DOI: 10.1002/adsc.201200516

Asymmetric Cyanation of α-Ketiminophosphonates Catalyzed by *Cinchona* Alkaloids: Enantioselective Synthesis of Tetrasubstituted α-Aminophosphonic Acid Derivatives from Trisubstituted α-Aminophosphonates

Javier Vicario,[a] José María Ezpeleta,[b] and Francisco Palacios[a,*]

[a] Departamento de Química Orgánica I, Centro de Investigación y Estudios Avanzados "Lucio Lascaray" – Facultad de Farmacia, Universidad del País Vasco, UPV/EHU, Paseo de la Universidad 7, 01006 Vitoria-Gasteiz, Spain
Fax: (+34)-945-013103; phone: (+34)-945-010756; e-mail: francisco.palacios@ehu.es

[b] Departamento de Física Aplicada, Facultad de Farmacia. Universidad del País Vasco, UPV/EHU, Paseo de la Universidad 7, 01006 Vitoria-Gasteiz, Spain

Received: June 12, 2012; Published online: September 28, 2012

This paper is dedicated in honour to Professor Henri-Jean Cristau on the occasion of his 70th birthday.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201200516.

Abstract: An enantioselective synthesis of tetrasubstituted α-phosphono-α-amino nitriles through asymmetric cyanation of α-ketiminophosphonates catalyzed by *Cinchona* alkaloids is reported. α-Ketiminophosphonates are generated, in a very efficient synthetic protocol, by oxidation of trisubstituted α-aminophosphonates.

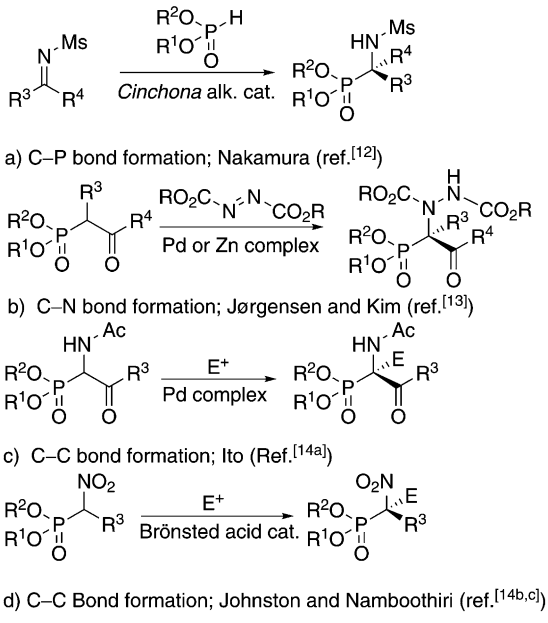
Keywords: aminonitriles; aminophosphonates; asymmetric catalysis; cyanation; imines

α-Aminophosphonates are structural analogues of α-amino acids, where the planar carboxylic acid has been substituted by a bulkier tetrahedral phosphonate group,[1] which have numerous applications[2] in medicinal and pharmaceutical sciences as haptens of catalytic antibodies,[3a] peptide mimetics,[3b] enzyme inhibitors,[3c] antibacterial agents[3d] as well as agrochemicals.[4] The biological activity of α-aminophosphonic acids is strongly dependent on their absolute configuration[5] and the stereoselective synthesis of α-aminophosphonic acid derivatives[6] is an imperative task in organic chemistry. The synthesis of optically active α-aminophosphonic acids was reported for the first time in 1972.[7] Based on the chiral auxiliary approach, some syntheses of optically active α-aminophosphonic acid derivatives have been reported[6] and, likewise, catalytic asymmetric methodologies[8] have also been reported, where the key step involves C–P, C–N and C–C bond formation.

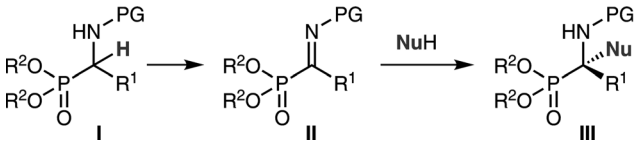
All-substituted stereogenic carbon centers are ubiquitous motifs in natural products and pharmaceutical agents and the efficient formation of tetrasubstituted centers is a crucial challenge in chemical synthesis.[9] However, the formation of tetrasubstituted centers from ketones and ketimines was unachievable for a long time, due to the poor electrophilic character of the carbonyl or the ketimine groups and to the additional steric hindrance on the substrate, and the enantiotopic faces of ketimines are not as easily discriminated as those of aldimines when asymmetric synthesis is sought.[10]

Only a few diastereoselective preparations of α-aminophosphonic acid derivatives can be applied to tetrasubstituted α-aminophosphonates,[11] and the asymmetric synthesis of tetrasubstituted α-aminophosphonates is limited to the *Cinchona* alkaloids-catalyzed hydrophosphonylation of sulfonylimines (Scheme 1, a),[12] Pd- or Zn-catalyzed enantioselective amination of β-ketophosphonates, using dialkyl azocarboxylate (Scheme 1, b).[13] and Pd-catalyzed allylation of β-keto-α-aminophosphonates (Scheme 1, c)[14a] or Brønsted acid-catalyzed addition of α-nitrophosphonates to electrophiles (Scheme 1, d).[14b,c]

Our group has been involved in the preparation of simple[15] and vinylic[16] α-aminophosphonates as well as of phosphadepsipeptides derived from α-aminophosphonates.[17] Continuing with our concern in aminophosphorus chemistry,[18] we believed that an enantioselective addition of nucleophiles to α-ketiminophosphonates would be a convenient pathway to access optically active tetrasubstituted α-aminophosphonates (Scheme 2) and that the generation of



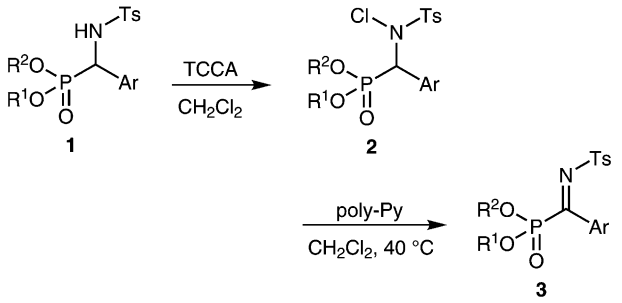
Scheme 1. Enantioselective synthesis of tetrasubstituted α-aminophosphonates.



Scheme 2. Strategy for the enantioselective synthesis of tetrasubstituted α-aminophosphonates.

α-ketiminophosphonates might be feasible by oxidation of the parent α-aminophosphonates. Consequently, this synthetic approach could be considered globally as a new route for the generation of tetrasubstituted α-aminophosphonates by the substitution of hydrogen in a trisubstituted α-aminophosphonate by a nucleophilic reagent and the complementary process ("umpolung reaction") of the electrophilic substitution of trisubstituted α-aminophosphonate (Scheme 1, c, d). We report herein an efficient synthesis of α-iminophosphonates derived from ketones (**II**, Scheme 2) as well as their synthetic applications as precursors of optically active tetrasubstituted α-aminophosphonates (**III**, Scheme 2) through a *Cinchona* alkaloid-catalyzed enantioselective Strecker reaction, using cheap and non-toxic pyruvonitrile.

Recently, we reported the synthesis of α-iminophosphonates derived from ketones through an aza-Wittig methodology.[16a,19] One of the drawbacks of this methodology[20] is that only *N*-aryl- or *N*-alkylphosphazenes can be used for the generation of the imine bond. Taking into account the moderate electrophilic character and the additional steric hindrance present in ketimine groups, we were mostly interested in ketimines **II** (Scheme 2) bearing an electron-withdrawing group at the nitrogen. These synthons would favor nucleophilic addition to the C=N double bond and at the same time would allow an easy deprotection of the nitrogen in an ultimate synthetic step.



Scheme 3. Synthesis of starting α-aminophosphonates **3**.

Construction of a carbon-nitrogen double bond from α-aminophosphonates **I** would imply the introduction of a good leaving group at the aminophosphonate to promote then its elimination with a base. Then, selective *N*-chlorination can be achieved by treatment of α-aminophosphonates **1** with trichloroisocyanuric acid (TCCA) in dichloromethane at 0 °C (Scheme 3). A large excess of inexpensive TCCA is normally required in order to decrease the reaction times, since higher reaction temperatures result not only in a faster reaction but also in the obtention of a mixture of *N*- and *C*-chlorinated aminophosphonates. In the case of α-aminophosphonates **1** holding large phosphonate groups ($R^1 = R^2 = i$-Pr), due to the higher steric hindrance present in the α-carbon, selective *N*-chlorination can be completed in a few hours at room temperature using an excess of TCCA. *N*-Chloroaminophosphonates **2** are unstable species and, in order to prevent the dechlorination reaction, they are readily used without purification after elimination of the solid residue by filtration. Nonetheless, their formation can be confirmed by ^{1}H NMR of the crude mixture, where a simplification (double doublet to doublet) coincident with a downfield shift of 1 ppm of the signal, corresponding to the methyne group attached to the phosphorus, as well as the disappearence of the broad doublet in the range 6–7 ppm, corresponding to the NH, are observed. ^{31}P NMR also shows an upfield shift of aproximate 3 ppm of the signal of the *N*-chloro α-aminophosphonates **2** relative to α-aminophosphonates **1**.

β-Elimination of HCl in *N*-chloro α-aminophosphonates **2** can be performed using pyridine as a base. Unfortunately, the resulting unstable α-iminophosphonates **3** cannot be separated from pyridine hydrochloride avoiding the hydrolysis of the imine bond. The use of an insoluble base in organic solvents as the promoter of the β-elimination reaction would allow the elimination of both the hydrochloride and the excess of base from the reaction solution. Finally, re-

fluxing overnight the resulting clear solution of *N*-chloroaminophosphonate **2** with an excess of poly(4-vinylpyridine) affords pure α-ketiminophosphonates **5** in very good yields (Scheme 3, 77–85% overall, See also the Supporting Information), after filtration and crystallization from diethyl ether.

With an efficient protocol in hand for the generation of α-ketiminophosphonates **3**, next we studied the organocatalytic asymmetric addition of nucleophiles to imines **3**. In this context, the Strecker reaction[21] is one of the most efficient methods for the preparation of α-aminonitriles, useful precursors of α-amino acids. A few catalytic systems have been developed for the enantioselective cyanation of ketimines to generate tetrasubstituted centers. This embraces organocatalysis, like thiourea-catalyzed addition of HCN to *N*-benzylimines[22] or *N*-*N*-dioxide-catalyzed addition of TMS-CN to *N*-tosylimines,[23] and metal catalysis such as Ti-catalyzed addition of TMS-CN or EtO_2C-CN to *N*-tosylimines[24] or Gd-catalyzed addition of TMS-CN to *N*-diphenylphosphinylimines.[25]

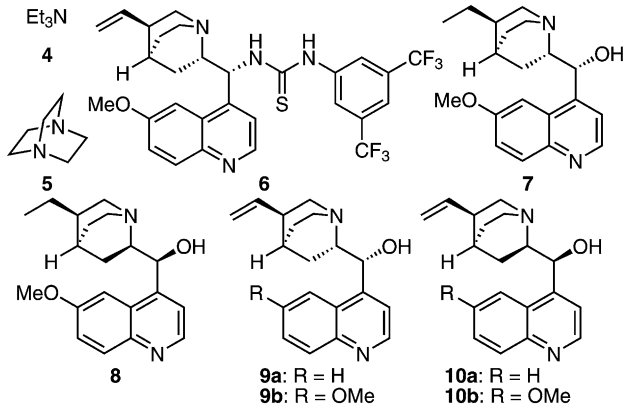
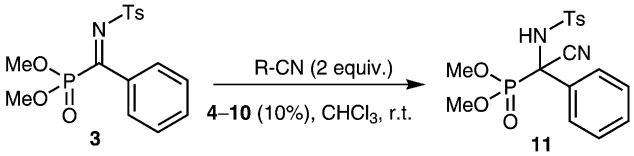


Figure 1. Catalysts tested in the asymmetric cyanation reaction of α-iminophosphonates **3**.

Cyanation of α-iminophosphonate **3** can be performed in a few hours by treatment with 2 equivalents of pyruvonitrile in the presence of a nucleophilic amine such as triethylamine **4** or 1,4-diazabicyclo-[2.2.2]octane **5** (Figure 1 and Table 1, entries 1 and 2).

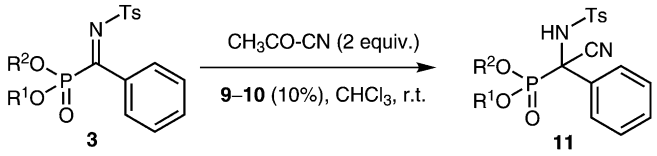
Then we tested the asymmetric cyanation in the presence of a catalytic quantity of *Cinchona* alkaloid derivatives (10%). Although bifunctional thiourea **6** catalyzed very efficiently the nucleophilic addition of cyanide, no significant enantiomeric excess was observed (Table 1, entry 3). Dihydroquinine (**7**) and dihydroquinidine (**8**) showed a modest enantioselectivity (Table 1, entries 4 and 5) as did other *Cinchona* alkaloids tested such as cinchonidine (**9a**), quinine (**9b**), cinchonine (**10a**) or quinidine (**10b**) (Table 1, entries 6–9). Given that a maximum enantiomeric excess of 36% was observed for quinidine (**10b**), several sources of cyanide were analyzed using **10b** as catalyst. While practically the same results were obtained using methyl cyanoformate (Table 1, entry 10), the use of tosyl cyanide or diethyl cyanophosphonate resulted in a drop in the conversions and enantioselectivities (Table 1, entries 11 and 12) and no trace of cyanated product was observed when trimethylsilyl cyanide was used (Table 1, entry 13). A strong dependence of the conversion and enantioselectivity with the electron-withdrawing character of cyanide substituent is concluded in this experiment. These results suggest that a source of cyanide with a strong electron-withdrawing group is needed in this reaction,

Table 1. Screening of catalysts and cyanide sources.



Entry	Catalyst	R-CN	Time [h]	Conversion [%]	*ee* [%]
1	**4**	CH_3CO-CN	12	100	–
2	**5**	CH_3CO-CN	12	100	–
3	**6**	CH_3CO-CN	3	95	15
4	**7**	CH_3CO-CN	48	100	17
5	**8**	CH_3CO-CN	48	100	−30
6	**9a**	CH_3CO-CN	48	100	24
7	**9b**	CH_3CO-CN	48	100	20
8	**10a**	CH_3CO-CN	48	100	−14
9	**10b**	CH_3CO-CN	48	100	−36
10	**10b**	MeO_2C-CN	48	100	−35
11	**10b**	Ts-CN	72	55	−11
12	**10b**	$(EtO)_2P(O)$-CN	72	50	−6
13	**10b**	TMS-CN	48	0	–

Table 2. Influence of the phosphorus substituent.



Entry	Compound	Catalyst	R^1	R^2	*ee* [%]
1	**9a**	**13b**	Bn	Bn	16
2	**9b**	**14b**	Bn	Bn	10
3	**10a**	**13a**	Bn	Bn	−20
4	**10b**	**14a**	Bn	Bn	−22
5	**9a**	**13b**	Me	Me	24
6	**9b**	**14b**	Me	Me	14
7	**10a**	**13a**	Me	Me	−20
8	**10b**	**14a**	Me	Me	−36
9	**9b**	**13b**	Et	Et	30
10	**10b**	**14b**	Et	Et	−38
11	**9a**	**13b**	*i*-Pr	*i*-Pr	80
12	**9b**	**14b**	*i*-Pr	*i*-Pr	58
13	**10a**	**13a**	*i*-Pr	*i*-Pr	−58
14	**10b**	**14a**	*i*-Pr	*i*-Pr	−60
15	**9b**	**13b**	Ph	Ph	6
16	**10b**	**14b**	Ph	Ph	−7
17	**9a**	**13b**	H_2C-$C(CH_3)_2$-CH_2		−1
18	**9b**	**14b**	H_2C-$C(CH_3)_2$-CH_2		0
19	**10a**	**13a**	H_2C-$C(CH_3)_2$-CH_2		−5
20	**10b**	**14a**	H_2C-$C(CH_3)_2$-CH_2		1

which may confer a high nucleophilic character to the cyanide carbon.

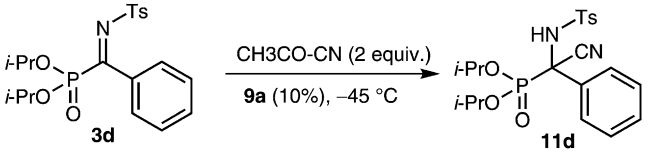
Taking advantage of our new protocol for the preparation of α-ketiminophosphonates **3**, we implemented an analysis of the influence of the phosphorus substituent on the enantioselectivity of the cyanation reaction using cinchonidine (**9a**), quinine (**9b**), cinchonine (**10a**) and quinidine (**10b**) as organocatalysts (Table 2).

The effect of acyclic aliphatic substituents at the phosphonate on the enantioselectivity of the reaction correlates with their Winstein–Holness A values.[26] For example, while an enantiomeric excess of 22% was observed for the dibenzylphosphonate **11a** with quinidine (**10b**) (Table 2 entry 4, $A_{Bn}=1.68$ kcal mol^{-1}), this value is increased to 36% and 38%, respectively, in the case of dimethyl and diethyl phosphonates **11b** and **11c** (Table 2, entries 8 and 10), with similar A values for their substituents ($A_{Me}=1.74$ kcal mol^{-1}, $A_{Et}=1.79$ kcal mol^{-1}). Then, as expected, the enantiomeric excess was increased to 60% for diisopropylphosphonate **3d** (Table 2, entry 13, $A_{i\text{-}Pr}=2.21$ kcal mol^{-1}). A special case is the use of diphenylphosphonate **3e**. In view of the high A value for the phenyl group ($A_{Ph}=2.80$ kcal mol^{-1}), the highest enantiomeric excess would be expected. Nevertheless, very low asymmetric induction is observed in the cyanation with quinine (**9b**) and quinidine (**10b**) (Table 2, entries 15 and 16). This result may be due to the planarity of the phenyl ring which allows a conformation with less steric crowding at the iminic carbon. Surprisingly, almost no enantioselectivity was observed in the cyanation of neopentylene phosphonate **3f** (Table 2, entries 17–20), where the free rotation of phosphonate substituents has been restricted by the presence of a cyclic structure (Table 2, entries 17–20). Finally, the best enantioselectivity (*ee* = 80%) was observed when the cyanation reaction of diisopropyl phosphonate was performed using cinchonidine (**9a**) as organocatalyst (Table 2, entry 11).

It is well known that a drop in the reaction temperature results normally in an increase in the enantioselectivity and, therefore, we studied the cinchonidine-catalyzed cyanation of diisopropyl phosphonate **3d** with pyruvonitrile at different temperatures. The enantiomeric excess is increased from 80% to 84% and 92% if the reaction temperature is lowered to 0 °C or −45 °C but, as a consequence, the reaction times are substantially increased. Further decrease of the temperature to −55 °C results in very low rates of conversion. Increasing the catalyst loading reduces significantly the reaction times but, unfortunately, still raising the catalyst loading to 25%, very low conversion rates are obtained at −55 °C. Finally, a decrease on the catalyst quantity to 5% results in lower conversions and a considerable decrease in the enantioselectivity.

Now, in order to examine the influence of the polarity of the solvent on the enantioselectivity of the process, the cinchonidine (**9a**)-catalyzed asymmetric cyanation of iminophosphonate **3d** was studied in different solvents. The dielectric constant (K_e)[27] and the

Table 3. Influence of the polarity of the solvent.



Entry	Solvent	E_T^N [kcal mol^{-1}]	K_e	Conversion [%]	*ee* [%]
1	CCl_4	0.052	2.24	65	10
2	toluene	0.099	2.39	85	52
3	Et_2O	0.117	4.34	79	23
4	DME	0.231	7.20	83	35
5	THF	0.207	7.58	95	65
6	$CHCl_3$	0.259	4.81	100	92
7	CH_2Cl_2	0.309	8.93	100	86
8	$Cl(CH_2)_2Cl$	0.327	10.6	100	63
9	AcN	0.460	37.5	100	46
10	*i*-PrOH	0.546	19.9	100	0
11	EtOH	0.654	24.6	100	0
12	MeOH	0.762	32.7	100	0

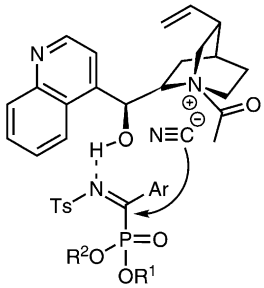


Figure 2. Possible transition state for asymmetric cyanation of α-iminophosphonates **3**.

normalized molar electronic translation energies (E_T^N)[28] are used as indicators of the polarity of the solvent (Table 3). Low conversions with modest enantiomeric excesses were observed when the reaction was performed in the least polar solvents, which may be attributable to the low solubility of the substrates and/or catalyst in those solvents at low temperature (Table 3, entries 1–5). A faster reaction with very good conversions was observed for more polar solvents (Table 3, entries 6–12). Within the good solubilizing solvents, the less polar one, chloroform, showed the best enantioselectivities (Table 3, entry 6). This inverse dependence of the enantioselectivity on the polarity of the solvent is probably due to a diminution in the difference of the energy of activation for the formation of the two enantiomers due to a stabilization of both possible diastereomeric transition states in a polar solvent, rational for reactions with ionic transition states.

It is noteworthy that a very fast reaction (12–24 h) with complete loss of the enantioselectivity is observed if alcohols are used as solvents (Table 3, entries 10–12). This might indicate a crucial role for the hydroxy group of *Cinchona* alkaloids in the transition state which may activate the substrate *via* hydrogen bonding with the iminic nitrogen as shown in Figure 2. This necessary catalyst-substrate coordination may be replaced by a solvent-substrate coordination in the presence of protic solvents, speeding up the reaction with a concomitant collapse of the enantioselectivity.

The absolute configuration of α-cyano-α-aminophosphonate **11d** was determined by X-ray diffraction.[29] Key features of the crystal structure of **11d** are its *S* configuration and a unit cell formed by a dimeric structure, where two intermolecular hydrogen bonds are established between the amine hydrogens and the phosphoryl oxygens. In order to tolerate this dimeric structure, the sulfonyl groups of both molecules adopt the opposite conformation as showed in Figure 3.

The generalization of the asymmetric cyanation of diisopropyl α-ketiminophosphonates **3** catalyzed by cinchonidine (**9a**) was put into effect using different

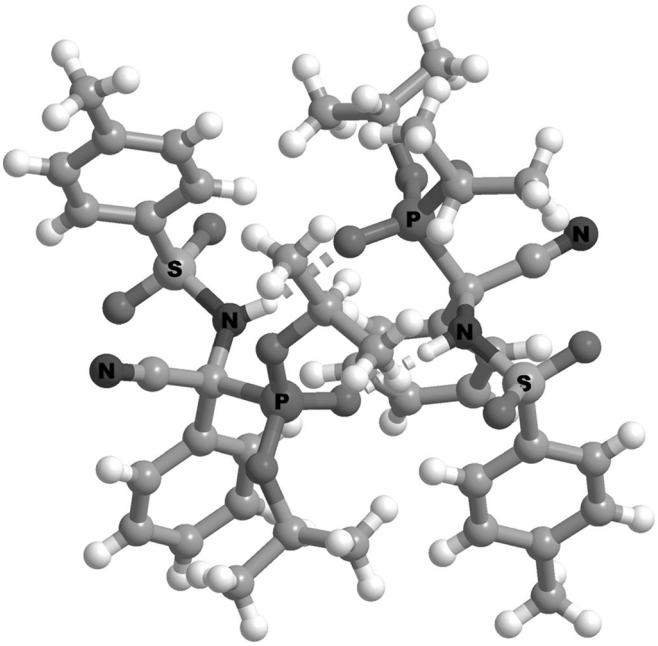
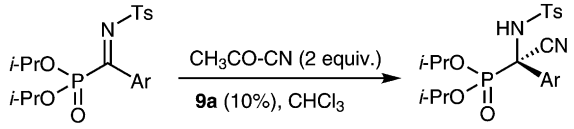


Figure 3. X-ray structure of (*S*)-**11d**.

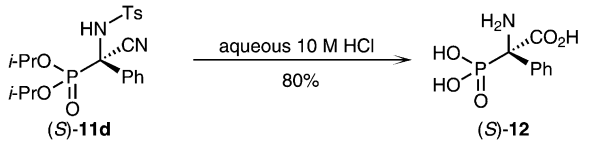
Table 4. Generalization of asymmetric cyanation reaction.



Entry	Compound	Ar	Yield[a] [%]	*ee* [%]
1	**11d**	Ph	80[b]	92, >99[d]
2	**11g**	*p*-CF_3-C_6H_4	78[b]	89, 95[d]
3	**11h**	*p*-NO_2-C_6H_4	75[b]	73, 82[d]
4	**11i**	*p*-MeO-C_6H_4	78[c]	88, 95[d]
5	**11j**	*p*-Cl-C_6H_4	77[c]	90, 98[d]

[a] Isolated yield after crystallization.
[b] Reaction at −45 °C.
[c] Reaction at 0 °C.
[d] % *ee* after crystallization.

aromatic α-substituents (Table 4). Compared with the model α-ketiminophosphonates **3d**, with a phenyl substituent at the α-carbon, a slight drop on the enantioselectivity is observed for the most reactive α-ketiminophosphonates **3g** and 3**h** (R = *p*-CF_3-C_6H_4, *p*-NO_2-C_6H_4), bearing electron-withdrawing substituents at the aromatic ring (Table 4, entries 2 and 3). In the case of α-ketiminophosphonates **3i** and **3j** (R = *p*-Cl-C_6H_4, *p*-MeO-C_6H_4), bearing electron-donating substituents at the aromatic ring (Table 4, entries 4 and 5), the cyanation reaction did not proceed at −45 °C, but raising the temperature to 0 °C afforded α-cyano-α-aminophosphonates **11i** and **11j** with satisfactory enantiomeric excesses. It is remarkable that in all



Scheme 4. Hydrolysis of α-cyano-α-aminophosphonate (*S*)-**11d**.

cases purification by crystallization from methanol affords of α-cyano-α-aminophosphonates **11** in very good yields (75 to 80%) and enantioselecitivies (82 to >99%).

Finally (*S*)-α-phosphonophenylglycine (*S*)-**12** was synthesized by simultaneous hydrolysis of nitrile, phosphonate and sulfonyl groups by treatment with 10 M hydrochloric acid (Scheme 4).

In summary we present here a new and general synthesis of α-iminophosphonates derived from ketones and an efficient strategy for the enantioselective synthesis of tetrasubstituted α-aminophosphonic acid derivatives from trisubstituted α-aminophosphonates through a global substitution of the hydrogen atom by a nucleophilic reagent, where the key step is an asymmetric cyanation of α-ketiminophosphonates catalyzed by *Cinchona* alkaloids. The new approach for the synthesis tetrasubstituted α-aminophosphonates with the addition of a nucleophilic reagent in the α position, not easily available by alternative methods, involves a C–C bond formation through addition of a carbon nucleophile, to phosphorylated iminic systems. This represents also a useful entry for asymmetric cyanation of ketimines and for the first time of inexpensive and non-toxic pyruvonitrile being used as cyanide source for the asymmetric synthesis of tetrasubstituted α-amino nitriles. As far as we know, enantiopure phosphorated tetrasubstituted α-amino nitriles and α-amino acids **11** and **12** have not been reported so far.

Experimental Section

Procedure for the Asymmetric Cyanation of α-Ketiminophosphonates 3

A solution of α-ketiminophosphonate **3** (0.5 mmol) and cinchonidine (**9a**) (10%) in $CHCl_3$ under an N_2 atmosphere was cooled to −45 °C or 0 °C (see Table 4). Pyruvonitrile (71 μL, 1 mmol) was added and the mixture was stirred for 72 h at −45 °C or 0 °C. The resulting solution was concentrated under reduced pressure and the residue was purified by crystallization from EtOH to afford pure α-phosphono-α-amino nitriles **11**.

Acknowledgements

The present work has been supported by the Dirección General de Investigación del Ministerio de Ciencia e Innovación (CTQ2009-12156) and by Gobierno Vasco and Universidad del País Vasco (GV, IT 422-10; UPV, UFI-QOSYC 11/12). J. V. thanks the Ministerio de Ciencia e Innovación for a "Ramón y Cajal" contract.

References

[1] *Aminophosphonic and Aminophosphinic Acids. Chemistry and Biological Activity*, (Eds: V. P. Kukhar, H. R. Hudson), Wiley, Chichester, **2000**.
[2] a) K Van der Jeught, C. V. Stevens, *Chem. Rev.* **2009**, *109*, 2672–2702; b) L. Berlicki, P. Kafarski, *Curr. Org. Chem.* **2005**, *9*, 1829–1850; c) P. Kafarski, B. Lejczak, *Curr. Med. Chem: Anti-Cancer Ag.* **2001**, *1*, 301–312.
[3] a) R. Hirschmann, A. B. Smith III, C. M. Taylor, P. A. Benkovic, S. D. Taylor, K. M. Yager, P. A. Sprengeler, S. J. Venkovic, *Science* **1994**, *265*, 234–237; b) A. Macchiarulo, R. Pellicciari, *J. Mol. Graphics Modell.* **2007**, *26*, 728–739; c) M. Sieńczyk, L. Winiarski, P. Kasperkiewicz, M. Psurski, J. Wietrzyk, J. Oleksyszyn, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 7224–7227; d) F. R. Atherton, C. H. Hassall, R. W. Lambert, *J. Med. Chem.* **1986**, *29*, 29–40.
[4] D. Bonarska, H. Kleszczyńska, J. Sarapuk, *Cell Mol. Biol. Lett.* **2002**, *7,* 929–935.
[5] a) A. Mucha, P. Kafarski, L. Berlicki, *J. Med. Chem.* **2011**, *54*, 5955–5980; b) F. Orsini, G. Sello, M. Sisti, *Curr. Med. Chem.* **2010**, *17*, 264–289.
[6] M. Ordóñez, H. Rojas-Cabrera, C. Cativiela, *Tetrahedron* **2009**, *65*, 17–49.
[7] W. F. Gilmore, H. A. McBride, *J. Am. Chem. Soc.* **1972**, *94*, 4361.
[8] P. Merino, E. Marques-Lopez, R. P. Herrera, *Adv. Synth. Catal.* **2008***, 350*, 1195–1208.
[9] a) *Quaternary Stereocentres: Challenges and Solutions for Organic Synthesis*, (Eds: A. Baro, J. Christoffers), Wiley-VCH, Weinhein, **2006**; b) M. Shimizu, *Angew. Chem. Int. Ed.* **2011**, *50*, 5988–6000.
[10] O. Riant, J. Hannedouche, *Org. Biomol. Chem.* **2007**, *5*, 873–888.
[11] a) A. Studer, D. Seebach, *Heterocycles* **1995**, *40*, 357–378; b) M. Mikołajczyk, P. Łyżwa, J. Drabowicz, *Tetrahedron: Asymmetry* **1997**, *8*, 3991–3994; c) F. A. Davis, S. Lee, H. Yan, D. D. Titus, *Org. Lett.* **2001**, *3*, 1757–1760; d) Q. Chen, J. Li, C. Yuan, *Synthesis* **2008**, 2986–2990; e) E. Kuliszewska, M. Hanbauer, F. Hammerschmidt, *Chem. Eur. J.* **2008**, *14*, 8603–8614.
[12] S. Nakamura, M. Hayashi, Y. Hiramatsu, N. Shibata, Y. Funahashi T. Toru, *J. Am. Chem. Soc.* **2009**, *131,* 18240–18241.
[13] a) S. M. Kim, H. R. Kim, D. Y. Kim, *Org. Lett.* **2005**, *7,* 2309–2311; b) L. Bernardi, W. Zhuang, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 5772–5773.
[14] a) R. Kuwano, R. Nishio, Y. Ito, *Org. Lett.* **1999**, *1,* 837–839; b) J. C. Wilt, M. Pink, J. N. Johnston, *Chem. Commun.* **2008**, 4177–4179; c) K. Bera I. N. N. Namboothiri, *Org. Lett.* **2012**, *14*, 980–983.

[15] a) F. Palacios, A. M. Ochoa de Retana, J. I. Gil, J. M. Alonso, *Tetrahedron* **2004**, *60*, 8937–8947; b) J. Vicario, C. Alonso, J. M. de Los Santos, F. Palacios, *Curr. Org. Synth.* **2010**, *7*, 628–649.
[16] a) F. Palacios, J. Vicario, A. Maliszewska, D. Aparicio, *J. Org. Chem.* **2007**, *72*, 2682–2685; b) F. Palacios, A. M. Ochoa de Retana, A. Velez del Burgo, *J. Org. Chem.* **2011**, *76*, 9472–9477.
[17] a) F. Palacios, D. Aparicio, Y. Lopez, J. M. de Los Santos, *Tetrahedron* **2005**, *61*, 2815–2830; b) J. M. de Los Santos, R. Ignacio, D. Aparicio, F. Palacios, *J. Org. Chem.* **2007**, *72*, 5202–5206.
[18] F F. Palacios, C. Alonso, J. M. de Los Santos, *Chem. Rev.* **2005**, *105*, 899–931.
[19] J. Vicario, D. Aparicio, F. Palacios, *Phosphorus Sulfur Silicon Relat. Elem.* **2011**, *186*, 638–643.
[20] a) F. Palacios, C. Alonso, D. Aparicio, G. Rubiales, J. M. De Los Santos, *Tetrahedron* **2007**, *63*, 523–575; b) F. Palacios, C. Alonso, D. Aparicio, G. Rubiales, J. M. De Los Santos, in: *Organic Azides. Synthesis and Applications*, (Eds.: S. Bräse, K Banert), Wiley, & Sons, Chichester, U.K., **2010**, pp 437–468.
[21] A. Strecker, *Justus Liebigs Ann. Chem.* **1850**, *75*, 27–45.
[22] a) P. Vachal, E. N. Jacobsen, *Org. Lett.* **2000**, *2*, 867–870; b) P. Vachal, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 10012–11014.
[23] a) X. Huang, J. L. Huang, Y. H. Wen, X. M. Feng, *Adv. Synth. Catal.* **2006**, *348*, 2579–2584; b) Z. R. Hou, J. Wang, X. H. Liu, X. M. Feng, *Chem. Eur. J.* **2008**, *14*, 4484–4486.
[24] a) J. Wang, X. L. Hu, J. Jiang, S. H. Gou, X. Huang, X. H. Liu, X. M. Feng, *Angew. Chem.* **2007**, *119*, 8468–8470; b) J. Wang, W. Wang, W. Li, X. Hu, K. Shen, C. Tan, X. Liu, X. Feng, *Chem. Eur. J.* **2009**, *15*, 11642–11659.
[25] a) S. Masumoto, H. Usuda, M. Suzuki, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2003**, *125*, 5634–5635; b) N. Kato, T. Mita, M. Kanai, B. Therrien, M. Kawano, K. Yamaguchi, H. Danjo, Y. Sei, A. Sato, S. Furusho, M. Shibasaki, *J. Am. Chem. Soc.* **2006**, *128*, 6768–6769.
[26] *Stereochemistry of Organic Compounds*, (Eds.: E. L. Eliel, S. H. Wilen, L. N. Mander), Wiley, New York, **1994**.
[27] *Perry's Standard Tables and Formulas for Chemical Engineers*, (Ed.: J. G. Speight), McGraw-Hill, New York, **2003**.
[28] a) C. Reichardt, E. Harbusch-Görnert, *Liebigs Ann. Chem.* **1983**, 57–61; b) C. Reichardt, *Chem. Rev.* **1994**, *94*, 2319–2358.
[29] CCDC 871788 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

