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Diastereoselective and Enantiospecific Synthesis of γ-Substituted α,β-Unsaturated Nitriles from O-Protected Allylic Cyanohydrins

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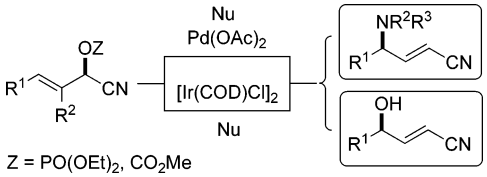

γ-Functionalized α,β-unsaturated nitriles are prepared diastereoselectively and enantiospecifically from enantioenriched cyanohydrin-*O*-phosphates and carbonates derived from α,β-unsaturated aldehydes, either by palladium or iridium-catalyzed nucleophilic allylic substitution reactions with different nucleophiles. Appropriate reaction conditions for dibenzylamine, benzylamine, sodium azide, NaOAc, tetra-*n*-butylammonium acetate (TBAA), the corresponding sodium salts of phenol and *N*-hydroxysuccinimide and the carbonucleophile sodium dimethyl malonate are described. Different substituted O-protected cyanohydrins, such as carbonates and phosphates, derived from crotonaldehyde, (*E*)-hex-2-enal, oct-2-enal, 2-methylbut-2-enal, and cinnamaldehyde are used as allylic substrates. The substitution takes place with total retention of the configuration for the (*E*)-γ-functionalized nitriles and with inversion of the configuration for the *Z*-isomers. In general, cyanohydrin-*O*-phosphates are the materials of choice to get the highest *E*-diastereoselectivity. Dibenzylamine is the best nucleophile for the synthesis of γ-nitrogenated α,β-unsaturated nitriles in the presence of either palladium or iridium catalysts when aliphatic compounds and cinnamaldehyde derivative are used (up to 98% dr). For the synthesis of γ-oxygenated α,β-unsaturated nitriles sodium or TBAA the reagents are selected to avoid epimerizations in up to 76% dr. Finally, the Tsuji−Trost reaction with sodium malonate works only under palladium catalysis in up to 70% dr.

Introduction

Enantiomerically enriched γ-functionalized α,β-unsaturated nitriles **1** and **2** are very important chiral building blocks in the total synthesis of natural products. These molecules are prone to undergo functional group transformations at both nitrile and γ-position substituent and classical carbon−carbon double bond reactions including electrocyclic rearrangements and Michael-type additions (Figure 1). γ-Hydroxy-α,β-unsaturated nitriles and their O-substituted derivatives **1** (R^3 = OH) have been used as chiral intermediates in the total synthesis of coriolic acid by the conversion of the nitrile to the aldehyde **7** (Figure 1).[1] The generation of the carboxylic acid **7** (R^4 = OH) from the nitrile was required to perform the final macrolactonization in the synthesis of the (+)-patulolide C.[2] A combined sequential carbon−carbon double bond reduction followed by oxidation of the nitrile group gave aldehyde **8**, which has been used in the total synthesis of the (+)-allocyathin B_2.[3] The transformation of the nitrile group into a primary alcohol, followed by the epoxidation of the double bond, afforded compound **9** as intermediate for the synthesis of a segment of the fish poisoning ciguatoxin CTX1B.[4] The Claisen−Johnson ortho ester rearrangement was studied in the reaction of allylic alcohols **1** with triethyl orthoacetate in refluxing xylene furnishing 3-cyano esters.[5] The Michael-type addition reactions onto the α,β-unsaturated nitrile moiety in compounds **1** have been employed for different synthetic purposes[6] such as in the modified Baylis−

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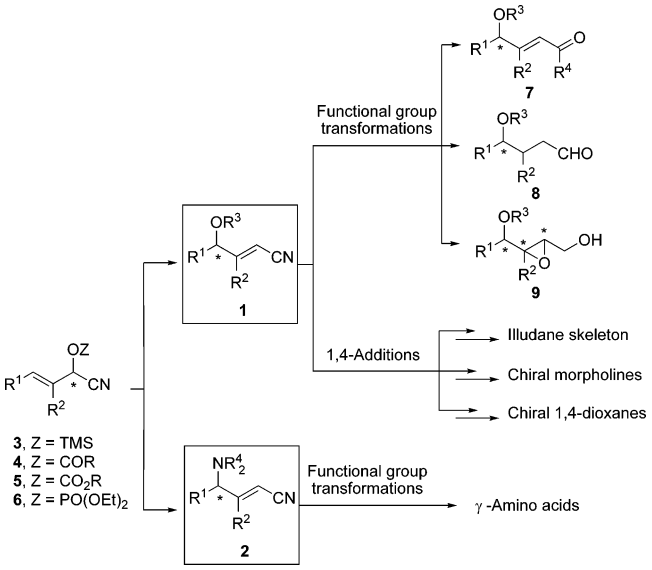

FIGURE 1. Preparation and main uses of compounds **1** and **2** in organic synthesis.

Hillman reaction, which served to obtain a cyclic intermediate employed in the synthesis of the illudane skeleton present in many toxic sesquiterpenes.[7] Intramolecular 1,4-additions onto chiral derivatives **1** have been exploited in the synthesis of enantiomerically enriched 1,4-dioxanes[8] and morpholines[9] by the direct attack of a sodium alkoxide or a sodium carbamate, respectively (Figure 1). Several intermediates containing the skeleton of **1** have been proposed in the reaction of racemic γ-oxo-α,β-unsaturated nitriles with Grignard reagents[10] through a sequential carbonyl addition−conjugated addition onto the resulting α,β-unsaturated nitriles.

In the case of γ-nitrogenated-α,β-unsaturated nitriles **2**, their application as chiral building blocks has been directed to the synthesis of γ-amino acids by functional group transformations involving the cyano and carbon−carbon double bond.[11,12] α,β-Unsaturated γ-amino acids are also attractive chiral building blocks in organic synthesis[12] and intriguing conformationally restricted amino acids, especially when they are incorporated into peptides as vinylogous amino acids.[13] γ-Aminobutyric acid (GABA)[14] is considered as an inhibitory neurotransmitter found in almost every region of the brain and spinal cord. In addition, GABA analogues have been used for many purposes. For example, they have been used as antineoplasic agents, as mood enhancement agents, tranquilizers, and analgesic drugs.[15] Very recently, a chiral nitrile **2** has been used in the determination of the absolute configuration of the *E*/*Z*-mixture products generated from preliminary palladium-catalyzed nucleophilic allylic substitution reaction of enantiomerically enriched cyanocarbonates **5**[12] (Figure 1).

Several diastereoselective synthetic sequences allow the preparation of chiral nitriles **1**, for example, the Wittig or Wittig-type reactions using chiral aldehydes or ketones,[7,16,17] the reaction between α-(arylsulfinyl)acetonitriles and aldehydes or ketones,[3,5,18,19] the oxyselenylation−deselenylation reaction of alkenes,[8,9,20−22] the addition of the cyanide anion to optically active epoxides,[23,24] the β-elimination reactions involving chiral dihydroxy nitriles,[25] and the cyanation reaction of vinyl iodides by copper cyanide.[26] Also, diastereoselective Wittig reactions were used for the preparation of aminonitriles **2**.[11] The most direct and simple synthetic approach to γ-substituted α,β-unsaturated nitriles **1** and **2** involves cyanohydrin derivatives **3**−**5**. The reduction of *O*-trimethylsilyl cyanohydrin **3** (Z = TMS) mediated by a Lewis acid,[4] thermal or palladium-catalyzed [3,3]-sigmatropic rearrangements of carbonates **5** (Z = CO_2R),[2] and the palladium-mediated dynamic kinetic resolution of these carbonates using a salen−palladium complex[27] (Figure 1) have been successively employed. However, the most important and versatile strategy for the synthesis of compounds **1** and **2** is the palladium-catalyzed nucleophilic allylic substitution reaction onto derivatives **4** and **5**. Racemic O-protected

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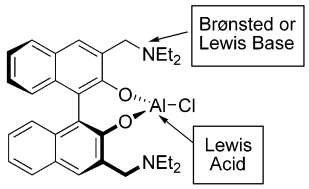

(*S*)-BINOLAM-AlCl **10**

FIGURE 2. Chiral bifunctional complex **10**.

cyanohydrins **4** and **5** have been transformed into γ-functionalized α,β-unsaturated nitriles by using NaOAc, sodium azide, and tin alkoxides as nucleophiles.[28] Enantioenriched *O*-acyl cyanohydrins **4** (Z = COR) have been used as allylic substrates in the reactions with sodium carboxylates,[1,29] and optically active cyanohydrin carbonates **5** (X = CO_2R) have been transformed into products **2** by reaction with sodium azide or trimethylsilyl azide.[12]

We have recently described the enantioselective cyanoformylation[30] and cyanophosphorylation[31] of aldehydes catalyzed by the bifunctional complex BINOLAM-AlCl **10** (Figure 2), which afforded enantiomerically enriched cyanohydrin-*O*-carbonates **5** and -phosphates **6**, respectively. Preliminary studies about the reactivity of these chiral phosphates **6**, derived from α,β-unsaturated aldehydes, in the palladium-catalyzed nucleophilic substitution with NaOAc and dibenzylamine allowed the diastereoselective and stereospecific generation of the compounds **1** (R^3 = Ac) and **2** (R^4 = *n*-Bu).[31] From these studies, we could establish that the compounds **1** and **2** with (*E*)-configuration were obtained with retention (double inversion) of the configuration and the *Z*-isomer with inversion of the configuration after the palladium-catalyzed nucleophilic substitution.[31] Usually allylic acetates **4** and, especially, carbonates **5** are used instead of the unknown (and not easily accessible) enantioenriched phosphates **6**.[32,33] The oxidative addition involved in this process onto allylic electrophiles to give allyl-substituted palladium(II) species is faster for allylic carbonates, while allylic phosphates and the analogous carboxylates possess a similar chemical behavior in this type of reaction.[34]

In this article, we describe a comprehensive study of the synthetic potential of the enantioenriched cyanohydrin-*O*-carbonates **5** and cyanohydrin-*O*-phosphates **6** to provide the corresponding γ-substituted α,β-unsaturated nitriles using heteronucleophiles and malonate as nucleophiles in the presence of palladium or iridium complexes as catalysts. The optimal conditions for each nucleophile and substrate, concerning the stereoselectivity and enantioselectivity, as well as the comparison between the carbonate and the phosphate as leaving groups will be evaluated.

Results and Discussion

As part of the very attractive family of cyanohydrins,[35] chiral cyanocarbonates **5**[30] and, for the first time, chiral cyanophosphates **6**[31] have been prepared by our research group in very high enantiomeric excess (ee) from aldehydes, in only one-step process, using chiral bifunctional[36] (*R*)- or (*S*)-BINOLAM-AlCl complexes **10** (Figure 2) as catalysts. Certainly, the preparation of the enantiomerically enriched cyanohydrin-*O*-phosphates **6** represented a synthetic task more difficult than the elaboration of the racemic ones,[37] and the chemical (non-enzymatic) procedures to achieve them were recently reported by us[31] and Shibasaki's group.[38] A priori, cyanohydrin-*O*-phosphates[39,40] resemble very exciting molecules due to their high functional density and the electrophilic character of the phosphate moiety, which has been the choice by nature in multiple biotransformations acting as the leaving group.

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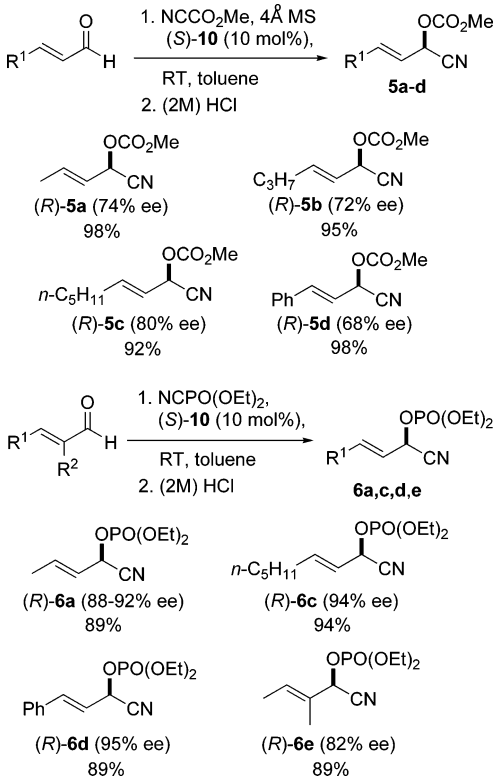
SCHEME 1. Enantioselective Synthesis of Cyanohydrin Derivatives 5 and 6



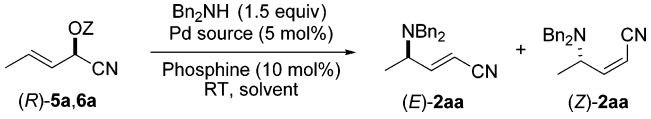
Unsaturated cyanohydrin-*O*-carbonates **5** and phosphates **6**, derived from α,*β*-unsaturated aldehydes, with (*R*)-configuration were the selected starting materials to run the allylic displacement of the carbonate and phosphate groups. They were obtained from the corresponding aldehydes employing a 10 mol % of the catalyst (*S*)-**10** and 3 equiv of methyl cyanoformate[30] and 1.1 equiv of diethyl cyanophosphonate, respectively, at room temperature under anhydrous conditions[31] (Scheme 1). 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%).[30,31] Particularly, the ee of the cyanohydrin-*O*-phosphate **6a** was very sensitive to the humidity present in the freshly distilled crotonaldehyde, the enantiomeric excesses being achieved in the range of 88−92%.

Nitrogenated Nucleophiles. Initially, the allylic phosphate **6a**, derived from crotonaldehyde, was selected for the optimization of the reaction conditions of each tested nucleophile, and dibenzylamine was chosen as the heteronucleophile in the model reaction, which will serve as a general pattern to be extended to other nitrogenated nucleophiles. The reactions were performed at room temperature employing a catalyst charge of 5 mol % of a palladium source and 10 mol % of the corresponding phosphine. To establish the best chemical yield and the best *E*/*Z*-ratio, palladium(II) acetate was first tested in acetonitrile as solvent and using several phosphines (Table 1, entries 1−3). The best *E*/*Z* ratio corresponded to the catalytic mixture composed of palladium(II) acetate (5 mol %)/1,2-bis(diphenylphosphino)ethane (dppe, 10 mol %), (Table 1, entry 2). Next, the effects of the different palladium sources such as palladium(II) acetate, tetrakis(triphenylphosphine)palladium(0), tris(dibenzylideneacetone)dipalladium(0), and *π*-allylpalladium(II) chloride dimer, with or without addition of phosphine, were analyzed, clearly indicating that the mixture $Pd(OAc)_2$/dppe gave the best (*E*)-**2aa**/(*Z*)-**2aa** ratio (Table 1 entries 2−8). The introduction of lower amounts of palladium produced lower chemical yields in uncompleted reactions. The influence of the solvent was studied with the mentioned catalytic mixture (Table 1, entries 2, 9−11) obtaining the highest selectivity in shorter reaction times in the reaction run in toluene (Table 1, entry 11). Other solvents as dichloromethane or THF gave the same chemical yields, affording (*E*)-**2**/(*Z*)-**2** ratios (94:6) lower than that of the reaction performed in the presence of toluene (Table 1, entries 9−11). The couple $Pd(OAc)_2$/tris(*o*-tolyl)phosphine was also tested and achieved a faster reaction with a lower (*E*)-**2aa**/(*Z*)-**2aa** ratio (Table 1, compare entries 11 and 12). For carbonate **5a**, a lower loading of $Pd(OAc)_2$ (3 mol %) was used, giving Ph_3P and dppe the same results in acetonitrile, although dppe showed cleaner reaction products (Table 1, entries 13 and 14). A noticeable reaction acceleration was observed in toluene that afforded a slightly better (*E*)-**2aa**/(*Z*)-**2aa** ratio and 5% of the α-substitution product (Table 1, entry 15). Despite lowering the reaction temperature at 0 and −10 °C, it was not possible to direct the reaction to give pure α-substitution product, achieving its maximum percentage when the reaction was performed at 0 °C (Table 1, entries 15−17). In any case, these α-substitution products were isolated and characterized because their separation from the (*E*)-**2**/(*Z*)-**2** mixtures was not possible. It can be concluded that the cyanohydrin-*O*-phosphate **6a** gave the highest *E*/*Z*-diastereomeric ratio of compound **2aa** using Pd(OAc)$_2$/dppe as catalyst and toluene as solvent. Although the analogous carbonate **5a** needed lower catalyst loading, competitive α−substitution occurred for this type of substrate.

By employing these reaction conditions, different cyanohydrin-protected carbonates **5** and phosphates **6** reacted with dibenzylamine or benzylamine, affording mixtures of (*E*)-**2a**/(*Z*)-**2a** (Table 2). Carbonate **5d**, derived from cinnamaldehyde, gave much better *E*/*Z*-diastereoselectivity than the crotonaldehyde derivative **5a** (Table 2, entries 1 and 2). Cyanophosphates **6a**,**d**,**e** derived from crotonaldehyde, cinnamaldehyde, and 2-methylbut-2-en-al, respectively, furnished good yields and high diastereomeric ratios (Table 2, entries 3−5). The less nucleophilic benzylamine reacted with cyanohydrin-*O*-phosphate **6a** under the optimized nucleophilic allylic substitution conditions, achieving diastereoselectivity similar to that exhibited by dibenzylamine, and the pure compound (*E*,*R*)-**2ba** was isolated after selective solubilization in hexanes with an overall retention of the configuration (Table 2, entry 6). On the other side, very high (*E*)-diastereoselection was detected in the reaction involving the cinnamaldehyde derivative (*R*)-**6d**, but surprisingly, (*E*,*R*)-**2bd** was isolated with a very significant loss of optical activity (Table 2, entry 7). Both reactions were completed in 2.5 h as revealed GC analysis. When cyanocarbonates **5a** and **5d** were submitted to the reaction conditions using benzylamine as nucleophile [$Pd(OAc)_2$ (3 mol %)/dppe (6 mol %), toluene, room temperature], the reaction did not occur as expected. While **5a** afforded a very complex mixture of unidentified products, including a low proportion of **2ba**, carbonate **5d** gave *N*-benzyl *O*-methyl carbamate **11** and the corresponding cyanohydrin **12d** as major reaction products as a consequence of the direct attack of the amine onto the carbonyl group (Scheme 2).

Iridium complexes also catalyzed this type of nucleophilic allylic substitutions.[33c,41] In this context, the catalyst [Ir(COD)Cl]$_2$ (2.5 mol %) promoted the nucleophilic substitution reaction of benzylamine onto chiral phosphate **6a**, in toluene, giving the

TABLE 1. Optimization of the Palladium-Catalyzed Allylic Substitution Reactions Using Dibenzylamine

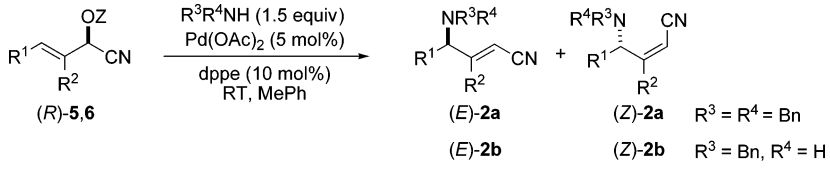


(*R*)-**5a**,**6a** (*E*)-**2aa** (*Z*)-**2aa**

	5a or **6a**								
entry	(% ee)	Z	Pd source	phosphine	solvent	time (h)	(*E*)-**2aa**/(*Z*)-**2aa**[a]	yield (%)[b]	ee (%)[c]
1	**6a** (88)	$PO(OEt)_2$	$Pd(OAc)_2$	Ph_3P	MeCN	12	(77)/(23)	85	88
2	**6a** (88)	$PO(OEt)_2$	$Pd(OAc)_2$	dppe[d]	MeCN	18	(86)/(14)	91	88
3	**6a** (88)	$PO(OEt)_2$	$Pd(OAc)_2$	dppp[e]	MeCN	> 24	(78)/(22)	<25	nd
4	**6a** (88)	$PO(OEt)_2$	$Pd_2(dba)_3$	−	MeCN	20	(73)/(27)	91	88
5	**6a** (88)	$PO(OEt)_2$	$Pd(Ph_3P)_4$	−	MeCN	12	(70)/(30)	92	88
6	**6a** (88)	$PO(OEt)_2$	(PdCl-π-allyl)$_2$	−	MeCN	18	(76)/(24)	90	88
7	**6a** (88)	$PO(OEt)_2$	$Pd(Ph_3P)_4$	dppe[d]	MeCN	17	(75)/(25)	90	88
8	**6a** (88)	$PO(OEt)_2$	(PdCl-π-allyl)$_2$	dppe[d]	MeCN	15	(78)/(22)	87	88
9	**6a** (88)	$PO(OEt)_2$	$Pd(OAc)_2$	dppe[d]	CH_2Cl_2[f]	12	(75)/(25)	91	88
10	**6a** (88)	$PO(OEt)_2$	$Pd(OAc)_2$	dppe[d]	THF	12	(87)/(23)	90	88
11	**6a** (90)	$PO(OEt)_2$	$Pd(OAc)_2$	dppe[d]	PhMe	6	(94)/(6)	89	90
12	**6a** (90)	$PO(OEt)_2$	$Pd(OAc)_2$	(*o*-Tol)$_3$P	PhMe	1	(83)/(17)	90	90
13	**5a** (74)	CO_2Me	$Pd(OAc)_2$[g]	Ph_3P	MeCN	20	(72)/(27)	80	74
14	**5a** (74)	CO_2Me	$Pd(OAc)_2$[g]	dppe[d]	MeCN	20	(72)/(27)	80	74
15	**5a** (74)	CO_2Me	$Pd(OAc)_2$[g]	dppe[d]	PhMe	1	(75)/(25)	94[h]	74
16	**5a** (74)	CO_2Me	$Pd(OAc)_2$[g]	dppe[d]	PhMe[i]	9	(87)/(13)	80[j]	74
17	**5a** (74)	CO_2Me	$Pd(OAc)_2$[g]	dppe[d]	PhMe[k]	20	(75)/(25)	94[l]	74

[a] Determined by ^{1}H NMR spectroscopy. [b] Isolated yield of the (*E*)-**2aa**/(*Z*)-**2aa** mixture after flash chromatography. [c] Enantiomeric excesses for both *E*- and *Z*-isomers, determined by chiral HPLC (Chiralcel OD-H). [d] dppe = 1,2-bis(diphenylphosphino)ethane. [e] dppp = 1,3-bis(diphenylphosphino)propane. [f] 10% of the corresponding α-substitution product was observed by ^{1}H NMR spectroscopy in the crude reaction mixture. [g] A 3 mol % charge of palladium(II) acetate and a 6 mol % of the phosphine were used. [h] 5% of the α-substitution product was identified by ^{1}H NMR. [i] Performed at 0 °C. [j] A 1:1 ratio of α- and γ-substitution products was identified by ^{1}H NMR. [k] Performed at −10 °C. [l] A 1:4 ratio of α- and γ-substitution products was identified by ^{1}H NMR.

TABLE 2. Palladium-Catalyzed Allylic Substitution Reactions onto 5 and 6 Using Dibenzylamine and Benzylamine



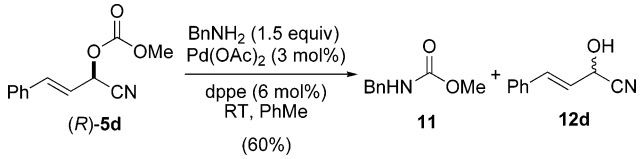
(*R*)-**5**,**6** (*E*)-**2a** (*Z*)-**2a** $R^3 = R^4 =$ Bn

(*E*)-**2b** (*Z*)-**2b** $R^3 =$ Bn, $R^4 =$ H

	5/**6**							
entry	(% ee)	R^1, R^2	Z	amine	time (h)	(*E*)-**2**/(*Z*)-**2**[a]	yield (%)[b]	ee (%)[c]
1	**5a** (74)[d]	Me, H	CO_2Me	Bn_2NH	1	(*E*)-**2aa** (75)/(*Z*)-**2aa** (25)	94[e]	74
2	**5d** (68)[d]	Ph, H	CO_2Me	Bn_2NH	20	(*E*)-**2ad** (99)/(*Z*)-**2ad** (1)	94	68[f]
3	**6a** (90)	Me, H	$PO(OEt)_2$	Bn_2NH	1	(*E*)-**2aa** (94)/(*Z*)-**2aa** (6)	90	90
4	**6d** (95)	Ph, H	$PO(OEt)_2$	Bn_2NH	10	(*E*)-**2ad** (95)/(*Z*)-**2ad** (5)	86	95[f]
5	**6e** (82)	Me, Me	$PO(OEt)_2$	Bn_2NH	24	(*E*)-**2ae** (90)/(*Z*)-**2ae** (10)	70	82[f]
6	**6a** (92)	Me, H	$PO(OEt)_2$	$BnNH_2$	2.5	(*E*)-**2ba** (93)/(*Z*)-**2ba** (7)	86	92[g]
7	**6d** (95)	Ph, H	$PO(OEt)_2$	$BnNH_2$	2.5	(*E*)-**2bd** (99)/(*Z*)-**2bd** (1)	91	31[g]

[a] Determined by ^{1}H NMR spectroscopy. [b] Isolated yield of the (*E*)-**2**/(*Z*)-**2** mixtures after flash chromatography. [c] Identical enantiomeric excesses for both *E*- and *Z*-isomers, determined by chiral HPLC (Chiralcel OD-H). [d] A 3 mol % charge of palladium(II) acetate and a 6 mol % of the phosphine were added. [e] 5% of the α-substitution product was identified by ^{1}H NMR. [f] Chiralpak AS. [g] Chiralpak AD.

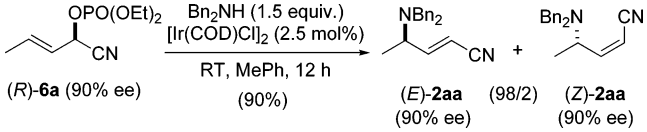
SCHEME 2. Side Reaction of Compound 5d with Benzylamine



(*R*)-**5d** **11** **12d**

highest (*E*)-**2aa**/(*Z*)-**2aa** ratio (98:2) in very good chemical yields with total retention of the configuration but in longer reaction times (12 h) than with $Pd(OAc)_2$ (Scheme 3). Unfortunately, no reaction occurred with carbonates **5** under identical reaction conditions. In the palladium-catalyzed addition of sodium azide onto carbonates, we observed a noticeable amount of the product resulting from the a-attack; however, this product was not observed when the reaction was performed with iridium. It has been reported that rhodium,[42] ruthenium,[43] and molybdenum[44] complexes also promoted the nucleophilic allylic substitution

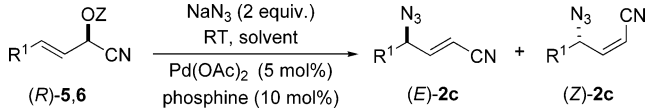
SCHEME 3. Iridium-Catalyzed Dibenzylamine Substitution onto 6a



(*R*)-**6a** (90% ee) (*E*)-**2aa** (90% ee) (98/2) (*Z*)-**2aa** (90% ee)

(41) (a) Miyabe, H.; Matsumura, A.; Moriyama, K.; Takemoto, Y. *Org. Lett.* **2004**, *6*, 4631−4634. (b) Lipowski, G.; Helmchem, G. *Chem. Commun.* **2004**, 116−117. (c) Miyabe, H.; Yoshida, K.; Yamauchi, M.; Takemoto, Y. *J. Org. Chem.* **2005**, *70*, 2148−2153.

TABLE 3. Palladium-Catalyzed Allylic Substitution Reactions Using Sodium Azide



(*R*)-**5**,**6** (*E*)-**2c** (*Z*)-**2c**

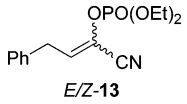
entry	5/6 (% ee)	R^1	Z	phosphine	solvent	time (h)	(*E*)-**2c**/(*Z*)-**2c**[a]	yield (%)[b]	ee (%)[c]
1	**5a** (74)	Me	CO_2Me	Ph_3P[d]	THF/H_2O[e]	24	(*E*)-**2ca** (84)/(*Z*)-**2ca** (16)	85	74
2	**5b** (72)	C_3H_7	CO_2Me	Ph_3P[d]	THF/H_2O[e]	24	(*E*)-**2cb** (84)/(*Z*)-**2cb** (16)	85	80[f]
3	**5b** (72)	C_3H_7	CO_2Me	Ph_3P[d]	THF[g]	24[h]	(*E*)-**2cb** (84)/(*Z*)-**2cb** (16)	85	80[f]
4	**6a** (92)	Me	$PO(OEt)_2$	Ph_3P	THF/H_2O[e]	24	(*E*)-**2ca** (72)/(*Z*)-**2ca** (28)	65	92
5	**6a** (92)	Me	$PO(OEt)_2$	dppe	THF/H_2O[e]	6	(*E*)-**2ca** (82)/(*Z*)-**2ca** (18)	85	92

[a] Determined by ^1H NMR spectroscopy. [b] Isolated yield of (*E*)-**2c**/(*Z*)-**2c** mixtures after flash chromatography. [c] Enantiomeric excesses for both *E*- and *Z*-isomers, determined by chiral HPLC (Chiralpak AD). [d] The reaction was performed with 3 mol % of palladium(II) acetate and 6 mol % of the corresponding phosphine. [e] 1:1 mixture (in volume). [f] Enantiomeric excesses for both *E*- and *Z*-isomers, determined by chiral HPLC (Chiralpak AS). [g] Anhydrous. [h] Trimethylsilyl azide (1.5 equiv) was used instead of sodium azide.

reactions with different regioselectivity, but in these title transformations neither carbonates **5** nor phosphates **6** gave any noticeable result. Thus, the iridium-catalyzed allylic substitution reaction represented a valuable alternative to prepare γ-dibenzylamino α,β-unsaturated nitriles only from chiral cyanohydrin-*O*-phosphates.

Sodium azide proved to be a very useful nucleophile in the palladium-catalyzed allylic substitution reaction onto racemic cyanoallylic carbonates, such as those described previously, employing mixtures of THF/water as solvent, $(Ph_3P)_4Pd$ as catalyst, and working at room temperature.[28e] In trying the same reaction conditions for chiral allylic carbonates **5** and phosphates **6**, we observed that the mixture $Pd(OAc)_2$/dppe or Ph_3P gave better results and cleaner reaction products. Thus, sodium azide reacted slowly with carbonate **5a** in approximately 1 d, employing $Pd(OAc)_2$ (3 mol %)/triphenylphosphine (6 mol %) and giving a 84:16 mixture of (*E*)-**2ca**/(*Z*)-**2ca** (Table 3, entry 1). Analogously, **5b** gave the same diastereoselectivity in both examples run with sodium azide or with trimethylsilyl azide[12] in anhydrous THF (Table 3, entries 2 and 3). Compound **5c** [derived from (*E*)-oct-2-enal] was inert under the described reaction conditions. Starting material (*R*)-**6a** afforded compounds (*E*)-**2ca** and (*Z*)-**2ca** in ratios dependent on the phosphine used; for example, the reaction involving dppe (10 mol %) as additive provided both yields (85%) and diastereomeric ratios (82:18) higher than those of the reaction performed with triphenylphosphine (10 mol %) (Table 3, compare entries 4 and 5). Unlike the reaction with carbonate **5a** with trimethylsilyl azide, cyanohydrin-*O*-phosphate **6a** did not afford the desired molecule (*E*)-**2ca**. Disappointingly, it was not possible to generate cinnamaldehyde derivatives (*E*)-**2cd** and (*Z*)-**2cd** in more than 10% yield, and instead the isomerized compound *E*/Z-**13** was generated in quantitative yield, as occurred in the reaction with the iridium complex (Figure 3). In the examples run with carbonates **5**, the use of dppe as ligand afforded very low conversions of the allylic substitution product.

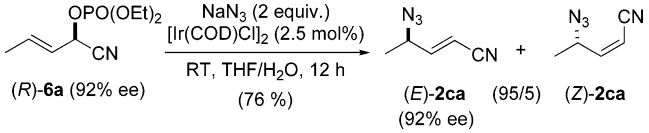
The phosphine-free iridium-catalyzed allylic substitution was also tested with $[Ir(COD)Cl]_2$ (2.5 mol %) in the allylic substitution reaction of sodium azide (2 equiv) onto alkene **6a**



E/*Z*-**13**

FIGURE 3. Compound *E*/*Z*-**13**.

SCHEME 4. Iridium-Catalyzed Substitution onto 6a with Sodium Azide



furnishing, such as occurred in the precedent reactions with dibenzylamine, the highest (*E*)-**2ca**/(*Z*)-**2ca** ratios (95:5) in a 1:1 mixture of THF/water (12 h) in good chemical yields (76%) (Scheme 4). Under these reaction conditions employing sodium azide, cyanophosphate **6d** yielded, basically, isomerized product **13**, and carbonate **5a** did not react at all.

All these results revealed that cyanohydrin-*O*-phosphates **6a**−**e** satisfactorily underwent both economical and chemical nucleophilic allylic substitution reactions with nitrogenated nucleophiles employing $Pd(OAc)_2$ (5 mol %)/dppe (10 mol %) as catalyst. Meanwhile, the $[Ir(COD)Cl]_2$ complex was a good alternative method to obtain and characterize almost pure (*E*,*R*)-**2ca** product from phosphate **6a**. Normally, the reactions of cyanohydrin-*O*-phosphates **6** were faster, or run in the same reaction times, than the corresponding reactions of carbonates **5**. On the other side, phosphates **6** and more versatile reagents than carbonates **5** (in terms of reactivity) were independent of the nucleophile used or structural backbone.

In general, the obtained compounds (*E*)-**2c** and (*Z*)-**2c** are very interesting α,β-unsaturated γ-amino nitriles. Usually, conventional functional group transformation operating under mild conditions is required to access enantiomerically enriched α,β-unsaturated γ-amino acids[13] or γ-amino acids (GABA).[15]

The already mentioned opposite configuration observed for (*E*)-**1** or -**2** versus (*Z*)-**1** or -**2** was clearly identified by the exhaustive HPLC analysis of each derivatized enantiomeric mixture of the diamine **14**, which was obtained in a parallel manner from enantiomerically enriched carbonate **5a** and phosphate **6a**. The simultaneous reduction of the carbon−carbon double bond and the nitrile group of (*E*)- and (*Z*)-**2aa** using lithium aluminum hydride, followed by protection of the resulting primary amine with benzoyl chloride in the presence of pyridine, led to *N*-benzoyl-1,4-diamine **14** (Scheme 5). The

(42) Leahy, D. K.; Evans, P. A. *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Ed.; Wiley-VCH: Weinheim, 2005; pp 191−214.
(43) Kondo, T.; Mitsudo, T. *Ruthenium in Organic Synthesis*; Wiley VCH: Weinheim, 2004; pp 129−151.
(44) (a) Belda, P. A.; Moberg, C. *Acc. Chem. Res.* **2004**, *37*, 159−167. (b) Krska, S. W.; Hughes, D.; Reamer, R. A.; Mathre, D. J.; Palucki, M.; Yasuda, N.; Sun, Y.; Trost, B. M. *Pure Appl. Chem.* **2004**, *76*, 625−633.

SCHEME 5. Determination of the Opposite Configuration of (*E*)- and (*Z*)-2aa

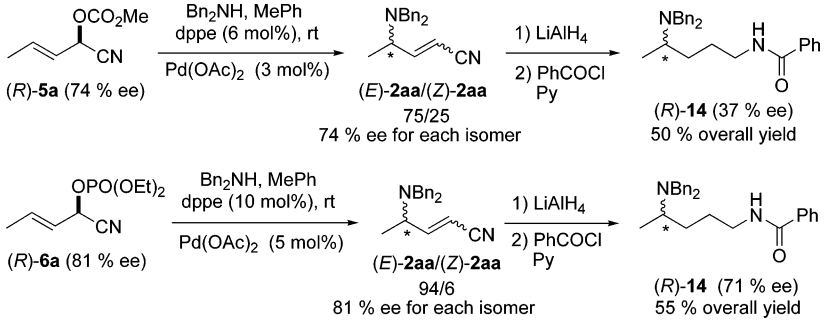
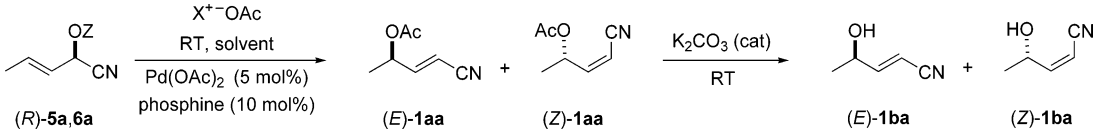


TABLE 4. Optimization of the Palladium-Catalyzed Allylic Substitution Reactions onto 6a and 5a Using NaOAc and TBAA



	5a or **6a**							product (*E*)-**1ba**	
entry	(% ee)	Z	XOAc (equiv)	phosphine	solvent	time (h)	(*E*)-**1aa**/(*Z*)-**1aa**[a]	yield (%)[b]	ee (%)[c]
1	**6a** (88)	$PO(OEt)_2$	NaOAc(4) [d]	Ph_3P	MeCN	20	(83)/(17)	78	88
2	**6a** (88)	$PO(OEt)_2$	NaOAc(4)[d]	dppe	MeCN	20	(78)/(22)	63	88
3	**6a** (88)	$PO(OEt)_2$	NaOAc(4)[d]	dppe	THF/H_2O[e]	24	(72)/(28)	50	88
4	**6a** (88)	$PO(OEt)_2$	TBAA (1.5)	dppe	THF	0.4	(70)/(30)	60	88
5	**6a** (88)	$PO(OEt)_2$	TBAA (1.5)	dppe	THF[f]	1	(78)/(22)	70	88
6	**6a** (92)	$PO(OEt)_2$	TBAA (1.5)	Ph_3P	THF	0.8	(81)/(19)	77	92
7	**6a** (88)	$PO(OEt)_2$	TBAA (1.5)	Ph_3P	THF[f]	1	(83)/(17)	78	88
8	**6a** (88)	$PO(OEt)_2$	TBAA (1.5)	$(o\text{-Tol})_3P$	THF	0.5	(78)/(22)	70	88
9	**5a** (74)	CO_2Me	NaOAc (4)[d]	Ph_3P	MeCN	20	(83)/(17)	77	74
10	**5a** (74)	CO_2Me	NaOAc (4)[d]	$(o\text{-Tol})_3P$	MeCN	24	(75)/(25)	70	74
11	**5a** (74)	CO_2Me	TBAA (1.5)	Ph_3P	THF	0.8	(82)/(18)	75	74

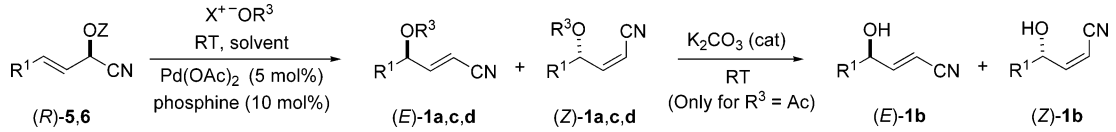
[a] Determined by ^1H NMR spectroscopy. [b] Isolated yield of allylic alcohols (*E*)-**1ba** after flash chromatography. [c] Identical enantiomeric excesses for both *E*- and *Z*-isomers of the compounds (*E*)-**1aa** and (*Z*)-**1aa** [determined by chiral HPLC (Chiralcel OD-H)] and (*E*)-**1ba** (determined by comparison between their optical rotations and the values reported in the literature). [d] AcOH (4 equiv) was added. [e] 1:1 mixture in volume. [f] Reaction run at 0 °C.

final ee obtained for the unknown compound **14** was determined by chiral HPLC analysis (Daicel Chiralpak AD).[31]

Oxygenated Nucleophiles. Several acetates were employed in the palladium-catalyzed nucleophilic substitution upon allylic electrophiles (*R*)-**5** or (*R*)-**6** for the preparation of γ-cyanoallylic alcohols **1**. The reaction was optimized with cyanohydrin-*O*-phosphates **6a** and carbonate **5a** and NaOAc (4 equiv) in the presence of AcOH (4 equiv) according to our previous experiences.[31] Due to high instability of the resulting unsaturated γ-acetoxy α,β-unsaturated nitriles (*E*)-**1a** and (*Z*)-**1a** during flash chromatography,[12] the obtained crude products were submitted to a very mild base-catalyzed hydrolysis with K_2CO_3 in MeOH,[1] affording, after purification, alcohols (*E*)-**1b** exclusively.[31] The optimized reaction conditions were applied to carbonate **5a** and also to another oxygenated nucleophile different from acetates. Thus, NaOAc (4 equiv) reacted sluggishly in acetonitrile with compound **6a** in the presence of AcOH (4 equiv), $Pd(OAc)_2$ (5 mol %), and Ph_3P (10 mol %), giving an 83:17 ratio of products (*E*)-**1aa**/(*Z*)-**1aa** in good chemical yield (Table 4, entry 1).[31] The substitution of the Ph_3P by dppe did not have the same positive effect as the analogous one described in the reaction involving dibenzylamine (see above), neither in a mixture THF/water nor in acetonitrile (Table 4, entries 2 and 3). The reaction did not occur in toluene as solvent. More soluble tetra-*n*-butylammonium acetate (TBAA) was an excellent reagent because it took very short reaction times to complete the allylic substitution reaction (Table 4, entries 4−8). For the particular reaction with this source of acetate, triphenylphosphine was a better ligand than $(o\text{-tolyl})_3P$ and dppe (Table 4, entries 4−6 and 8), giving the highest (*E*)-**1aa**/(*Z*)-**1aa** ratio by lowering the temperature to 0 °C (Table 4, entries 5 and 7). The same pattern of reactivity was observed in the reactions performed with cyanocarbonate **5a**, where acetonitrile was the selected solvent and triphenylphosphine was preferred over tris(*o*-tolyl)-phosphine (Table 4, entries 9 and 10). Surprisingly, with dppe the reaction did not work at all. The expected acceleration occurred when the reaction was run with TBAA, obtaining slightly lower (*E*)-**1aa**/(*Z*)-**1aa** ratios than the analogous reaction carried out with NaOAc (Table 4, entry 11). In this occasion, all the tests onto carbonates **5** were run with 5 mol % of palladium(II) acetate because uncompleted reactions were observed after 1 d when 3 mol % of the metal salt was added. To summarize, the best reaction conditions for both reagents were $Pd(OAc)_2$ (5 mol %)/Ph_3P (10 mol %) as catalytic mixture, room temperature, and acetonitrile (when using NaOAc) and THF (when using TBAA) as solvents.

With these optimized reaction conditions in hand, several chiral carbonates (**5a**, **5b**, and **5c**) were allowed to react with both NaOAc (Table 5 entries 1, 3, and 5) and TBAA (Table 5, entries 2, 4, and 6). At room temperature, both acetates gave an identical (*E*)-**1a**/(*Z*)-**1a** ratio and chemical yield for each particular chiral carbonate but required different reaction times, while NaOAc took 24 h to complete the reaction that TBAA just needed 1 h to complete. No reaction was observed when cinnamaldehyde derivative **5d** was employed as starting material. Cyanohydrin-*O*-phosphates **6a** and **6c**, together with

TABLE 5. Palladium-Catalyzed Allylic Substitution Reactions with Oxygenated Nucleophiles onto 5 and 6



	5/6								product 1			
entry	(% ee)	R^1	Z	$X^+ -OR^3$ (equiv)	phosphine	solvent	time (h)	(*E*)-**1**/(*Z*)-**1**[a]	R^3	No.	yield (%)[b]	ee (%)[c]
1	**5a** (74)	Me	CO_2Me	NaOAc (4)[d]	Ph_3P	MeCN	20	(*E*)-**1aa** (83)/(*Z*)-**1aa** (17)	H	**1ba**	77	74
2	**5a** (74)	Me	CO_2Me	TBAA (1.5)	Ph_3P	THF	0.8	(*E*)-**1aa** (82)/(*Z*)-**1aa** (18)	H	**1ba**	82	74
3	**5b** (72)	C_3H_7	CO_2Me	NaOAc (4)[d]	Ph_3P	MeCN	24	(*E*)-**1ab** (88)/(*Z*)-**1ab** (12)	H	**1bb**	80	72
4	**5b** (72)	C_3H_7	CO_2Me	TBAA (1.5)	Ph_3P	THF	1	(*E*)-**1ab** (88)/(*Z*)-**1ab** (12)	H	**1bb**	80	72
5	**5c** (80)	C_5H_{11}	CO_2Me	NaOAc (4)[d]	Ph_3P	MeCN	24	(*E*)-**1ac** (81)/(*Z*)-**1ac** (19)	H	**1bc**	83	80
6	**5c** (80)	C_5H_{11}	CO_2Me	TBAA (1.5)	Ph_3P	THF	1	(*E*)-**1ac** (81)/(*Z*)-**1ac** (19)	H	**1bc**	83	80
7	**6a** (88)	Me	$PO(OEt)_2$	NaOAc (4)[d]	Ph_3P	MeCN	20	(*E*)-**1aa** (83)/(*Z*)-**1aa** (17)	H	**1ba**	78	88
8	**6a** (92)	Me	$PO(OEt)_2$	TBAA (1.5)	Ph_3P	THF	0.8	(*E*)-**1aa** (81)/(*Z*)-**1aa** (19)	H	**1ba**	89	92
9	**6c** (94)	C_5H_{11}	$PO(OEt)_2$	NaOAc (4)[d]	Ph_3P	MeCN	24	(*E*)-**1ac** (81)/(*Z*)-**1ac** (19)	H	**1bc**	73	94
10	**6c** (94)	C_5H_{11}	$PO(OEt)_2$	TBAA (1.5)	Ph_3P	THF	1.5	(*E*)-**1ac** (78)/(*Z*)-**1ac** (22)	H	**1bc**	74	94
11	**6a** (90)	Me	$PO(OEt)_2$	NaOPh	dppe	THF[e]	1.5	(*E*)-**1ca** (79)/(*Z*)-**1ca** (21)	Ph	**1ca**	85[f,g]	16[f,h]
12	**6a** (90)	Me	$PO(OEt)_2$	Na−NHSu[i]	dppe	THF[e]	9	(*E*)-**1da** (78)/(*Z*)-**1da** (22)	Su[j]	**1da**	90[f,g]	90[f,h]

[a] Determined by ^1H NMR spectroscopy. [b] Isolated yield of allylic alcohols (*E*)-**1b** after flash chromatography. [c] Identical enantiomeric excesses for both *E*- and *Z*-isomers of the compounds (*E*)-**1a** and (*Z*)-**1a** [determined by chiral HPLC (Chiralcel OD-H)] and (*E*)-**1b** and (*Z*)-**1b** (determined by comparison between their optical rotations and the values reported in the literature). [d] AcOH (4 equiv) was added. [e] Anhydrous. [f] Mixture of (*E*)-**1** and (*Z*)-**1** compounds. [g] Isolated yield of compounds (*E*)-**1c**,**d** and (*Z*)-**1c**,**d**, after flash chromatography. [h] Identical enantiomeric excesses for both *E*- and *Z*-isomers of the compounds (*E*)-**1c**,**d** and (*Z*)-**1c**,**d** [determined by chiral HPLC (Chiralpak AS)]. [i] Sodium salt of the *N*-hydroxysuccinimide (Na−NHSu). [j] Succinimide.

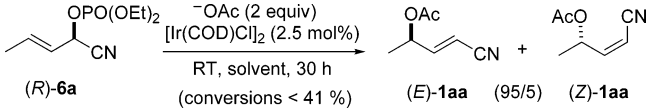
triphenylphosphine as additive, afforded a better ratio of compounds (*E*)-**1ac**/(*Z*)-**1ac** using NaOAc than the equivalent reaction performed with TBAA, taking longer reaction times (Table 5, entries 9 and 10). Once more, the cinnamaldehyde-derived cyanohydrin-*O*-phosphate **6d** did not afford the desired reaction product despite modification of all of the possible parameters, and isomerized compound (*E*/*Z*)-**13** was obtained as the major product.

Product (*E*)-**1bc**, which is the intermediate in the synthesis of coriolic acid, was achieved by Griengl and Johnson in a four-step process (involving enzymatic generation of the nonracemic cyanohydrin followed by acylation) in 55% overall yield from the initial (*E*)-oct-2-enal.[1] However, with our combined methodology, it was possible to employ only a three-step sequence to obtain compound (*E*)-**1bc** in a 66−67% overall yield, with an optical purity of 80 or 94% ee for the routes involving cynocarbonate **5c** or cyanophosphate **6c**.

Each enantiomeric excess of acetates (*E*)-**1a**/(*Z*)-**1a** was determined by chiral HPLC analysis (Chiralcel OD-H), while the optical purity of allylic alcohol was evaluated according to the relationship between their optical rotation and the values reported in the literature for pure original samples. Consequently, the sign of the optical rotation of the purified allylic alcohols (*E*)-**1ba**,[31] (*E*)-**1bb**,[29] and (*E*)-**1bc**[1] ensured the absolute configuration of the newly generated stereocenters.

When other oxygenated nucleophiles such as phenol and *N*-hydroxysuccinimide (previously deprotonated by reaction with sodium hydride) were allowed to react with cyanophosphate **6a** under the optimized reaction conditions discussed before [Pd(OAc)$_2$ (5 mol %)/Ph_3P (10 mol %)], we obtained chemical yields and diastereomeric ratios of compounds (*E*)-**1ca**/(*Z*)-**1ca** lower than those in the reaction run with dppe as additive (79:21) (Table 5, entry 11). In this last example, almost racemized products (*E*)-**1ca** and (*Z*)-**1ca** were obtained. However, in the presence of dppe as ligand, the *N*-hydroxysuccinimide sodium salt[41c] proved to be a good nucleophile under these reaction conditions giving, rather than with Ph_3P, a better (*E*)-**1da**/(*Z*)-**1da** ratio and chemical yield (Table 5, entry 12).

SCHEME 6. Iridium-Catalyzed Substitution onto 6a with NaOAc and TBAA

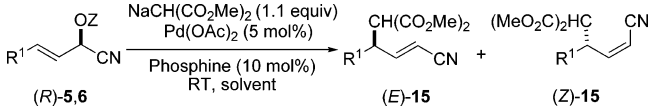


If evaluating the entries and data depicted in Tables 4 and 5, we can assume that there is not an appreciable difference between working with phosphates **6** and carbonates **5**, but analyzing the aspect of crude ^1H NMR spectra, we found that chiral phosphates **6** furnished cleaner transformations. For oxygenated nucleophiles, it was not possible to establish a common rule as succeeded for the nitrogenated nucleophiles. The optimal reaction conditions with acetates required the catalytic mixture Pd(OAc)$_2$/Ph_3P at room temperature. Nevertheless, the catalyst formed by Pd(OAc)$_2$ and dppe was preferred in the allylic substitution reaction involving sodium phenolate and *N*-hydroxysuccinimide sodium salt.

The iridium complex [Ir(COD)Cl]$_2$ (2.5 mol %) was also tested in the allylic substitution reaction of cyanohydrin derivative **6a** with NaOAc in acetonitrile or TBAA in THF, giving, in both cases, poor conversions (41 and 25% after 30 h, respectively) but in very good (*E*)-**1aa**/(*Z*)-**1aa** ratios (95:5) (Scheme 6). Also, the iridium complex was ineffective in the reaction of the acetates onto **6d** in the presence of the standard catalytic mixture.

Sodium Dimethyl Malonate as Nucleophile. A stabilized carbon nucleophile as sodium dimethyl malonate was chosen for the palladium-catalyzed allylic substitution reaction (also called the Tsuji−Trost reaction)[32] employing Pd(OAc)$_2$ as palladium source in light of the results of the experiments performed with heteronucleophilic reagents. By using THF as solvent, we found that dppe proved to be the more suitable ligand for this reaction than Ph_3P, obtaining the best (*E*)-**15a**/(*Z*)-**15a** ratio in very good yield and short reaction times (Table 6, entries 1 and 2). Toluene was not so efficient a solvent as THF, exhibiting a worse diastereomeric ratio at room temper-

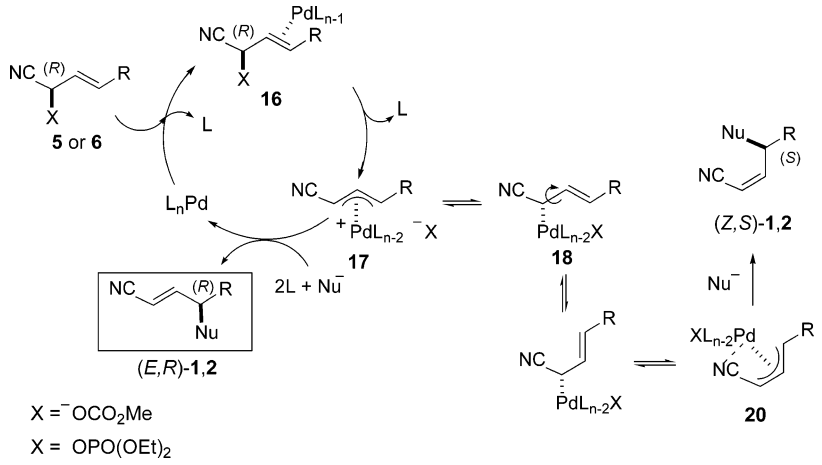
TABLE 6. Palladium-Catalyzed Allylic Substitution Reactions Using Sodium Dimethyl Malonate



	5/6								
entry	(% ee)	R^1	Z	phosphine	solvent	time (h)	(*E*)-**15**/(*Z*)-**15**[a]	yield (%)[b]	ee (%)[c]
1	**6a** (88)	Me	$PO(OEt)_2$	Ph_3P	THF	12	(*E*)-**15a** (58)/(*Z*)-**15a** (42)	71	88
2	**6a** (88)	Me	$PO(OEt)_2$	dppe	THF	1	(*E*)-**15a** (85)/(*Z*)-**15a** (15)	80	88
3	**6a** (88)	Me	$PO(OEt)_2$	dppe	PhMe	6	(*E*)-**15a** (78)/(*Z*)-**15a** (22)	80	88
4	**6d** (95)	Ph	$PO(OEt)_2$	dppe	THF	3	(*E*)-**15d** (99)/(*Z*)-**15d** (1)	80	16[d]
5	**5a** (74)	Me	CO_2Me	dppe	THF	4	(*E*)-**15a** (80)/(*Z*)-**15a** (20)	93	74
6	**5a** (74)	Me	CO_2Me	PPh_3	THF	4	(*E*)-**15a** (50)/(*Z*)-**15a** (50)	92	74

[a] Determined by ^1H NMR spectroscopy. [b] Isolated yield after flash chromatography. [c] Identical enantiomeric excesses for both *E*- and *Z*-isomers, determined by chiral HPLC (Chiralpak AD). [d] Enantiomeric excesses for both *E*- and *Z*-isomers were determined by chiral HPLC (Chiralpak AS).

SCHEME 7. Opposite Absolute Configuration in (*E*)-1,2 and (*Z*)-1,2



ature (Table 6, compare entries 2 and 3). Cinnamaldehyde-derived cyanophosphate **6d** reacted with sodium dimethyl malonate in 3 h, but the corresponding pure (*E*)-**15d** was isolated with a notable degree of racemization (16% ee from a 95% ee of **6d**; Table 6, entry 4). The racemization could not be avoided by lowering the temperature to 0 °C, because in this experiment the reaction raised 10% of conversion after 8 h. Although usually allylic carbonates reacted under neutral conditions, the reaction of dimethyl malonate with allylic carbonates **5** did not take place after 1 d. For this reason, sodium dimethyl malonate was used, affording the corresponding product **15** in good yields together with a catalyst charge of $Pd(OAc)_2$ (5 mol %)/dppe (10 mol %). The influence of the phosphine in this type of reaction is crucial in some cases; for example, carbonate **5a** afforded a high (*E*)-**15a**/(*Z*)-**15a** ratio when using dppe, while a 1:1 mixture of products (*E*)-**15a** and (*Z*)-**15a** was achieved with triphenylphosphine (Table 6, entries 5 and 6).

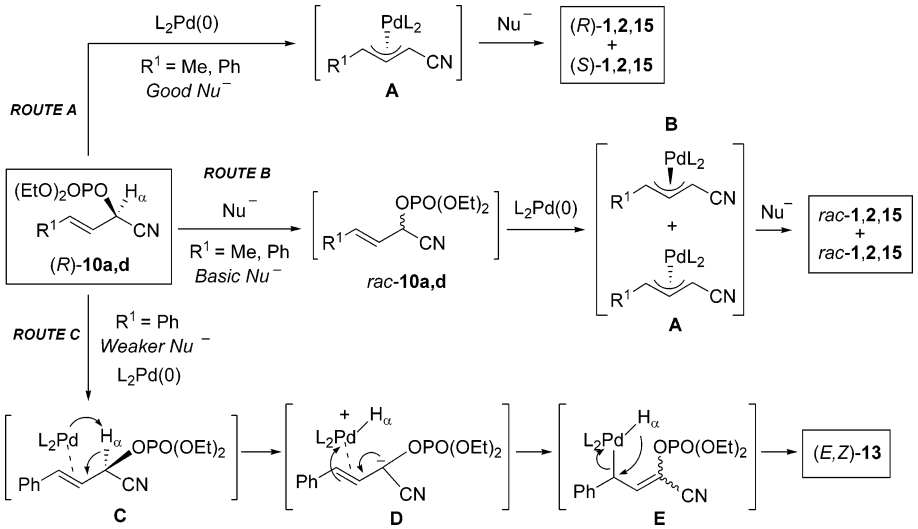
The employment of the iridium complex $[Ir(COD)Cl]_2$ (2.5 mol %) was not as advantageous as in the precedent heteronucleophilic substitutions: the reaction was very slow, it was not complete after 3 days (<40%), and its presence in the allylic substitution reaction onto compound **6d** did not avoid the almost total racemization.

Mechanistic Aspects. The already mentioned stereochemical outcome of the cyanohydrin-*O*-phosphates described previously[12,31] can be extended to the corresponding reactions performed with carbonates **5** and is consistent with the reaction mechanism reported for allylic carbonates[12,28e] where the methyl carbonate anion remains ligated to the palladium atom.[45] The expected double inversion involving intermediate **16** easily explains why the major *E*-isomer of **1**, **2**, or **15** should possess the (*R*)-configuration. In addition, since η^3-allyl palladium **17** is in equilibrium with η^3-allyl palladium **20** by means of a $\eta^3-\eta^1$ shift to **18**, bond rotation, and $\eta^1-\eta^3$ shift. This species should give rise upon nucleophilic attack to the *Z*-isomer-**1**, -**2**, or -**15** with the opposite (*S*)-configuration (Scheme 7). It is also possible that the sequence of intermediate species **17**, **18**, and **20**, favored by affinity of the palladium atom to the nitrile group, is responsible for the notable amounts of the *Z*-isomers obtained in all of the examples described in this work. The regiochemistry of the Pd- and Ir-catalyzed nucleophilic allylic substitution can be justified by the apparent manifestation of the energy-lowering effect of the olefinic conjugative overlap with the p-orbitals in the cyano group as reported by Deardorff et al.[28e]

The observed racemization in products (*E*)-**2bd** and (*Z*)-**2bd** (resulting from the nucleophilic attack of benzylamine; Table 2), (*E*)-**1ca** and (*Z*)-**1ca** (resulting from the nucleophilic attack of sodium phenoxide), and (*E*)-**15d**/(*Z*)-**15d** could be due to the high acidity of the H_α proton of the cyanohydrin-*O*-phosphates **6**. The normal course of the reaction should be represented by Route A (Scheme 8), but the presence of a basic nucleophile promoted the partial racemization just before the coordination of the palladium atom to the alkene, such as that described in Route B (Scheme 8). This fact was also justified by the results obtained in the direct cyanophosphorylation reaction of enan-

(45) Cantat, T.; Agenet, N.; Jutand, A.; Pleixats, R.; Moreno-Mañas, M. *Eur. J. Org. Chem.* **2005**, 4277−4286.

SCHEME 8. Reaction Mechanisms in Palladium-Catalyzed Allylic Substitution Reactions onto Compounds 6a,d



tiomerically enriched cyanohydrins catalyzed by bases[12] and by the studies of racemization of enantiomerically enriched cyanohydrin-*O*-phosphates in the presence of 1 equiv of amine.[46] According to these data, the bulkier dibenzylamine was the unique reagent able to react cleanly with substrate (*R*)-**6d** through Route A, avoiding undesired epimerizations and isomerizations.

The increased extended conjugation effect underwent the α-carbon in molecule **6d** and probably caused an increment of the acidity of its H_α, unlike the acidity of H_α of the molecules **6a**,**c**,**e** and **5**. This hypothesis can support the easy and fast palladium(0)-catalyzed isomerization of the double bond[34,47] in **6d** (Scheme 8, Route C). Presumably, compound (*E*/*Z*)-**13** was generated after the initial double bond palladium(0) coordination (intermediate **C**), followed by a nucleophilic attack of the palladium(0) atom onto H_α. The result of this step would be a C–H insertion of palladium to give the carbanionic intermediate **D**. The hydride transfer from the palladium atom to the allylic moiety and the regeneration of the catalytically active palladium(0) species in intermediate **E** completed the process.[34] Perhaps the driving force that governs this fast abstraction of the acidic hydrogen, rather than the attack onto phosphate unit, is the generation of a more stable trisubstituted conjugated alkene (*E*/*Z*)-**13**. We reckon essential the presence of the stable carbanion, drawn in intermediate **D**, to explain the variable ratios of *E*/*Z*-**13** obtained in the crude reaction products. Compound **13** was obtained as clean product in the absence of nucleophiles when phosphate **6d** was allowed to react with $Pd(OAc)_2$ (5 mol %)/dppe (10 mol %). However, the related carbonate **5d** did not undergo any transformation under the previous mentioned conditions. In general, working with **6d**, weaker nucleophiles permitted the acceleration of Route C in detriment of the expected Route A using the appropriate palladium/phosphine catalytic system (see Tables 1, 3, and 4 and Scheme 8). Although it was not indicated in Scheme 8, Routes B and C can be connected because a first racemization, promoted by a basic and weak nucleophile, followed by a further isomerization cannot be discarded.

Conclusions

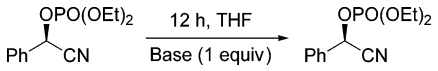
In general, enantioenriched cyanohydrin-*O*-phosphates, derived from α,β-unsaturated aldehydes, are better substrates than carbonates for the metal-catalyzed regiospecific nucleophilic allylic substitution reactions affording γ-substituted α,β-unsaturated nitriles with higher (*E*)-diastereoselectivity. From all tested nitrogenated nucleophiles, such as dibenzylamine, benzylamine, sodium azide, and trimethylsilyl azide, dibenzylamine was the most efficient and diastereoselective reagent for the preparation of enantioenriched γ-nitrogenated α,β-unsaturated nitriles under palladium or iridium catalysis with overall retention of the configuration. In the case of oxygenated nucleophiles, sodium and tetra-*n*-tetrabutylammonium acetates, sodium phenolate and the sodium salt of *N*-hydroxysuccinimide were the best reagents, the latter being faster concerning the reaction rates. However, these oxygenated nucleophiles failed when cinnamaldehyde-derived O-protected cyanohydrins were used as substrates. In addition, oxygenated nucleophiles also gave poor results under the iridium-catalyzed reaction conditions. Finally, for sodium dimethyl malonate $Pd(OAc)_2$/dppe was the catalytic mixture and THF was the selected solvent to give the optimal results onto crotonaldehyde-derived cyanohydrins, whereas the cinnamaldehyde derivative did not afford the desired result.

The studies of palladium versus iridium catalysis revealed that palladium catalysts accelerated the reaction in detriment of the *E*/*Z* ratio, which is lower than that obtained by the more expensive iridium complex although employing larger reaction times. Iridium catalysis allowed us to obtain pure *E*-isomers in the cases of dibenzylamine and sodium azide, but it give poor conversions with acetates and no reaction occurred with sodium dimethyl malonate.

Experimental Section

Synthesis of (2*R*,3*E*)-2-(Diethylphosphoryloxy)-3-methylpent-3-enenitrile (6e). 6e was prepared as described previously[31] in 2 h time. After purification by flash chromatography, a colorless oil

(46) The racemization of cyanohydrin-*O*-phosphate derived from benzaldehyde has been evaluated in the presence of 1 equiv of nitrogenated bases at room temperature, in THF (under an inert atmosphere) during 12 h. The results of the table below clearly demonstrate a stronger basic character of the benzylamine and triethylamine versus dibenzylamine, *N*-methylimidazole (NMI), and pyridine.



(47) *Handbook of Organopalladium Chemistry for Organic Systems*; Negishi, E., Ed.; Wiley: New York, 2002; Vol. II, Chapter VII.3, p 2783.

was obtained in 89% yield. $[\alpha]^{25}_D$ −13.8 (*c* 1.5, $CHCl_3$, 82% ee); 82% ee from HPLC: Daicel Chiralpak AD, $\lambda = 210$ nm, *n*-hexane/2-propanol 95:5, 1 mL/min, $t_r = 10.8$ and *14.1* min; R_f 0.54 (*n*-hexane/ethyl acetate 3:2); IR (neat): ν 2225, 1664, 1264, 1031 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.30−1.39 (m, 6H), 1.70 (d, $J = 7.9$ Hz, 3H), 1.80 (s, 3H), 4.09−4.22 (m, 4H), 5.36 (d, $J = 8.4$ Hz, 1H), 5.89 ppm (q, $J = 6.7$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.7, 13.5, 15.9, 64.6, 115.8, 128.2, 129.5 ppm; MS (EI): *m*/*z* = 247 (M^+, 6%), 191 (18), 155 (56), 127 (63), 99 (100); HRMS calcd for $C_{12}H_{14}N_2$ (M^+): 186.1157; found: 186.1154.

Synthesis of α,β-Unsaturated γ-Aminonitriles (2aa, 2adb, 2aea 2ba, and 2bd). In a round-bottomed flask, a solution of the compound **5** or **6** (0.40 mmol) in toluene (2 mL) was stirred at room temperature, and then $Pd(OAc)_2$ (2.7 mg, 0.012 mmol, 3 mol % or 4.5 mg, 0.02 mmol, 5 mol %) and dppe (10 mg, 0.024 mmol, 6 mol % or 16 mg, 0.04 mmol, 10 mol %) were added. After being stirred for 10 min, the corresponding amine (1.5 equiv, 0.6 mmol) was added, and the reaction was stirred at the same temperature. When the reaction was judged complete, water (12 mL) and ethyl acetate (3 × 5 mL) were added. The organic layer was dried ($MgSO_4$) and evaporated to give the crude compounds, which were purified by flash chromatography to obtain pure γ-aminonitriles. The identical procedure was utilized when the reaction was carried out using $[Ir(COD)Cl]_2$ (2.5 mol %) instead of the $Pd(OAc)_2$/dppe mixture.

(2*E*,4*R*)-4-(*N*,*N*-Dibenzylamino)pent-2-enenitrile (2aa):[31] Pale yellow oil. $[\alpha]^{25}_D$ +154.9 (*c* 2.0, $CHCl_3$, 90% ee *E*/*Z* 98:2); 90% ee from HPLC: Daicel Chiralcel OD-H, $\lambda = 254$ nm, *n*-hexane/2-propanol 95:5, 1.0 mL/min, $t_r = 8.1$ and 13.9 (*Z*), *10.3* and 11.8 min (*E*); R_f 0.53 (*Z*) and 0.60 (*E*) (*n*-hexane/ethyl acetate 4:1); IR (neat): ν 2222, 1636 cm^{-1}; ^1H NMR for the *E*-isomer (300 MHz, $CDCl_3$): δ 1.21 (d, $J = 6.9$ Hz, 3H), 3.50 (m, 1H), 3.58 (s, 4H), 5.48 (d, $J = 16.5$ Hz, 1H), 6.78 (dd, $J = 16.5$ and 5.3 Hz, 1H), 7.22−7.37 ppm (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.1, 53.7, 54.4, 100.1, 117.4, 127.1, 128.3, 128.4, 139.2, 157.4 ppm; ^1H NMR for the *Z*-isomer (300 MHz, $CDCl_3$): δ 1.29 (d, $J = 6.9$ Hz, 3H), 3.52 and 3.77 (2xd, $J = 14.4$ Hz, 4H), 5.41 (d, $J = 11.2$ Hz, 1H), 6.54 (m, 1H), 7.22−7.37 ppm (m, 11H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.4, 54.2, 55.3, 100.2, 117.4, 127.2, 128.3, 128.4, 139.3, 155.5 ppm. MS (EI): *m*/*z* 276 (M^+, 2%), 261 (21), 91 (100). HRMS calcd for $C_{19}H_{20}N_2$ (M^+): 276.3801; found: 276.3805.

(2*E*,4*R*)-4-(*N*,*N*-Dibenzylamino)-4-phenylbut-2-enenitrile (2ad): Colorless prisms. Mp 105 °C (from *n*-hexane/ethyl acetate); $[\alpha]^{20}_D$ −2.2 (*c* 1.5, $CHCl_3$, 95% ee); 95% ee from HPLC: Daicel Chiralpak AS, $\lambda = 254$ nm, *n*-hexane/2-propanol 97:3, 1 mL/min, $t_r = 7.6$ and 8.3 min; R_f 0.76 (*n*-hexane/ethyl acetate 3:2); IR (KBr): ν 2220, 1627 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.51 and 3.63 (2xd, $J = 13.9$, 4H), 4.43 (d, $J = 7.2$ Hz, 1H), 5.60 (d, $J = 16.4$ Hz, 1H), 6.62 (dd, $J = 16.4$, 7.2 Hz, 1H), 7.23−7.43 ppm (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 53.9, 64.4, 102.5, 117.1, 127.3, 128.1, 128.4, 128.5, 128.6, 128.9, 137.3, 138.7, 154.3 ppm; MS (EI): *m*/*z* = 338 (M^+, 9%), 247 (20), 142 (25), 115 (24), 91 (100); HRMS calcd for $C_{24}H_{22}N_2$ (M^+): 338.1783; found: 338.1779.

CAUTION: Azido compounds may represent an explosion hazard when concentrated under vacuum or as stored material. A safety shield and appropriate handling procedures are recommended.

CAUTION: Trimethylsilyl azide is an extremely toxic agent.

Synthesis of α,β-Unsaturated γ-Azidonitriles (2c). To a solution of compound **5** or **6** (0.4 mmol), $Pd(OAc)_2$ (2.7 mg, 0.012 mmol, 3 mol % or 4.5 mg, 0.02 mmol, 5 mol %), and phosphine (6 mol % or 10 mol %) in a (1:1) THF/H_2O mixture, NaN_3 (52 mg, 0.8 mmol, 2 equiv) was added. When the reaction was judged complete, the THF was evaporated under vacuo, and ethyl acetate (2 × 10 mL) was added. The organic layers were dried ($MgSO_4$) and evaporated to obtain a crude unpurified product as yellow oil.

The same procedure was employed using $[Ir(cod)Cl]_2$ (2.5% mol) instead of a palladium source.

(2*E*,4*R*)-4-Azidopent-2-enenitrile (2ca):[12] Colorless oil. $[\alpha]^{25}_D$ −14.2 (*c* 0.8, $CHCl_3$, 92% ee); {lit.[12] $[\alpha]^{25}_D$ −38.7 (*c* 1.870, $CHCl_3$, 81% ee)}; 92% ee from HPLC: Daicel Chiralpak AS, $\lambda = 254$ nm, *n*-hexane/2-propanol 99:1, 1 mL/min, $t_r = 18.8$ and *17.8* min; R_f 0.63 (*n*-hexane/ethyl acetate 3:2); IR (neat): ν 2225, 2113 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.39 (d, $J = 6.8$ Hz, 3H), 4.19 (m, 1H), 5.60 (d, $J = 16.8$ Hz, 1H), 6.60 ppm (dd, $J = 16.8$, 1.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.1, 57.6, 101.3, 116.7, 152.3 ppm.

Synthesis of α,β-Unsaturated γ-Acetoxynitriles (1a). In a round-bottomed flash was stirred, at the corresponding temperature, a mixture of compound **5** or **6** (0.4 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 5 mol %), and triphenylphosphine (11 mg, 0.04 mmol, 10 mol %) in acetonitrile (4 mL). Then NaOAc (131 mg, 1.6 mmol, 4 equiv) and AcOH (93 μL, 1.6 mmol, 4 equiv) were added, and stirring was continued at the same temperature. When the reaction was judged complete, the solvent was evaporated, water (5 mL) was added, and it was extracted with ethyl acetate (2 × 10 mL). The combined organic layers were dried ($MgSO_4$) to obtain the crude compounds (*E*)-**1a** and (*Z*)-**1a**.

The identical procedure was employed when tetra-*n*-buthylammonium acetate (1.5 equiv) was used instead of NaOAc and AcOH and replacing acetonitrile by THF (4 mL).

(2*E*,4*R*)-4-Acetoxypent-2-enenitrile (1aa):[31] Sticky pale yellow oil. 88% ee from HPLC: Daicel Chiralcel OD-H, $\lambda = 210$ nm, hexane/2-propanol 97:3, 0.6 mL/min, $t_r = 17.5$, *19.6* min (*Z*) and *20.7*, 27.7 (*E*) min; ^1H NMR (300 MHz, $CDCl_3$): δ 1.36 (d, $J = 6.7$ Hz, 3H), 2.09 (s, 3H), 5.39−5.49 (m, 1H), 5.54 (d, $J = 16.3$ Hz, 1H), 6.65 ppm (dd, $J = 16.3$, 4.9 Hz, 1H). ^{13}C NMR δ 13.9, 35.4, 72.0, 100.5, 116.6, 152.0, 170.1.

(2*E*,4*R*)-4-Acetoxyhept-2-enenitrile (1ab):[29] Pale yellow oil. 80% ee from HPLC, Daicel Chiralcel OD-H, $\lambda = 210$ nm, *n*-hexane/2-propanol 99:1, 0.5 mL/min, t_r (*Z*-isomer) = 17.5 and **20.2** min, t_r (*E*-isomer) = *18.0* and 24.6 min); R_f 0.77 (*n*-hexane/ethyl acetate 3:2). IR (neat): ν 2226, 1740, 1641 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.91−0.96 (t, $J = 7.1$ Hz, 3H), 1.25−1.35 (m, 2H), 1.56−1.65 (m, 2H), 2.10 (s, 3H), 5.37 (q, $J = 5.2$ Hz, 1H), 5.50 (d, $J = 16.4$ Hz, 1H), 6.63 (dd, $J = 16.4$, 5.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.7, 18.0, 20.7, 35.4, 72.0, 100.0, 116.5, 151.9, 169.8. MS (EI) *m*/*z*: 167 (M^+, 4%), 124 (45), 108 (100). HRMS calcd for $C_9H_{13}NO_2$: 167.0946; found: 167.0947.

Synthesis of γ-Hydroxynitriles 1b by Hydrolysis of α,β-Unsaturated γ-Acetoxynitriles (1a).[1,31] To a solution of compounds **1a** (0.8 mmol) in dry methanol (5 mL) solid potassium carbonate was added (28 mg, 0.2 mmol) and the mixture was stirred at room temperature during 16 h. Then, silica was added, and the mixture was stirred another 5 min, After that, the suspension was filtered and evaporated, and the crude residue was purified by flash chromatography to obtain pure γ-hydroxynitriles **9**.

(2*E*,4*R*)-4-Hydroxypent-2-enenitrile (1ba):[27,31] Colorless oil; $[\alpha]^{25}_D$ −51.5 (*c* 0.9, $CHCl_3$) 98% ee; {lit.[31] $[\alpha]^{25}_D$ −51.5 (*c* 0.9, $CHCl_3$) 98% ee}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.33 (d, $J = 7.0$ Hz, 3H), 3.40 (br s, 1H, OH), 4.50 (ddq, $J = 7.0$, 3.9, 0.9 Hz, 1H), 5.65 (dd, $J = 16.3$, 0.9 Hz, 1H), 6.75 (dd, $J = 16.3$, 3.9 Hz, 1H); ^{13}C NMR (75 MHz, $CHCl_3$): δ 22.3, 66.8, 97.9, 117.3, 157.8.

(2*E*,4*R*)-4-Hydroxyhept-2-enenitrile (1bb):[29] Colorless oil. $[\alpha]^{25}_D$ −12.2 (*c* 0.3; $CHCl_3$, 72% ee); IR (neat): ν 3432, 2224, 1630 cm^{-1}. ^1H NMR (300 MHz, $CHCl_3$): δ 0.93−0.98 (m, 3H), 1.23−1.28 (m, 4H), 3.22 (br s, 1H), 4.34 (m, 1H), 5.67 (d, $J = 16.2$ Hz, 1H), 6.75 (dd, $J = 4.0$, 16.2 Hz, 1H). ^{13}C NMR (300 MHz, $CHCl_3$): δ 13.8, 19.1, 39.2, 73.8, 98.2, 117.0, 156.9. MS (EI) *m*/*z*: 96 (M^+ − 29, 5%), 85 (11), 58 (100). HRMS calcd for $C_7H_{11}NO$ (M^+): 125.1722; found: 125.1730.

(2*E*,4*R*)-4-Hydroxynon-2-enenitrile (1bc):[31] Colorless oil. $[\alpha]^{25}_D$ −37.0 (*c* 1.0, $CHCl_3$, 94% ee) [lit.[31] $[\alpha]^{25}_D$ −37.0 (*c* 1.0, $CHCl_3$), 94% ee)]; IR (neat): ν 3439, 2225, 1634 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.87−0.91 (t, $J = 6.6$, 3H), 1.23−1.61 (m, 8H), 4.31 (m, 1H), 5.67 (d, $J = 16.4$ Hz, 1H), 6.75 ppm (dd, $J = 16.4$, 4.0

Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9, 22.4, 24.7, 31.5, 36.4, 71.0, 98.7, 117.3, 156.6 ppm.

Palladium-Catalyzed Nucleophilic Substitution Reaction with Sodium Phenoxide and *N*-Hydroxysuccinimide Sodium Salt.[41c] The corresponding sodium salt, previously formed by reaction of phenol (57 mg, 0.6 mmol) or *N*-hydroxysuccinimide (69 mg, 0.6 mmol) with sodium hydride (24 mg, 0.6 mmol, 60% dispersion in mineral oil) in dry THF for 1 h, was added to a solution containing compound **6a** (69 mg, 0.4 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 5 mol %), and dppe (16 mg, 0.04 mmol, 10 mol %) in dry THF and under inert atmosphere (argon). The mixture was stirred until it was judged complete. Then, the solvent was evaporated, and water (5 mL) and ethyl acetate (2 × 10 mL) were added. The organic layers were dried ($MgSO_4$) and evaporated to give the crude compounds, which were purified by flash chromatography to afford the corresponding pure compounds (*E*)-**1ca**/(*Z*)-**1ca** and (*E*)-**1da**/(*Z*)-**1da**.

(2*E*,4*R*)-4-(2,5-Dioxopyrrolidin-1-yloxy)pent-2-enenitrile [(*E*)-1da]: Colorless oil. $[\alpha]^{25}_D$ +66.1 (*c* 1.5, $CHCl_3$, 90% ee); 90% ee from HPLC: Daicel Chiralpak AS, λ = 215 nm, *n*-hexane/2-propanol 70:30, 1 mL/min, t_r = *19.8* and 35.8 min; R_f 0.25 (*n*-hexane/ethyl acetate 3:2); IR (neat): ν 2227, 1786, 1721 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.48 (d, *J* = 6.4 Hz, 3H), 2.73 (s, 4H), 4.85 (m, 1H), 5.68 (d, *J* = 16.4 Hz, 1H), 6.71 ppm (dd, *J* = 16.4, 6.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.7, 25.3, 81.6, 102.9, 116.0, 151.2, 171.2 ppm; MS (EI): *m*/*z* 194 (M^+, 0.2%), 179 (0.15), 96 (2), 80 (100); HRMS calcd for $C_8H_7N_2O_3$ ($M^+ - CH_3$): 179.0456; found: 179.0458.

(2*Z*,4*S*)-4-(2,5-Dioxopyrrolidin-1-yloxy)pent-2-enenitrile [(*Z*)-1da]: Colorless oil. $[\alpha]^{25}_D$ +10.9 (*c* 1.5, $CHCl_3$, 90% ee); 90% ee from HPLC: Daicel Chiralpak AS, λ = 215 nm, *n*-hexane/2-propanol 70:30, 1 mL/min, t_r = 30.7 and *43.2* min; R_f 0.29 (*n*-hexane/ethyl acetate 3:2); IR (neat): ν 2227, 1786, 1721 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.55 (d, *J* = 6.5 Hz, 3H), 2.73 (s, 4H), 5.15 (m, 1H), 5.49 (d, *J* = 11.0 Hz, 1H), 6.71 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.4, 25.4, 80.5, 103.1, 114.5, 151.3, 171.1 ppm. MS (EI): *m*/*z* 194 (M^+, 0.2%), 179 (0.15), 96 (2), 80 (100); HRMS calcd for $C_8H_7N_2O_3$ ($M^+ - CH_3$): 179.0456; found: 179.0454.

Palladium-Catalyzed Allylic Substitution Reactions with Sodium Dimethyl Malonate. General Procedure. A suspension of $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 5 mol %) and phosphine (0.1 mmol) in the solvent shown in Table 5 (5 mL) was stirred at room temperature for 15 min. Then, compound **5** or **6** (0.4 mmol) and sodium dimethyl malonate (0.4 mmol) suspended in THF (1.5 mL) were successively added. The reaction mixture was stirred at room temperature for the period of time shown in Table 5. The solvent was evaporated, water (5 mL) was added, and this aqueous phase was extracted with ethyl acetate (2 × 10 mL). The resulting organic phase was dried ($MgSO_4$) and evaporated, yielding products (*E*)-**15** and (*Z*)-**15** after flash chromatography.

Methyl (3*R*,4*E*)-5-Cyano-3-methyl-2-(methoxycarbonyl)pent-4-enoate (15a): Pale yellow oil. $[\alpha]^{25}_D$ +26.7 (*c* 1, $CHCl_3$); 88% ee from HPLC: Daicel Chiralpak AD, λ = 210 nm, hexane/2-propanol 98:2, 1.0 mL/min, t_r = 11.4 and *13.3* *Z*-isomer and *13.9* and 15.9 min *E*-isomer; R_f 0.59 (*n*-hexane/ethyl acetate 3:2); IR (neat): ν 2223, 1731, 1633. ^{1}H NMR (300 MHz, $CDCl_3$): *E*-isomer δ 1.14 (d, *J* = 6.9 Hz, 3H), 3.09 (m, 1H), 3.38 (d, *J* = 7.8 Hz, 1H), 3.73 (s, 6H), 5.40 (d, *J* = 16.5 Hz, 1H), 6.70 (dd, *J* = 16.5 and 8.1 Hz, 1H). ^{1}H NMR (300 MHz, $CDCl_3$): *Z*-isomer δ 1.19 (d, *J* = 6.9 Hz), 3.43−3.50 (m, 2H), 3.75 (s, 3H), 5.35 (d, *J* = 11.2 Hz, 1H), 6.55 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): *E*-isomer δ 16.8, 37.2, 52.6, 56.1, 100.9, 116.9, 155.6, 167.7. ^{13}C NMR (75 MHz, $CDCl_3$): *Z*-isomer δ 17.8, 36.4, 52.6, 56.1, 100.2, 115.2, 154.7, 167.7. MS (EI): *m*/*z* = 211 (M^+, 1%), 179 (12), 151 (54), 136 (19), 119 (100), 101 (53). HRMS calcd for $C_{10}H_{13}NO_4$: 211.0845; found: 211.0849.

Methyl (3*R*,4*E*)-5-Cyano-2-(methoxycarbonyl)-3-phenylpent-4-enoate (15d):[28] Colorless oil. $[\alpha]^{25}_D$ −4.3 (*c* 1.2, $CHCl_3$, 16% ee); 16% ee from HPLC Daicel Chiralpak AS, λ = 215 nm, *n*-hexane/2-propanol 99:1, 1 mL/min, t_r = *36.6* and 38.2 min; R_f 0.53 (*n*-hexane/ethyl acetate 3:2); IR (neat): ν 2221, 1738, 1633, 1298, 1030 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.78 (s, 6H), 3.87 (d, *J* = 10.4 Hz, 1H), 4.24 (m, 1H), 5.34 (dd, *J* = 1.2, 16.2 Hz, 1H), 6.89 (dd, *J* = 16.2, 8.1 Hz), 7.18 (m, 2H), 7.29−7.38 ppm (m, 3H); ^{13}C NMR δ 48.6, 52.8, 56.1, 102.1, 116.7, 128.0, 128.2, 129.2, 136.6, 153.4, 167.1 ppm; MS (EI): *m*/*z* = 273 (M^+, 7.2%), 241 (22), 209 (100), 182 (28), 181 (40), 154 (34), 153 (51), 127 (23), 115 (26), 104 (75); HRMS calcd for $C_{15}H_{15}NO_4$: 273.1001; found: 273.0998.

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Supporting Information Available: General experimental details, physical and spectroscopic data of compounds **2ae**, **2ba**, **2bd**, **2cb**, **14**, **1ac**, **1ca**, *E*-**13**, *Z*-**13**, as well as the ^{1}H NMR and ^{13}C NMR spectra of new compounds **6e**, **2ad**, **2ae**, **2ba**, **2bd**, **1ca**, *E*-**1da**, *Z*-**1da**, *E*-**13**, *Z*-**13**, and **15a** and NOESY bidimensional representation of compounds *E*-**13** and *Z*-**13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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