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Enantioenriched cyanohydrin *O*-phosphates: Synthesis and applications as chiral building blocks*

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Abstract: Aluminum complexes of the chiral (*R*)- or (*S*)-3,3'-bis(diethylaminomethyl)-1,1'-bi-2,2'-naphthol (BINOLAM) ligand behave as efficient catalysts for the enantioselective cyanation-*O*-functionalization of aldehydes, thereby leading to enantiomerically enriched *O*-silyl, *O*-methoxycarbonyl, or *O*-phosphate derivatives of cyanohydrins. The enantioenriched cyanohydrin-*O*-phosphates are useful for the synthesis of several enantioenriched compounds such as α-hydroxy esters, β-amino alcohols, and γ-substituted α,β-unsaturated nitriles. Natural products such as (–)-aegeline and (–)-tembamide have been prepared in this manner.

Keywords: asymmetric catalysis; cyanohydrins; binolam; aluminum; palladium; copper.

INTRODUCTION

Asymmetric catalysis [1] is a powerful synthetic approach to access a variety of enantiomerically enriched building blocks useful for numerous fields of modern organic synthesis. Many strategies have been developed, the simultaneous (dual activation) of electrophile and nucleophile by appropriately designed bifunctional catalysts [2] being one of the most elegant and effective. In particular, this concept has been successfully implemented for the asymmetric cyanation of carbonyl compounds which led to the synthesis of a variety of enantiomerically pure cyanohydrin derivatives [2], which have been shown to be highly valuable building blocks for the synthesis of pharmaceuticals and natural products [3]. Specifically, Shibasaki and coworkers pioneered the use of aluminum derivatives of 2,2'-dihydroxy-1,1'-binaphthalene (BINOL) having phosphinoylmethyl arms at C3 and C3', as bifunctional catalysts for the direct enantioselective silylcyanation of aldehydes with trimethylsilyl cyanide (TMSCN) [4]. We chose instead to use aminofunctionalized arms, and thus we employed (*R*)- or (*S*)-3,3'-bis(diethylaminomethyl)-1,1'-bi-2,2'-naphthol (BINOLAM) **1** as ligands for the in situ preparation of monometallic (aluminum) catalysts which were proven to be capable of performing the enantioselective cyanation/*O*-protection of aldehydes. In this work, we review our findings regarding the use of (*R*)- or (*S*)-BINOLAM-AlCl complex **2** for the enantioselective synthesis of cyanohydrin derivatives, and their conversion into valuable building blocks for synthesis.

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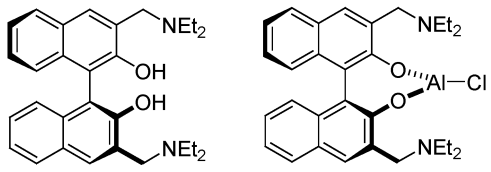
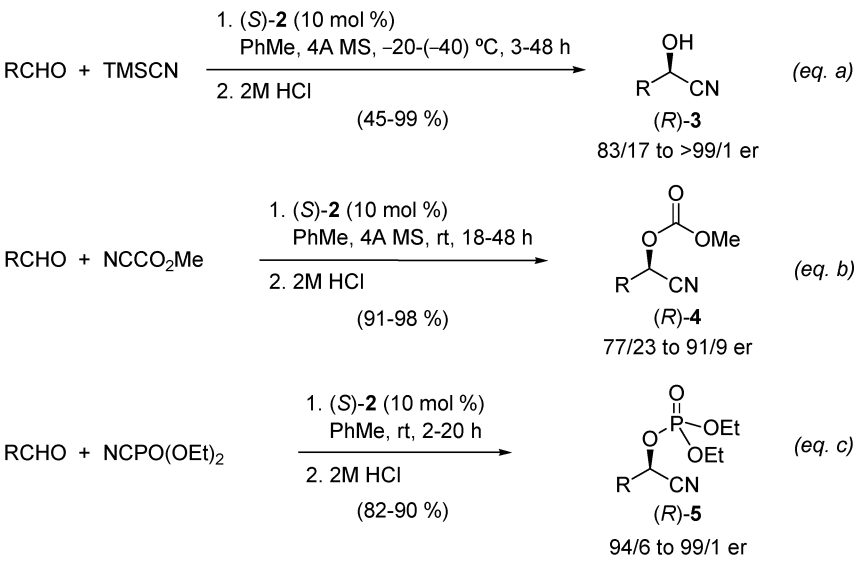
RESULTS AND DISCUSSION

Enantiomerically enriched (*R*)- or (*S*)-BINOLAM **1**, which can be prepared from either optically pure (*R*)- or (*S*)-BINOL [5] or (*R*)- or (*S*)-2,2'-dihydroxy-1,1'-binaphthalene-3,3'-dicarboxylic acid [6], have been employed as catalyst precursor for the enantioselective addition of diethylzinc to aldehydes [5b], for the enantioselective alkylation of the aldimine Schiff bases of alanine esters [7], as well as in the Michael addition of 2-(trimethylsilyloxy)furans to oxazolidinone enoates [8].

We first explored the direct asymmetric synthesis of cyanohydrin derivatives of (*R*)-**3** [4,9] catalyzed by (*S*)-BINOLAM-AlCl complex **2** (10 mol %), by reacting aldehydes with TMSCN in the presence of triphenylphosphine oxide and 4 Å molecular sieves, in anhydrous toluene at low temperature (–20 °C for aromatic and heteroaromatic aldehydes, and –40 °C for both α,β-unsaturated and aliphatic aldehydes), thereby giving rise to products in almost quantitative yields and er ranging from 83/17 to >99/1 (Scheme 1, eq. a). Acidic hydrolysis of the crude mixture of cyanohydrin and *O*-TMS-cyanohydrin was required for obtaining pure cyanohydrins. In so doing, we were able to recover the chiral ligand (*S*)-BINOLAM **1** (>95 % and >99/1 er) almost quantitatively and, most importantly, further reuse of it as catalyst in subsequent batches led to no detectable loss of efficiency [10].



(*S*)-BINOLAM **1** (*S*)-BINOLAM-AlCl **2**



Scheme 1 Synthesis of enantiomerically enriched cyanohydrin derivatives **3**, **4**, and **5**.

Due to the lability of cyanohydrins **3** and their *O*-TMS derivatives to basic and even neutral media, we decided to search for the enantioselective synthesis of more robust *O*-protected cyanohydrin derivatives. In particular, we have explored the direct, one-pot enantioselective synthesis of *O*-methoxycarbonyl cyanohydrins (*R*)-**4** [11] and *O*-phosphate cyanohydrins (*R*)-**5** [12] using bifunctional (*R*)- or (*S*)-**2** complexes as catalysts for these transformations.

Actually, configurationally stable, enantiomerically enriched *O*-methoxycarbonyl cyanohydrins (*R*)-**4** [13] were obtained in almost quantitative chemical yields and good-to-excellent er by addition of methyl cyanoformate to prochiral aldehydes of all kinds under very mild reaction conditions (4 Å MS was required as additive) in the presence of "in situ" generated **2**. The formally analogous titanium or zinc derivatives were found to be unsuitable catalysts for the reaction (Scheme 1, eq. b).

We then discover the first enantioselective synthesis of cyanohydrin *O*-phosphates (*R*)-**5**. We found that aldehydes reacted very efficiently with commercial diethyl cyanophosphonate in the presence of catalyst **2**, generated "in situ" by mixing equimolar amounts of Me_2AlCl and (*S*)-**1** in toluene at room temperature. Configurationally stable cyanophosphates (*R*)-**5** were obtained in short reaction times, in very good chemical yields and excellent enantioselectivities in the absence of external additives at room temperature (Scheme 1, eq. c, and Table 1). Aromatic, α,β-unsaturated, and aliphatic aldehydes were suitable substrates for this reaction, thereby demonstrating the wide applicability of this transformation. Relevant features of this new enantioselective synthesis were unveiled when attempting to synthesize enantiomerically pure **5** by direct or indirect functionalization of enantioenriched cyanohydrins. Thus: (a) extensive racemization was observed when attempting the direct reaction with either diethyl cyanophosphonate or diethyl chlorophosphate under basic conditions [12]; (b) the two-step synthesis involving the initial formation of the cyanohydrin phosphite followed then by oxidation to the corresponding phosphate also produced considerable racemization [12]. Moreover, the enantioselective cyanophosphorylation reported more recently by Shibasaki's group, which involves a more sophisticated bimetallic YLi_3-trisbinaphthoxide complex (YLB) [14], did not improve the results illustrated in Scheme 1 (eq. c) and Table 1 [12]. In all of the reactions depicted in Scheme 1, the corresponding cyanohydrin derivatives (*S*)-**3**, (*S*)-**4**, and (*S*)-**5** were obtained in the same yields and enantiomeric purity using the catalytic complex (*R*)-**2**.

Table 1 Enantioselective synthesis of enantioenriched cyanohydrin *O*-phosphates **5**.

Entry	Aldehyde	Time (h)	(*R*)-**5**	Yield (%)	er (%)
1	PhCHO	4	**5a**	89	99/1
2	4-Cl-C_6H_4CHO	20	**5b**	88	98/2
3	4-(MeO)-C_6H_4CHO	10	**5c**	87	99/1
4	3-(PhO)-C_6H_4CHO	2	**5d**	90	98.5/1.5
5	2-Cl-C_6H_4CHO	4	**5e**	89	98.5/1.5
6	(*E*)-MeCH=CHCHO	2	**5f**	89	94/6
7	(*E*)-C_5H_{11}CH=CHCHO	6	**5g**	90	97/3
8	(*E*)-PhCH=CHCHO	7	**5h**	82	97.5/2.5
9	C_6H_{13}CHO	3	**5i**	90	99/1
10	$PhCH_2CH_2CHO$	2	**5j**	90	96/4

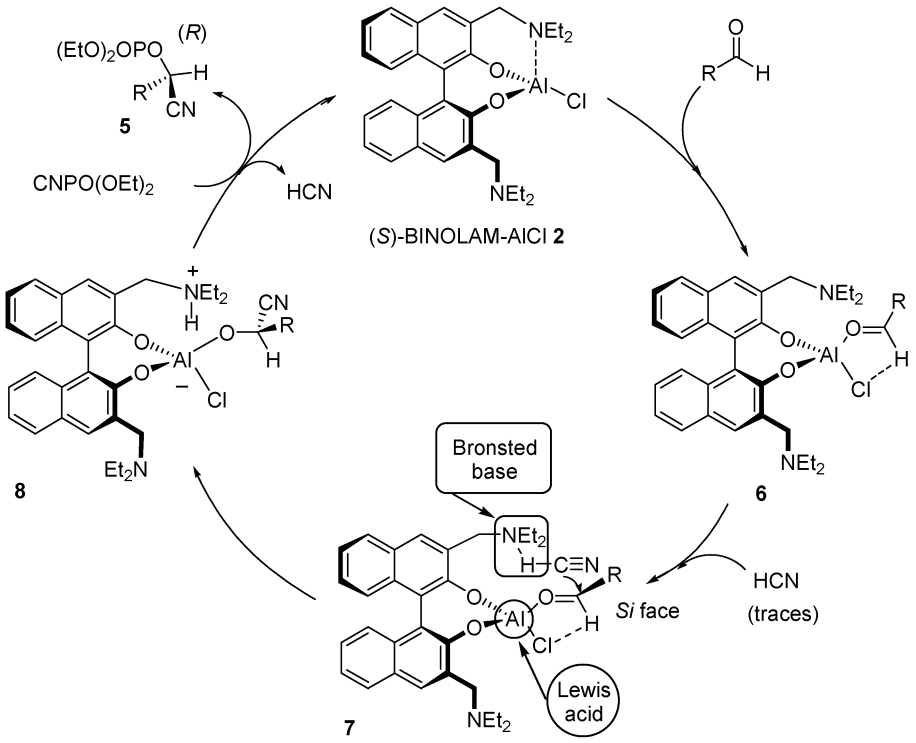
A considerable effort has been invested in clarifying the mechanism of these transformations promoted by catalysts (*R*)- or (*S*)-**2** in the enantioselective synthesis of cyanohydrin derivatives **3**, **4**, and **5**. All evidences (experimental results, nonlinear effects observed in the synthesis of cyanohydrin *O*-phosphates, and ab initio and DFT calculations) led to the following conclusions:

- Catalyst **2** is in equilibrium with oligomeric species.
- The analysis of ^{27}Al NMR data suggests a rapidly equilibrating penta–tetracoordinated aluminum species.
- The catalyst appears to work as a bifunctional species. The crucial role of the diethylaminomethyl arms in ligating HCN was indirectly proved by the competition with an added external base (Et_3N), which led to a intense lowering of ee. The reluctance of the analogous aluminum derivative obtained from (*S*)-BINOL to act as a enantioselective catalyst as it led to almost racemic

product. Also, NMR detection of HCN in all the commercially available cyanide sources can then trigger the catalytic cycle.

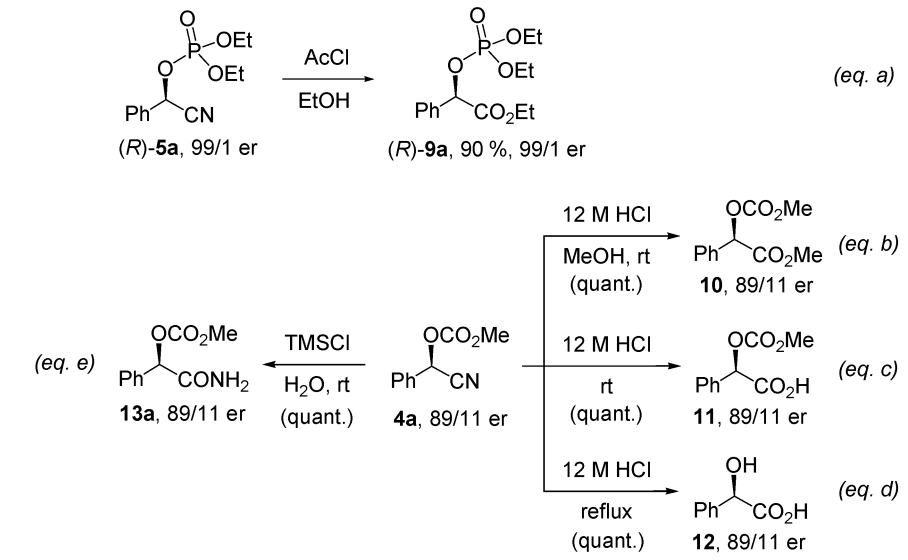
- DFT studies support the capacity of catalyst **2** to act as a bifunctional catalyst, triple complexes being found as stationary points.

Accordingly, we postulate that catalyst **2** works as a bifunctional Lewis acid/Brønsted base (LABB) system, the aluminum acting as Lewis acid in binding the carbonyl group of the aldehyde and the amino arm by capturing freely available hydrogen cyanide, the stereochemically relevant operation thus being the subsequent enantioselective hydrocyanation. The eventual *O*-functionalization of this adduct will led to the observed products and HCN for the next cycle. It can thus be said that the overall enantioselective cyanosilylation, cyanoformylation, and cyanophosphorylation are the consequence of two consecutive operations occurring at the catalytic cycle, namely, enantioselective hydrocyanation followed by *O*-functionalization [12a] (Scheme 2).



Scheme 2 Mechanistic proposal based on the bifunctional role of (*S*)-**2** complex.

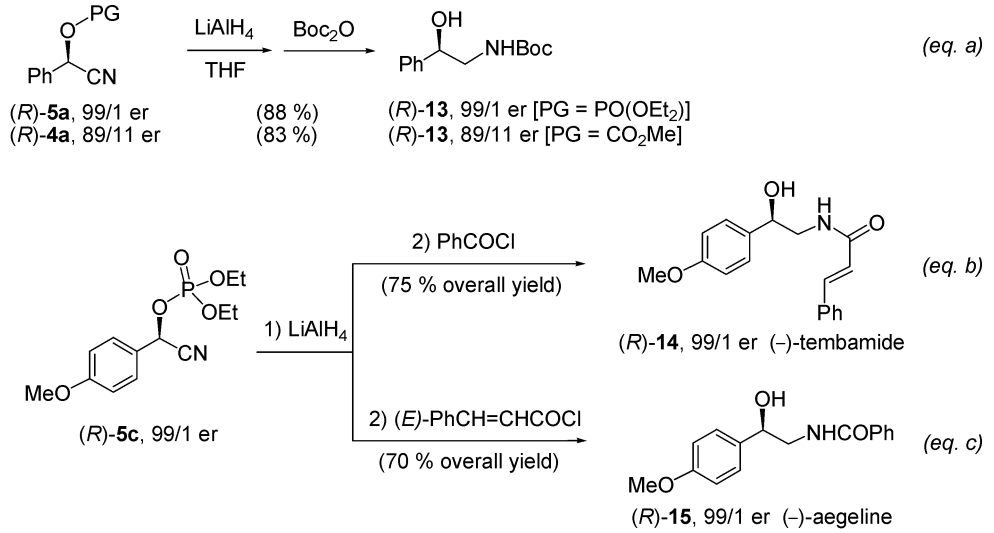
The nature of cyanocarbonates **4** and cyanophosphates **5** encouraged us to study the most common transformations of these highly functionalized molecules in order to obtain chiral building blocks for synthesis. Direct S_N2 displacement of cyanide, or direct addition of Grignard reagents onto the nitrile group, or even the selective hydrolysis of the phosphate group were not successful, as they led to racemized products or very complex reaction mixtures. Ethanolysis of the cyano group took place satisfactorily by treatment of (*R*)-**5** with a mixture of acetyl chloride/ethanol (Scheme 3, eq. a), thereby leading to enantioenriched *O*-phosphoryl α-hydroxy esters **9** in very good chemical yield and a slight racemization only. On the other hand, *O*-methoxycarbonyl cyanohydrins **4** could be transformed into the corresponding enantiomerically enriched *O*-methoxycarbonyl α-hydroxy ester **10**, the *O*-methoxycarbonyl α-hydroxy acid **11**, or the α-hydroxy acid **12** under appropriate acidic conditions, as illustrated



Scheme 3 Hydrolysis of **4** and **5**.

in Scheme 3 (eqs. b, c, and d, respectively). Moreover, mild treatment of **4** with TMSCl in water (Scheme 3, eq. e) [11a] led to enantiomerically pure *O*-methoxycarbonyl α-hydroxy amide **13a**.

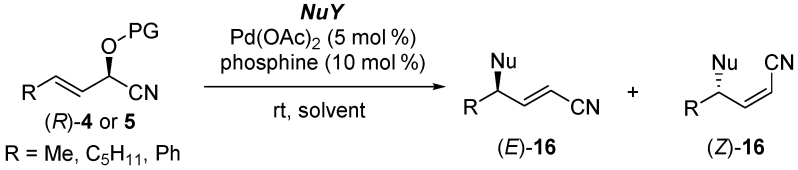
Treatment of chiral, non-racemic **4** or **5** with $LiAlH_4$ (Scheme 4, eq. a) [11,12] led to enantiomerically enriched β-amino alcohols **11** by the simultaneous reduction of the nitrile group and cleavage of the *O*-protecting group. Subsequent *N*-Boc-protection yielded enantiomerically enriched products **13**. This synthetic sequence allowed us to synthesize natural products (–)-tembamide **13** and (–)-aegeline **14** starting from the corresponding cyanohydrin *O*-phosphate **5c** [12a], as illustrated in Scheme 4 (eqs. b and c).



Scheme 4 β-Amino alcohols resulting from reduction of **4** and **5**. Synthesis of (–)-tembamide and (–)-aegeline.

Enantiomerically enriched β,γ-unsaturated cyanohydrin *O*-phosphates **5f**, **g**, and **h** derived from the corresponding α,β-unsaturated aldehydes, should be capable of undergoing allylic substitutions, thereby leading to enantiopure α,β-unsaturated nitriles **16** possessing a chiral center at the γ-position, which have been proven to be valuable chiral building blocks [15,16]. We have carried out a comprehensive study of the reaction conditions for both palladium-catalyzed and organocopper-promoted allylic substitutions upon β,γ-unsaturated cyanohydrin *O*-phosphates as summarized in Schemes 5 and 6.

Nitrogen-, oxygen-, and carbon-based nucleophiles were examined as reagents for palladium-catalyzed allylic substitution, for which purpose they were allowed to react with cyanohydrin *O*-phosphates **5f–h** or *O*-methoxycarbonyl cyanohydrins **4** in the presence of $Pd(OAc)_2$ (5 mol %) and a selected phosphine (10 mol %), as illustrated in Scheme 4 [16]. Separable mixtures of enantiomerically enriched (*E*) and (*Z*) γ-substituted α,β-unsaturated nitriles **16** were obtained, in both cases with enantiomeric excesses which matched that of the starting material, however, with the only exception of cinamaldehyde derivative (*R*)-**5h**. Interestingly, we found that configuration at the chiral center of (*Z*)-**16** was opposite to that of (*E*)-**16**. In most cases, the initial configuration of the starting cyanophosphates was maintained in both final (*E*)- and (*Z*)-products. Iridium-catalyzed allylic substitution worked upon phosphates **5**, whereas cyanocarbonates **4** were unreactive. Using iridium complex $[Ir(Cod)Cl]_2$ as catalyst and several heteronucleophiles, phosphates **5** were converted into enantioenriched γ-substituted α,β-unsaturated nitriles **16** in high (*E/Z*)-ratios (>95/5 in all examples tested), although reactions required quite long reaction times and chemical yields were lower. The enantioenriched alcohol (*E*)-**16** (Nu = OH, R = C_5H_{11}), an advanced precursor in the synthesis of coriolic acid, was obtained in a shorter sequence after mild hydrolysis of the acetate precursor in higher overall yield and enantiomeric ratio than that reported in the literature [17].

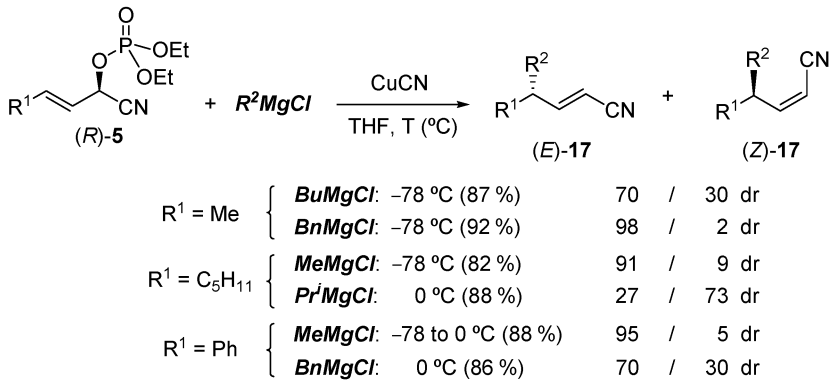


Bn$_2$NH: dppe, PhMe (86-90 %)	up to 95	/	5 dr
BnNH$_2$: dppe, PhMe (86-91 %)	up to 99	/	1 dr
NaN$_3$: dppe, THF/H_2O (65-85 %)	up to 82	/	18 dr
NaOAc: PPh_3, MeCN (73-89 %)	up to 83	/	17 dr
TBAA: PPh_3, THF (74-89 %)	up to 81	/	19 dr
NaCH(CO$_2$Me)$_2$: dppe, THF (71-80 %)	up to 85	/	15 dr

TBAA: tetra-*n*-butylammonium acetate

Scheme 5 Nucleophilic allylic substitution reaction onto **4** and **5** catalyzed by Pd-complexes.

Metal-catalyzed allylic substitutions and direct allylic substitutions with preformed organometalic reagents are generally considered complementary to each other because the former employs soft nucleophiles whilst the latter is applicable also to hard nucleophiles such as Grignard or organozinc reagents [18]. In practice, we found that allylic phosphates (*R*)-**5** undergo allylic substitution reaction (S_N2') with freshly prepared organocopper species generated "in situ" from CuCN and the appropriate Grignard reagent (excess is required) at low temperatures (Scheme 6). Unfortunately, *O*-methoxycarbonyl cyanohydrins **4** decomposed under these reaction conditions.



Scheme 6 Nucleophilic allylic substitution onto (*R*)-**5** promoted by organocopper species.

As illustrated in Scheme 6, the general trend for the direct allylic substitution with "in situ" generated organocopper species is that major products are (*E*)-α,β-unsaturated nitriles **17a–c**. However, this rule breaks down for hindered organocopper such as that generated from Pr^{i}MgCl/CuCN. In all cases, however, a very low degree of racemization was observed (Scheme 5) [19]. Assignment of absolute configurations of these new compounds **17** required conversion into other chiral compounds with known absolute configuration. In particular, ozonolysis of α,β-unsaturated nitriles **17a–c** furnished the corresponding aldehydes whose absolute configuration was determined by comparison of their optical rotation with that published in the literature. A couple of important conclusions can be drawn from this study: (a) as expected, organocopper attack occurs *anti* to the phosphate leaving group; (b) (*E*)-**17** and (*Z*)-**17** products possess opposite absolute configurations [19], the anomalous high proportion of the (*Z*)-isomer **17** [20] being perhaps originated by coordination of the nitrile group to the active copper species, thereby directing the cuprate attack.

CONCLUSIONS

Nonracemic BINOLAM-AlCl complexes **2** can act as bifunctional catalysts in the asymmetric cyanosilylation, cyanoformylation, and cyanophophorylation of aldehydes. The recovery of the chiral ligand (*R*)- or (*S*)-**1** was achieved at the end of the process. The presumed mechanism would involve a hydrocyanation followed by *O*-protection. Both cyanocarbonates and cyanophosphates are valuable starting materials in the palladium-catalyzed allylic nucleophilic substitution. However, whilst chiral cyanoformates are more versatile molecules than cyanophosphates in the chemoselective hydrolysis of their corresponding functional groups, cyanophosphates are better substrates for copper-catalyzed nucleophilic allylic substitutions. These cyanohydrin derivatives can be used for the preparation of enantioenriched β-amino alcohols, α-hydroxy acids derivatives, and γ-substituted α,β-unsaturated nitriles.

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