem.* 2008, 3344

12 For selected reviews, see: (a) Ł. Albrecht, A. Albrecht, H. Krawczyk and K. A. Jørgensen, *Chem. Eur. J.* 2010, **16**, 28; (b) P. Merino, E. Marqués-López and R. P. Herrera, *Adv. Synth. Catal.* 2008, **350**, 1195; (c) D. Zhao and R. Wang, *Chem. Soc. Rev.* 2012, **41**, 2095; (d) M. Dzięgielewski, J. Pięta, E. Kamińska and Ł. Albrecht, *Eur. J. Org. Chem.* DOI: 10.1002/ejoc.201403184.

13 For selected organocatalytic examples, see: (a) G. D. Joly and E. N. Jacobsen, *J. Am. Chem. Soc.* 2004, **126**, 4102; (b) D. Pettersen, M. Marcolini, L. Bernardi, F. Fini, R. P. Herrera, V. Sgarzani and A. Ricci, *J. Org. Chem.* 2006, **71**, 6269; (c) S. Nakamura, H. Nakashima, A. Yamamura, N. Shibata and T. Toru, *Adv. Synth. Catal.* 2008, **350**, 1209; (d) T. Akiyama, H. Morita, J. Itoh and K. Fuchibe, *Org. Lett.* 2005, **7**, 2583; (e) X. Cheng, R. Goddard, G. Buth and B. List, *Angew. Chem. Int. Ed.* 2008, **47**, 5079; (f) F. Fini, G. Micheletti, L. Bernardi, D. Pettersen, M. Fochi and A. Ricci, *Chem. Commun.* 2008, 4345; (g) X. Fu, W.-T. Loh, Y. Zhang, T. Ma, H. Liu, J. Wang and C.H. Tan, *Angew. Chem. Int. Ed.* 2009, **48**, 7387.

14 For organocatalytic examples, see: (a) J. C. Wilt, M. Pink and J. N. Johnston, *Chem. Commun.* 2008, 4177; (b) J. Vicario, J. M. Ezpeleta and F. Palacios, *Adv. Synth. Catal.* 2012, **354**, 2641; (c) K. Bera and I. N. N. Namboothiri, *Org. Lett.* 2012, **14**, 980; (d) C. B. Tripathi, S. Kayal and S. Mukherjee, *Org. Lett.* 2012, **14**, 3296; (e) W.-Y. Han, J.-Q. Zhao, Z.-J. Wu, X.-M. Zhang and W.-C. Yuan *J. Org. Chem.* 2013, **78**, 10541; (f) Y.-M. Cao, F.-F. Shen, F.-T. Zhang, J.-L. Zhang and R. Wang, *Angew. Chem. Int. Ed.* 2014, **53**, 1862.

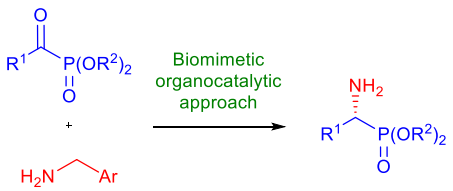
15 (a) A. Martell, *Acc. Chem. Res.* 1989, **22**, 115; (b) A. Hjelmencrantz and U. Berg, *J. Org. Chem.* 2002, **67**, 3585;

16 (a) X. Xiao, Y. Xie, C. Su, M. Liu, and Y. Shi, *J. Am. Chem. Soc.* 2011, **133**, 12914; (b) X. Xiao, M. Liu, C. Rong, F. Xue, S. Li, Y. Xie and Y. Shi, *Org. Lett.* 2012, **14**, 5270.

17 For a review, see: (a) J. T. Mohr, A. Y. Hong and B. M. Stoltz, *Nature Chem.* 2009, **1**, 359; for selected base-catalyzed enantioselective isomerizations, see: (b) Y. Wu, R. P. Singh and L. Deng, *J. Am. Chem. Soc.* 2011, **133**, 12458; (c) Y. Wu and L. Deng, *J. Am. Chem. Soc.* 2012, **134**, 14334.

18 C. Yuan, C. Xu and Y. Zhang, *Tetrahedron* 2003, **59**, 6095.

View Article Online
DOI: 10.1039/C4CC09477H



Graphical abstract

A novel biomimetic approach to the biologically relevant α-aminophosphonates via the base-catalyzed transamination process is demonstrated for the first time. The reaction sequence utilizes condensation of the corresponding benzylamine with acylphosphonates followed by the isomerization of the double bond via a deprotonation/enantioselective protonation protocol. Hydrolysis of the imines thus obtained affords highly enantiomerically enriched α-aminophosphonates. The nature-inspired reaction sequence benefits from the operational simplicity and readily available starting materials.