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

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Dedicated to Prof. Henri B. Kagan for his pivotal contributions in asymmetric synthesis

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Enantiomerically enriched cyanohydrin *O*-phosphates, prepared by enantioselective cyanophosphorylation of α,β-unsaturated aldehydes, react regioselectively at the γ-position with organocuprates derived from alkyl Grignard reagents and CuCN 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 °C and (*Z*) when it is carried out at higher temperatures (0 °C). A high level of transfer of the chirality in the new stereocentre, corresponding to a stereospecific *anti* attack onto the cyanophosphate, is observed. 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 have been 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 between an organometallic reagent and a chiral electrophilic substrate can be employed for this purpose, but many side reactions – such as isomerisations, eliminations and partial racemisations – are unfortunately associated with these processes.[1] Nowadays, 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. In particular, in allylic nucleophilic substitution reactions, the palladium-catalysed process requires soft nucleophiles, whilst copper catalysts allow the use of hard nucleophiles including Grignard and organozinc reagents. Recent advances in the asymmetric allylic substitutions promoted by copper complexes make these transformations much more interesting.[5a] Out of all the possible combinations, the techniques most frequently used in organic synthesis are the employment of chiral organocuprates in stoichiometric amounts,[5,6] the use of chiral catalytic copper(II) reagents,[5,7] and reactions performed with chiral substrates and organocuprates,[5,8] with employment of allylic acetates, carbonates and phosphates.

It has been demonstrated that simple allylic phosphates are appropriate substrates with which to develop this process efficiently through a γ-*anti*-S_N2' stereocontrolled process.[6] The enantiomerically enriched unsaturated cyanophosphates **1**[9,10] (Scheme 1) would be promising candidates to undergo these type of displacements. Previous works have revealed their potential as chiral building blocks in the synthesis of the optically active (*E*)- and (*Z*)-γ-substituted α,β-unsaturated nitriles **2** through palladium- or iridium-catalysed allylic nucleophilic substitutions.[9] As part of an ongoing survey of the synthetic applications of the cyanohydrin-*O*-phosphates **1** as chiral building blocks we focused our attention on their direct nucleophilic allylic substitution, mediated by organocuprates. Only the regioselective reactions between stoichiometric amounts of lithium organocuprates and racemic cyanophosphates have been reported, with different diastereoselectivities having been obtained, depending on the reaction conditions applied, but favouring the final (*Z*) configuration necessary for the synthesis of racemic (±)-manicone, (±)-nuciferal and both isomers of (±)-nuciferol.[11] In this article the results of S_N2' substitutions achieved through the 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** are described (Scheme 1).[12] These chiral α,β-unsaturated

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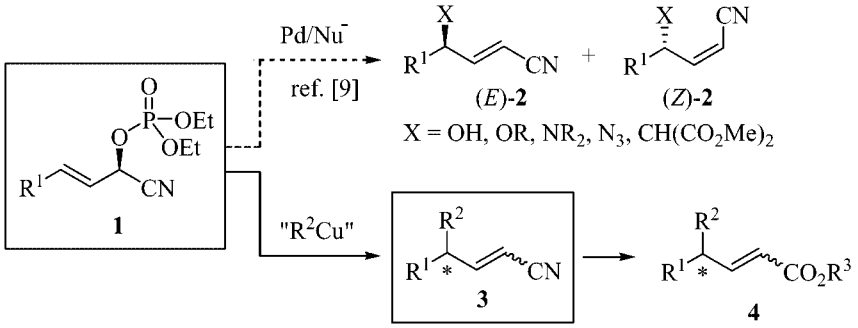
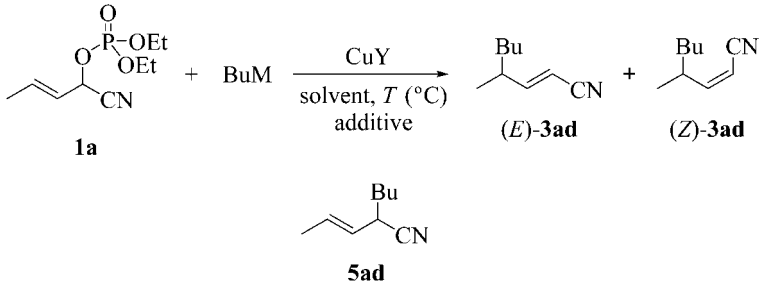


Scheme 1.

nitriles **3** can be regarded as direct precursors, through simple alcoholysis, of valuable chiral (*E*)-Michael acceptors, such as optically enriched α,β-unsaturated esters **4**, mainly with (*E*) configurations. These compounds **4** have recently been prepared by stereoselective methyl cuprate addition onto allylic bromides followed by crossed metathesis with methyl acrylate.[7a] More highly functionalised chiral α,β-unsaturated esters of type **4** have also been obtained through a one-pot process involving a sequential organocatalytic asymmetric Mannich reaction and a Horner–Wadsworth–Emmons olefination.[13]

Results and Discussion

Reactions between organocopper reagents and allylic electrophiles are normally influenced by multiple parameters, many of them apparently negligible, but actually being crucial at the end of the transformation for the regioselectivity, diastereoselectivity, reaction time, yields etc.[5] Initially we searched for optimal reaction conditions for the allylic substitution reaction, comparing the results with the analogous findings published in the literature for racemic cyanohydrin *O*-phosphates.[11] These tests were performed with the racemic cyanophosphate **1a** as starting material, this being obtained in quantitative yield from crotonaldehyde and diethyl cyanophosphonate in the absence of solvent and with the use of catalytic amounts of triethylamine (10 mol-%) over 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, delivering the product derived from the attack of the alkyl group onto the phosphorus atom, together with variable amounts of the γ-substitution product (*Z*)-**3ad** and the α-substitution product **5ad** (Scheme 2), as has been described previously.[11] However, when an organocopper reagent, freshly generated by mixing *n*-butylmagnesium bromide or chloride (instead of *n*-butyllithium) and a copper(I) source, was used under argon in



Scheme 2.

Table 1. Optimization of S_N2' reactions between organocopper compounds and racemic cyanophosphate **1a**.

Entry	*n*BuM[a]	CuY[b]	Additive	Solvent	*T* [°C]	*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

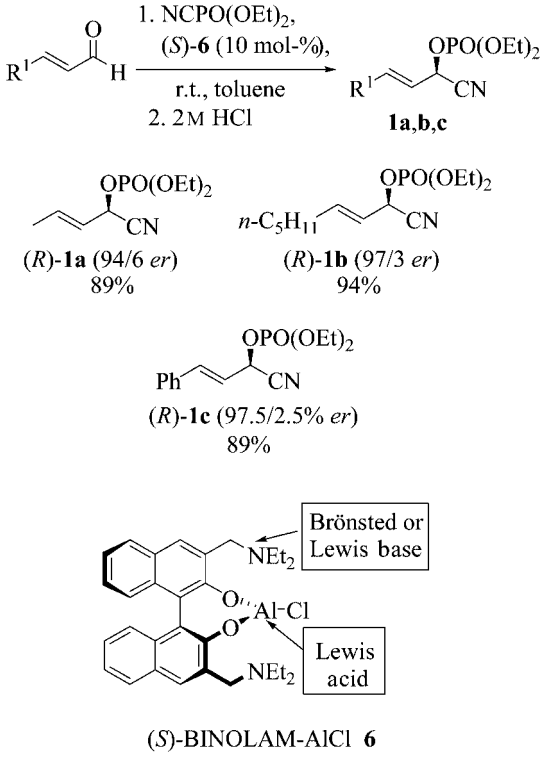
[a] 3 Equiv. of Grignard reagent was added. [b] 1.5 Equiv. of copper(I) salt was added. [c] Determined on the crude reaction product by ^{1}H NMR spectroscopy. [d] Determined on the crude reaction product by ^{1}H NMR spectroscopy. [e] 1.5 Equiv. of TMSCl was added. [f] Previously formed at –30 °C by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

THF or diethyl ether as solvents, the reaction proceeded cleanly at low temperatures and with high conversions to give products **3ad** regioselectively (Scheme 2 and Table 1). The first parameter studied was the effect of the nature of the halide in the Grignard reagent, with use of CuCN as copper salt in both reactions, at –78 °C and in 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 *n*BuMgCl was employed than with *n*BuMgBr. The role of the solvent was impressive: the difference between the use of anhydrous THF and diethyl ether at –78 °C is shown in Entries 1 and 3 in Table 1. The replacement of THF with diethyl ether at this temperature resulted, after 15 h, in a very low degree of conversion (25%), approximately the same level of conversion that had originally been obtained after 1.5 h. When the reaction temperature was 0 °C the isomer (*Z*)-**3ad** was obtained as the major product, but with low diastereoselectivity (Table 1; compare Entries 1 and 4). When the Cu^I source was modified, with use of $CuBr{\cdot}SMe_2$ in place of CuCN, the reaction at –78 °C took place with a high level of diastereoselection for the (*Z*)-**3ad** product, but unfortunately with a low conversion (Table 1, Entry 5), whilst at 0 °C the reaction failed, a complex mixture of undesired products being obtained in the crude reaction mixture (Table 1, Entry 6).

Once we had found the optimal S_N2' reaction conditions for **1a** [CuCN (1.5 equiv.) as Cu^I source, *n*-BuMgCl (3 equiv.) in THF and at –78 °C], the influence of some additives was evaluated. TMSCl (1.5 equiv.) was used as an additive because it acts as a complexating agent with organocopper reagents, promoting the allylic substitution (S_N2') process over the α-substitution (S_N2) process.[15] When the reaction was carried out at –78 °C it was complete after 1 hour, slightly favouring the formation of the (*Z*)-**3** isomer (Table 1, Entry 7), and this trend was slightly higher when the reaction was carried out at 0 °C (Table 1, Entry 8). In both cases the (*E*/*Z*) diastereoselectivity was similar to that observed in the reactions run in the absence of additives (Table 1, compare Entries 4 and 8). The employment of nBuCu·BF_3[11] at several temperatures resulted in very low yields of compounds **3** (Table 1, Entry 9).

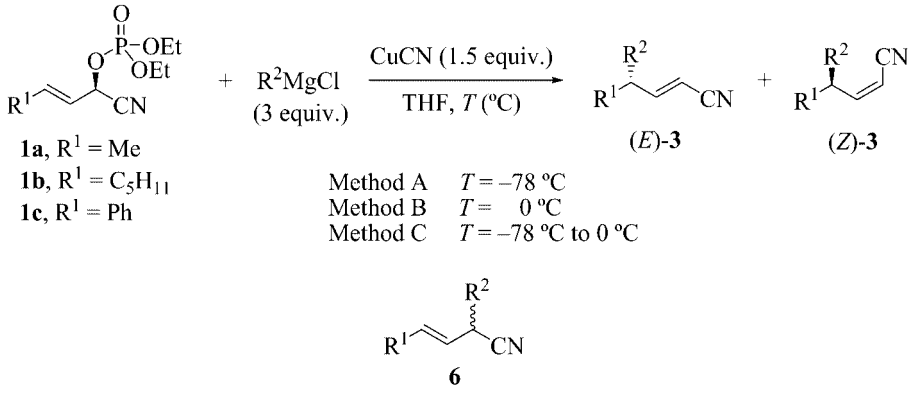
Reactions performed with substoichiometric amounts of copper(I) salts and stoichiometric amounts of the organomagnesium reagent (at a range of temperatures of –78 to 0 °C) did not give satisfactory results: complex mixtures of decomposition products were obtained in the crude reaction product due to the high reactivity of the cyanophosphate **1a**.[9] Identical behaviour was observed when organozinc compounds were used instead of the Grignard reagents. Other Grignard reagents, such as arylmagnesium halides, gave the γ-substitution products at very low levels of conversion, the major products being the biaryl compounds originating from homocoupling. In addition, reactions with cuprates also failed in the cases 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** being prepared in very high *er*s from aldehydes[9,10] in a one-step process with chiral bifunctional[16] (*R*)- or (*S*)-BINOLAM-AlCl complexes **6** as catalysts.[9] This method required 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 in order to recover the (*S*)-3,3′-bis(diethylaminomethyl)-1,1′-bi(2-naphthol) [(*S*)-BINOLAM] chiral ligand almost quantitatively (up to 91%).[9] During the preparation of (*R*)-**1a** on large scales (0.5 g) we noticed that its enantiomeric ratio (*er*) was very sensitive to the moisture present in the freshly distilled crotonaldehyde, the achieved enantiomeric excesses being 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 (previously generated by mixing alkylmagnesium chlorides with CuCN) in dry THF was carried out at –78 °C (Method A), at 0 °C (Method B) or by addition of the organocopper species at –78 °C and allowing the temperature to reach 0 °C (Method C) (Scheme 4). The reactions between the enantiomerically enriched allylic cyanophosphonate **1a**, derived from crotonaldehyde, and the organocoppers formed with *n*-butyl- or benzylmagnesium chloride were very fast at –78 °C, giving the (*E*) diastereoisomer **3a** as the major product by Method A (Table 2, Entries 1 and 8), whereas Method B gave poorer diastereoselectivities. Unfortunately, a small reduction in *er* in the final products **3**



Scheme 4.

(in relation to the original enantiomeric ratio in cyanophosphate **1a**) was observed. In addition, the reaction with the *n*-butyl derivative in the presence of TMSCl also gave satisfactory results, although in this case the reduction in enantioselectivity was slightly larger (Table 2, Entry 3). In contrast, when isopropyl- or *tert*-butylmagnesium chloride were used to form the organocopper reagent, better chirality transfer was achieved under Method B conditions, with *er* values of 93.5:6.5 or 90:10, respectively, being obtained and the (*Z*) product being 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 °C (Method A) and in lower yields (Table 2, Entries 4 and 6).

Similar behaviour was observed when the chiral allylic cyanophosphate **1b**, derived from (*E*)-oct-2-enal, was employed, with the use of methylmagnesium chloride as precursor for the organocopper reagent thus furnishing compound (*E*)-**3ba** almost exclusively, in very high yield and without any degree of racemisation by either Method A or B (Table 2, Entries 10 and 11). On the other hand, the use

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

of a bulkier group such as isopropyl in the organocopper reagent did not result in any reaction at all under the conditions described for Method A (Table 2, Entry 12), but the (*E*/*Z*) isomers of **3bc** were obtained in good yield and with the same *er* as in the original cyanophosphate **1b** in the range of temperatures described for methods B and C (Table 2, Entries 13 and 14). At this point, in order to eliminate the carbon–carbon double bond isomerisation caused by the cuprate residues in the initial addition, we ran two experiments. In the first, a equimolar mixture of (*E*/*Z*)-**3bc** was added to a completed reaction with an excess of *i*PrMgCl/CuCN to provide, after 1 h at 0 °C, 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*) ratio in the resulting **3bc** generated from the analogous reaction at 0 °C (Table 2, Entry 13) was determined by ^{1}H NMR spectroscopy after 1.5, 3 and 6 h, with exactly the same *dr* (27:73) always being measured.

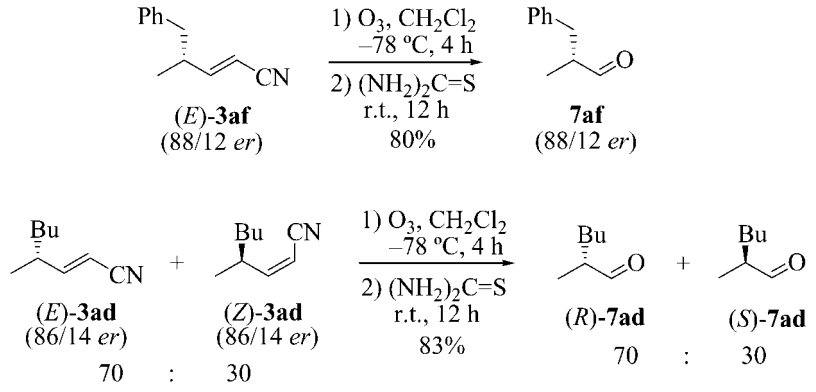
Surprisingly, the use of *n*-butylmagnesium chloride for the generation of the organocopper reagent gave almost equimolecular amounts of (*E*/*Z*)-**3bd** when the reaction was carried out by Method A (Table 2, Entry 15). An increase in temperature (Method B) resulted, predominantly, in the formation of the (*Z*) isomer of **3bd** (Table 2, Entry 16), whilst in the case of benzylmagnesium chloride, (*E*)-**3bf** was mainly obtained with a slight degree of racemisation (Table 2, Entries 17 and 18). It is worth noting 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 characterised as a very reactive and easily racemisable molecule in Pd-catalysed reactions involving moderately to strongly basic reagents.[9] The addition reaction with the cuprate generated from methylmagnesium chloride was carried out by Methods A, B and C (Table 2, Entries 19–21), with a very high (*E*/*Z*) ratio in **3ca** being obtained under the last set of reaction conditions in very good yields and, surprisingly, with only a slight loss of optical purity (Table 2, Entry 21). The reaction failed with Method A, whilst in the case of Method B the (*E*/*Z*) ratio in **3ca** dropped to 76:24 (Table 2, Entries 19 and 20). With ethyl and *n*-butyl organocopper compounds (Table 2, Entries 22–25) Method A was better 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 more basic *n*-butyl group promoted the greatest racemisation in this series, as had also been the case when **1a** was selected as starting material (Table 2, compare Entries 1 and 24). In this example, a considerable proportion of the α-substitution product **5cd** was obtained (27%). When isopropyl- or benzylmagnesium chlorides were employed under the reaction conditions described by Method A the reaction failed. Nevertheless, Methods B and C were effective, product **3cc** being obtained in both cases, with a reversal of the diastereomeric ratio in the case of isopropylmagnesium chloride (Table 2, Entries 27 and 28). However, the benzylic product (*E*)-**3cf** was isolated in a better yield when Method B was essayed (Table 2, Entries 29 and 30). It can be concluded that only slight reductions in the *er* were observed in the case of the cyanophosphate **1c**.

In summary, we note that (*E*) isomers **3** were mainly obtained at low temperatures, that (*Z*) isomers **3** were the major diastereoisomers isolated when the reactions were performed at 0 °C, and that no carbon–carbon double bond isomerisation was observed when the reactions were allowed to continue for 6 h. Cuprates containing *i*Pr or *t*Bu groups gave almost identical (*E*/*Z*) ratios in the products **3a** at the same temperature and, in particular, afforded equimolar diastereomeric mixtures at –78 °C. The highest proportions of (*E*) isomers **3** were obtained when methyl- and benzylmagnesium chlorides were employed at very low temperatures, whereas the highest (*Z*) selectivities for molecules **3** were identified in the reactions run with cuprates derived from *n*-butyl- and isopropylmagnesium chlorides at 0 °C. The α-substitution product **5** was detected only when the cuprate generated with *n*-butylmagnesium chloride was allowed to react with substrates **1a** and **1c** at –78 °C. Racemisation occurred to greater extents when *n*-butylmagnesium chloride was allowed to react with phosphates **1a** and **1c**, but isopropylmagnesium chloride hardly caused loses of enantiomeric purity. When benzyl-, methyl- and *tert*-butylmagnesium chlorides were used, the final products **3** were obtained with low degrees of racemisation independently of the selected temperature of the reaction.

With the aims of determining the absolute configurations of compounds **3** and of confirming the predicted *anti* attack, the transformation of compounds **3** into the known aldehydes **7** was undertaken. Ozonolysis was carried out in dichloromethane at –78 °C and, after a reductive treatment with thiourea, the final aldehydes **7** were obtained in very good yields (Scheme 5). In the reaction carried out with the pure (2*E*,4*R*)-**3af**, aldehyde (*R*)-**7af** was generated in high yield and without loss of enantiomeric purity, which was confirmed by chiral HPLC analysis (CHIRACEL OJ). The suggested the (*R*) absolute configuration (note the priority change around the new stereogenic centre from the original allylic cyanophosphates), resulting from the expected *anti* attack of the copper species onto the allylic cyanophosphate, was confirmed by comparison of the 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 (according to the already mentioned *anti* addition of the organocopper reagent) be around 70:30. Unfortunately, the separation of the two enantiomers either by chiral HPLC or by GC was impossible, but the specific rotation of the **7ad** aldehyde mixture was compared with the reported data[18] and confirmed the (*R*) absolute configuration of the more abundant enantiomer in the mixture.

With regard to the mechanism of the alkylation process, when a substrate containing a good leaving group in an allylic position is treated with a organocopper reagent, two processes can occur: S_N2 (attack at the α-position) and/or



Scheme 5.

S_N2' (attack at the γ-position). This regioselectivity is mainly determined by the natures of the starting material (in terms of its steric and electronic properties), the leaving group and the copper reagent used.[5a,5c] If we assume that the phosphate is a very good leaving group and is not coordinated to the organocuprate, the more important effects to explain the preference for the γ-position should involve the steric requirements of both the substrate and the reagent. It has been reported that the reaction takes place through copper–double bond starting coordination, followed by oxidative addition to the double bond to form the π-allyl copper intermediate, which progresses through a reductive elimination to afford the S_N2' product if this reductive elimination is fast enough, or to afford the 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 in our case, which could explain the high regioselectivity observed.[5a,5c] This stereospecific reaction takes place with absolute configuration inversion, due to the *anti* attack of the organocopper reagent with respect to the leaving group.[5c] Corey et al. proposed an explanation based on frontier orbital theory for this behaviour, in which the organocopper reagents, unlike carbonucleophiles, have *d*-filled orbitals which can interact with the double bond π* orbital in the γ-position and more weakly with the σ* orbital of the carbon-leaving group bond (C–X)[19] (Figure 1).

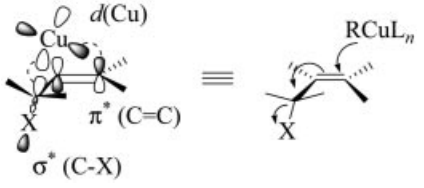
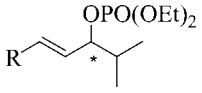


Figure 1. Proposed interaction of the frontier orbitals previous to the S_N2' reaction.

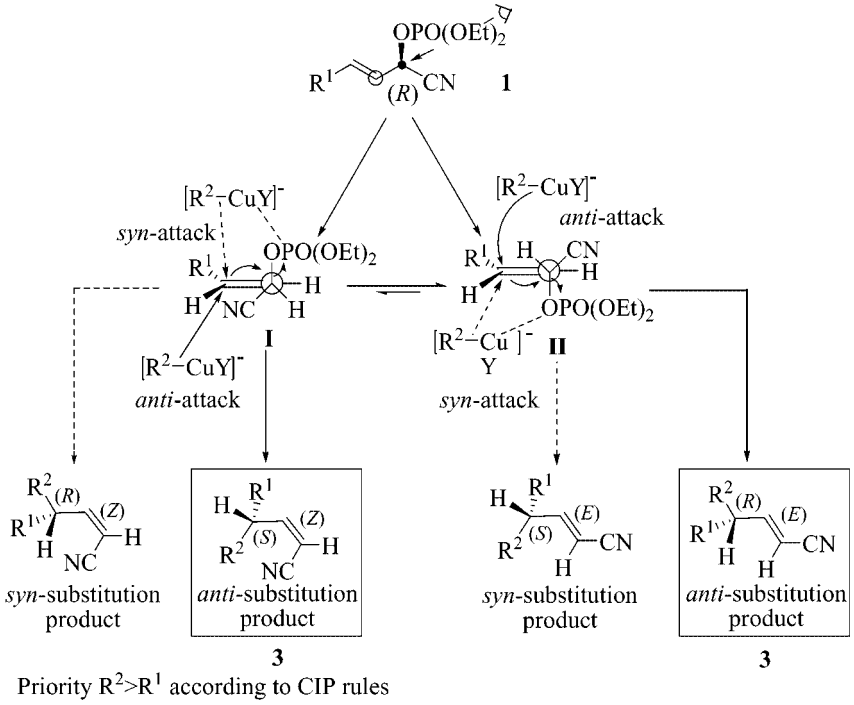
As a consequence of such *anti* attacks onto optically active cyanophosphates, both the leaving group (phosphate) and the cuprate have to be essentially antiperiplanar (ap) in the transition state. Of all of the possible conformations, the most effective overlapping between σ* orbital [C-OPO(OEt)$_2$] 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, which is not involved here in strong interactions with the rest of the substituents. With this conformation *anti* substitution can take place if there is no coordination between leaving group and copper atom in the organocopper reagent attacking the allylic cyanophosphate, or *syn* substitution may occur if this coordination exists (Scheme 6).

The *anti* attack at the less sterically hindered *anti* side in conformer **II** should result in the formation, with total inversion of the configuration, of the diastereoisomer (*E,R*)-**3**, whilst the same mode of attack on conformer **I** should produce the diastereoisomer (*Z,S*)-**3**. It is necessary to note that, despite the mentioned configuration inversion, the product **3** and the enantioenriched allylic cyanophosphate have the same stereogenic descriptors, due to the change in priorities around the stereogenic centre (Scheme 6).



8

Disregarding the coordination between phosphate group and copper complexes, it was initially expected that the (*E*) isomer should be the major product according to the precedent work, in which a isopropyl group was present in compound **8** instead of the nitrile group.[6] However, the amounts of the (*Z*) isomers obtained were unusually large. We believe that the coordinative power between the nitrile group and the copper species is responsible for this behaviour, so rotamers **I** and **II** have 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 should remain closer to the coordination sphere of the copper atom, so that the resulting metallic aggregate, coordinated



Scheme 6.

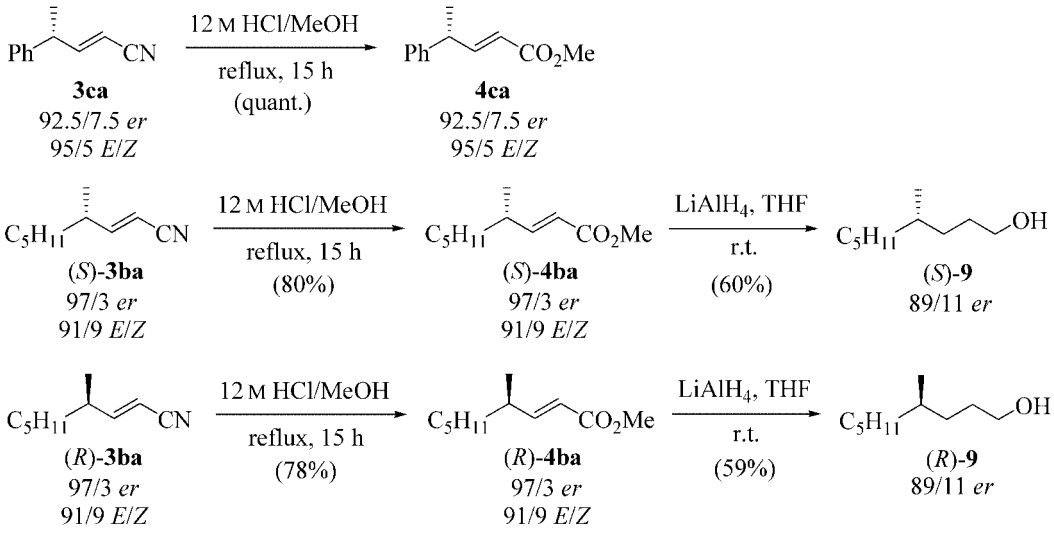
to the nitrile group, would be very bulky and would favour the approach of the methyl group through the less sterically hindered conformer **II**. In fact, the highest (*E*/*Z*) ratios of all the series of reactions were obtained with methylmagnesium bromide (Table 2, Entries 1, 10 and 21).

Obviously, the amount of the (*Z*) isomer increased when the temperature of the reaction was higher (Methods B and C). At –78 °C (Method A), the highest percentage of the (*Z*) isomer was achieved with use of 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), in which 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 that a higher (*E*/*Z*) ratio should be expected, though not so elevated as that 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, especially compound **1c**, in basic media.[9] Although the alkyl cuprates are not so strong bases as Grignard reagents, they can still promote this type of side processes.

The potential of the enantiomerically enriched unsaturated nitriles **3** as chiral building blocks was next examined through the preparation of the α,β-unsaturated esters **4** by acidic hydrolysis of the nitrile group. The best reactions condition were found to involve the use of concentrated hydrochloric acid in methanol at reflux for 15 h, generating the products **4ba** and **4ca** in 80% and quantitative yields, respectively (Scheme 7). This methodology represented a simpler and more 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 from the cyanohydrin *O*-phosphate (*R*)-**1b**, was the synthesis of the enantiomerically enriched (*S*)-4-methylnonan-1-ol (**9**), the enantiomer of the sex pheromone of the yellow mealworm *Tenebrio molitor* L.[21] The enantiomer (*R*)-**4ba**, obtained by the step described in Scheme 7, was reduced both at the carbon–carbon double bond and at the ester group with lithium aluminium hydride to give the alcohol **9** in 48% yield. The low optical rotation value {$[\alpha]_D$ = –0.51 (*c* = 2, $CHCl_3$); ref.[21] $[\alpha]_D$ = +0.63 ($CHCl_3$, unknown concentration)} was not a very reliable datum for determining the *er* of the natural product (*R*)-**9**, but it was consistent 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 also prepared (46% overall yield) by the same route, starting from cyanohydrin *O*-phosphate (*S*)-**1b**, which was enantioselectively generated by use of (*R*)-BINOLAM-AlCl **6** (Scheme 7). This four-step access to enantiomerically enriched compounds **9** contrasts with the previously reported syntheses, involving eight and seven steps starting from chiral (*S*)-(+)-dihydromyrcene[21a] and methyl (*R*)-3-methylglutarate,[21e] respectively.



Scheme 7.

Conclusions

It can be concluded that enantiomerically enriched (*E*)-α,β-unsaturated nitriles possessing alkyl groups at stereogenic centres in their γ-positions can be prepared regio- and diastereoselectively by alkylation of cyanohydrin *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 levels of racemisation and it could be regarded as a complementary transformation to the palladium-catalysed allylic substitution process, which allows the introduction of heteronucleophiles and malonates. Although each substrate required a different set of optimal reaction conditions, we can state 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 °C (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, especially with methyl and benzyl cuprates, whereas anomalously high proportions of the (*Z*) isomers were observed when more dissociation-prone Grignard reagents (*n*-butyl, isopropyl and *tert*-butyl) were employed, and d) in general, low degrees of racemisation were observed, especially 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 newly created sterocentres in both (*Z*) and (*E*) diastereomers. The nitrile group might possibly be able to assist the S_N2' addition to enantiomerically enriched cyanohydrin *O*-phosphates, favouring the formation of these isomers. 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 in only four steps from the starting aldehyde.

Experimental Section

General Remarks: IR spectra were recorded on a Nicolet 510 P-FT instrument, and only the structurally most relevant bands are listed. NMR spectra were determined on a Bruker AC 300 machine, with $CDCl_3$ as solvent and TMS as internal standard, unless otherwise stated. Low-resolution electron impact (EI) mass spectra were obtained at 70 eV on a Shimadzu QP-5000 instrument, and low-resolution electrospray ionization (ESI) mass spectra were obtained on a Finnigan VG Platform. HRMS (EI) were recorded on a Finnigan MAT 95S machine. 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 were visualised under UV light at 254 nm. GC analyses were carried out in a HP-5890SB instrument and chiral HPLC analyses were run in a Jasco 2000 series (the chiral column and wavelength used is given for each compound, the major enantiomer being denoted in bold format). The retention times for each isomer are reported in cases in which it was possible to achieve the perfect separation of the four isomers; otherwise only the retention times of the major isomers obtained are reported. Merck silica gel 60 (0.040–0.063 mm) was employed for flash chromatography.

General Procedure for Allylic Substitution by Organocopper Addition

Method A: A solution of Grignard reagent (3 mmol, in THF) was added under Ar at –78 °C to a cooled suspension of CuCN (1.5 mmol, 134 mg) in dry THF (2 mL). The mixture was then stirred for 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 °C until 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 concentrated to provide the crude compounds, which were purified by flash chromatography to afford pure products **3**.

Method B: Same as Method A but at 0 °C.

Method C: A solution of Grignard reagent (3 mmol, in THF) was added under Ar at –78 °C to a cooled suspension of CuCN (1.5 mmol, 134 mg) in dry THF (2 mL). The mixture was then stirred for 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 rise slowly to 0 °C (approx. 1.5 h). Ethyl acetate (10 mL) and an 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 concentrated to provide the crude compounds, which were purified by flash chromatography to afford pure products **3**.

(2*E*,4*R*)-4-Methyloct-2-enenitrile (3ad): (Table 2, Entry 1, 119 mg, 87%). Pale yellow oil. $[\alpha]_D^{25}$ = –9.0 (*c* = 0.4, $CHCl_3$ for the (*E*)/(*Z*) mixture, 70:30) [72% *ee* for each isomer by HPLC; DAICEL CHIRALPAK AS, λ = 206 nm, *n*-hexane, 1 mL min^{-1}, 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, 3 H, CH_3), 1.07 (d, *J* = 6.6 Hz, 3 H, CH_3), 1.24–1.40 (m, 6 H, 3 × CH_2), 2.29 (m, 1 H, C*H*CH_3), 5.27 (d, *J* = 16.4 Hz, 1 H, CHCN), 6.60 (dd, *J* = 16.4, 7.9 Hz, 1 H, 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 (CH_2CH), 37.7 (*C*HCH_3), 98.0 (*C*HCN), 117.7 (CN), 161.4 (*C*H=CHCN) ppm.

(*Z*) Isomer: ^{1}H NMR (300 MHz): δ_H = 0.88 (t, *J* = 6.9 Hz, 3 H, CH_3), 1.07 (d, *J* = 6.4 Hz, 3 H, CH_3), 1.24–1.40 (m, 6 H, 3 × CH_2), 2.74 (m, 1 H, C*H*CH_3), 5.25 (d, *J* = 10.8 Hz, 1 H, CHCN), 6.25 (t, *J* = 10.8 Hz, 1 H, 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 (CH_2CH), 37.0 (*C*HCH_3), 97.8 (*C*HCN), 116.1 (CN), 160.7 (*C*H=CHCN) ppm. IR (neat): $\tilde{\nu}$ = 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: $C_8H_{12}N$ [M – Me]$^+$ calcd. 122.0969, found 122.0968.

(2*Z*,4*S*)-4,5-Dimethylhex-2-enenitrile (3ac): (Table 2, Entry 5, 109 mg, 89%). Colourless oil. $[\alpha]_D^{25}$ = –19.3 (*c* = 1.0, $CHCl_3$ for the (*E*)/(*Z*) mixture, 35:65) [87% *ee* for each isomer from HPLC; DAICEL CHIRALPAK AS, λ = 215 nm, *n*-hexane/propan-2-ol, 99:1, 1 mL min^{-1}, 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 [2 × d, *J* = 6.7 Hz, 2 × 3 H, CH(CH_3)$_2$], 1.01 (d, *J* = 6.9 Hz, 3 H, CH_3C*H*), 1.64 [m, 1 H, C*H*(CH_3)$_2$], 2.15 (m, 1 H, C*H*CH=CH), 5.26 (dd, *J* = 16.4, 1.1 Hz, 1 H, CHCN), 6.65 (dd, *J* = 16.4, 8.1 Hz, 1 H, 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 [2 × d, *J* = 6.8 Hz, 2 × 3 H, CH(CH_3)$_2$], 1.04 (d, *J* = 6.7 Hz, 3 H, CH_3C*H*), 1.60 [m, 1 H, C*H*(CH_3)$_2$], 2.56 (m, 1 H, C*H*CH=CH), 5.28 (d, *J* = 10.8 Hz, 1 H, CHCN), 6.32 (t, *J* = 10.8 Hz, 1 H, 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): $\tilde{\nu}$ = 2221, 1626 cm^{-1}. MS (EI): *m*/*z* (%) = 123 [*M*]$^+$ (0.03), 81 (100), 80 (40), 54 (19). HRMS: $C_8H_{13}N$ calcd. 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. $[\alpha]_D^{25}$ = –18.1 (*c* = 1.0, $CHCl_3$ for the (*E*)/(*Z*) mixture, 37:63) [80% *ee* for each isomer from HPLC; DAICEL CHIRALPAK AS, λ = 215 nm, *n*-hexane, 0.8 mL min^{-1}, 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, 9 H (CH_3)$_3$], 0.98 (d, *J* = 6.9 Hz, 3 H, CH_3CH), 2.08 (m, 1 H, C*H*CH_3), 5.28 (d, *J* = 16.4 Hz, 1 H, CHCN), 6.70 (dd, *J* = 16.4, 9.0 Hz, 1 H, 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, 9 H, (CH_3)$_3$], 0.99 (d, *J* = 6.9 Hz, 3 H, CH_3CH), 2.58 (m, 1 H, C*H*CH_3), 5.29 (d, *J* = 10.9 Hz, 1 H, CHCN), 6.39 (t, *J* = 10.9 Hz, 1 H, 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): $\tilde{\nu}$ = 2222, 1631 cm^{-1}. MS (EI): *m*/*z* (%) = 122 [*M* – Me]$^+$ (27.5), 105 (11), 95 (13), 81 (59), 80 (21), 57 (100). HRMS: $C_8H_{12}N$ [*M* – Me]$^+$ calcd. 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. $[\alpha]_D^{25}$ = –71.2 (*c* = 0.8, $CHCl_3$) [78% *ee* from HPLC; DAICEL CHIRALPAK AS, λ = 215 nm, *n*-hexane/propan-2-ol, 99:1, 1 mL min^{-1}, 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, 3 H, CH_3), 2.66 (m with s at 2.64, 3 H, CH_2 and C*H*CH_3), 5.20 (d, *J* = 16.4 Hz, 1 H, CHCN), 6.67 (dd, *J* = 16.4, 6.7 Hz, 1 H, C*H*=CHCN), 7.11 (m, 2 H, ArH), 7.22–7.32 (m, 3 H, 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): $\tilde{\nu}$ = 2222, 1632 cm^{-1}. MS (EI): *m*/*z* (%) = 171 [*M*]$^+$ (5.1), 91 (100), 65 (15), 106 (24), 92 (13), 91 (92). HRMS: $C_{12}H_{13}N$ calcd. 171.1048, found 171.1052.

(2*E*,4*S*)-4-Methylnon-2-enenitrile (3ba): (Table 2, Entry 10, 124 mg, 82%). Pale yellow oil. $[\alpha]_D^{25}$ = +24.4 (*c* = 0.5, $CHCl_3$ for the (*E*)/(*Z*) mixture, 91:9) [94% *ee* from HPLC; DAICEL CHIRALPAK AS, λ = 215 nm, *n*-hexane, 1 mL min^{-1}, 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, 3 H, CH_3CH$_2$), 1.03 (d, *J* = 6.7 Hz, 3 H, CH_3CH), 1.21–1.35 (m, 8 H, 4 × CH_2), 2.29 (m, 1 H, C*H*CH_3), 5.26 (d, *J* = 16.4 Hz, 1 H, CHCN), 6.60 (dd, *J* = 16.4, 7.9 Hz, 1 H, C*H*=CHCN) ppm. ^{13}C NMR (75 MHz): δ_C = 13.8 (*C*H_3CH$_2$), 18.8 (CH_2), 22.4 (CH_3CH), 26.6, 31.1, 31.6 (3 × CH_2), 37.7 (*C*HCH_3) 98.0 (*C*H.CN), 119.1 (CN), 161.3 (*C*H=CHCN) ppm. IR (neat): $\tilde{\nu}$ = 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: $C_9H_{14}N$ [*M* – Me]$^+$ calcd. 136.1126, found 136.1124.

(2*Z*,4*S*)-4-Isopropylnon-2-enenitrile (3bc): (Table 2, Entry 13, 158 mg, 88%). Pale yellow oil. $[\alpha]_D^{25}$ = +25.1 (*c* = 0.5, $CHCl_3$ for the (*E*)/(*Z*) mixture, 27:73) [94% *ee* for each isomer from HPLC; DAICEL CHIRALPAK AS, λ = 215 nm, *n*-hexane, 1 mL min^{-1}, 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, 9 H, CH_3CH$_2$ and 2 × CH_3CH), 1.25–1.34 (m, 8 H, 4 × CH_2), 1.56 (m, 1 H, C*H*CH_3), 1.92 (m, 1 H, C*H*CH=CH), 5.25 (d, *J* = 16.4 Hz, 1 H,

CHCN), 6.50 (dd, J = 16.4, 9.9 Hz, 1 H, C*H*=CHCN) ppm. ^{13}C NMR (75 MHz): δ_C = 14.2 (*C*H$_3$CH$_2$), 18.9 and 20.6 (2 × CH$_3$), 27.0, 31.2, 31.7 and 31.8 (4 × CH$_2$), 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, 9 H, CH$_3$CH$_2$ and 2 × CH$_3$CH), 1.25–1.34 (m, 8 H, 4 × CH$_2$), 1.68 (m, 1 H, CHCH$_3$), 2.45 (m, 1 H, CHCH=CH), 5.36 (d, J = 10.9 Hz, 1 H, CHCN), 6.26 (t, J = 10.9 Hz, 1 H, C*H*=CHCN) ppm. ^{13}C NMR (75 MHz): δ_C = 14.0 (*C*H$_3$CH$_2$), 19.0, 20.6 (2 × CH$_3$), 22.5, 27.1, 31.4 and 31.8 (4 × CH$_2$), 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): $\tilde{\nu}$ = 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: $C_{12}H_{21}N$ calcd. 179.1674, found 179.1677.

(2*Z*,4*R*)-4-Butylnon-2-enenitrile (3bd): (Table 2, Entry 16, 168 mg, 87%). Yellow oil. $[\alpha]_D^{25}$ = +2.1 (c = 1, $CHCl_3$ for the (*E*)/(*Z*) mixture, 32:68) [94% *ee* from HPLC; DAICEL CHIRALPAK AS, λ = 215 nm, *n*-hexane, 0.8 mL min^{-1}, 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, 6 H, 2 × CH$_3$CH$_2$), 1.26–1.39 (m, 10 H, 5 × CH$_2$), 1.46 (m, 4 H, 2 × CH$_2$CH), 2.12 (m, 1 H, CHCH$_2$), 5.26 (d, J = 16.4 Hz, 1 H, CHCN), 6.49 (dd, J = 16.4, 9.2 Hz, 1 H, 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 (5 × CH$_2$), 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, 6 H, 2 × CH$_3$CH$_2$), 1.26–1.39 (m, 10 H, 5 × CH$_2$), 1.46 (m, 4 H, 2 × CH$_2$CH), 2.62 (m, 1 H, CHCH$_2$), 5.31 (d, J = 10.9 Hz, 1 H, CHCN), 6.19 (t, J = 10.9 Hz, 1 H, 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 (5 × CH$_2$), 42.7 (*C*HCH$_2$), 99.1 (*C*HCN), 117.6 (CN), 160.7 (*C*H=CHCN) ppm. IR (neat): $\tilde{\nu}$ = 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: $C_{12}H_{20}N$ [*M* – Me]$^+$ calcd. 178.1595, found 178.1600.

(2*E*,4*R*)-4-Benzylnon-2-enenitrile (3bf): (Table 2, Entry 17, 186 mg, 81%). Colourless, sticky oil. $[\alpha]_D^{25}$ = –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/propan-2-ol, 99.5:0.5, 0.8 mL min^{-1}, 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, 3 H, CH$_3$), 1.25–1.35 (m, 6 H, 3 × CH$_2$), 1.67 (m, 2 H, CH$_2$CH), 2.44 (m, 1 H, CHCH$_2$), 2.58 and 2.78 (2 × m, 2 H, CH$_2$Ph), 5.11 (dd, J = 16.4, 0.6 Hz, 1 H, CHCN), 6.51 (dd, J = 16.4, 9.0 Hz, 1 H, C*H*=CHCN), 7.11–7.18 (m, 3 H, ArH), 7.21–7.31 (m, 2 H, ArH) ppm. ^{13}C NMR (75 MHz): δ_C = 13.9 (CH$_3$), 22.5, 31.6, 33.5 and 37.9 (4 × CH$_2$), 40.7 (*C*HCH$_2$), 45.8 (*C*H$_2$Ph), 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, 3 H, CH$_3$), 1.25–1.35 (m, 6 H, 3 × CH$_2$), 1.67 (m, 2 H, CH$_2$CH), 2.58 and 2.78 (2 × m, 3 H, CH$_2$Ph and CHCH$_2$), 5.24 (d, J = 10.8 Hz, 1 H, CHCN), 6.19 (t, J = 10.8 Hz, 1 H, C*H*=CHCN), 7.11–7.18 (m, 3 H, ArH), 7.21–7.31 (m, 2 H, ArH) ppm. ^{13}C NMR (75 MHz): δ_C = 13.9 (CH$_3$), 25.4, 31.7, 33.9 and 37.9 (4 × CH$_2$), 41.1 (*C*HCH$_2$), 44.1 (CH$_2$Ph), 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): $\tilde{\nu}$ = 2221, 1611 cm^{-1}. MS (EI): *m*/*z* (%) = 227 [*M*]$^+$ (12), 92 (9), 91 (100). HRMS: $C_{16}H_{21}N$ calcd. 227.1674, found 227.1669.

(2*E*,4*R*)-4-Phenylpent-2-enenitrile (3ca):[22] (Table 2, Entry 21, 138 mg, 88%). Colourless oil. $[\alpha]_D^{25}$ = +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/propan-2-ol, 99:1, 1 mL min^{-1}, 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, 3 H, CH$_3$), 3.59–3.65 (m, 1 H, CHPh), 5.27 (dd, J = 16.4, 1.1 Hz, 1 H, CHCN), 6.88 (dd, J = 16.4, 6.3 Hz, 1 H, C*H*=CHCN), 7.17–7.28 (m, 2 H, ArH), 7.33–7.36 (m, 3 H, 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): $\tilde{\nu}$ = 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. $[\alpha]_D^{25}$ = +8.3 (c = 0.7, $CHCl_3$) (80% *ee* from HPLC; DAICEL CHIRALPAK AD, λ = 215 nm, *n*-hexane/propan-2-ol, 99.5:0.5, 0.5 mL min^{-1}, 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, 3 H, CH$_3$), 1.82–1.93 (m, 2 H, CH$_2$), 3.26–3.33 (m, 1 H, CHPh), 5.25 (d, J = 16.4 Hz, 1 H, CHCN), 6.84 (dd, J = 16.4, 7.3 Hz, 1 H, C*H*=CHCN), 7.12–7.27 (m, 2 H, ArH), 7.29–7.37 (m, 3 H, 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): $\tilde{\nu}$ = 2221, 1613 cm^{-1}. MS (EI): *m*/*z* (%) = 171 [*M*]$^+$ (25.4), 143 (15), 142 (86), 116 (18), 115 (100). HRMS: $C_{12}H_{13}N$ calcd. 171.1048, found 171.1049.

(2*Z*,4*S*)-4-Phenylhex-2-enenitrile (3cb): (Table 2, Entry 22, 148 mg, 86%). Colourless oil. $[\alpha]_D^{25}$ = +68.1 (c = 0.2, $CHCl_3$) (80% *ee* from HPLC; DAICEL CHIRALPAK AD, λ = 215 nm, *n*-hexane/propan-2-ol, 99.5:0.5, 0.5 mL min^{-1}, 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, 3 H, CH$_3$), 1.76–1.88 (m, 2 H, CH$_2$), 3.75–3.82 (m, 1 H, CHPh), 5.33 (d, J = 10.8 Hz, 1 H, CHCN), 6.53 (t, J = 10.8 Hz, 1 H, C*H*=CHCN), 7.12–7.27 (m, 2 H, ArH), 7.29–7.37 (m, 3 H, 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): $\tilde{\nu}$ = 2221, 1613 cm^{-1}. MS (EI): *m*/*z* (%) = 171 [*M*]$^+$ (25.4), 143 (15), 142 (86), 116 (18), 115 (100). HRMS: $C_{12}H_{13}N$ calcd. 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/propan-2-ol 99.5:0.5, 0.5 mL min^{-1}, t_r = 21.0 and **22.4** min, (*E*) isomer) and DAICEL CHIRACEL OJ, λ = 215 nm, *n*-hexane/propan-2-ol, 99:1, 0.5 mL min^{-1}, 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, 3 H, CH$_3$), 1.21–1.37 (m, 4 H, 2 × CH$_2$), 1.73–1.86 (m, 2 H, CH$_2$), 3.39 (m, 1 H, CHPh), 5.25 (d, J = 16.4 Hz, 1 H, CHCN), 6.85 (dd, J = 16.4, 7.5 Hz, 1 H, C*H*=CHCN), 7.12–7.25 (m, 2 H, ArH), 7.29–7.40 (m, 3 H, ArH) ppm. ^{13}C NMR (75 MHz): δ_C = 13.8 (CH$_3$), 22.4, 29.4 and 34.2 (3 × CH$_2$), 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, 3 H, CH$_3$), 1.21–1.37 (m, 4 H, 2 × CH$_2$), 1.73–1.86 (m, 2 H, CH$_2$), 3.90 (m, 1 H, CHPh), 5.72 (d, J = 10.8 Hz, 1 H, CHCN), 6.54 (t, J = 10.8 Hz, 1 H, C*H*=CHCN), 7.12–7.25 (m, 2 H, ArH), 7.29–7.40 (m, 3 H, 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): $\tilde{\nu}$ = 2221, 1617 cm^{-1}. MS (EI): *m*/*z* (%) = 199 [*M*]$^+$ (21.7), 143 (100), 142

(62), 116 (29), 115 (70). HRMS: $C_{14}H_{17}N$ calcd. 199.1361, found 199.1358.

(2*Z*,4*S*)-5-Methyl-4-phenylhex-2-enenitrile (3cc): (Table 2, Entry 27, 154 mg, 83%). Colourless oil. $[\alpha]_D^{25}$ = +158.9 (c = 1.0, $CHCl_3$ for the (*E*)/(*Z*) mixture, 39:61) [90% *ee* for each isomer from HPLC; DAICEL CHIRALPAK AS, λ = 215 nm, *n*-hexane, 1 mL min^{-1}, 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, 3 H, CH_3), 0.98 (d, J = 6.7 Hz, 3 H, CH_3), 2.04 (m, 1 H, C*H*CH_3), 3.01 (t, J = 9.0 Hz, 1 H, C*H*CH=CH), 5.31 (dd, J = 16.2, 0.9 Hz, 1 H, CHCN), 6.89 (dd, J = 16.2, 9.0 Hz, 1 H, C*H*=CHCN), 7.10–7.27 (m, 2 H, ArH), 7.31–7.38 (m, 3 H, ArH) ppm. ^{13}C NMR (75 MHz): δ_C = 20.7 and 20.8 (2 × CH_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, 3 H, CH_3), 1.01 (d, J = 6.7 Hz, 3 H, CH_3), 2.04 (m, 1 H, C*H*CH_3), 3.50 (t, J = 10.2 Hz, 1 H, C*H*CH=CH), 5.32 (d, J = 10.8 Hz, 1 H, CHCN), 6.62 (t, J = 10.8, 9.0 Hz, 1 H, C*H*=CHCN), 7.10–7.27 (m, 2 H, ArH), 7.31–7.38 (m, 3 H, ArH) ppm. ^{13}C NMR (75 MHz): δ_C = 20.5 and 20.6 (2 × CH_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): $\tilde{\nu}$ = 2222, 1619 cm^{-1}. MS (EI): *m*/*z* (%) = 185 $[M]^+$ (6.9), 143 (100), 115 (23). HRMS: $C_{13}H_{15}N$ calcd. 185.1204, found 185.1206.

(2*E*,4*R*)-4,5-Diphenylpent-2-enenitrile (3cf): (Table 2, Entry 29, 200 mg, 86%). Colourless oil. $[\alpha]_D^{25}$ = +10.5 (c = 2.0, $CHCl_3$ for the (*E*)/(*Z*) mixture, 70:30) [85% *ee* for each isomer from HPLC; DAICEL CHIRALPAK AS, λ = 209 nm, *n*-hexane/propan-2-ol, 99:1, 0.7 mL min^{-1}, t_r = 16.5 and **17.2** min, (*Z*) isomer, and 25.1 and **26.7** min, (*E*) isomer)]; TLC: R_f = 0.45 for the (*Z*) isomer, 0.39 for the (*E*) isomer (*n*-hexane/ethyl acetate, 4:1).

(*E*) Isomer: ^{1}H NMR (300 MHz): δ_H = 3.07 (m, 2 H, CH_2), 3.71 (m, 1 H, CHPh), 5.12 (dd, J = 16.4, 1.5 Hz, 1 H, CHCN), 6.87 (dd, J = 16.4, 7.2 Hz, 1 H, C*H*=CHCN), 7.12–7.25 (m, 4 H, ArH), 7.29–7.40 (m, 6 H, 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 (2 × m, 2 H, CH_2), 4.18 (m, 1 H, CHPh), 5.24 (d, J = 10.8 Hz, 1 H, CHCN), 6.60 (t, J = 10.8 Hz, 1 H, C*H*=CHCN), 7.12–7.25 (m, 4 H, ArH), 7.29–7.40 (m, 6 H, 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): $\tilde{\nu}$ = 2221 (CN), 1629 (C=C) cm^{-1}. MS (EI): *m*/*z* (%) = 233 $[M]^+$ (6.2), 115 (7), 91 (100). HRMS: $C_{17}H_{15}N$ calcd. 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 at –78 °C through a solution of product **3a** (0.25 mmol) in dichloromethane (3 mL) 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 overnight. The reaction mixture was concentrated and the crude mixture was 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*) {ref.[17] $[\alpha]_D^{23}$ = –4.42 (c = 4, MeOH) 94% *ee* (*S*) enantiomer} (76% *ee* from HPLC; DAICEL CHIRACEL OJ, λ = 254 nm, *n*-hexane/propan-2-ol, 99:1, 0.7 mL min^{-1}, t_r = **10.2** and 12.2 min). ^{1}H NMR (300 MHz): δ_H = 1.05 (d, J = 7.1 Hz, 3 H, CH_3), 1.21 (m, 1 H, CH), 3,35 (2 × d, J = 12.5 Hz, 2 H, CH_2), 7.14–7.35 (m, 5 H, ArH), 9.75 (d, 1 H, 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), {ref.[18] $[\alpha]_D^{25}$ = –19.7 {c = 5.8, $CHCl_3$ 99% *ee* (*R*) enantiomer}. ^{1}H NMR (300 MHz): δ_H = 0.92 (m, 3 H, CH_3), 1.10 (d, J = 7.1 Hz, 3 H, CH_3CH), 1.22–1.74 (m, 6 H, 3 × CH_2), 2.42 (m, 1 H, CH), 9.62 (d, 1 H, 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 °C overnight. An aqueous saturated solution of $NaHCO_3$ (10 mL) was then added to neutralise the acidic medium. MeOH was then removed by evaporation, and ethyl acetate was added. The organic layer was separated, dried ($MgSO_4$) and concentrated to afford the crude compounds, which were purified by flash chromatography to provide the pure esters **4**.

Methyl (2*E*,4*S*)-4-Methylnon-2-enenoate [(*S*)-4ba]: (37 mg, 80%). Pale yellow oil. $[\alpha]_D^{25}$ = +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, 3 H, CH_3CH$_2$), 1.04 (d, J = 6.7 Hz, 3 H, CH_3CH), 1.26–1.41 (m, 8 H, 4 × CH_2), 2.28 (m, 1 H, C*H*CH_3), 3.73 (s, 3 H, OCH_3), 5.77 (d, J = 15.7 Hz, 1 H, CHCN), 6.86 (dd, J = 15.7, 7.9 Hz, 1 H, 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_3CH), 26.6, 31.1, 31.6 (3 × CH_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): $\tilde{\nu}$ = 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: $C_{10}H_{17}O_2$ calcd. 169.1248, found 169.1244.

Methyl (2*E*,4*R*)-4-Methylnon-2-enenoate [(*R*)-4ba]: (36 mg, 78%). Pale yellow oil. $[\alpha]_D^{25}$ = –31.8 (c = 0.8, $CHCl_3$ for the (*E*)/(*Z*) mixture, 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, 3 H, CH_3CH$_2$), 1.04 (d, J = 6.7 Hz, 3 H, CH_3CH), 1.26–1.41 (m, 8 H, 4 × CH_2), 2.28 (m, 1 H, C*H*CH_3), 3.73 (s, 3 H, OCH_3), 5.77 (d, J = 15.7 Hz, 1 H, CHCN), 6.86 (dd, J = 15.7, 7.9 Hz, 1 H, 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_3CH), 26.6, 31.1, 31.6 (3 × CH_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): $\tilde{\nu}$ = 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: $C_{10}H_{17}O_2$ calcd. 169.1248, found 169.1249.

Methyl (2*E*,4*R*)-4-Phenylpent-2-enenoate (4ca):[7a] (47 mg, 99%). Colourless oil. $[\alpha]_D^{25}$ = +15.5 (c = 0.3, $CHCl_3$ for the (*E*)/(*Z*) mixture, 95:5). ^{1}H NMR (300 MHz): δ_H = 1.43 (d, J = 7.0 Hz, 3 H, CH_3CH), 3.62 (m, 1 H, C*H*CH_3), 3.72 (s, 3 H, CH_3O), 5.80 (dd, J = 15.7, 1.5 Hz, 1 H, $CHCO_2Me$), 7.20 (dd, J = 15.7, 6.4 Hz, 1 H, C*H*=CHCN), 7.25–7.39 (m, 3 H, ArH), 7.28–7.36 (m, 2 H, 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 for 15 h. The reaction mixture was quenched with H_2SO_4 (1 M, 5 mL) and ethyl acetate (10 mL) and the organic residue was purified by flash chromatography (36 mg, 48% overall yield from **3ba** mixtures).

Compound (*S*)-9: $[\alpha]_D^{25}$ = +0.51 (*c* = 2, $CHCl_3$, 78% *ee*), ref.[21a] $[\alpha]_D^{25}$ = +0.63 ($CHCl_3$), ref.[21e] $[\alpha]_D^{25}$ = +1.97 (neat). ^1H NMR (300 MHz): δ_H = 0.92 (m, 6 H, $2\times CH_3$), 0.99–1.77 (m, 13 H, C*H*CH_3 and $6\times CH_2$), 2.8 (s, 1 H, OH), 3.61 ppm (t, *J* = 6.6 Hz, 2 H, CH_2O). MS (EI): *m*/*z* (%) = 158 $[M - 1]^+$ (2), 140 (3), 112 (16), 97 (24), 84 (36), 69 (100), 57 (93), 41 (100).

Compound (*R*)-9: $[\alpha]_D^{25}$ = +0.48 (*c* = 2, $CHCl_3$, 78% *ee*), ref.[21a] $[\alpha]_D^{25}$ = +0.63 ($CHCl_3$), ref.[21e] $[\alpha]_D^{25}$ = +1.97 (neat). ^1H NMR (300 MHz): δ_H = 0.92 (m, 6 H, $2\times CH_3$), 0.99–1.77 (m, 13 H, C*H*CH_3 and $6\times CH_2$), 2.8 (s, 1 H, OH), 3.61 ppm (t, *J* = 6.6 Hz, 2 H, CH_2O). MS (EI): *m*/*z* (%) = 158 $[M - 1]^+$ (1), 140 (1), 112 (19), 97 (24), 84 (38), 69 (100), 57 (90), 41 (100).

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