European Journal of Organic Chemistry

S_N2' Alkylation of Chiral Allylic Cyanohydrin *O*-Phosphates with Organocuprates

Alejandro Baeza, Carmen Nájera* and José M. Sansano
Departamento de Química Orgánica, Facultad de Ciencias, and Instituto de Síntesis Orgánica (ISO), Universidad de Alicante.
Apdo. 99, 03080 Alicante, Spain.
Fax: +34 965903549
E-mail: cnajera@ua.es

Dedicated to Prof. Henri B. Kagan for its pivotal contribution in asymmetric synthesis

Received (will be filled in by the editorial staff)

copper / allylic substitution / asymmetric synthesis/ unsaturated nitriles/cyanophosphates

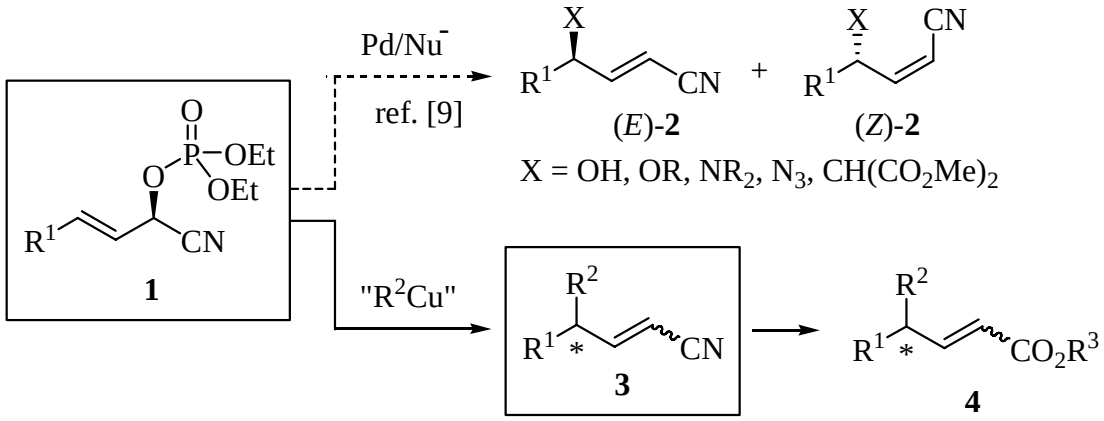
Abstract: Enantiomerically enriched cyanohydrin *O*-phosphates, prepared by enantioselective cyanophosphorylation of α,β-unsaturated aldehydes, react regioselectively with organocuprates derived from alkyl Grignard reagents and CuCN at the γ-position to afford chiral γ-alkyl substituted α,β-unsaturated nitriles. The configuration of the new C-C double bond is mainly *E* when the reaction is performed at –78 ºC and *Z* at higher temperatures (0 ºC). A high transfer of the chirality in the new stereocentre is observed according to a stereospecific *anti*-attack onto the cyanophosphate. Enantiomerically enriched (*E*)-γ-alkylated α,β-unsaturated esters are prepared after subsequent methanolysis in a three step sequence from the corresponding α,β-unsaturated aldehydes. In addition, the synthesis of (*R*)-4-methylnonan-1-ol, also known as the sex pheromone of the yellow mealworm *Tenebrio molitor* L, and its (*S*)-enantiomer are carried out in a four-step route from (*E*)-oct-2-enal.

Introduction

The generation of a non-functionalised stereogenic centre is not a very easy task in modern organic chemistry. Traditionally, the reaction of an organometallic reagent with a chiral electrophilic substrate can be employed for this purpose, but unfortunately, many side reactions, such as isomerisations, eliminations and partial racemisations are associated to these processes.[1] Nowadays, the transformations involving asymmetric Michael-type addition of organometallics,[1][2] hydrogenations,[1]-[3] isomerisations,[1][2] cyclopropanations,[1][2] some C-C or C-H insertions,[1][2] and allylic nucleophilic substitutions[1][2][4][5] are mainly employed in order to achieve these fully alkylated/arylated stereocenters. Particularly, in allylic nucleophilic substitution reactions, the palladium catalysed process requires soft nucleophiles whilst copper catalyst allows the use of hard nucleophiles including Grignard and organozinc reagents. Recent progresses in the asymmetric allylic substitutions promoted by copper complexes make these transformations much more interesting. [5a] From all the possible combinations, the

employment of chiral organocuprates in stoichiometric amounts,[5][6] the use of chiral catalytic copper(II) reagents,[5][7] and the reactions performed with chiral substrates and organocuprates,[5][8] are the most frequently used in organic synthesis, employing allylic acetates, carbonates and phosphates.

It has been demonstrated that simple allylic phosphates are appropriate substrates to develop efficiently this process through a γ-*anti*-S_N2' stereocontrolled process.[6] The enantiomerically enriched unsaturated cyanophosphates **1**[9][10] would be promising candidates to underwent these type of displacements. In previous works, it was revealed their potential as chiral building blocks in the synthesis of the optically active (*E*)- and (*Z*)-γ-substituted α,β-unsaturated nitriles **2** using a palladium- or iridium-catalysed allylic nucleophilic substitution.[9] As a continuing survey on the synthetic applications of the cyanohydrin-*O*-phosphates **1** as chiral building blocks we focused our attention in the direct nucleophilic allylic substitution mediated by organocuprates onto them. It has been only reported the regioselective reaction of stoichiometric amounts of lithium-organocuprates onto racemic cyanophosphates obtaining different diastereoselectivities, depending on the applied reaction conditions, favouring the final (*Z*)-configuration necessary for the synthesis of the racemic (±)-manicone, (±)-nuciferal and both isomers of (±)-nuciferol.[11] In this article the results of the S_N2' by addition of organocuprates onto enantiomerically enriched β,γ-unsaturated cyanophosphates **1** for the synthesis of the corresponding optically active α,β-unsaturated nitriles **3** and their esters **4** will be described (Scheme 1).[12] These chiral α,β-unsaturated nitriles **3** can be considered as direct precursors of valuable chiral (*E*)-Michael acceptors, such as optically enriched α,β-unsaturated esters **4**, mainly with *E*-configuration, by simple alcoholysis. These compounds **4** have been recently prepared using a stereoselective methyl cuprate addition onto allylic bromides followed by crossed metathesis with methyl acrylate.[7a] More functionalised chiral α,β-unsaturated esters of the type **4** have been obtained in a one-pot sequential organocatalytic asymmetric Mannich reaction followed by a Horner-Wadsworth-Emmons olefination.[13]



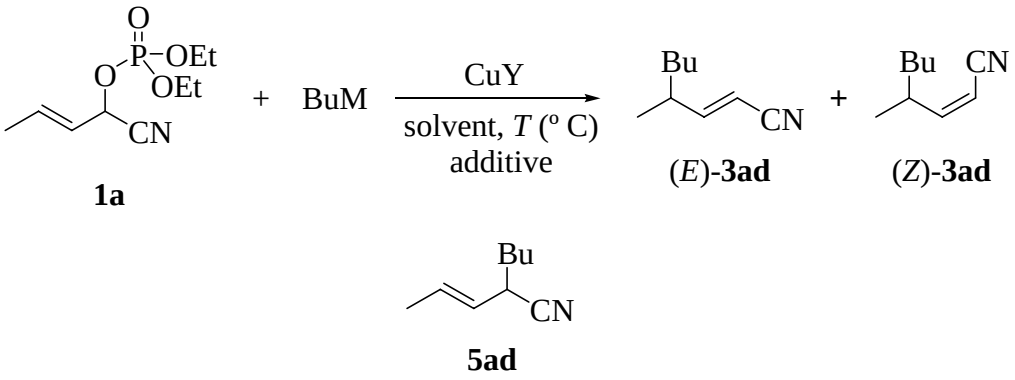
Scheme 1

Results and Discussion

The reaction of organocopper reagents onto allylic electrophiles is normally influenced by multiple parameters, many of them apparently negligible but at the end of the transformation become

crucial in the regioselectivity, diastereoselectivity, reaction time, yields, etc.[5] Initially we searched for the optimal reaction conditions for the allylic substitution reaction comparing the results with the analogous published in the literature for racemic cyanohydrin *O*-phosphates.[11] These tests were performed using the racemic cyanophosphate **1a** as starting material, which was obtained in quantitative yield from crotonaldehyde and diethyl cyanophosphonate in absence of solvent and using catalytic amounts of triethylamine (10 mol%) in 5 min at room temperature.[14] When *n*-butyllithium and stoichiometric amounts of CuCN were employed to form the corresponding organocopper reagent, the reaction was not reproducible, obtaining the product derived from the attack of the alkyl group onto the phosphorous atom, together with variable amounts of the γ-substitution product (*Z*)-**3ad** and the α-substitution product **5ad**, such as it was previously described.[11] However, when a organocopper reagent, freshly generated by mixing *n*-butylmagnesium bromide or chloride (instead of *n*-butyllithium) with a copper(I) source under an argon atmosphere, in THF or diethyl ether as solvents, the reaction proceeded cleanly at low temperatures and with high conversions to give regioselectively products **3ad** (Scheme 2 and Table 1). The first parameter studied was the effect of the halogenide nature of the Grignard reagent using in both reactions CuCN as copper salt, at –78 ºC, and THF as solvent (Table 1, entries 1 and 2). The reaction took place with total conversion within 1 h, but the (*E/Z*)-ratio of **3ad** was higher when it was employed ^{n}BuMgCl rather than ^{n}BuMgBr. The role of the solvent was impresive, the difference between using anhydrous THF or diethyl ether at –78 ºC is shown in entries 1 and 3 of the Table 1. The change of THF by diethyl ether afforded, after 15 h, a very low conversion (25%) at this temperature, approximately the same conversion that the obtained after 1.5 h. When the temperature of the reaction was 0 ºC the (*Z*)-**3ad**-isomer was obtained as major product but with low diastereoselectivity (Table 1, compare entries 1 and 4). When it was modified the Cu(I) source, using CuBr·SMe_2 instead of CuCN, at –78 ºC the reaction took place with a high diastereoselection for the (*Z*)-**3ad** product, but unfortunately with a low conversion (Table 1, entry 5) and the reaction failed at 0 ºC, obtaining a complex mixture of undesired products in the reaction crude (Table 1, entry 6).

Once we found the optimal S_N2' reaction conditions onto **1a** [CuCN (1.5 equiv.) as Cu(I) source, *n*-BuMgCl (3 equiv.) in THF and at –78 ºC], the influence of some additives was evaluated. TMSCl was used as additive (1.5 equiv.) because it acts as complexating agent with organocopper reagent, favouring the allylic substitution (S_N2') process over the α-substitution process (S_N2).[15] When the reaction was carried out at –78 ºC it was complete after 1 hour, slightly favouring the formation of (*Z*)-**3**-isomer (Table 1, entry 7). This trend was slightly higher when the reaction was carried out at 0 ºC (Table 1, entry 8). In both cases, the (*E/Z*)-diastereoselection was similar to the ratio isolated in the reaction run in absence of additives (Table 1, compare entries 4 and 8). The employment of ^{n}BuCu·BF_3[11] at several temperatures gave very low yields of compounds **3** (Table 1, entry 9).



Scheme 2

Table 1. Optimization of the S_N2' reaction of organocopper compounds onto racemic cyanophosphate **1a**.

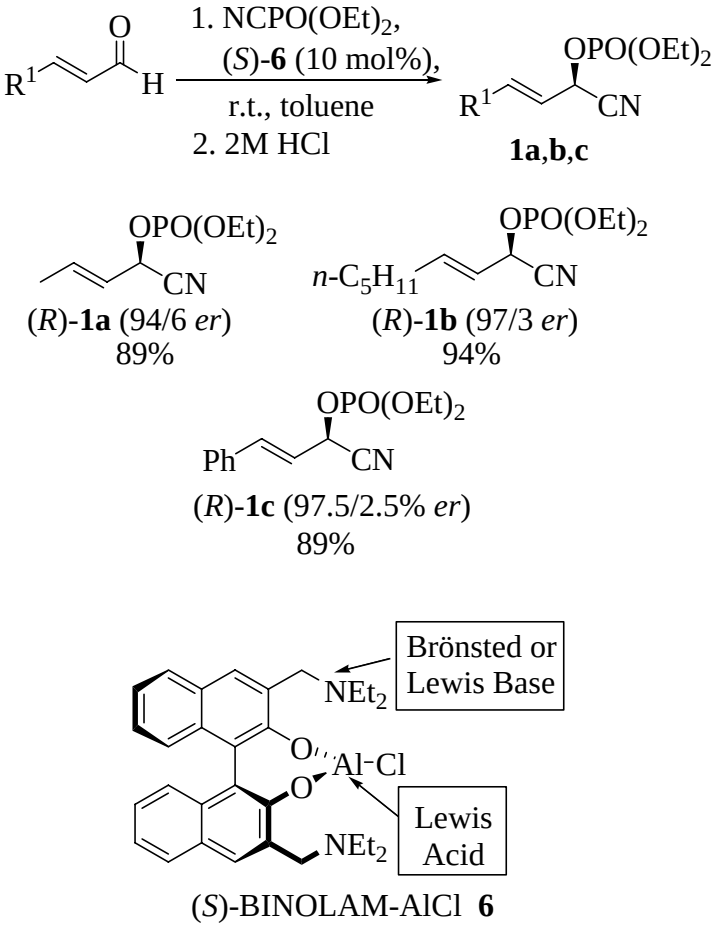
Entry	^{n}BuM [a]	CuY[b]	Additive	Solvent	*T* [ºC]	*t* [h]	Conv. [%][c]	(*E*/*Z*)-**3**[d]
1	^{n}BuMgCl	CuCN	—	THF	–78	1	100	70:30
2	^{n}BuMgBr	CuCN	—	THF	–78	1	100	55:45
3	^{n}BuMgCl	CuCN	—	Et_2O	–78	1.5	20	40:60
4	^{n}BuMgCl	CuCN	—	THF	0	1	100	40:60
5	^{n}BuMgCl	CuBr·SMe_2	—	THF	–78	2	35	12:88
6	^{n}BuMgCl	CuBr·SMe_2	—	THF	0	1.5	—	—
7	^{n}BuMgCl	CuCN	TMSCl[e]	THF	–78	1	100	44:56
8	^{n}BuMgCl	CuCN	TMSCl[e]	THF	0	1	100	38:62
9	^{n}BuCu[f]	—	BF_3[g]	THF	–78	1.5	10	37:63

[a] 3 equiv. of Grignard reagent were added. [b] 1.5 equiv. of copper(I) salt were added. [c] Determined by ^{1}H-NMR spectroscopy of the reaction crude. [d] Determined by ^{1}H-NMR spectroscopy of the reaction crude. [e] 1.5 equiv. of TMSCl were added. [f] Previously formed at –30 ºC by mixing ^{n}BuLi (2.4 equiv.) and CuI (1.2 equiv.). [g] 1.2 equiv. of BF_3·Et_2O were added.

The reaction performed with substoichiometric amounts of copper(I) salts and stoichiometric amounts of the organomagnesium reagent (at a range of temperatures of –78 to 0 ºC) did not give satisfactory results; a complex mixture of decomposition products was obtained in the reaction crude due to the high reactivity of the cyanophosphate **1a**.[9] An identical behaviour was observed when organozinc compounds, instead of the Grignard reagents, were used. Other Grignard reagents, such as arylmagnesium halides, gave the γ-substitution products in very low conversions, the biaryl compound originated from the homocoupling reaction being the major product. In addition, the reaction with cuprates failed in the case of other *O*-protected cyanohydrins, such as the methyl *O*-carbonate or the *O*-benzoyl cyanohydrin derived from crotonaldehyde.

The optimal reaction conditions were implemented with chiral cyanophosphates **1**. These chiral cyanohydrin derivatives **1** have been prepared in very high *er* from aldehydes, [9][10] in only one step process, using chiral bifunctional[16] (*R*)- or (*S*)-BINOLAM-AlCl complex **6** as catalysts.[9] This method

required a 10 mol% of the catalyst (*S*)-**6** and 3 equiv. of diethyl cyanophosphonate at room temperature under anhydrous conditions (Scheme 3).[9] The additional treatment of the reaction mixture in acidic media was made with the aim to recover the chiral ligand (*S*)-3,3'-bis(diethylaminomethyl)-1,1'-bi(2-naphthol) (*S*)-BINOLAM almost quantitatively (up to 91%).[9] During the preparation of (*R*)-**1a** in a large scale (0.5 g) we noticed that its enantiomeric ratio (*er*) was very sensitive to the humidity present in the freshly distilled crotonaldehyde, the enantiomeric excesses being achieved in the range of 88 to 92%.



Scheme 3

The temperature range of the allylic nucleophilic substitution was adapted on the basis of the reactivity and steric hindrance of the alkylmagnesium chlorides. In this way, the reaction carried out with an excess of organocopper species (generated previously by mixing alkylmagnesium chlorides with CuCN) in dry THF was carried out at –78 ºC (method A), at 0 ºC (method B) or by adding the organocopper species at –78 ºC and allowing the temperature to reach 0 ºC (method C) (Scheme 4). The reaction of the enantiomerically enriched allylic cyanophosphonate **1a**, derived from crotonaldehyde, with the organocopper formed with *n*-butyl or benzylmagnesium chloride was very fast at –78 ºC giving the (*E*)-diastereoisomer **3a** as major product following the method A (Table 2, entries 1 and 8), whereas method B gave poorer diastereoselectivities. Unfortunately, a small loss of *er* in the final products **3** was observed versus the original enantiomeric ratio of cyanophosphate **1a**. In addition, the reaction with the *n*-

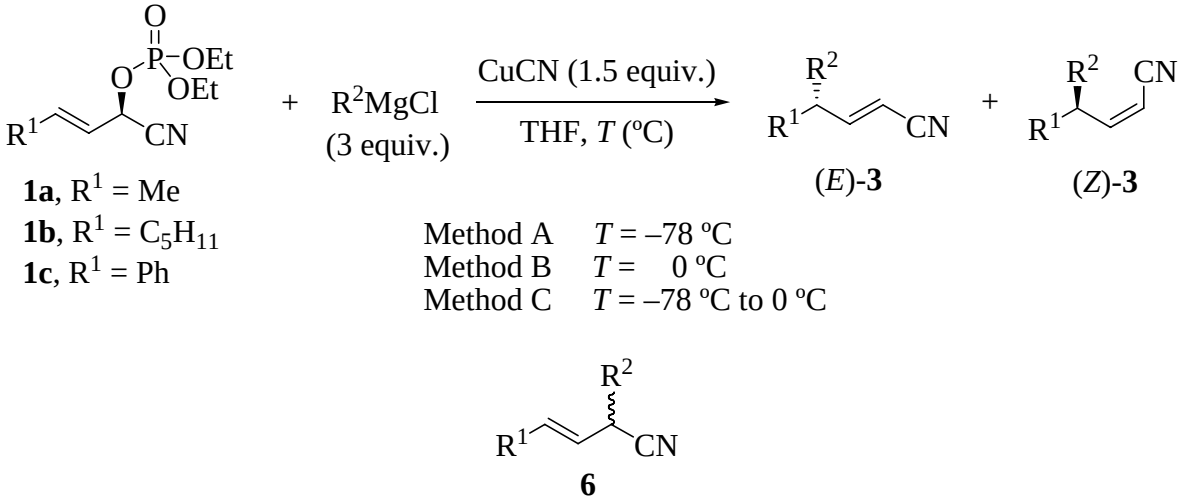
butyl derivative in presence of TMSCl also gave satisfactory results, although in this case the loss of enantioselectivity was slightly higher (Table 2, entry 3). In contrast, when isopropyl or *tert*-butylmagnesium chloride were used to form the organocopper reagent, a better transfer of chirality was achieved using method B conditions, obtaining 93.5:6.5 or 90:10 *er*, respectively, being the (*Z*)-product the major isomer in both cases (Table 2, entries 5 and 7), whereas almost equimolecular mixtures of both isomers (*E*/*Z*)-**3** were obtained at –78 ºC (method A) in lower yields (Table 2, entries 4 and 6).

When the chiral allylic cyanophosphate **1b**, derived from (*E*)-2-octenal was used, a similar behaviour was observed. Thus, the use of methylmagnesium chloride as precursor of the organocopper reagent furnished almost exclusively the compound (*E*)-**3ba** in very high yield and with any racemisation degree either with method A or B (Table 2, entries 10 and 11). In other hand, the use of a bulkier group as isopropyl in the organocopper reagent did not react at all under the conditions described for method A (Table 2, entry 12), but with the range of temperatures described for methods B and C (*E*/*Z*)-isomers **3bc** were obtained in good yield and with the same *er* that the original cyanophosphate **1b** (Table 2, entries 13 and 14). At this point, in order to discard the double carbon-carbon bond isomerisation caused by the cuprate residues of the initial addition, we run two experiments. In the first one, a equimolar mixture of (*E/Z*)-**3bc** was added to a completed reaction with excess of $Pr^{i}MgCl$/CuCN obtaining, after 1 h at 0 ºC, just the sum of the known reaction (27:73, Table 2, entry 13) and the added 1:1 mixture. In a second test, the (*E/Z*)-mixture of the resulting **3bc**, generated from analogous reaction at 0 ºC (Table 2, entry 13), was determined by ^{1}H NMR spectroscopy after 1.5, 3 and 6 h, obtaining exactly the same dr (27:73).

Surprisingly, the use of *n*-butylmagnesium chloride for the generation of the organocopper reagent gave almost equimolecular amounts of (*E*/*Z*)-**3bd** when the reaction was carried out using method A (Table 2, entry 15). The increasing temperature (method B) led, predominantly, to the formation of (*Z*)-isomer **3bd** (Table 2, entry 16). In the case of benzylmagnesium chloride, (*E*)-**3bf** was mainly obtained with slight degree of racemisation (Table 2, entries 17 and 18). It is worthy to note that compounds **1b** gave the corresponding S_N2' products **3b** without any loss of enantiomeric purity.

The chiral allylic cyanohydrin-*O*-phosphate **1c**, derived from cinnamaldehyde, has been classified as a very reactive and easily racemisable molecule in the Pd-catalysed reactions involving moderate to strong basic reagents.[9] The addition reaction with the cuprate generated from methylmagnesium chloride was carried out following methods A, B and C (Table 2, entries 19-21) obtaining under last reaction conditions a very high (*E/Z*)-ratio of **3ca** in very good yields and surprisingly with a slight loss of optical purity (Table 2, entry 21). The reaction failed using method A and (*E*/*Z*)-ratio of **3ca** dropped to (76:24) in the case of method B (Table 2, entries 19 and 20). For ethyl and *n*-butyl organocopper compounds (Table 2, entries 22-25) the method A was preferred rather than method B (Table 2, entries 23 and 25), because better yields and higher proportions of the (*E*)-**3** compounds were obtained, whilst method C gave the same result as method A. Again, the most basic *n*-butyl group promoted the highest racemisation of this series such as occurred when **1a** was selected as starting material (Table 2, compare entries 1 and 24). In this example, considerable proportion of the α-substitution product **5cd** was obtained (27%). When isopropyl or benzylmagnesium chlorides were employed following the reaction conditions described by method A, the reaction failed. Nevertheless, methods B and C were effective, obtaining with both of them product **3cc** with reversal diastereomeric ratio in the case of isopropylmagnesium chloride (Table 2, entries 27 and 28). However, the benzylic product (*E*)-**3cf** was isolated with better yield when

method B was essayed (Table 2, entries 29 and 30). It can be concluded that only a slight loss of the *er* was observed in the case of the cyanophosphate **1c**.



Scheme 4

Table 2. Allylic substitution onto enantioenriched cyanophosphates.

Entry	**1** (*er*)	R^2	Method	*t* [h]	**3**	(*E*)-**3**/(*Z*)-**3** [a]	Yield [%][b]	*er*[c]
1	**1a** (94:6)	^{n}Bu	A	1	**3ad**	70:30[d]	87	86:14
2	**1a** (94:6)	^{n}Bu	B	1	**3ad**	40:60	88	86:14
3	**1a** (94:6)	^{n}Bu	B[e]	1	**3ad**	38:62	83	82:18
4	**1a** (94:6)	^{i}Pr	A	1	**3ac**	48:52	67	93.5:6.5
5	**1a** (94:6)	^{i}Pr	B	1	**3ac**	35:65	89	93.5:6.5
6	**1a** (94:6)	^{t}Bu	A	2.5	**3ae**	58:42	72	90:10
7	**1a** (94:6)	^{t}Bu	B	1.5	**3ae**	37:63	85	90:10
8	**1a** (94:6)	Bn	A	1.5	**3af**	92:8	92	88:12
9	**1a** (94:6)	Bn	B	2	**3af**	70:30	43	88:12
10	**1b** (97:3)	Me	A	2	**3ba**	91:9	82	97:3
11	**1b** (97:3)	Me	B	1	**3ba**	61:39	89	97:3
12	**1b** (97:3)	^{i}Pr	A	3	**3bc**	nd	<20	nd
13	**1b** (97:3)	^{i}Pr	B	1.5	**3bc**	27:73	88	97:3
14	**1b** (97:3)	^{i}Pr	C	1.5	**3bc**	51:49	89	97:3
15	**1b** (97:3)	^{n}Bu	A	2	**3bd**	54:46	80	97:3
16	**1b** (97:3)	^{n}Bu	B	1	**3bd**	32:68	87	97:3
17	**1b** (97:3)	Bn	A	4	**3bf**	85:15	81	93.5:6.5[f]
18	**1b** (97:3)	Bn	B	2	**3bf**	61:39	84	93.5:6.5[f]
19	**1c** (97.5:2.5)	Me	A	2.5	**3ca**	nd	nd	nd
20	**1c** (97.5:2.5)	Me	B	1	**3ca**	76:24	89	92.5:7.5
21	**1c** (97.5:2.5)	Me	C	3	**3ca**	95:5	88	92.5:7.5
22	**1c** (97.5:2.5)	Et	A	1.5	**3cb**	69:31	86	90:10

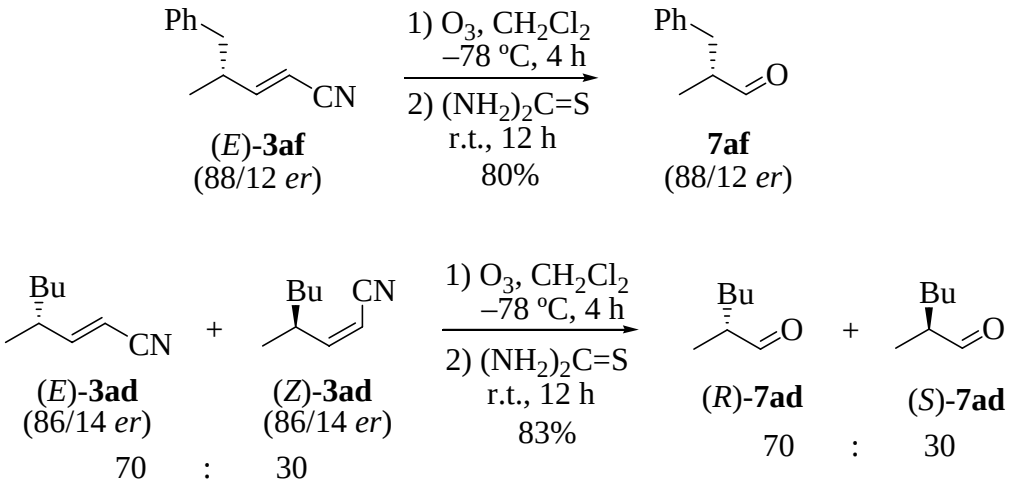
23	**1c** (97.5:2.5)	Et	B	1	**3cb**	52:48	88	90:10
24	**1c** (97.5:2.5)	^{n}Bu	A	1	**3cd**	87:13[g]	86	79:21[h]
25	**1c** (97.5:2.5)	^{n}Bu	B	1	**3cd**	nd	<20	nd
27	**1c** (97.5:2.5)	^{i}Pr	B	1	**3cc**	39:61	83	95:5
28	**1c** (97.5:2.5)	^{i}Pr	C	3	**3cc**	60:40	53	95:5
29	**1c** (97.5:2.5)	Bn	B	2.5	**3cf**	70:30	86	92.5:7.5
30	**1c** (97.5:2.5)	Bn	C	3	**3cf**	68:32	47	92.5:7.5

[a] Determined by ^{1}H-NMR spectroscopy of crude products. [b] Isolated yield of pure compounds after flash chromatography. [c] Determined by chiral HPLC analysis (Chiralpak AS), being the same in both pure isomers *E* and *Z* . [d] 7% of α-substitution was obtained. [e] 1.5 equiv. of TMSCl were added. [f] Determined by chiral HPLC analysis (Chiralcel OJ), being the same in both isomers (*E* and *Z*). [g] A 27% of α-substitution was obtained. [h] The *er* of γ- and α-substitution products were determined by chiral HPLC analysis (Chiralcel OJ), being the same in all products. nd = not determined.

In summary, of we notice that (*E*)-isomers **3** were mainly obtained at low temperatures and (*Z*)-isomers **3** were the major diastereoisomers isolated when the reaction was performed at 0 ºC and no carbon-carbon double bond isomerisation was observed when the reaction was allowed for 6 h. Cuprates containing ^{i}Pr or ^{t}Bu groups gave almost identical (*E*/*Z*)-ratios of products **3a** at the same temperature and, particularly, afforded equimolar diastereomeric mixtures at –78 ºC. The highest proportions of (*E*)-isomers **3** were obtained when employing methyl- and benzylmagnesium chlorides at very low temperatures. Whereas, the highest (*Z*)-selectivity for molecules **3** was identified in the reactions run with cuprates derived from *n*-butyl and isopropylmagnesium chlorides at 0 ºC. The α-substitution product **5** was detected only when the cuprate generated with *n*-butylmagnesium chloride reacted with substrates **1a** and **1c** at –78 ºC. The racemisation occurred in larger extensions when *n*-butylmagnesium chloride reacted with phosphates **1a** and **1c**, however isopropylmagnesium chloride hardly caused loses of enantiomeric purity. When benzyl-, methyl- and *tert*-butylmagnesium chlorides were used final products **3** were obtained with a low degree of racemisation independently of the selected temperature of the reaction.

With the aim to determine the absolute configuration of compounds **3** and to confirm the predicted *anti*-attack, the transformation of compounds **3** to the known aldehydes **7** was designed. The ozonolysis was carried out in dichloromethane, at –78 ºC and, after a reductive treatment using thiourea, the final aldehydes **7** were obtained in very good yields (Scheme 5). From the reaction carried out with the pure (2*E*,4*R*)-**3af**, aldehyde (*R*)-**7af** was generated in high yields and without loss of enantiomeric purity, which was confirmed by chiral HPLC analysis (Chiracel OJ). The suggested absolute (*R*)-configuration (note the priority change around the new stereogenic centre from original allylic cyanophosphates), caused by expected *anti*-attack of the copper species onto allylic cyanophosphate, was confirmed by comparison of specific rotation with the reported values.[17] When the ozonolysis was performed with the 70:30 (*E*/*Z*)-mixture of compound **3ad**, the aldehyde **7ad** was obtained in high yield (83%). If we consider that (*E*)- and (*Z*)-isomers have opposite absolute configuration, the expected enantiomeric ratio for this mixture should be, (according to the already mentioned *anti*-addition of the organocopper

reagent), around 70:30. Unfortunately, the separation of both enantiomers was impossible neither by chiral HPLC nor by GC. However, the specific rotation of aldehydes **7ad** mixture was compared with the reported data[18] confirming the (*R*)-absolute configuration of the more abundant enantiomer of the mixture.



Scheme 5

Concerning the mechanism of the alkylation process, when a substrate containing a good leaving group in allylic position is treated with a organocopper reagent two processes can occur: S_N2 (upon α-position attack) and/or S_N2' (upon γ-position attack). This regioselectivity is determined, mainly, by starting material nature (in accordance with its steric and electronic properties), leaving group nature and copper reagent which are used. [5a][5c] If we assumed that the phosphate is a very good leaving group and is not coordinated to the organocuprate, the more important effects to explain the γ-position preference would came from steric requirements of both the substrate and the reagent. It is described that the reaction takes place upon a copper-double bond starting coordination, followed by oxidative addition to double bond to form the π-allyl copper intermediate, which evolves upon a reductive elimination to S_N2' product if this reductive elimination is fast enough, or to S_N2 product if it is not. This fast reductive elimination is favoured by the presence of electron-withdrawing groups in the organocopper reagent, as is our case, which could explain the high regioselectivity observed. [5a][5c] This stereospecific reaction takes place with absolute configuration inversion, due to *anti*-attack of organocopper reagent with respect to the leaving group.[5c] Corey et al. proposed, based on frontier-orbital theory, an explanation to this behaviour in which the organocopper reagents, in contrast with carbonucleophiles, have *d* fulfilled orbitals which can interact with double bond π* orbital in γ-position and more weakly with σ* orbital of carbon-leaving group bond (C-X)[19] (Figure 1).

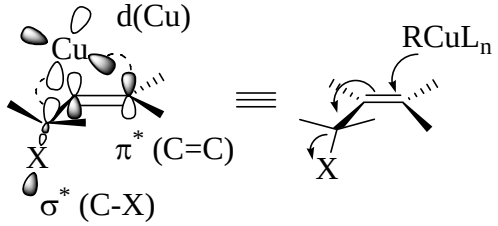
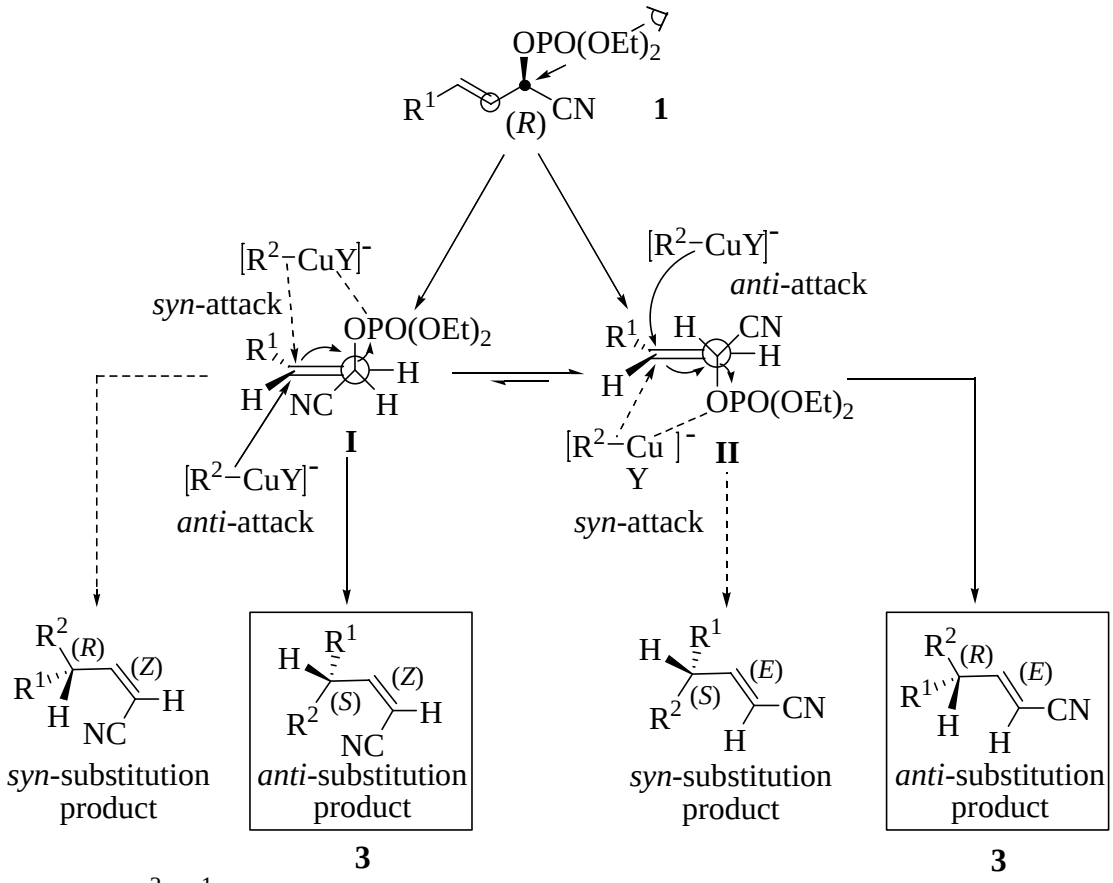


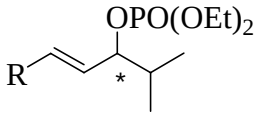
Figure 1

As consequence of this *anti*-attack onto optically active cyanophosphates both, the leaving group (phosphate) and the cuprate have to be essentially antiperiplanar (ap) in the transition-state. From all of the possible conformations, the more effective overlapping between σ* orbital [C-OPO(OEt)$_2$] and *d* orbital of the copper atom takes place in conformations **I** and **II** (Scheme 6). Conformation **II** is slightly more stable due to the linear cyano group does not represent enough high interactions with the rest of substituents. Onto this conformations can take place the *anti*-substitution if there is not coordination between leaving group and copper atom of organocopper reagent which attacks onto allylic cyanophosphate, or *syn*-substitution if this mentioned coordination exists (Scheme 6).



Scheme 6

The *anti*-attack onto the less sterically hindered *anti*-side onto the conformer **II** led to the formation, with total inversion of the configuration, of (*E*,*R*)-**3** diastereoisomer. This same attack onto conformer **I** produces (*Z*,*S*)-**3** diastereoisomer. It is necessary to note that, despite of the mentioned configuration inversion, the product **3** and the enantioenriched allylic cyanophosphate have the same stereogenic descriptors due to the change of priority around stereogenic centre (Scheme 6). Discarding the coordination between phosphate group and copper complexes it was initially expected that the (*E*)-isomer would be the major product according to the precedent work where a isopropyl group in



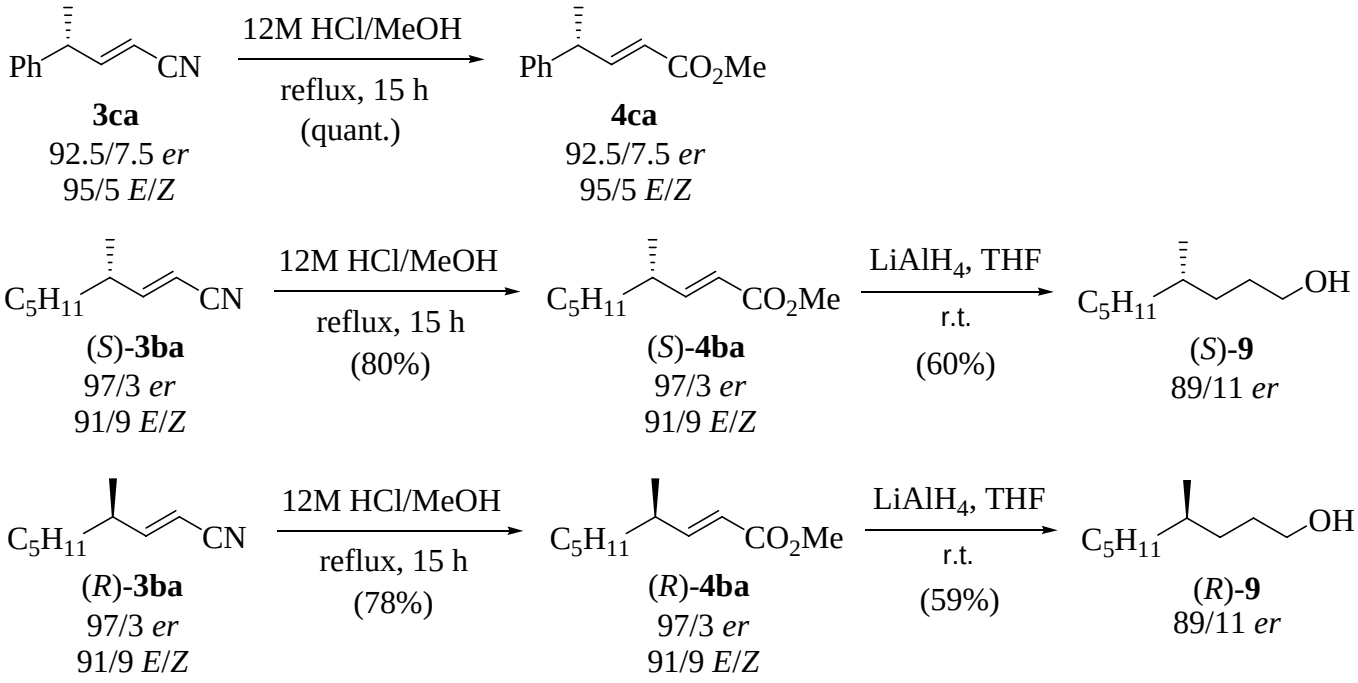
8

compound **8**, instead of the nitrile group, was present.[6] However, the amounts of the (*Z*)-isomers obtained were exceptionally too large. We reckon that the coordinative power of the nitrile group to the copper species is the responsible of this behaviour, so rotamers **I** and **II** must to be reconsidered as well as the nature of the Grignard reagent. The estimated values of dissociation energies (*D* in kcal mol^{-1}) for the C-Mg bond in methyl-, ethyl-, *n*-butyl-, isopropyl-, and *tert*-butylmagnesium bromides are 60, 49, 51, 44 and 42, respectively.[20] The higher dissociation energy of the methylmagnesium bromide would imply that magnesium cation remains closer to the coordination sphere of the copper atom, so the resulting metallic aggregate, coordinated to the nitrile group, would be very bulky and would favour the approach of the methyl group by the less sterically hindered conformer **II**. In fact, with methylmagnesium bromide the highest (*E*/*Z*)-ratios of all series of reactions were obtained (Table 2, entries 1, 10 and 21).

Obviously, the amount of the (*Z*)-isomer increased when the temperature of the reaction was higher (methods B and C). At –78 ºC (method A), the highest percentage of the (*Z*)-isomer was achieved by the most dissociated isopropyl group, whilst ethyl-, *n*-butyl-, and *tert*-butylmagnesium bromides gave very similar (*E*/*Z*)-ratios demonstrating that steric hindrance is not important in this mechanism (Table 2, compare entries 1, 2, 4, 5 6, 7 and 23). These data suggest that conformer **I** (or a rotamer very close in energy), where the nitrile is coordinated to a more simple copper complex (relatively free of magnesium), compete seriously with the rotamer **II**. The examples run with benzylmagnesium bromide deserve to be treated separately (Table 2, entries 8, 9, 17 and 18) because the benzylic group is very large (compared with Me, Et, ^{i}Pr, ^{n}Bu and ^{t}Bu) but its dissociation energy is 47 kcal mol^{-1} (similar to EtMgBr, ^{i}PrMgBr, ^{n}BuMgBr and ^{t}BuMgBr), so it would be expected a higher (*E*/*Z*)-ratio but not so elevated as the obtained when the MeMgBr was used as reagent for the formation of cuprates. Finally, the racemisation observed in some cases can arise from the well known sensitivity of the cyanophosphates in basic media especially compound **1c**.[9] Although the alkyl cuprates are not so strong bases as Grignard reagents but can promote this type of side processes.

The interest of enantiomerically enriched unsaturated nitriles **3** as chiral building blocks was next examined by preparing the α,β-unsaturated esters **4** through an acidic hydrolysis of the nitrile group. The best condition reactions were found using concentrated hydrochloric acid in methanol under reflux for 15 h generating the products **4ba** and **4ca** in 80% and quantitative yields (Scheme 7). This methodology represented a more simple and straightforward route than the already published one for the construction of the alkene **4ca**.[7a] Another application of the α,β-unsaturated nitrile (*E*,*S*)-**3ba**, prepared by the cyanohydrin *O*-phosphate (*R*)-**1b** was the synthesis of the enantiomerically enriched (*S*)-4-methylnonan-1-ol **9**, which is the enantiomer of the sex pheromone of the yellow mealworm *Tenebrio molitor* L.[21] The enantiomer (*R*)-**4ba**, obtained following the step described in Scheme 7, was reduced both the carbon-carbon double bond and the ester group with lithium aluminium hydride to give alcohol **9** in 48% yield. The low optical rotation value {$[\alpha]_D$ = –0.51 (*c* 2, $CHCl_3$); lit.[21] $[\alpha]_D$ = +0.63 ($CHCl_3$) (unknown concentration) was not a very reliable data for determining the *er* of natural product (*R*)-**9** but it was in agreement with the expected 89:11 *er* from the precursor (*E*,*R*)- and (*Z*,*S*)-**3ba** mixtures obtained during the nucleophilic allylic substitution reaction. Analogously, the natural product (*R*)-**9** {$[\alpha]_D$ = +0.48 (*c* 2, $CHCl_3$)} was prepared (46% overall yield) by the same route starting from cyanohydrin *O*-phosphate (*S*)-**1b**, which was enantioselectively generated with (*R*)-BINOLAM-AlCl **6** (Scheme 7). This four step access to enantiomerically enriched compounds **9** contrasted with the previously reported synthesis

involving eight and seven steps starting from chiral (*S*)-(+)-dihydromyrcene[21a] and methyl (*R*)-3-methylglutarate,[21e] respectively.



Scheme 7

Conclusion

It can be conclude that enantiomerically enriched (*E*)-α,β-unsaturated nitriles with an alkyl group at the stereogenic centre in γ-position can be prepared regio- and diasteroselectively by alkylation of cyanohydrins *O*-phosphates with organocuprates. These were the more appropriate substrates for this transformation because neither enantiomerically enriched cyanoformates nor *O*-benzoyl cyanohydrins underwent this nucleophilic allylic substitution. The reaction can be carried out in short times and with low racemisations and it could be considered as complementary transformation to the palladium-catalysed allylic substitution process, which allowed the introduction of heteronucleophiles and malonates. Although each substrate required a different set of optimal reaction conditions, we can assume that: a) when substrates **1a** and **1b** (derived from crotonaldehyde and oct-2-enal, respectively) were allowed to react at lower temperatures (method A) the (*E*)-isomer was the major isolated product and higher proportions of the (*Z*)-isomer were always achieved at 0 ºC (method B), b) substrate **1c** (derived from cinnamaldehyde) was more sensitive to the reaction conditions and to the type of cuprate, c) in most of cases the major (*E*)-diastereoselectivity was obtained specially with methyl and benzyl cuprates, whereas anomalous high proportions of the (*Z*)-isomers were observed when more dissociable Grignard reagents (*n*-butyl, isopropyl, and *tert*-butyl) were employed, d) in general, low racemisation degrees were detected specially for the cyanohydrin *O*-phosphate **1b**. The reaction mechanism involved an *anti*-attack of the organocopper species onto the allylic cyanophosphate as can deduced by the resulting configuration in the new created sterocenter in both (*Z*)- and (*E*)-diasteromers. Possibly the nitrile group would be able to

assist the S_N2' addition onto enantiomerically enriched cyanohydrin *O*-phosphates favouring the formation of this isomers. The methanolysis of these enantiomerically enriched α,β-unsaturated nitriles has allowed the preparation of (*E*)-γ-alkylated α,β-unsaturated esters in only three steps from the starting α,β-unsaturated aldehydes. This strategy can be applied to the synthesis of the sex pheromone (*S*)- and (*R*)-4-methylnonan-1-ol in a straightforward manner employing only four steps from the starting aldehyde.

Acknowledgements

This work has been supported by the DGES of the Spanish Ministerio de Educación y Ciencia (MEC) (CTQ2004-00808/BQU) and Generalitat Valenciana (CTIOIB/2002/320, GRUPOS03/134 and GV05/144) and by the University of Alicante. A. Baeza also thanks Generalitat Valenciana for a pre-doctoral fellowship (CTBPRB/2002/107).

Experimental Section

General Remarks: IR spectra were recorded on a Nicolet 510 P-FT, and only the structurally most relevant bands are listed. NMR spectra were performed on a Bruker AC-300 machine, using $CDCl_3$ as solvent and TMS as internal standard, unless otherwise stated. Low-resolution electron impact (EI) mass spectra were obtained at 70eV on a Shimadzu QP-5000, and low-resolution electrospray ionization (ESI) mass spectra were obtained on a Finnigan VG Platform. HRMS (EI) were recorded on a Finnigan MAT 95S. Microanalyses were carried out by the Microanalyses Service of the University of Alicante. Optical rotations were measured on a Perkin Elmer 341 polarimeter. Analytical TLC was performed on Schleicher & Schuell F1400/LS silica gel plates, and the spots visualized under UV light at 254 nm. GC analyses were done in a HP-5890SB and chiral HPLC analyses were run in a Jasco 2000 series (the chiral column and wavelength used is given for each compound, remarking in bold format the major enantiomer). The retention times for each isomer will be reported in the cases when it was possible the perfect separation of the four isomers, otherwise only the retention times of the major isomers obtained will be reported. For flash chromatography Merck silica gel 60 (0.040-0.063 mm) was employed.

General procedure to the allylic substitution by organocopper addition:

Method A: To a cooled suspension of CuCN (1.5 mmol, 134 mg) in dry THF (2 mL) at –78 ºC was added a solution of Grignard reagent (3 mmol, in THF) under Ar. The mixture was then stirred during 30 min. and a solution of the corresponding allylic cyanophosphate **1** (1 mmol) in dry THF (1 mL) was added at the same temperature. Stirring was continued at –78 ºC till the reaction was judged complete by GC. Ethyl acetate (10 mL) and aqueous saturated solution of NH_4Cl (10 mL) were added at room temperature. The mixture was stirred for 30 min and the organic layer was separated, dried ($MgSO_4$) and evaporated to obtain the crude compounds, which were purified by flash chromatography affording pure products **3**.

Method B: To a cooled suspension of CuCN (1.5 mmol, 134 mg) in dry THF (2 mL) at –78 ºC was added a solution of Grignard reagent (3 mmol, in THF) under Ar. The mixture was then stirred during 30 min. and a solution of the corresponding allylic cyanophosphate **1** (1 mmol) in dry THF (1 mL) was added at the same temperature. Stirring was continued whilst the temperature was allowed to raise slowly 0 ºC (aprox. 1.5 h). Ethyl acetate (10 mL) and aqueous saturated solution of NH_4Cl (10 mL) were added at room temperature. The mixture was stirred for 30 min and the organic layer was separated, dried

($MgSO_4$) and evaporated to obtain the crude compounds, which were purified by flash chromatography affording pure products **3**.
Method C: Same as method A but at 0º C.

(2*E*,4*R*)-4-Methyloct-2-enenitrile (3ad): (Table 2, entry 1, 119 mg, 87%). Pale yellow oil; $[\alpha]^{25}_{D}$ = –9.0 (*c* = 0.4, $CHCl_3$ for the mixture *E:Z* 70:30) [72% *ee* for each isomer from HPLC; DAICEL CHIRALPAK AS, λ = 206 nm, *n*-hexane, 1 mL/min, t_r = **12.3** and 13.2 min (*E*-isomer)]; TLC: R_f 0.82 (*n*-hexane/ethyl acetate, 4:1); *E*-isomer ^{1}H NMR (300 MHz): δ_H 0.88 (t, *J* = 6.9 Hz, 3H, CH_3), 1.07 (d, *J* = 6.6 Hz, 3H, CH_3), 1.24-1.40 (m, 6H, 3xCH_2), 2.29 (m, 1H, C*H*CH_3), 5.27 (d, *J* = 16.4 Hz, 1H, CHCN), 6.60 (dd, *J* = 16.4, 7.9 Hz, 1H, C*H*=CHCN) ppm; ^{13}C NMR (75 MHz): δ_C 13.9 (CH_3), 18.8 (*C*H_3CH), 22.5 (CH_2), 29.2 (CH_2), 35.3 (*C*H_2CH), 37.7 (*C*HCH_3), 98.0 (*C*HCN), 117.7 (CN), 161.4 (*C*H=CHCN); (*Z*)-isomer ^{1}H NMR (300 MHz): δ_H 0.88 (t, *J* = 6.9 Hz, 3H, CH_3), 1.07 (d, *J* = 6.4 Hz, 3H, CH_3), 1.24-1.40 (m, 6H, 3xCH_2), 2.74 (m, 1H, C*H*CH_3), 5.25 (d, *J* = 10.8 Hz, 1H, CHCN), 6.25 (t, *J* = 10.8 Hz, 1H, C*H*=CHCN) ppm; ^{13}C NMR (75 MHz): δ_C 13.9 (CH_3), 19.9 (*C*H_3CH), 22.5 (CH_2), 29.3 (CH_2), 35.9 (*C*H_2CH), 37.0 (*C*HCH_3), 97.8 (*C*HCN), 116.1 (CN), 160.7 (*C*H=CHCN) ppm; IR (neat): ν = 2222, 1631 cm^{-1}; MS (EI): *m/z* (%) = 137 $[M]^+$ (0.3), 94 (18), 84 (24), 83 (29), 82 (19), 81 (100), 80 (48); HRMS calcd for $C_8H_{12}N$ (M^+ - Me): 122.0969; found 122.0968.

(2*Z*,4*S*)-4,5-Dimethylhex-2-enenitrile (3ac): (Table 2, entry 5, 109 mg, 89%). Colourless oil; $[\alpha]^{25}_{D}$ = –19.3 (*c* = 1.0, $CHCl_3$ for the mixture *E*:*Z* 35:65) [87% *ee* for each isomer from HPLC; DAICEL CHIRALPAK AS, λ = 215 nm, *n*-hexane/2-propanol 99:1, 1 mL/min, t_r = **5.2** and 5.7 min, (*Z*-isomer) and **5.9** and 6.2 min, (*E*-isomer)]; TLC: R_f 0.87 (*n*-hexane/ethyl acetate, 9:1); (*E*)-isomer ^{1}H NMR (300 MHz): δ_H 0.86 and 0.88 (2xd, *J* = 6.7 Hz, 2x3H, CH(CH_3)$_2$], 1.01 (d, *J* = 6.9 Hz, 3H, CH_3C*H*), 1.64 [m, 1H, C*H*(CH_3)$_2$], 2.15 (m, 1H, C*H*CH=CH), 5.26 (dd, *J* = 16.4 , 1.1 Hz, 1H, CHCN), 6.65 (dd, *J* = 16.4 , 8.1 Hz, 1H, C*H*=CHCN) ppm; ^{13}C NMR (75 MHz): δ_C 17.3 (CH_3), 19.6 and 19.9 [(CH_3)$_2$], 32.4 [*C*H(CH_3)$_2$], 43.2 (*C*HCH_3), 98.8 (*C*HCN), 117.5 (CN), 159.5 (*C*H=CHCN) ppm; (*Z*)-isomer ^{1}H NMR (300 MHz): δ_H 0.88 and 0.93 [2xd, *J* = 6.8 Hz, 2x3H, CH(CH_3)$_2$], 1.04 (d, *J* = 6.7 Hz, 3H, CH_3C*H*), 1.60 [m, 1H, C*H*(CH_3)$_2$], 2.56 (m, 1H, C*H*CH=CH), 5.28 (d, *J* = 10.8 Hz, 1H, CHCN), 6.32 (t, *J* = 10.8 Hz, 1H, C*H*=CHCN) ppm; ^{13}C NMR (75 MHz): δ_C 15.7 (CH_3), 19.5, 19.6 [(CH_3)$_2$], 32.9 [*C*H(CH_3)$_2$], 44.0 (*C*HCH_3), 98.4 (*C*HCN), 117.1 (CN), 160.2 (*C*H=CHCN) ppm; IR (neat): ν = 2221, 1626 cm^{-1}; MS (EI): *m/z* (%) = 123 $[M]^+$ (0.03), 81 (100), 80 (40), 54 (19); HRMS calcd for $C_8H_{13}N$: 123.1048; found 123.1052.

(2*Z*,4*S*)-4,5,5-Trimethylhex-2-enenitrile (3ae): (Table 2, entry 7, 116 mg, 85%). Colourless oil; $[\alpha]^{25}_{D}$ = –18.1 (*c* = 1.0, $CHCl_3$ for the mixture *E*:*Z* 37:63) [80% *ee* for each isomer from HPLC; DAICEL CHIRALPAK AS, λ = 215 nm, *n*-hexane, 0.8 mL/min, t_r = **12.9** and 13.4 min, (*Z*-isomer) and **17.3** and 18.6 min, (*E*-isomer)]; TLC: R_f 0.84 (*n*-hexane/ethyl acetate, 9:1); (*E*)-isomer ^{1}H NMR (300 MHz): δ_H 0.87 [s, 9H, (CH_3)$_3$], 0.98 (d, *J* = 6.9 Hz, 3H, CH_3CH), 2.08 (m, 1H, C*H*CH_3), 5.28 (d, *J* = 16.4 Hz, 1H, CHCN), 6.70 (dd, *J* = 16.4, 9.0 Hz, 1H, C*H*=CHCN) ppm; ^{13}C NMR (75 MHz): δ_C 14.8 (*C*H_3CH), 27.1 [(CH_3)$_3$], 46.7 [*C*(CH_3)$_3$], 48.3 (*C*HCH_3), 98.6 (*C*HCN), 117.4 (CN), 158.6 (*C*H=CHCN) ppm; (*Z*)-isomer ^{1}H NMR (300 MHz): δ_H 0.90 [s, 9H, (CH_3)$_3$], 0.99 (d, *J* = 6.9 Hz, 3H, CH_3CH), 2.58 (m, 1H, C*H*CH_3), 5.29 (d, *J* = 10.9 Hz, 1H, CHCN), 6.39 (t, *J* = 10.9 Hz, 1H, C*H*=CHCN) ppm; ^{13}C NMR (75 MHz): δ_C 14.2 (*C*H_3CH), 27.3 [(CH_3)$_3$], 46.7 [*C*(CH_3)$_3$], 48.3 (*C*HCH_3), 99.3 (*C*HCN), 117.2 (CN), 159.4 (*C*H=CHCN) ppm; IR (neat): ν = 2222, 1631 cm^{-1}; MS (EI): *m/z* (%) = 122 [M^+- Me] (27.5), 105 (11), 95 (13), 81 (59), 80 (21), 57 (100); HRMS calcd for $C_8H_{12}N$ (M^+ - Me): 122.0969; found 122.0970.

(2*E*,4*R*)-4-Methyl-5-phenylpent-2-enenitrile (3af): (Table 2, entry 8, 158 mg, 92%). Colourless oil; $[\alpha]^{25}_{D}$ = –71.2 (*c* = 0.8, $CHCl_3$) [78% *ee* from HPLC; DAICEL CHIRALPAK AS, λ = 215 nm, *n*-hexane/2-propanol 99:1, 1 mL/min, t_r = 11.6 and **12.4** min, (*E*-isomer) and t_r = **10.9** and 13.6 min, (*Z*-isomer)]; TLC: R_f 0.43 (*n*-hexane/ethyl acetate, 9:1); ^{1}H NMR (300 MHz): δ_H 1.07 (d, *J* = 6.4 Hz, 3H, CH_3), 2.66 (m with s at 2.64, 3H, CH_2 and C*H*CH_3), 5.20 (d, *J* = 16.4 Hz, 1H, CHCN), 6.67 (dd, *J* =

16.4,6.7 Hz, 1H, C*H*=CHCN), 7.11 (m, 2H, ArH), 7.22-7.32 (m, 3H, ArH) ppm; ^{13}C NMR (75 MHz): δ_C 18.4 (CH_3), 39.4 (*C*HCH$_3$), 42.1 (CH_2), 98.7 (*C*HCN), 117.5 (CN), 126.5, 128.5, 129.0 and 138.6 (ArC), 159.9 (*C*H=CHCN) ppm; IR (neat): ν = 2222, 1632 cm^{-1}; MS (EI): *m/z* (%) = 171 [M^+] (5.1), 91 (100), 65 (15), 106 (24), 92 (13), 91 (92); HRMS calcd for $C_{12}H_{13}N$: 171.1048; found 171.1052.

(2*E*,4*S*)-4-Methylnon-2-enenitrile (3ba): (Table 2, entry 10, 124 mg, 82%). Pale yellow oil; $[\alpha]^{25}_D$ = +24.4 (*c* = 0.5, $CHCl_3$ for the mixture *E*:*Z* 91:9) [94% *ee* from HPLC; DAICEL CHIRALPAK AS, λ = 215 nm, *n*-hexane, 1 mL/min, t_r = 12.5 and **13.2** min (*E*-isomer) and t_r = **12.9** and 13.4 min, (*Z*-isomer)]; TLC: R_f 0.82 (*n*-hexane/ethyl acetate, 9:1); ^{1}H NMR (300 MHz): δ_H 0.88 (t, *J* = 6.6 Hz, 3H, C*H*$_3$CH$_2$), 1.03 (d, *J* = 6.7 Hz, 3H, C*H*$_3$CH), 1.21-1.35 (m, 8H, 4xCH$_2$), 2.29 (m, 1H, C*H*CH$_3$), 5.26 (d, *J* = 16.4 Hz, 1H, CHCN), 6.60 (dd, *J* = 16.4, 7.9 Hz, 1H, C*H*=CHCN) ppm; ^{13}C NMR (75 MHz): δ_C 13.8 (*C*H$_3$CH$_2$), 18.8 (CH$_2$), 22.4 (CH$_3$CH), 26.6, 31.1, 31.6 (3xCH$_2$), 37.7 (*C*HCH$_3$) 98.0 (*C*H.CN), 119.1 (CN), 161.3 (*C*H=CHCN) ppm; IR (neat): ν = 2223, 1631 cm^{-1}; MS (EI): *m/z* (%) = 151 [M]$^+$ (1.0), 136 (31), 122 (18), 109 (19), 108 (38), 98 (33), 97 (34), 94 (36), 83 (31), 82 (23), 81 (100), 80 (56); HRMS calcd for $C_9H_{14}N$ (M^+ - Me): 136.1126; found 136.1124.

(2*Z*,4*S*)-4-Isopropylnon-2-enenitrile (3bc): (Table 2, entry 13, 158 mg, 88%). Pale yellow oil; $[\alpha]^{25}_D$ = +25.1 (*c* = 0.5, $CHCl_3$ for the mixture *E*:*Z* 27:73) [94% *ee* for each isomer from HPLC; DAICEL CHIRALPAK AS, λ = 215 nm, *n*-hexane, 1 mL/min, t_r = 6.1 and **7.7** min, (*Z*-isomer) and 9.5 and **9.7** min, (*E*-isomer)]; TLC: R_f 0.87 (*n*-hexane/ethyl acetate, 9:1); (*E*)-isomer ^{1}H NMR (300 MHz): δ_H 0.82-0.95 (m, 9H, C*H*$_3$CH$_2$ and 2xC*H*$_3$CH), 1.25-1.34 (m, 8H, 4xCH$_2$), 1.56 (m, 1H, C*H*CH$_3$), 1.92 (m, 1H, C*H*CH=CH), 5.25 (d, *J* = 16.4 Hz, 1H, CHCN), 6.50 (dd, *J* = 16.4, 9.9 Hz, 1H, C*H*=CHCN) ppm; ^{13}C NMR (75 MHz): δ_C 14.2 (*C*H$_3$CH$_2$), 18.9 and 20.6 (2xCH$_3$), 27.0, 31.2, 31.7 and 31.8 (4xCH$_2$), 31.8 (*C*HCH$_2$), 50.7 (*C*HCH$_2$), 100.0 (*C*HCN), 117.2 (CN), 159.0 (*C*H=CHCN) ppm; (*Z*)-isomer ^{1}H NMR (300 MHz): δ_H 0.82-0.95 (m, 9H, C*H*$_3$CH$_2$ and 2xC*H*$_3$CH), 1.25-1.34 (m, 8H, 4xCH$_2$), 1.68 (m, 1H, C*H*CH$_3$), 2.45 (m, 1H, C*H*CH=CH), 5.36 (d, *J* = 10.9 Hz, 1H, CHCN), 6.26 (t, *J* = 10.9 Hz, 1H, C*H*=CHCN) ppm; ^{13}C NMR (75 MHz): δ_C 14.0 (*C*H$_3$CH$_2$), 19.0, 20.6 (2xCH$_3$), 22.5, 27.1, 31.4 and 31.8 (4xCH$_2$), 31.8 (*C*HCH$_2$), 48.9 (*C*HCH$_3$), 99.9 (*C*HCN), 117.1 (CN), 158.3 (*C*H=CHCN) ppm; IR (neat): ν = 2224, 1625 cm^{-1}; MS (EI): *m/z* (%) = 179 [M]$^+$ (0.5), 137 (60), 108 (19), 95 (24), 94 (50), 81 (28), 80 (100); HRMS calcd for $C_{12}H_{21}N$: 179.1674; found 179.1677.

(2*Z*,4*R*)-4-Butylnon-2-enenitrile (3bd): (Table 2, entry 16, 168 mg, 87%). Yellow oil; $[\alpha]^{25}_D$ = +2.1 (*c* = 1, $CHCl_3$ for the mixture *E*:*Z* 32:68) [94% *ee* from HPLC; DAICEL CHIRALPAK AS, λ = 215 nm, *n*-hexane, 0.8 mL/min, t_r = 8.0 and **8.4** min (*Z*-isomer)]; TLC: R_f 0.61 (*n*-hexane/ethyl acetate, 9:1); (*E*)-isomer ^{1}H NMR (300 MHz): δ_H 0.88 (m, 6H, 2xC*H*$_3$CH$_2$), 1.26-1.39 (m, 10H, 5xCH$_2$), 1.46 (m, 4H, 2xC*H*$_2$CH), 2.12 (m, 1H, C*H*CH$_2$), 5.26 (d, *J* = 16.4 Hz, 1H, CHCN), 6.49 (dd, *J* = 16.4, 9.2 Hz, 1H, C*H*=CHCN) ppm; ^{13}C NMR (75 MHz): δ_C 13.9 (CH$_3$), 16.1 (CH$_2$), 22.5 (CH$_3$), 22.7, 26.7, 29.3, 30.3, 31.7 and 33.9 (5xCH$_2$), 44.1 (*C*HCH$_2$), 99.1 (*C*HCN), 116.5 (CN), 160.0 (*C*H=CHCN) ppm; (*Z*)-isomer ^{1}H NMR (300 MHz): δ_H 0.88 (m, 6H, 2xC*H*$_3$CH$_2$), 1.26-1.39 (m, 10H, 5xCH$_2$), 1.46 (m, 4H, 2xC*H*$_2$CH), 2.62 (m, 1H, C*H*CH$_2$), 5.31 (d, *J* = 10.9 Hz, 1H, CHCN), 6.19 (t, *J* = 10.9 Hz, 1H, C*H*=CHCN) ppm; ^{13}C NMR (75 MHz): δ_C 14.0 (CH$_3$), 16.2 (CH$_2$), 22.7 (CH$_3$), 22.6, 26.8, 29.3, 30.9, 31.8 and 34.5 (5xCH$_2$), 42.7 (*C*HCH$_2$), 99.1 (*C*HCN), 117.6 (CN), 160.7 (*C*H=CHCN) ppm; IR (neat): ν = 2221, 1621 cm^{-1}; MS (EI): *m/z* (%) = 193 [M]$^+$ (0.5), 164 (27), 136 (31), 124 (50), 123 (27), 110 (35), 108 (31), 95 (29), 94 (39), 83 (29), 81 (36), 80 (100); HRMS calcd for $C_{12}H_{20}N$ (M^+ - Me): 178.1595; found 178.1600.

(2*E*,4*R*)-4-Benzylnon-2-enenitrile (3bf): (Table 2, entry 17, 186 mg, 81%). Colourless sticky oil; $[\alpha]^{25}_D$ = –22.1 (*c* = 1.4, $CHCl_3$ for the mixture *E*:*Z* 85:15) [87% *ee* from HPLC; DAICEL CHIRALCEL OJ, λ = 215 nm, *n*-hexane/2-propanol 99.5:0.5, 0.8 mL/min, t_r = 16.3 and **21.2** min (*E*-isomer) and t_r = 11.6 and 12.0 (*Z*)-isomer]; TLC: R_f 0.52 (*n*-hexane/ethyl acetate, 9:1); (*E*)-isomer ^{1}H NMR (300 MHz): δ_H 0.88 (m, 3H, CH$_3$), 1.25-1.35 (m, 6H, 3xCH$_2$), 1.67 (m, 2H, C*H*$_2$CH), 2.44 (m, 1H, C*H*CH$_2$), 2.58 and 2.78 (2xm, 2H, CH$_2$Ph), 5.11 (dd, *J* = 16.4, 0.6 Hz, 1H, CHCN), 6.51 (dd, *J* = 16.4, 9.0 Hz, 1H, C*H*=CHCN),

7.11-7.18 (m, 3H, ArH), 7.21-7.31 (m, 2H, ArH) ppm; ^{13}C NMR (75 MHz): δ_C 13.9 (CH_3), 22.5, 31.6, 33.5 and 37.9 (4xCH_2), 40.7 (*C*HCH_2), 45.8 (*C*H_2Ph), 99.8 (*C*HCN), 117.4 (CN), 125.9, 128.3, 128.5 and 138.7 (ArC), 159.2 (*C*H=CHCN) ppm; (*Z*)-isomer ^{1}H NMR (300 MHz): δ_H 0.88 (m, 3H, CH_3), 1.25-1.35 (m, 6H, 3xCH_2), 1.67 (m, 2H, CH_2CH), 2.58 and 2.78 (2xm, 3H, CH_2Ph and C*H*CH_2), 5.24 (d, *J* = 10.8 Hz, 1H, CHCN), 6.19 (t, *J* = 10.8 Hz, 1H, C*H*=CHCN), 7.11-7.18 (m, 3H, ArH), 7.21-7.31 (m, 2H, ArH) ppm; ^{13}C NMR (75 MHz): δ_C 13.9 (CH_3), 25.4, 31.7, 33.9 and 37.9 (4xCH_2), 41.1 (*C*HCH_2), 44.1 (CH_2Ph), 99.7 (*C*HCN), 117.4 (CN), 126.3, 128.3, 129.0 and 140.8 (ArC), 158.5 (*C*H=CHCN) ppm; IR (neat): ν = 2221, 1611 cm^{-1}; MS (EI): *m/z* (%) = 227 [*M*]$^+$ (12), 92 (9), 91 (100); HRMS calcd for $C_{16}H_{21}N$: 227.1674; found 227.1669.

(2*E*,4*R*)-4-Phenylpent-2-enenitrile (3ca):[22] (Table 2, entry 21, 138 mg, 88%). Colourless oil; $[\alpha]^{25}_D$ = +58.7 (*c* = 1.0, $CHCl_3$ for the mixture *E*:*Z* 95:5) (85% *ee* from HPLC; DAICEL CHIRALPAK AS, λ = 215 nm, *n*-hexane/2-propanol 99:1, 1 mL/min, t_r = 8.8 and **9.8** min.); TLC: R_f 0.52 (*n*-hexane/ethyl acetate, 4:1); ^{1}H NMR (300 MHz): δ_H 1.42 (d, *J* = 7.1 Hz, 3H, CH_3), 3.59-3.65 (m, 1H, CHPh), 5.27 (dd, *J* = 16.4, 1.1 Hz, 1H, CHCN), 6.88 (dd, *J* = 16.4, 6.3 Hz, 1H, C*H*=CHCN), 7.17-7.28 (m, 2H, ArH), 7.33-7.36 (m, 3H, ArH) ppm; ^{13}C NMR (75 MHz): δ_C 19.7 (CH_3), 43.0 (CHPh), 98.9 (*C*HCN), 117.2 (CN), 127.2, 127.3, 128.9 and 141.7 (ArC), 159.2 (*C*H=CHCN) ppm; IR (neat): ν = 2224, 1637 cm^{-1}; MS (EI): *m/z* (%) =157 [*M*]$^+$ (67), 156 (71), 142 (100), 129 (25), 115 (81).

(2*E*,4*R*)-4-Phenylhex-2-enenitrile (3cb): (Table 2, entry 22, 15 mg, 9%). Colourless oil; $[\alpha]^{25}_D$ = +8.3 (*c* = 0.7, $CHCl_3$) (80% *ee* from HPLC; DAICEL CHIRALPAK AD, λ = 215 nm, *n*-hexane/2-propanol 99.5:0.5, 0.5 mL/min, t_r = **17.6** and 20.2 min.); R_f 0.73 (*n*-hexane/ethyl acetate, 4:1); ^{1}H NMR (300 MHz): δ_H 0.89 (m, 3H, CH_3), 1.82-1.93 (m, 2H, CH_2), 3.26-3.33 (m, 1H, CHPh), 5.25 (d, *J* = 16.4 Hz, 1H, CHCN), 6.84 (dd, *J* = 16.4, 7.3 Hz, 1H, C*H*=CHCN), 7.12-7.27 (m, 2H, ArH), 7.29-7.37 (m, 3H, ArH) ppm; ^{13}C NMR (75 MHz): δ_C 11.9 (CH_3), 27.5 (CH_2), 51.1 (CHPh), 99.4 (*C*HCN), 116.1 (CN), 127.2, 127.7, 128.9, 141.4 (ArC), 158.4 (*C*H=CHCN) ppm; IR (neat): ν = 2221, 1613 cm^{-1}; MS (EI): *m/z* (%) = 171 [*M*]$^+$ (25.4), 143 (15), 142 (86), 116 (18), 115 (100); HRMS calcd for $C_{12}H_{13}N$: 171.1048; found 171.1049.

(2*Z*,4*S*)-4-Phenylhex-2-enenitrile (3cb): (Table 2, entry 22, 148 mg, 86%). Colourless oil; $[\alpha]^{25}_D$ = +68.1 (*c* = 0.2, $CHCl_3$) (80% *ee* from HPLC; DAICEL CHIRALPAK AD, λ = 215 nm, *n*-hexane/2-propanol 99.5:0.5, 0.5 mL/min, t_r = **20.6** and 23.2 min.); R_f 0.73 (*n*-hexane:ethyl acetate, 4:1); ^{1}H NMR (300 MHz): δ_H 0.93 (m, 3H, CH_3), 1.76-1.88 (m, 2H, CH_2), 3.75-3.82 (m, 1H, CHPh), 5.33 (d, *J* = 10.8 Hz, 1H, CHCN), 6.53 (t, *J* = 10.8 Hz, 1H, C*H*=CHCN), 7.12-7.27 (m, 2H, ArH), 7.29-7.37 (m, 3H, ArH) ppm; ^{13}C NMR (75 MHz): δ_C 11.8 (CH_3), 28.2 (CH_2), 50.0 (CHPh), 98.6 (*C*HCN), 117.4 (CN), 127.1, 127.3, 128.9, 140.5 (ArC), 157.5 (*C*H=CHCN) ppm; IR (neat): ν = 2221, 1613 cm^{-1}; MS (EI): *m/z* (%) = 171 [*M*]$^+$ (25.4), 143 (15), 142 (86), 116 (18), 115 (100); HRMS calcd for $C_{12}H_{13}N$: 171.1048; found 171.1049.

(2*E*,4*R*)-4-Phenyloct-2-enenitrile (3cd): (Table 2, entry 24, 171 mg, 86%). Colourless oil; [58% *ee* for each isomer from HPLC; DAICEL CHIRALPAK AS, λ = 215 nm, *n*-hexane/2-propanol 99.5:0.5, 0.5 mL/min, t_r = 21.0 and **22.4** min, (*E*-isomer) and DAICEL CHIRACEL OJ, λ = 215 nm, *n*-hexane/2-propanol 99:1, 0.5 mL/min, t_r = 18.3 and **23.6** min, (*Z*-isomer), 32.5 and **35.0** min, (α-substitution)]; TLC: R_f 0.58 (*n*-hexane/ethyl acetate, 4:1); (*E*)-isomer ^{1}H NMR (300 MHz): δ_H 0.84-0.96 (m, 3H, CH_3), 1.21-1.37 (m, 4H, 2xCH_2), 1.73-1.86 (m, 2H, CH_2), 3.39 (m, 1H, C*H*Ph), 5.25 (d, *J* = 16.4 Hz, 1H, CHCN), 6.85 (dd, *J* = 16.4, 7.5 Hz, 1H, C*H*=CHCN), 7.12-7.25 (m, 2H, ArH), 7.29-7.40 (m, 3H, ArH) ppm; ^{13}C NMR (75 MHz): δ_C 13.8 (CH_3), 22.4, 29.4 and 34.2 (3xCH_2), 49.4 (*C*HPh), 99.2 (*C*HCN), 117.1 (CN), 127.2, 127.7, 128.7 and 140.7 (ArC), 158.7 (*C*H=CHCN) ppm; (*Z*)-isomer ^{1}H NMR (300 MHz): δ_H 0.84-0.96 (m, 3H, CH_3), 1.21-1.37 (m, 4H, 2xCH_2), 1.73-1.86 (m, 2H, CH_2), 3.90 (m, 1H, C*H*Ph), 5.72 (d, *J* = 10.8 Hz, 1H, CHCN), 6.54 (t, *J* = 10.8 Hz, 1H, C*H*=CHCN), 7.12-7.25 (m, 2H, ArH), 7.29-7.40 (m, 3H, ArH) ppm; ^{13}C NMR (75 MHz): δ_C 13.9 (CH_3), 22.5, 29.3 and 34.9 (CH_2), 48.3

(*C*HPh), 98.4 (*C*HCN), 116.0 (CN), 127.1, 127.3, 128.9 and 141.6 (ArC), 157.7 (*C*H=CHCN) ppm; IR (neat): ν = 2221, 1617 cm^{-1}; MS (EI): *m/z* (%) = 199 $[M]^+$ (21.7), 143 (100), 142 (62), 116 (29), 115 (70); HRMS calcd for $C_{14}H_{17}N$: 199.1361; found 199.1358.

(2Z,4S)-5-Methyl-4-phenyl-hex-2-enenitrile (3cc): (Table 2, entry 27, 154 mg, 83%). Colourless oil; $[\alpha]^{25}_D$ = +158.9 (*c* = 1.0, $CHCl_3$ for the mixture *E*:*Z* 39:61) [90% *ee* for each isomer from HPLC; DAICEL CHIRALPAK AS, λ = 215 nm, *n*-hexane, 1 mL/min, t_r = 16.5 and **19,9** min, (*Z*-isomer) and 27.0 and **30.0** min, (*E*-isomer)]; TLC: R_f 0.59 (*n*-hexane/ethyl acetate, 4:1); (*E*)-isomer ^{1}H NMR (300 MHz): δ_H 0.78 (d, *J* = 6.7 Hz, 3H, CH_3), 0.98 (d, *J* = 6.7 Hz, 3H, CH_3), 2.04 (m, 1H, C*H*CH_3), 3.01 (t, *J* = 9.0 Hz, 1H, C*H*CH=CH), 5.31 (dd, *J* = 16.2 , 0.9 Hz, 1H, CHCN), 6.89 (dd, *J* = 16.2, 9.0 Hz, 1H, C*H*=CHCN), 7.10-7.27 (m, 2H, ArH), 7.31-7.38 (m, 3H, ArH) ppm; ^{13}C NMR (75 MHz): δ_C 20.7 and 20.8 (2xCH_3), 32.6 ($CHCH_3$), 57.9 (CHPh), 99.9 (*C*HCN), 116.1 (CN), 127.1, 128.0, 128.8 and 140.5 (ArC), 157.7 (*C*H=CHCN) ppm; (*Z*)-isomer ^{1}H NMR (300 MHz): δ_H 0.78 (d, *J* = 6.7 Hz, 3H, CH_3), 1.01 (d, *J* = 6.7 Hz, 3H, CH_3), 2.04 (m, 1H, C*H*CH_3), 3.50 (t, *J* = 10.2 Hz, 1H, C*H*CH=CH), 5.32 (d, *J* = 10.8 Hz, 1H, CHCN), 6.62 (t, *J* = 10.8, 9.0 Hz, 1H, C*H*=CHCN), 7.10-7.27 (m, 2H, ArH), 7.31-7.38 (m, 3H, ArH) ppm; ^{13}C NMR (75 MHz): δ_C 20.5 and 20.6 (2xCH_3), 32.9 ($CHCH_3$), 56.3 (CHPh), 98.9 (*C*HCN), 116.2 (CN), 127.0, 127.8, 128.9 and 141.1 (ArC), 157.0 (*C*H=CHCN) ppm; IR (neat): ν = 2222, 1619 cm^{-1}; MS (EI): *m/z* (%) = 185 $[M]^+$ (6.9), 143 (100), 115 (23); HRMS calcd for $C_{13}H_{15}N$: 185.1204; found 185.1206.

(2*E*,4*R*)-4,5-Diphenylpent-2-enenitrile (3cf): (Table 2, entry 29, 200 mg, 86%). Colourless oil; $[\alpha]^{25}_D$ = +10.5 (*c* = 2.0, $CHCl_3$ for the mixture *E*:*Z* 70:30) [85% *ee* for each isomer from HPLC; DAICEL CHIRALPAK AS, λ = 209 nm, *n*-hexane/2-propanol 99:1, 0.7 mL/min, t_r = 16.5 and **17.2** min, (*Z*-isomer) and 25.1 and **26.7** min, (*E*-isomer)]; TLC: R_f 0.45 (*Z*-isomer), 0.39 (*E*-isomer) (*n*-hexane/ethyl acetate: 4:1); (*E*)-isomer ^{1}H NMR (300 MHz): δ_H 3.07 (m, 2H, CH_2), 3.71 (m, 1H, CHPh), 5.12 (dd, *J* = 16.4, 1.5 Hz, 1H, CHCN), 6.87 (dd, *J* = 16.4, 7.2 Hz, 1H, C*H*=CHCN), 7.12-7.25 (m, 4H, ArH), 7.29-7.40 (m, 6H, ArH) ppm; ^{13}C NMR (75 MHz): δ_C 29.7 (CH_2), 51.2 (CHPh), 100.2 (*C*HCN), 117.2 (CN), 126.5, 126.6, 127.4, 127.7, 128.5, 128.9, 129.0 and 138.2 (ArC), 157.2 (*C*H=CHCN) ppm; (*Z*)-isomer ^{1}H NMR (300 MHz): δ_H 3.07-3.12 and 3.17-3.21 (2xm, 2H, CH_2), 4.18 (m, 1H, CHPh), 5.24 (d, *J* = 10.8 Hz, 1H, CHCN), 6.60 (t, *J* = 10.8 Hz, 1H, C*H*=CHCN), 7.12-7.25 (m, 4H, ArH), 7.29-7.40 (m, 6H, ArH) ppm; ^{13}C NMR (75 MHz): δ_C 29.3 (CH_2), 49.9 (CHPh), 100.2 (*C*HCN), 115.1 (CN), 126.5, 127.2, 127.3, 127.4, 128.3, 128.4, 129.1 and 140.1 (ArC), 156.2 (*C*H=CHCN) ppm; IR (neat): ν = 2221 (CN), 1629 (C=C) cm^{-1}; MS (EI): *m/z* (%) = 233 $[M]^+$ (6.2), 115 (7), 91 (100); HRMS calcd for $C_{17}H_{15}N$: 233.1204; found 233.1199.

General procedure for the synthesis of the enantioenriched aldehydes 7 by ozonolysis of compounds 3a.[23]

A stream of oxygen and ozone was passed through a solution of product **3a** (0.25 mmol) in dichloromethane (3 mL) at –78 ºC for 30 min. The blue solution was the purged with a stream of argon for 10 min, thiourea (0.3 mmol, 34 mg) was added and the resulting solution was allowed to warm to room temperature over 30 min. The reaction was concentrated and the crude mixture purified by flash chromatography to yield pure aldehydes **7**.

(***R*)-2-Methyldihydrocinnamaldehyde (7af):**[17] (30 mg, 80%). Colourless oil; $[\alpha]_D^{20}$ = +7,0 (*c* = 0.7, MeOH, 76% ee), {lit. $[\alpha]_D^{23}$ = –4,42 (*c* = 4, MeOH) 94% *ee* (*S*) enantiomer}[17] (76% *ee* from HPLC; DAICEL CHIRACEL OJ, λ = 254 nm, *n*-hexane/2-propanol 99:1, 0.7 mL/min, t_r = **10.2** and 12.2 min.); ^{1}H NMR (300 MHz): δ_H 1.05 (d, *J* = 7.1 Hz, 3H, CH_3), 1.21 (m, 1H, CH), 3,35 (2xd, *J* = 12.5 Hz, 2H, CH_2), 7.14-7.35 (m, 5H, ArH), 9.75 (d, 1H, *J* = 1.7 Hz, CHO) ppm.

(*R*)-2-Methylhexanal (7ad): [18] (24 mg, 83%) Colourless oil; $[\alpha]_D^{20}$ = –10.2 (*c* = 1.0, $CHCl_3$) (30% *ee* estimated), {lit. $[\alpha]_D^{25}$ = –19.7 (*c* = 5.8, $CHCl_3$ 99% *ee* (*R*) enantiomer}[18]; ^{1}H NMR (300 MHz): δ_H 0.92 (m, 3H, CH_3), 1.10 (d, *J* = 7.1 Hz, 3H, C*H*$_3$CH), 1.22-1.74 (m, 6H, 3xCH_2), 2.42 (m, 1H, CH), 9.62 (d, 1H, *J* = 2.0 Hz, CHO) ppm; MS (EI): *m/z* (%) = 114 $[M]^+$ (1.3), 85 (6), 70 (6), 58 (100), 57 (26).

General procedure for the synthesis of the enantioenriched esters 4.

A mixture of compound **3ba** or **3ca** (0.25 mmol), MeOH (2 mL) and concentrated aqueous HCl (2 mL) was heated at 90 ºC overnight. Then, an aqueous saturated solution of $NaHCO_3$ (10 mL) was added to neutralize the acidic media. MeOH was then removed by evaporation, and ethyl acetate was added. The organic layer was separated, dried ($MgSO_4$) and evaporated to afford the crude compounds, which were purified by flash chromatography obtaining the pure esters **4**.

Methyl (2*E*,4*S*)-4-methylnon-2-enenoate [(*S*)-4ba]: (37 mg, 80%). Pale yellow oil; $[\alpha]^{25}_D$ = +31.7 (*c* = 0.8, $CHCl_3$ for the mixture *E*:*Z* 91:9); TLC: R_f 0.39 (*n*-hexane/ethyl acetate, 4:1); ^{1}H NMR (300 MHz): δ_H 0.88 (t, *J* = 6.6 Hz, 3H, C*H*$_3$CH$_2$), 1.04 (d, *J* = 6.7 Hz, 3H, C*H*$_3$CH), 1.26-1.41 (m, 8H, 4xCH_2), 2.28 (m, 1H, C*H*CH$_3$), 3.73 (s, 3H, OCH_3), 5.77 (d, *J* = 15.7 Hz, 1H, CHCN), 6.86 (dd, *J* = 15.7, 7.9 Hz, 1H, C*H*=CHCN) ppm; ^{13}C NMR (75 MHz): δ_C 14.0 (*C*H$_3$CH$_2$), 18.8 (CH_2), 22.4 (CH$_3$CH), 26.6, 31.1, 31.6 (3xCH_2), 37.7 (*C*HCH$_3$), 51.4 (OCH_3), 119.1 (*C*HCN), 155.1 (*C*H=CHCN), 161.4 (CO) ppm; IR (neat): ν = 2860, 1725, 1655, 1265 cm^{-1}; MS (EI): *m/z* (%) = 184 $[M]^+$ (3.5), 153 (44), 128 (100), 127 (73), 114 (31), 110 (77), 109 (20), 97 (25), 96 (72), 95 (51); HRMS calcd for $C_{10}H_{17}O_2$: 169.1248; found 169.1244.

Methyl (2*E*,4*R*)-4-methylnon-2-enenoate [(*R*)-4ba]: (36 mg, 78%). Pale yellow oil; $[\alpha]^{25}_D$ = –31.8 (*c* = 0.8, $CHCl_3$ for the mixture *E*:*Z* 91:9); TLC: R_f 0.39 (*n*-hexane/ethyl acetate, 4:1); ^{1}H NMR (300 MHz): δ_H 0.88 (t, *J* = 6.6 Hz, 3H, C*H*$_3$CH$_2$), 1.04 (d, *J* = 6.7 Hz, 3H, C*H*$_3$CH), 1.26-1.41 (m, 8H, 4xCH_2), 2.28 (m, 1H, C*H*CH$_3$), 3.73 (s, 3H, OCH_3), 5.77 (d, *J* = 15.7 Hz, 1H, CHCN), 6.86 (dd, *J* = 15.7, 7.9 Hz, 1H, C*H*=CHCN) ppm; ^{13}C NMR (75 MHz): δ_C 14.0 (*C*H$_3$CH$_2$), 18.8 (CH_2), 22.4 (CH$_3$CH), 26.6, 31.1, 31.6 (3xCH_2), 37.7 (*C*HCH$_3$), 51.4 (OCH_3), 119.1 (*C*HCN), 155.1 (*C*H=CHCN), 161.4 (CO) ppm; IR (neat): ν = 2860, 1725, 1655, 1265 cm^{-1}; MS (EI): *m/z* (%) = 184 $[M]^+$ (3.5), 153 (44), 128 (100), 127 (73), 114 (31), 110 (77), 109 (20), 97 (25), 96 (72), 95 (51); HRMS calcd for $C_{10}H_{17}O_2$: 169.1248; found 169.1249.

Methyl (2*E*,4*R*)-4-phenylpent-2-enenoate (4ca):[7a] (47 mg, 99%). Colourless oil; $[\alpha]^{25}_D$ = +15.5 (*c* = 0.3, $CHCl_3$ for the mixture *E*:*Z* 95:5); ^{1}H NMR (300 MHz): δ_H 1.43 (d, *J* = 7.0 Hz, 3H, C*H*$_3$CH), 3.62 (m, 1H, C*H*CH$_3$), 3.72 (s, 3H, CH_3O), 5.80 (dd, *J* = 15.7, 1.5 Hz, 1H, $CHCO_2Me$), 7.20 (dd, *J* = 15.7, 6.4 Hz, 1H, C*H*=CHCN), 7.25-7.39 (m, 3H, ArH), 7.28-7.36 (m, 2H, ArH) ppm; MS (EI): *m/z* (%) = 190 $[M]^+$ (20), 159 (21), 131 (100), 130 (59), 129 (40), 116 (20), 119 (58), 91 (28).

Synthesis of (*S*)- and (*R*)-4-methylnonan-1-ol (9).[21] Crude compound **4ba** (0.5 mmol, 68 mg) was treated with $LiAlH_4$ (1.5 mmol, 58 mg) in anhydrous THF (2 mL) at room temperature during 15 h. The reaction mixture was quenched with 1M H_2SO_4 (5 mL) and ethyl acetate (10 mL) and the organic residue purified by flash chromatography (36 mg, 48% overall yield from **3ba** mixtures).
(*S*)-9: $[\alpha]^{25}_D$ = +0.51 (*c* = 2, $CHCl_3$, 78% *ee*) , lit.[21a] $[\alpha]^{25}_D$ = +0.63 ($CHCl_3$), lit.[21e] $[\alpha]^{25}_D$ = +1.97 (neat). ^{1}H NMR (300 MHz): δ_H 0.92 (m, 6H, 2xCH_3), 0.99-1.77 (m, 13H, C*H*CH$_3$ and 6xCH_2), 2.8 (s, 1H, OH), 3.61 ppm (t, *J* = 6.6 Hz, 2H, CH_2O); MS (EI): *m/z* (%) = 158 ($[M]^+$–1, 2), 140 (3), 112 (16), 97 (24), 84 (36), 69 (100), 57 (93), 41 (100).
(*R*)-9: $[\alpha]^{25}_D$ = +0.48 (*c* = 2, $CHCl_3$, 78% *ee*) , lit.[21a] $[\alpha]^{25}_D$ = +0.63 ($CHCl_3$), lit.[21e] $[\alpha]^{25}_D$ = +1.97 (neat). ^{1}H NMR (300 MHz): δ_H 0.92 (m, 6H, 2xCH_3), 0.99-1.77 (m, 13H, C*H*CH$_3$ and 6xCH_2), 2.8 (s, 1H, OH), 3.61 ppm (t, *J* = 6.6 Hz, 2H, CH_2O); MS (EI): *m/z* (%) = 158 ($[M]^+$–1, 1), 140 (1), 112 (19), 97 (24), 84 (38), 69 (100), 57 (90), 41 (100).

References

[1] *Comprehensive Asymmetric Catalysis*. Eds. E.N. Jacobsen, A. Pfaltz, H. Yamamoto, Springer: Berlin, 1999-2004.

[2] *Catalytic Asymmetric Synthesis*. Ed. I. Ojima, Wiley-VCH: New York, 2000.

[3] S. Bell, B. Wüstenberg, S. Kaiser, F. Menges, T. Netscher, A. Pfaltz, *Science* **2006**, *311*, 642-644.

[4] *Handbook of Organopalladium Chemistry*. Ed. E. Negishi, Wiley-Interscience: New York, 2002 vol. II, Chp.V.2, p. 1669.

[5] [5a] A. Alexakis, C. Malan, L. Lea, K. Tissot-Croset, D. Polet, C. Falciola *Chimia* **2006**, *60*, 124-130. [5b] H. Yorimitsu, K. Oshima, *Angew. Chem. Int. Ed.* **2005**, *44*, 4435-4439. [5c] *Modern Organocopper Chemistry*. Ed. N. Krause, Wiley-VCH: Weinheim, 2002. [5d] E. Nakamura, S. Mori, *Angew. Chem. Int. Ed.* **2000**, *39*, 3750-3771.

[6] For a recent example, see: R. K. Dieter, V. K. Gore, N. Chen, *Org. Lett.* **2004**, *6*, 763-766.

[7] For recent examples, see: [7a] F. López, A. W. van Zijl, A. J. Minnaard, B. L. Feringa, *Chem. Commun.* **2006**, 409-411. [7b] J. J. Veldhuizen, J. E. Campbell, R. E. Giudici, A. H. Hoveyda *J. Am. Chem. Soc.* **2005**, *127*, 6877-6882. [7c] K. E. Murphy, A. H. Hoveyda, *Org. Lett.* **2005**, *7*, 1255-1258. [7d] A. O. Larsen, W. Len, C. Nieto-Overhuber, J. E. Campbell, A. H. Hoveyda, *J. Am. Chem. Soc*. **2004**, *126*, 11130-11131.

[8] For recent examples, see: [8a] D. Soorukram, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 3686-3689. [8b] P. Demel, M. Keller, B. Breit, *Chem. Eur. J.* **2006**, *12*, 6669-6683. [8c] C. Herber, B. Breit, *Chem. Eur. J.* **2006**, *12*, 6684-6691. [8d] A. Whitehead, M. D. McReynolds, J. D. Moore, P. R. Hanson, *Org. Lett.* **2005**, *7*, 3375-3378. [8e] D. Soorukram, P. Knochel, *Org. Lett.* **2004**, *6*, 2409-2411. [8f] U. Piarelli, C. Claverie, P. Danbos, C. Gennari, A. J. Minnaard, B. L. Feringa, *Org. Lett.* **2003**, *5*, 4493-4496. [8g] U. Piarelli, C. Claverie, P. Danbos, M. Roux, C. Gennari, *Angew. Chem. Int. Ed.* **2003**, *42*, 234-236.

[9] [9a]A. Baeza, J. Casas, C. Nájera, J. M. Sansano, *J. Org. Chem.* **2006**, *71*, 3837-3848. [9b] A. Baeza, C. Nájera, J. M. Sansano, J. M. Saá, *Chem. Eur. J.* **2005**, *11*, 3849-3862. [9c] A. Baeza, J. Casas, C. Nájera, J. M. Sansano, J. M. Saá, *Angew. Chem. Int. Ed.* **2003**, *42*, 3143-3146.

[10] For other synthesis of chiral cyanophosphates, see: [10a]N. Yamagiwa, Y. Abiko, M. Sugita, J. Tian, S. Matsunaga, M. Shibasaki, *Tetrahedron: Asymmetry* **2006**, *17*, 566-573. [10b]Y. Abiko, N. Yamagiwa, M. Sugita, J. Tian, S. Matsunaga, M. Shibasaki, *Synlett* **2004**, 2434-2436.

[11] R. Yoneda, S. Harusawa, T. Kurihara, *J. Chem. Soc., Perkin Trans. 1* **1988**, 3163-3168.

[12] A part of these results have been presented in the 16th IUPAC International Conference on Organic Synthesis, Mérida (Mexico), June 2006.

[13] W.-W. Liao, I. Ibrahem, A. Córdova, *Chem. Commun.* **2006**, 674-676.

[14] A. Baeza, C. Nájera, J. M. Sansano, *Arkivoc* **2005**, *ix*, 353-363. www.arkat.usa.org.

[15] M. Kimura, T. Yamazaki, T. Kitazume, T. Kubota, *Org. Lett.* **2004**, *6*, 4651.

[16] For reviews about bifunctional catalysis see: [16a] M. Kanai, N. Kato, E. Ichikawa, M. Shibasaki, *Synlett* **2005**, 1491-1508. [16b] M. Kanai, N. Kato, E. Ichikawa, M. Shibasaki, *Pure Appl. Chem.* **2005**, *77*, 2047-2052. [16c] J.-M. Ma, D. Cahard, *Angew. Chem. Int. Ed.* **2004**, *43*, 4566-4583. [16d] M. Shibasaki, M. Kanai, K. Funabashi, *Chem. Commun.* **2002**, 1189-1199. [16e] S. Matsunaga, T. Ohshima, M. Shibasaki, *Adv. Synth. Catal.* **2002**, *344*, 3-15. [16f] H. Gröger, *Chem. Eur. J.* **2001**, *7*, 5246-5251.

[17] M. V. Rangaishenvi, B. Singaram, H. C. Brown, *J. Org. Chem.* **1991**, *56*, 3286-3294

[18] S. W. Goldstein, L. E. Overman, M. H. Rabinowitz, *J. Org. Chem.* **1992**, *57*, 1179-1190.

[19] N. W. Boaz, E. J. Corey, *Tetrahedron Lett*. **1984**, *25*, 3063-3065.

[20] *Grignard Reagents, New Developments*. Ed. H. G. Richey, Jr., Wiley: Chichester, 2000.

[21] [21a] G. Y. Ismuratov, M. P. Yakovleva, A. V. Galyautdinova, G. A. Tolstikov, *Chem. Nat. Prod.* **2003**, *39*, 31-33. [21b] T. Kitahara, S.-H. Kang, *Proc. Japan. Acad., Ser. B* **1994**, *70*, 181-184. [21c] V. N. Odinikov, G. Yu. Ishmuratov, O. V. Sokol'skaya, M. P. Yakovleva, R. Ya. Kharisov, E. P. Serebryakov, G. A. Tolstikov, *Russ. Chem. Bull.* **1993**, *42*, 1244-1245. [21d] S.Genard, H. Patin, *Bull. Soc. Chim. Fr.*

1991, 397-406. [21e] A. Carpita, E. De Magistris, R. Rossi, *Gazz. Chim Ital.* **1989**, *119*, 99-105. [21f] Y. Tanaka, H. Honda, K. Ohsawa, I. Yamamoto, *Pesticide Sci.* **1989**, 14, 197-202.
[22] [22a] S. Kojima, T. Fukuzaki, A. Yamakawa, Y. Murai, *Org. Lett.* **2004**, *6*, 3917-3920. [22b] F. Effenberger, S. Oßwald, *Tetrahedron: Asymmetry* **2001**, *12*, 2581-2587.
[23] D. J. Wardrop, M. S. Burge, *J. Org. Chem.* **2005**, *70*, 10271-10284.

Layout 1:

((Catch Phrase))

((Text for Table of Contents))

((Insert TOC Graphic here))

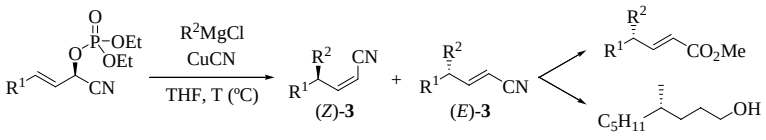
((Author(s), Corresponding Author(s)*)) …….. Page No. – Page No.

((Title))

Keywords: ((Keyword 1 / Keyword 2 / Keyword 3 / Keyword 4 / Keyword 5))

Layout 2:

Cyanohydrin *O*-phosphates as chiral building blocks.



Alejandro Baeza, Carmen Nájera* and José M. Sansano Page No. – Page No.

S_N2' Alkylation of Chiral Allylic Cyanohydrin *O*-Phosphates with Organocuprates

Keywords: (copper / allylic substitution / asymmetric synthesis/ unsaturated nitriles/cyanophosphates)