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Enantioselective Synthesis of *O*-Methoxycarbonyl Cyanohydrins: Chiral Building Blocks Generated by Bifunctional Catalysis with BINOLAM-AlCl

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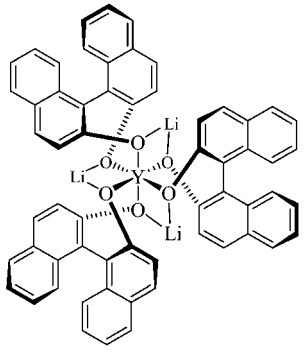
(*R*)- or (*S*)-BINOLAM-AlCl, generated in situ, work as bifunctional catalysts in promoting the enantioselective cyanoalkoxycarbonylation of aldehydes. The reaction is wide in scope and the mechanistic evidence gathered suggests the intervention of an indirect process involving enantioselective hydrocyanation by HCN, followed by *O*-alkoxycarbonylation. The resultant *O*-alkoxycarbonyl cyanohydrins are shown to be important chiral building blocks for synthesis. Chemoselective hydrolysis can thus be directed either to provide enantioenriched β-hydroxy esters, or acids, or instead to give *O*-methoxycarbonyl β-hydroxy acids, esters, or amides. In addition, the enantiopure cyanocarbonates can be converted into β-amino alcohols by reduction with lithiumaluminium hydride.

Introduction

The introduction of XCN across a double bond (generically defined as a cyanation reaction) is a useful C_1 homologation methodology in organic synthesis. In particular, both racemic and nonracemic cyanation[1] of carbon–oxygen or carbon–nitrogen double bonds are of considerable importance because the introduced cyano group can easily be transformed into numerous other functional groups. Unprotected cyanohydrins resulting from hydrocyanations (X = H) are unstable compounds, and *O*-protection is therefore generally required for safe synthetic applications, as well as for ensuring their configurational stability, if appropriate. Some *O*-protected derivatives such as *O*-TMS cyanohydrins are still too labile (partial desilylation is a common undesired reaction taking place during manipulation). Easy access to other enantiomerically pure *O*-protected cyanohydrins is therefore a current goal of asymmetric catalysis, as they should be valuable building blocks for organic synthesis.

Racemic *O*-acyl,[2] *O*-bis-alkoxyphosphoryl,[3] and *O*-alkoxycarbonyl cyanohydrins[2b,2d,4] can be prepared in single operations through a variety of procedures. However, the catalytic, enantioselective cyanation of either C=O or C=N double bonds is a topic of current interest in the field of asymmetric synthesis.[1] A successful one-step enantioselective cyanation (actually a cyanoalkoxycarbonylation) of ketones (not aldehydes) promoted by *cinchona* alkaloid-derived tertiary amines has been reported by Deng,[5] whilst Shibasaki and co-workers have achieved the enantioselective cyanoalkoxycarbonylation of aldehydes in up to 98% *ee*s by use of the heterobimetallic complex (*S*)-YLi_3-tris(binaphthoxide) (YLB) **1**.[6] Belokon and North[7a] and Moberg[7b] instead used the bimetallic titanium complex **2**, derived from a chiral salen ligand, as catalyst, thereby obtaining the desired *O*-alkoxycarbonyl cyanohydrins in up to 99% and 96% *ee*s, respectively.



(*S*)-YLi_3tris(binaphthoxide) = YLB

1

The power of bifunctional catalysis[8] has an especial relevance for enantioselective cyanide addition onto C=X bonds, and the pioneering dual-motif structures reported by Shibasaki et al., based on a chiral BINOL skeleton **3** and a modified carbohydrate structure,[8e] were undoubtedly suitable ligands for the enantioselective cyanosilylation

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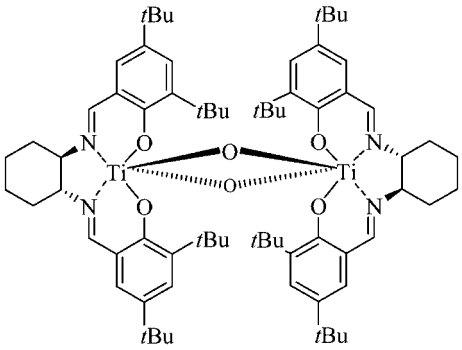

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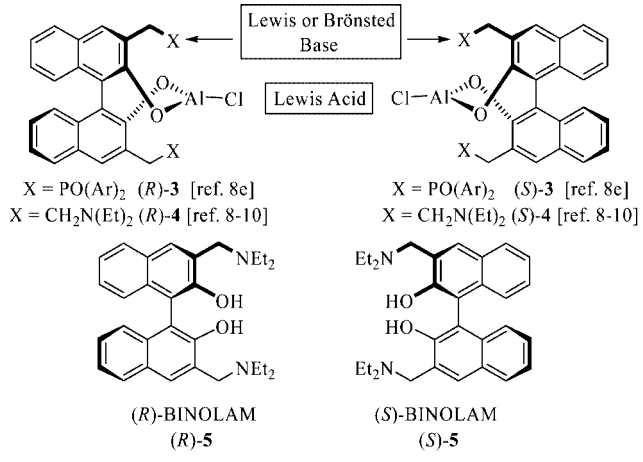
of aldehydes and ketones, respectively.[8e] Presumably the scant enantioselection exhibited by these ligands in the asymmetric cyanocarbonylation of aldehydes forced the development of an alternative catalytic complex such as **1**. In contrast, we have recently found that the monometallic bifunctional **4** is an excellent catalyst for the cyanosilylation[9] or cyanophosphorylation[10] of aldehydes, whilst the cyanobenzoylation of aldehydes was achieved with the same catalytic complex but containing titanium(IV) instead.[11] For the current work,[12] we explored the enantioselective cyanoalkoxycarbonylation of aldehydes by use of the monometallic bifunctional aluminium complexes (*R*)- and (*S*)-BINOLAM-AlCl **4**,[9–11] generated from the corresponding chiral ligands (*R*)- and (*S*)-3,3′-bis(diethylaminomethyl)-1,1′-bi(2-naphthol) (**5**).[13] These types of complexes bear two non-canceling centers capable of acting a priori either as an LALB (Lewis acid-Lewis base) or an LABB (Lewis acid-Brönsted base) system capable of activating electrophilic and nucleophilic reagents simultaneously.[8] By using a combination of approaches, including extensive DFT calculations, we have recently shown that these reactions are in fact likely to be the result of a catalytic cycle involving enantioselective hydrocyanation (an LABB reaction) coupled to subsequent *O*-functionalization in the turnover step.[10b]



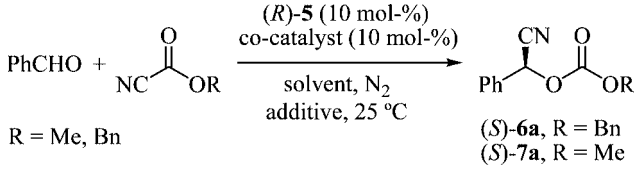
We now report a detailed account of the enantioselective cyanoalkoxycarbonylation of aldehydes catalyzed by the monometallic, bifunctional aluminium complexes (*R*)- and (*S*)-BINOLAM-AlCl **4**, as well as some useful transformations of the resulting products into valuable enantiopure building blocks for organic synthesis.

Results and Discussion

Enantioselective Cyano *O*-Alkoxycarbonylation

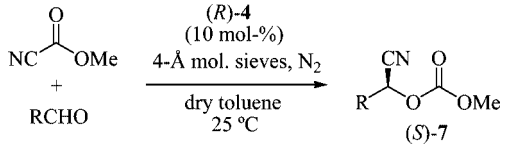
In our search for the ideal reaction conditions to achieve this goal, we studied the reaction between benzaldehyde and benzyl cyanoformate (1.5 equiv.), in dry toluene at room temperature in the presence, or not, of some metal-containing co-catalysts (10 mol-%, Scheme 1 and Table 1, Entries 1–6) and enantiomerically pure (*S*)-BINOLAM (10 mol-%). The reaction failed completely in the absence of co-catalyst, as well as in the presence of $Ti(OiPr)_2Cl_2$ (Table 1, Entries 1 and 3), and gave a poor result when $Ti(OiPr)_4$ was added as co-catalyst (Table 1, Entry 2). When working with aluminium-based catalysts we found that the one made from Me_3Al gave null results in terms of enantioselection (Table 1, Entry 4). Fortunately, we found that employment of catalyst **4**, prepared in situ by mixing (*R*)-BINOLAM **5** with commercial dimethylaluminium chloride (Table 1, Entry 5), rather than diethylaluminium chloride (Table 1, Entry 6), gave encouraging results. From previous experiences it seems that diethylaluminium chloride does not react as rapidly with ligand **5** as dimethylaluminium chloride does, and can itself act as a Lewis acid, favoring the racemic catalytic process. Methyl cyanoformate (Table 1, Entry 7) was found to be the reagent of choice (instead of benzyl cyanoformate), as in this way we were able to avoid the presence of some benzyl alcohol in the crude reaction mixtures after workup. Since the reaction was quite slow even at room temperature, we then looked for additives[14] and found that the reaction rate increased significantly when 4 Å molecular sieves (50 mg/0.25 mmol of aldehyde), previously dried at 120 °C for 4 h,[15] were added to the reaction mixture (Table 1, Entry 8), albeit with no change whatsoever in chemical yield and stereochemical outcome. This behavior was suggestive of a slow turnover reaction (probably that of *O*-alkoxycarbonylation, with the concomitant freeing of HCN). Triphenylphosphane oxide was also tested as additive, but no improvement was observed (Table 1, Entry 9), in apparent contrast with observations for the enantioselective cyanosilylation of aldehydes, also catalyzed by **4**.[9] Working with toluene or dichloromethane (Table 1, Entries 8 and 10) gave similar values of enantioselection (thoroughly expressed as *er*), the former being selected as the optimal solvent due to some marginally better chemical yields obtained. THF, however, was found to be an inappropriate solvent for this reaction (Table 1, Entry 11). The use of lower or higher temperatures did not give rise to significant changes either in enantioselectivity or in chemical yield of the process. Finally, no obvious improvement was observed by working with the same reaction conditions tested for the asymmetric cyanobenzoylation of aldehydes, with $Ti(OiPr)_4$/(*S*)-BINOLAM catalyst (10 mol-%) in THF as solvent at room temperature

(Table 1, Entry 12).[11] The enantiomeric ratios of products **6a** and **7a** were determined by chiral HPLC analysis with a Daicel Chiralcel OD-H column (for more details, see Exp. Sect.). Their absolute configurations were unambiguously assigned by comparison of their optical rotation values with those of pure samples obtained by treatment of enantiomerically enriched cyanohydrins[9,12] with benzyl and/or methyl chloroformate in the presence of pyridine, in dichloromethane as solvent.



Scheme 1.

Overall, the results obtained for the above cyano *O*-alkoxycarbonylation were found to be similar, in terms of chemical yield, to those found for the analogous cyano *O*-alkoxyphosphorylation, though slightly poorer in terms of enantioselectivity, a result a priori consistent with a slow turnover step. The scope of cyano *O*-alkoxycarbonylation also paralleled that of the cyano *O*-alkoxyphosphorylation,[10] as shown in Scheme 2 and Table 2. Aromatic aldehydes thus reacted almost quantitatively to give **7** in up to 78% *ee* (Table 2, Entries 1–8). As in the case of the cyano *O*-alkoxyphosphorylation,[10] the reactions of heteroaromatic aldehydes such as pyridine-3-carboxaldehyde took place with high chemical yields but with very low enantioselection (2% *ee*; see Table 2, Entry 9), an indication that both reactions probably proceed through a common mechanism involving an LABB enantioselective hydrocyanation followed by *O*-functionalization. In accordance with this analysis, basic aldehydes such as pyridine-3-carboxaldehyde showed strong competition by the racemic mechanism as the pyridine nitrogen atom can act as a base in capturing HCN, in competition with the amino arm. Apparently, the less basic thiazole nitrogen [$pK_{a\ (thiazole)}$ = 2.4][16] does not compete so efficiently, and so the cyano *O*-alkoxycarbonylated product (*R*)-**7i** is accordingly obtained in excellent yield and with good enantioselectivity (86:14 *er*; see Table 2, Entry 11). This compound has been employed as a key intermediate in the synthesis of epothilones A and B.[10,12,17] Furfural reacted with a good chemical yield, but with only modest enantioselectivity (Table 2, Entry 10). Both conjugated and aliphatic aldehydes also gave good enantiomeric ratios and almost quantitative chemical yields. Disappointingly, ketones did not undergo the reaction under the above reaction conditions. As expected, enantiomerically enriched carbonates (*R*)-**7** were isolated in identical chemical yield and enantiomeric purity when (*S*)-BINOLAM-AlCl (*S*)-**4** was employed as catalyst (Scheme 2 and Table 2, Entries 1 and 2). This behavior is in full agreement with the *SSR*/*RRS* mnemonic rule for the stereochemical outcome of cyanophosphorylations catalyzed by BINOLAM-AlCl,[10] which states that the (*S*) catalyst promotes the attack at the *Si* face, thereby giving rise to the (*R*)-cyanohydrin derivative, and the opposite: the (*R*) catalyst induces attack at the *Re* face, thereby giving rise to the (*S*)-cyanohydrin derivative. The apparently anomalous case of furfural, which affords (*R*)-**7h** with use of the complex (*R*)-**4** (Table 2, Entry 10) can be explained simply by the different priority of substituents according to CIP rules. As described previously,[10–13] ligands (*S*)- or (*R*)-**5** could be almost quantitatively (95%) recovered by extractive workup and subsequently reused without any loss of activity (Table 2, Entry 3).



Scheme 2.

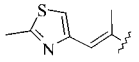
Several other pieces of indirect evidence suggest a common LABB dual mechanism involving enantioselective hydrocyanation followed by *O*-functionalization for both the cyano *O*-phosphorylation[10] and the cyano *O*-alkoxycarb-

Table 1. Optimization of the reaction conditions for the catalytic, enantioselective synthesis of *O*-alkoxycarbonylated cyanohydrins (*S*)-**6a** and (*S*)-**7a**.

Entry	R	Co-catalyst[a]	Additive	Solvent	Time [h][b]	Product	Yield [%][c]	*er*[d]
1	Bn	–	–	toluene	96	**6a**	–	–
2	Bn	$Ti(OiPr)_4$	–	toluene	24	**6a**	91	63:37
3	Bn	$Ti(OiPr)_2Cl_2$	–	toluene	48	**6a**	–	–
4	Bn	Me_3Al	–	toluene	3	**6a**	>95	50:50
5	Bn	Me_2AlCl	–	toluene	72	**6a**	53	88:12
6	Bn	Et_2AlCl	–	toluene	5	**6a**	>95	56:44
7	Me	Me_2AlCl	–	toluene	72	**7a**	94	89:11
8	Me	Me_2AlCl	4-Å mol. sieves	toluene	28	**7a**	94	89:11
9	Me	Me_2AlCl	4-Å, mol. sieves, Ph_3PO	toluene	60	**7a**	92	88:12
10	Me	Me_2AlCl	4-Å mol. sieves	CH_2Cl_2	28	**7a**	87	89:11
11	Me	Me_3Al	4-Å mol. sieves	THF	44	**7a**	80	76:24
12	Me	$Ti(OiPr)_4$	–	THF	8	**7a**	85	66:34

[a] Reactions were carried out in the presence of 10 mol-% of the BINOLAM-MX catalyst generated in situ from a 1:1 mixture of enantiopure ligand and co-catalyst. [b] Reactions were monitored by GC. [c] Isolated yield of pure crude compounds determined by ^1H NMR spectroscopy. [d] Determined by chiral HPLC (Daicel Chiralcel OD-H).

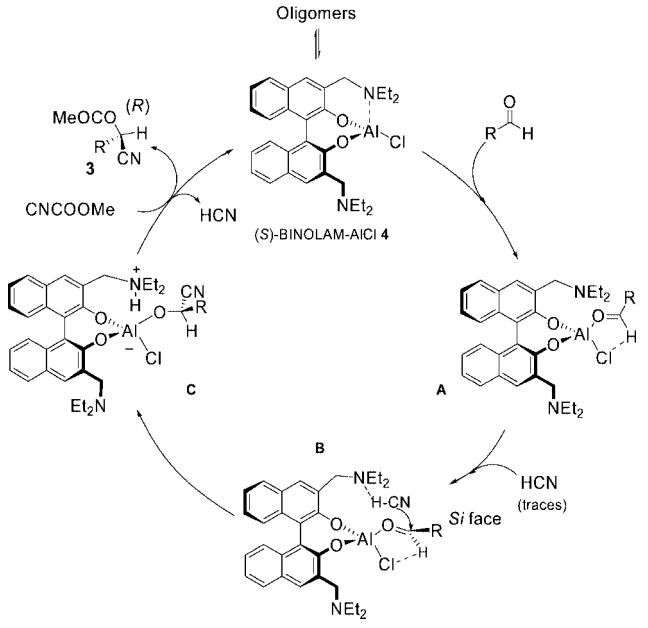
Table 2. Synthesis of cyanocarbonates **7**.

Entry	R	**4**	$CNCO_2Me$ [equiv.]	Time [h]	Product	Yield [%][a]	*er*[b]
1	Ph	(*R*)	3	28	(*S*)-**7a**	>98	89/11
2	Ph	(*S*)	3	28	(*R*)-**7a**	>98	89/11
3	Ph[c]	(*R*)	3	30	(*S*)-**7a**	92	89/11
4	4-$MeOC_6H_4$	(*R*)	4	20	(*S*)-**7b**	>98	89/11
5	2-naphthyl	(*R*)	4	48	(*S*)-**7c**	>98	85/15
6	6-MeO-2-naphthyl	(*S*)	4	55	(*R*)-**7d**	96	85/15
7	2-ClC_6H_4	(*R*)	4	35	(*S*)-**7e**	>98	68/32
8	4-ClC_6H_4	(*S*)	4	22	(*R*)-**7f**	>98	90/10[d]
9	3-pyridyl	(*R*)	4	12	(*S*)-**7g**	96	52/48[d]
10	2-furyl	(*R*)	4	19	(*R*)-**7h**	95	77/23[d]
11		(*S*)	7	28	(*R*)-**7i**	93	86/14[d]
12	(*E*)-MeCH=CH	(*S*)	1.5	20	(*R*)-**7j**	>98	87/13[d]
13	(*E*)-PhCH=CH[e]	(*S*)	4	24	(*R*)-**7k**	95	84/16
14	Me_2C=CH	(*R*)	4	18	(*S*)-**7l**	>98	91/9
15	(*E*)-$Me(CH_2)_2$CH=CH	(*S*)	4	21	(*R*)-**7m**	95	86/14
16	(*E*)-$Me(CH_2)_4$CH=CH	(*S*)	4	28	(*R*)-**7n**	92	90/10
17	$PhCH_2$	(*S*)	4	35	(*R*)-**7o**	>98	67/33[d]
18	$PhCH_2CH_2$	(*R*)	4	20	(*S*)-**7p**	>98	79/21[f]
19	$Me(CH_2)_5$	(*R*)	3	24	(*S*)-**7q**	91	84/16[f]
20	*c*-C_6H_{11}	(*S*)	4	20	(*R*)-**7r**	94	78/22[f]

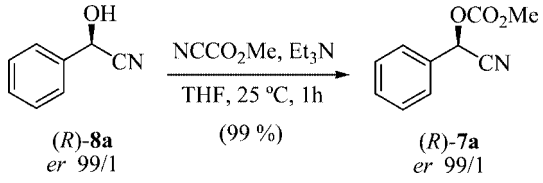
[a] Isolated yield of pure crude compounds determined by ^1H NMR spectroscopy and GC. [b] Determined by chiral HPLC (Daicel Chiralcel OD-H). [c] Reaction carried out with a recovered chiral ligand (*R*)-**3**. [d] Determined by chiral HPLC (Daicel Chiralpak AD). [e] 500 mg of 4 Å MS were used with 0.25 mmol of aldehyde. [f] Determined by chiral GC (γ-cyclodextrin).

onylation. Thus, as in the case of cyanophosphorylations, we found that the attempted cyanoalkoxycarbonylation of benzaldehyde carried out with (*S*)-BINOL-AlCl, which lacks the amino arm, was completely unsuccessful (0% yield after 48 h). Moreover, the addition of a competing external base such as triethylamine (20 mol-%) to the otherwise standard reactions conditions lowered the enantioselection of the reaction (**7a** was obtained in 65:35 *er*), while simultaneously increasing the reaction rate (3 h, 99% yield), consistently with the proposed hydrocyanation plus *O*-alkoxycarbonylation mechanism. In support of the involvement of HCN in the hydrocyanation step we found that: a) commercial methyl cyanoformate contains trace amounts of hydrogen cyanide observable by ^{13}C NMR (δ =109.8 ppm), b) addition of D_2O gives rise to a triplet centered at δ = 111.0 ppm, and c) a suspension of 4-Å mol. sieves and methyl chloroformate shows a small peak centered at δ = 109.8 ppm. In addition, a positive nonlinear effect (NLE)[18] was also observed for the enantioselective cyano *O*-alkoxycarbonylation of aldehydes, though weaker than that observed in the corresponding asymmetric cyano *O*-alkoxyphosphorylations.[10] The existence of all these common features for both types of reactions suggest a common mechanism characterized by a catalytic cycle involving a BINOLAM-AlCl species **4** with a highly coordinated[19,20] central aluminium atom (supported by the wide band centered at δ = 47.5 ppm detected by ^{27}Al NMR spectroscopy[21]) capable of coordinating both HCN (through the amino arm) and an aldehyde through a strong Al–O interaction and a weaker H–Cl one (complex **B**),[22] as illustrated in Scheme 3. We suspect that the minor, though relevant, differences between the two reactions occur at the turnover step, which in the case of the cyano *O*-alkoxycarbonylation of aldehydes is a slow step, thereby facilitating the occurrence of racemic hydrocyanations. In an attempt to address this possibility we carried out the standard reaction with an excess of methyl cyanoformate (10 equiv. relative to the aldehyde), the result being an acceleration of the overall process. In support of this proposal we found that (*S*)-mandelonitrile **8a** was transformed in the corresponding derivative **7a** by treatment with methyl cyanoformate (1.2 equiv.) and triethylamine (1.2 equiv.) in THF at room temperature, in excellent chemical yield and enantiomeric excess (Scheme 4).[23]

We explored some basic chemistry and functional group transformations undergone by the obtained chiral cyanocarbonates **7**. To the best of our knowledge, only Shibasaki et al. have demonstrated that chiral β,γ-unsaturated cyanohydrin *O*-carbonates undergo thermal [3,3]-sigmatropic rearrangements, to afford optically active γ-oxy-α,β-unsaturated nitriles.[6b] In search of chemoselective hydrolysis of the functional group-containing cyanocarbonates, we therefore first studied the transformation of cyanocarbonate (*R*)-**7i** into the corresponding α-hydroxy ester (*R*)-**9i** which we achieved in 82% yield simply by heating at reflux in aqueous, acidic ethanol by the procedure described in the literature for the total syntheses of epothilones A and B[17] (Scheme 5). The observed operations, namely alcoholysis of the cyano group and transesterification at the carbonate moiety, must take place at quite different rates, as shown by



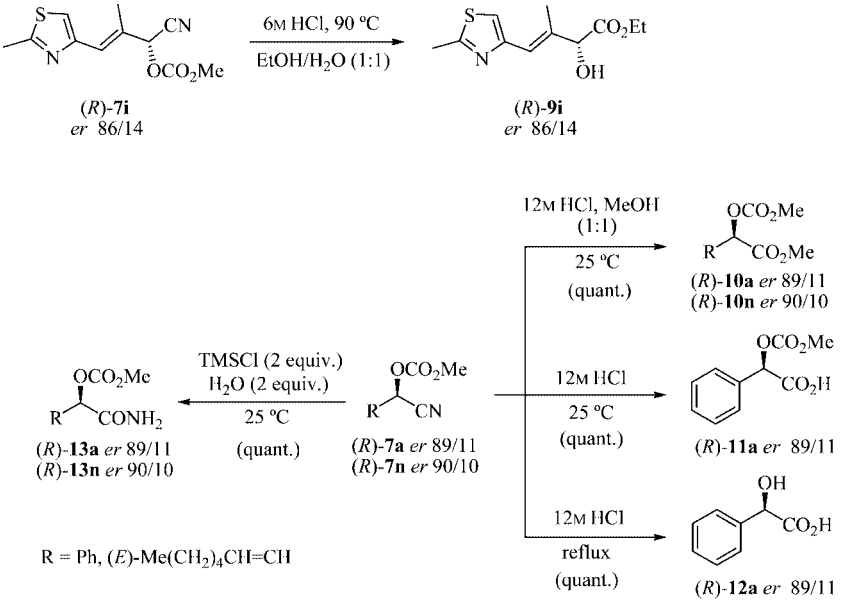
Scheme 3.



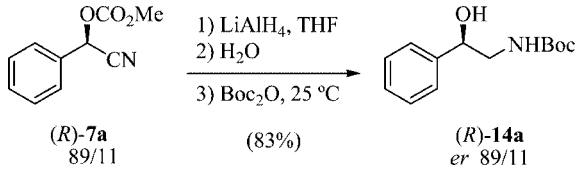
Scheme 4.

the fact that working at room temperature results in alcoholysis only of the cyano group: cyanocarbonate (*R*)-**7a** can be cleanly converted into the methyl ester of the (*R*)-*O*-methoxycarbonyl mandelic acid (*R*)-**10a** (95% yield, 89:11 *er*, by GC with γ-cyclodextrin) by use of a 1:1 mixture of hydrochloric acid (12 M) and methanol at room temperature (Scheme 5). Analogously, compound **7n** could be converted into the corresponding *O*-protected hydroxy ester **10n** in quantitative yield and with no apparent racemization (90:10 *er*). Accordingly, hydrolysis of (*R*)-**7a** with concentrated hydrochloric acid either at room temperature or at 100 °C furnished the (*R*)-*O*-methoxycarbonyl mandelic acid (*R*)-**11a** and the (*R*)-mandelic acid (*R*)-**12a**, respectively, in quantitative yields in both cases (Scheme 5). No noticeable racemization was observed (Scheme 6), in spite of the high temperature of operation applied. The enantiomeric purities of (*R*)-**9i** and (*R*)-**12a** were determined by comparison of their optical rotations with those reported in the literature, whilst that of (*R*)-**11a** was determined by ^{1}H NMR experiments with use of (*S*)-1-phenylethylamine as chiral resolving agent. The direct transformation of the cyano compound (*R*)-**7a** into the corresponding amide (*R*)-**13a** was achieved quantitatively under milder reaction conditions,[24] namely treatment with a mixture of TMSCl/H_2O at room temperature (Scheme 5). Under identical conditions, the cyanohydrin derivative **7n** yielded the amide **13n** quantitatively (see Experimental Section). Their enantiomeric purities (expressed as *er*) were determined by chiral HPLC analysis (Daicel Chiralcel OD-H). α-Hydroxyamides of this kind and their derivatives are frequently encountered as parts of natural products such as, for example, the neuropeptide antho-RNamide.[25]

Reduction of cyanocarbonate (*R*)-**7a** with lithiumaluminium hydride and subsequent standard *N*-Boc protection gave rise to enantiopure, *N*-Boc-protected β-amino alcohol (*R*)-**14a** in good yield (Scheme 6), with complete retention of configuration. The optical purity of carbamate (*R*)-**14a** was evaluated by comparison of its optical rotation with that described in the literature.[26] In contrast, reduction of



Scheme 5.



(*R*)-**7a** 89/11 (83%) (*R*)-**14a** *er* 89/11

Scheme 6.

7a with nickel(II) chloride in the presence of di-*tert*-butyl dicarbonate[27] gave the overreduced *N*-Boc-phenethylamine in very high yield (82%).

Conclusion

In summary, we have developed a one-pot asymmetric synthesis of chiral cyanocarbonates in good chemical yield and with good enantioselection by means of a catalytic, enantioselective cyano *O*-alkoxycarbonylation of aldehydes. Methyl cyanoformate was used rather than benzyl cyanoformate because higher yields were obtained and also because the reaction was cleaner, avoiding secondary reaction products. Reaction conditions are very mild and allow one to work at room temperature, and the chiral ligand (BINOLAM), recovered unaltered upon workup, can be reused. All available evidence is consistent with a catalytic cycle involving enantioselective hydrocyanation promoted by BINOLAM-AlCl, followed by a turnover-limiting step involving *O*-alkoxycarbonylation. This dual mechanism (supported by the poor results obtained when optically active BINOL was used) is analogous to that proposed for the BINOLAM-AlCl cyanophosphorylation.[10b] Enantiopure cyanocarbonates are configurationally very stable compounds (much more so than the analogous cyanophosphates), useful for accessing a variety of α-hydroxyacid derivatives, by means of simple transformations, which exhibited very interesting chemoselectivity and very good chemical yields.

Experimental Section

General Remarks: Melting points were determined with a Reichert Thermovar hot plate apparatus, and are uncorrected. IR spectra were recorded with a Nicolet 510 P-FT instrument, and only the structurally most relevant bands are listed. NMR spectra were performed with Bruker AC 300 and DRX 500 machines, 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 with a Shimadzu QP-5000 instrument, and low-resolution electrospray ionization (ESI) mass spectra were obtained with a Finnigan VG Platform. HRMS (EI) were recorded with a Finnigan MAT 95S. Microanalyses were carried out by the Microanalyses Service of the University of Alicante. Optical rotations were measured with a Perkin–Elmer 341 polarimeter. Analytical TLC was performed on Schleicher & Schuell F1400/LS silica gel plates, and the spots were visualized under UV light at 254 nm. Chiral GC analysis were performed in an HP-5890 apparatus with a WCOT γ-cyclodextrin column (0.25 μm thick), and chiral HPLC analysis were run with a Shimadzu LC-10AD detector SPD-10A and a Jasco 2000 series (the chiral column and wavelength used are given for each compound, the major enantiomer being marked in bold format). For flash chromatography Merck silica gel 60 (0.040–0.063 mm) was employed.

General Procedure for the Synthesis of Chiral Cyanocarbonates 6 and 7: Dimethylaluminium chloride (1 M solution in hexanes, 0.025 mmol, 25 μL) was added under argon to a suspension of (*R*)- or (*S*)-BINOLAM[13a,28] (11.4 mg, 0.025 mmol) and molecular sieves (4 Å, 200 mg per mmol aldehyde, previously dried at 120 °C for 4 h) in anhydrous toluene (1 mL), and the resulting mixture was stirred at room temperature for 1 h. The corresponding freshly distilled aldehyde (0.25 mmol) and the appropriate cyanoformate (1.5–7 equiv., see Table 1 and Table 2) were then added in that order. The reaction mixture was then stirred for the time given in Table 1 or Table 2. When the reaction was judged complete (monitoring by ^1H NMR spectroscopy), aqueous HCl (2 M, 2 mL) and ethyl acetate (2 mL) were added, and stirring was continued for 10 min. The biphasic mixture was filtered through a celite pad and the organic phase was separated, dried ($MgSO_4$), and concentrated under vacuum. The residue was purified by percolation through a silica gel column, thereby affording pure compounds **6** and **7**. At this point, the acidic aqueous phase was treated with a buffered solution (1 M NH_3/1 M NH_4Cl) and extracted with ethyl acetate (2 × 10 mL). The organic phases were combined, dried ($MgSO_4$), and evaporated, thereby yielding back (*R*)- or (*S*)-BINOLAM (11 mg, 96%).

(*S*)-2-(Benzyloxycarbonyloxy)-2-phenylacetonitrile (6a):[29] Colorless oil. $[a]_D^{25}$ = –9.1 (*c* = 1.0, $CHCl_3$) (78% *ee* by HPLC, Daicel Chiralcel OD-H, λ = 254 nm, *n*-hexane/propan-2-ol, 99:1, 0.7 mL min^{-1}, t_r = 17.7 and **20.1** min). TLC: R_f = 0.79 (*n*-hexane/ethyl acetate, 3:2). ^1H NMR: δ_H = 5.26 (s, 2 H, CH_2), 6.29 (s, 1 H, CNCH), 7.40 (s, 5 H, ArH), 7.42–7.56 (m, 5 H, ArH) ppm. ^{13}C NMR: δ_C = 66.5 (CH_2), 70.9 (*C*HCN), 115.6 (CN), 127.8, 128.4, 128.5, 128.6, 128.8, 129.2, 131.0, 134.0 (ArC), 154.9 (OCOO) ppm. IR (neat): $\tilde{\nu}$ = 2252, 1758 cm^{-1}. MS (EI): *m*/*z* (%) = 151 [*M* – 116]$^+$ (1), 117 (79), 107 (34), 91 (100), 77 (28). HRMS calcd. for $C_{16}H_{13}NO_3$: 267.0895; found 267.0920.

(*S*)-2-(Methoxycarbonyloxy)-2-phenylacetonitrile (7a):[30] Colorless oil. $[a]_D^{25}$ = –10.1 (*c* = 1.8, $CHCl_3$) (78% *ee* by HPLC, Daicel Chiralcel OD-H, λ = 254 nm, *n*-hexane/propan-2-ol, 99:1, 1.0 mL min^{-1}, t_r = 11.0 and **14.0** min). TLC: R_f = 0.70 (*n*-hexane/ethyl acetate, 3:2). ^1H NMR: δ_H = 3.87 (s, 3 H, CH_3O), 6.27 (s, 1 H, CHCN), 7.47 (m, 3 H, ArH), 7.54 (m, 2 H, ArH) ppm. ^{13}C NMR: δ_C = 55.8 (CH_3O), 66.5 (*C*HCN), 115.6 (CN), 127.8, 129.2, 130.6, 131.1 (ArC), 154.0 (OCOO) ppm. IR (neat): $\tilde{\nu}$ = 2250, 1759 cm^{-1}. MS (EI): *m*/*z* (%) = 191 [*M*]$^+$ (30), 116 (100), 105 (49), 89 (25). HRMS calcd. for $C_{11}H_{21}NO_2$: 191.0582; found 191.0559.

(*S*)-2-(Methoxycarbonyloxy)-2-(4-methoxyphenyl)acetonitrile (7b): Pale yellow oil. $[a]_D^{25}$ = +24.7 (*c* = 2.0, $CHCl_3$) (78% *ee* by HPLC, Daicel Chiralcel OD-H, λ = 254 nm, *n*-hexane/propan-2-ol, 99:1, 1.0 mL min^{-1}, t_r = 14.9 and **19.5** min). TLC: R_f = 0.65 (*n*-hexane/ethyl acetate, 3:2). ^1H NMR: δ_H = 3.86, 3.88 (2 × s, 6 H, $PhOCH_3$, $COOCH_3$), 6.23 (s, 1 H, CHCN), 6.98 (d, *J* = 8.8 Hz, 2 H, ArH), 7.50 (d, *J* = 8.8 Hz, 2 H, ArH) ppm. ^{13}C NMR: δ_C = 55.3, 55.8 ($COOCH_3$, $PhOCH_3$), 66.3 (*C*HCN), 114.8 (ArC), 115.8 (CN), 123.1, 129.6 (ArC), 154.0 (OCOO), 161.3 ($ArCOCH_3$) ppm. IR (neat): $\tilde{\nu}$ = 2244, 1758 cm^{-1}. MS (EI): *m*/*z* (%) = 221 [*M*]$^+$ (15), 146 (100), 145 (92), 135 (11), 116 (11), 103 (12). HRMS calcd. for $C_{11}H_{11}NO_4$: 221.0688; found 221.0684.

(*S*)-2-(Methoxycarbonyloxy)-2-(2-naphthyl)acetonitrile (7c):[29] Colorless oil. $[a]_D^{25}$ = +9.3 (*c* = 2.0, $CHCl_3$) (70% *ee* by HPLC, Daicel Chiralcel OD-H, λ = 254 nm, *n*-hexane/propan-2-ol, 99:1, 1.0 mL min^{-1}, t_r = 27.2 and **29.7** min). TLC: R_f = 0.62 (*n*-hexane/

ethyl acetate, 3:2). ^{1}H NMR: δ_H = 3.89 (s, 3 H, OCH_3), 6.44 (s, 1 H, CHCN), 7.57 (m, 3 H, ArH), 7.90 (m, 3 H, ArH), 8.04 (s, 1 H, ArH) ppm. ^{13}C NMR: δ_C = 55.8 ($COOCH_3$), 66.7 (*C*HCN), 115.6 (CN), 124.0, 127.0, 127.6, 127.7, 128.0, 128.2, 128.3, 129.4, 132.7, 133.9, (ArC), 154.0 (OCOO) ppm. IR (neat): $\tilde{\nu}$ = 2249, 1770 cm^{-1}. MS (EI): *m*/*z* (%) = 241 [*M*]$^+$ (20), 165 (100), 156 (23), 139 (21), 127 (22). HRMS calcd. for $C_{14}H_{11}NO_3$: 241.0739; found 241.0732.

(*R*)-2-(Methoxycarbonyloxy)-2-(6-methoxy-2-naphthyl)acetonitrile (7d): Pale yellow oil. $[\alpha]_D^{25}$ = –10.4 (*c* = 1.0, $CHCl_3$) (70% *ee* by HPLC, Daicel Chiralcel OD-H, λ = 254 nm, *n*-hexane/propan-2-ol, 99:1, 1.0 mL min^{-1}, t_r = **23.7** and 27.0 min). TLC: R_f = 0.64 (*n*-hexane/ethyl acetate, 3:2). ^{1}H NMR: δ_H = 3.88, 3.94 (2×s, 6 H, $COOCH_3$ and $ArOCH_3$), 6.45 (s, 1 H, CHCN), 7.21 (m, 2 H, ArH), 7.53 (m, 1 H, ArH), 7.80 (m, 2 H, ArH), 7.96 (s, 1 H, ArH) ppm. ^{13}C NMR: δ_C = 55.2, 55.8 ($COOCH_3$ and $ArCOCH_3$), 66.8 (*C*HCN) 105.6 (ArC), 115.7 (*C*CN), 119.9, 124.7, 125.8, 127.9, 128.0, 129.8, 135.4 (ArC), 154.0 (OCOO), 158.9 (ArC) ppm. IR (neat): $\tilde{\nu}$ = 2254, 1774 cm^{-1}. MS (EI): *m*/*z* (%) = 271 [*M*]$^+$ (25), 207 (25), 196 (100), 185 (10), 167 (17), 153 (54), 127 (37), 114 (9). HRMS calcd. for $C_{15}H_{13}NO_4$: 271.0844; found 271.0839.

(*S*)-2-(2-Chlorophenyl)-2-(methoxycarbonyloxy)acetonitrile (7e): Colorless oil. $[\alpha]_D^{25}$ = –10.3 (*c* = 2.0, $CHCl_3$) (36% *ee* by HPLC, Daicel Chiralcel OD-H, λ = 254 nm, *n*-hexane/propan-2-ol, 99:1, 1.0 mL min^{-1}, t_r = 10.0 and **11.8** min). TLC: R_f = 0.70 (*n*-hexane/ethyl acetate, 3:2). ^{1}H NMR: δ_H = 3.89 (s, 3 H, CH_3O), 6.62 (s, 1 H, CHCN), 7.39–7.45 (m, 3 H, ArH), 7.71–7.74 (m, 1 H, ArH) ppm. ^{13}C NMR: δ_C = 55.9 (CH_3O), 63.7 (*C*HCN), 114.8 (CN), 127.6, 128.8, 129.3, 130.1, 131.9, 133.3 (ArC), 153.7 (OCOO) ppm. IR (neat): $\tilde{\nu}$ = 2247, 1765 cm^{-1}. MS (EI): *m*/*z* (%) = 225 [*M*]$^+$ (3), 224 (25), 150 (100), 149 (76), 139 (72), 114 (42), 75 (16). HRMS calcd. for $C_{10}H_8NClO_3$: 225.0192; found 225.0193.

(*R*)-2-(4-Chlorophenyl)-2-(methoxycarbonyloxy)acetonitrile (7f): Pale yellow oil. $[\alpha]_D^{25}$ = –3.4 (*c* = 1.1, $CHCl_3$) (80% *ee* by HPLC, Daicel Chiralpak AD, λ = 254 nm, *n*-hexane/propan-2-ol, 90:10, 1.0 mL min^{-1}, t_r = **12.4** and 13.6 min). TLC: R_f = 0.72 (*n*-hexane/ethyl acetate, 3:2). ^{1}H NMR: δ_H = 3.90 (s, 3 H, CH_3O), 6.26 (s, 1 H, CHCN), 7.44–7.53 (m, 4 H, ArH) ppm. ^{13}C NMR: δ_C = 55.9 (CH_3O), 65.7 (*C*HCN), 115.2 (CN), 128.1, 129.2, 129.5, 130.8 (ArC), 153.8 (OCOO) ppm. IR (neat): $\tilde{\nu}$ = 2254, 1760 cm^{-1}. MS (EI): *m*/*z* (%) = 225 [*M*]$^+$ (3), 224 (25), 149 (98), 148 (100), 139 (40), 123 (17), 114 (42). HRMS calcd. for $C_{10}H_8NClO_3$: 225.0192; found: 225.0188.

2-(Methoxycarbonyloxy)-2-(3-pyridyl)acetonitrile (7g): Colorless oil. HPLC: Daicel Chiralpak AD, λ = 254 nm, *n*-hexane/propan-2-ol, 99:1, 1.0 mL min^{-1}, t_r = 19.2 and 20.4 min. TLC: R_f = 0.17 (*n*-hexane/ethyl acetate, 3:2). ^{1}H NMR: δ_H = 3.90 (s, 3 H, OCH_3), 6.32 (s, 1 H, CHCN), 7.43 (dd, *J* = 7.9, 4.8 Hz, 1 H, NCHC*H*), 7.92 (d, *J* = 7.9 Hz, 1 H, CCH), 8.74 (d, *J* = 4.8 Hz, 1 H, NCH), 8.79 (s, 1 H, NCHC) ppm. ^{13}C NMR: δ_C = 55.9 (OCH_3), 64.2 (*C*HCN), 114.8 (CN), 123.8, 127.2, 135.3, 148.8, 151.6 (ArC), 153.6 (OCOO) ppm. IR (neat): $\tilde{\nu}$ = 2247, 1767 cm^{-1}. MS (EI): *m*/*z* (%) = 192 [*M*]$^+$ (42), 137 (13), 133 (17), 117 (100), 106 (81), 90 (27), 78 (22), 63 (34), 51 (22). HRMS calcd. for $C_9H_8N_2O_3$: 192.0535, found: 192.0539.

(*R*)-2-Furyl-2-(methoxycarbonyloxy)acetonitrile (7h): Pale yellow oil. $[\alpha]_D^{25}$ = +6.4 (*c* = 1.0, $CHCl_3$) (44% *ee* by HPLC, Daicel Chiralpak AD, λ = 210 nm, *n*-hexane/propan-2-ol, 99:1, 1.0 mL min^{-1}, t_r = 12.9 and **14.6** min). TLC: R_f = 0.78 (*n*-hexane/ethyl acetate, 3:2). ^{1}H NMR: δ_H = 3.89 (s, 3 H, OCH_3), 6.36 (s, 1 H, CHCN), 6.46 (dd, *J* = 3.3, 1.9 Hz, 1 H, OCHC*H*), 0.75 (d, *J* = 3.3 Hz, 1 H, OCCH), 7.53 (d, *J* = 1.9 Hz, 1 H, OC*H*CH) ppm. ^{13}C NMR: δ_C = 55.9 ($COOCH_3$), 59.3 (*C*HCN), 111.1 (OCH*C*H), 113.0 (OC*C*H), 113.6 (CN), 143.4 (O*C*CH), 145.2 (O*C*HCH), 153.8 (OCOO) ppm. IR (neat): $\tilde{\nu}$ = 2254, 1763 cm^{-1}. MS (EI): *m*/*z* (%) = 181 [*M*]$^+$ (18), 106 (100), 95 (14), 77 (40). HRMS calcd. for $C_8H_7NO_4$: 181.0375; found 181.0376.

(2*R*,3*E*)-2-(Methoxycarbonyloxy)-3-methyl-4-(2-methyl-1,3-thiazol-4-yl)but-3-enenitrile (7i): Colorless oil. $[\alpha]_D^{25}$ = –20.2 (*c* = 1.1, $CHCl_3$) (72% *ee* by HPLC, Daicel Chiralpak AD, λ = 254 nm, *n*-hexane/propan-2-ol, 80:20, 1.0 mL min^{-1}, t_r = **14.7** and 17.3 min). TLC: R_f = 0.55 (*n*-hexane/ethyl acetate, 3:2). ^{1}H NMR: δ_H = 2.23 (s, 3 H, CH_3CH), 2.65 (s, 3 H, CH_3CN), 3.80 (s, 3 H, $COCH_3$), 5.70 (s, 1 H, CHO), 6.68 (s, 1 H, NCHC), 7.06 (s, 1 H, SCHC) ppm. ^{13}C NMR: δ_C = 14.7 (CH_3CHCH), 19.2 (CH_3CN), 55.5 (OCH_3), 70.3 (CN*C*HO), 115.0 (CN), 119.5 (SCH), 125.7 (NC*C*H), 128.5 (SCH*C*), 150.8 (CH_3CCH), 154.0 (OCOO), 165.5 (CH_3CS) ppm. IR (neat): $\tilde{\nu}$ = 2256, 1762 cm^{-1}. MS (EI): *m*/*z* (%) = 252 [*M*]$^+$ (18), 220 (33), 193 (62), 177 (100), 166 (34), 151 (10), 135 (55), 109 (20), 97 (63). HRMS calcd. for $C_{11}H_{12}SN_2O_3$: 252.0568; found 252.0568.

(2*R*,3*E*)-2-(Methoxycarbonyloxy)pent-3-enenitrile (7j): Pale yellow oil. $[\alpha]_D^{25}$ = –9.2 (*c* = 2.0, $CHCl_3$) (74% *ee* by HPLC, Daicel Chiralpak AD, λ = 210 nm, *n*-hexane/propan-2-ol, 99:1, 1.0 mL min^{-1}, t_r = **7.6** and 9.2 min.). TLC: R_f = 0.83 (*n*-hexane/ethyl acetate, 3:2). ^{1}H NMR: δ_H = 1.83 (d, *J* = 6.6 Hz, 3 H, CH_3CH), 3.87 (s, 3 H, $COCH_3$), 5.58–5.68 (m, 2 H, CHCN and CNCHC*H*), 6.22 (m, 1 H, CHCH=C*H*) ppm. ^{13}C NMR: δ_C = 17.6 (CH_3CH), 55.6 ($COCH_3$), 65.0 (*C*HCN), 115.2 (CN), 120.8 (OCH*C*H), 136.4 (CH_3CH), 153.9 (OCOO) ppm. IR (film): $\tilde{\nu}$ = 2254, 1759 cm^{-1}. MS (EI): *m*/*z* (%) = 155 [*M*]$^+$ (7), 96 (19), 80 (95), 69 (40), 59 (45), 53 (100). HRMS calcd. for $C_7H_9NO_3$: 155.0582; found 155.0582.

(2*R*,3*E*)-2-(Methoxycarbonyloxy)-4-phenylbut-3-enenitrile (7k): Colorless oil. $[\alpha]_D^{25}$ = –11.6 (*c* = 1.0, $CHCl_3$) (68% *ee* by HPLC, Daicel Chiralcel OD-H, λ = 254 nm, *n*-hexane/propan-2-ol, 99:1, 0.5 mL min^{-1}, t_r = **39.1** and 42.1 min). TLC: R_f = 0.71 (*n*-hexane/ethyl acetate, 3:2). ^{1}H NMR: δ_H = 3.89 ($COCH_3$), 5.90 (d, *J* = 6.8 Hz, 1 H, CHCN), 6.22 (dd, *J* = 16.0, 6.8 Hz, 1 H, C*H*CHCN), 7.00 (d, *J* = 16.0 Hz, 1 H, CHAr), 7.35–7.42 (m, 5 H, ArH) ppm. ^{13}C NMR: δ_C = 55.8 ($COCH_3$), 65.2 (*C*HCN), 115.0 (CN), 117.7 (OCH*C*H), 127.2, 128.8, 129.5, 134.2 (ArC), 138.4 (PhCH), 154.0 (OCOO) ppm. IR (neat): $\tilde{\nu}$ = 2255, 1769 cm^{-1}. MS (EI): *m*/*z* (%) = 217 [*M*]$^+$ (5), 185 (8), 158 (44), 141 (100), 131 (18), 115 (84), 103 (18), 89 (10). HRMS calcd. for $C_{12}H_{11}NO_3$: 217.0738; found 217.0718.

(*S*)-2-(Methoxycarbonyloxy)-4-methylpent-3-enenitrile (7l): Colorless oil. $[\alpha]_D^{25}$ = +26.5 (*c* = 0.88, $CHCl_3$) (82% *ee* by HPLC, Daicel Chiralpak AD, λ = 210 nm, *n*-hexane/propan-2-ol, 99:1, 0.5 mL min^{-1}, t_r = 11.3 and **12.5** min). TLC: R_f = 0.87 (*n*-hexane/ethyl acetate, 3:2). ^{1}H NMR: δ_H = 1.81, 1.83 (2×s, 6 H, 2×CCH_3), 3.85 (s, 3 H, OCH_3), 5.39 (d, *J* = 9.2 Hz, 1 H, CCH), 5.87 (d, *J* = 9.2 Hz, 1 H, CHCN) ppm. ^{13}C NMR: δ_C = 18.6, 25.6 (2×C*C*H$_3$), 55.6 ($COCH_3$), 61.6 (*C*HCN), 115.1 (*C*HCHCN), 116.0 (CN), 145.0 [$(CH_3)_2C$], 154.1 (OCOO) ppm. IR (neat): $\tilde{\nu}$ = 2243, 1759 cm^{-1}. MS (EI): *m*/*z* (%) = 169 [*M*]$^+$ (11), 94 (81), 83 (12), 77 (22), 66 (100). HRMS calcd. for $C_8H_{10}NO_3$: 168.0660; found 168.0682.

(2*R*,3*E*)-2-(Methoxycarbonyloxy)hex-3-enenitrile (7m):[2b,4c] Colorless oil. $[\alpha]_D^{25}$ = –14.7 (*c* = 1.0, $CHCl_3$) (72% *ee* by HPLC, Daicel Chiralcel OD-H, λ = 210 nm, *n*-hexane/propan-2-ol, 99:1, 0.5 mL min^{-1}, t_r = **12.0** and 12.8 min). TLC: R_f = 0.77 (*n*-hexane/ethyl acetate, 3:2). ^{1}H NMR: δ_H = 0.92 (t, *J* = 7.3 Hz, 3 H, CH_2CH_3), 1.46 (qt, *J* = 22.0, 7.3 Hz, 2 H, CH_2CH_3), 2.12 (m, 2 H, $CH_2CH_2CH_3$), 3.86 (s, 3 H, OCH_3), 5.55–5.69 (m, 2 H, CHCN and CNCHC*H*), 6.18 (m, 1 H, CH_2CH) ppm. ^{13}C NMR: δ_C = 13.4 (CH_3CH_2), 21.4 (CH_3CH_2), 33.9 ($CH_3CH_2CH_2$), 55.6 ($COCH_3$),

65.1 (*C*HCN), 115.2 (CN), 119.6 (*C*HCHCN), 141.2 (CH_2CH), 153.9 (OCOO) ppm. IR (neat): $\tilde{\nu}$ = 2254, 1759 cm^{-1}. MS (EI): *m/z* (%) = 183 $[M]^+$ (0.01), 154 (8), 142 (18), 106 (100), 92 (39), 80 (70), 66 (28), 59 (52), 52 (37). HRMS calcd. for $C_9H_{13}NO_3$: 183.0895; found 183.0896.

(2*R*,3*E*)-2-(Methoxycarbonyloxy)oct-3-enenitrile (7n): Colorless oil. $[\alpha]_D^{25}$ = –12.0 (*c* = 2.0, $CHCl_3$) (80% *ee* by HPLC, Daicel Chiralcel OD-H, λ = 210 nm, *n*-hexane/propan-2-ol, 95:5, 0.5 mL min^{-1}, t_r = **9.6** and 10.8 min). TLC: R_f = 0.72 (*n*-hexane/ethyl acetate, 3:2). ^1H NMR: δ_H = 0.89 (t, *J* = 6.7 Hz, 3 H, CH_3CH_2), 1.25–1.30 (m, 4 H, 2×CH_2), 1.40–1.45 (m, 2 H, CH_2), 2.13 (m, 2 H, CH_2CH), 3.86 (s, 3 H, OCH_3), 5.54–5.61 (m, 1 H, CNCHC*H*), 5.66–5.68 (m, 1 H, CHCN), 6.20 (dt, *J* = 14.6, 7.2 Hz, 1 H, CH_2CH) ppm. ^{13}C NMR: δ_C = 13.8 (CH_3CH_2), 22.3, (CH_3CH_2), 27.8 ($CH_3CH_2CH_2$), 31.1 ($CHCH_2CH_2$), 31.9 ($CHCH_2$), 55.6 ($COCH_3$), 65.1 (*C*HCN), 115.2 (CN), 119.4 (CNCH*C*H), 141.5 (CH_2CH), 154.0 (OCOO) ppm. IR (neat): $\tilde{\nu}$ = 2249, 1763 cm^{-1}. MS (EI): *m/z* (%) = 211 $[M]^+$ (2), 154 (34), 136 (22), 120 (31), 106 (38), 93 (46), 80 (99), 69 (57), 55 (100). HRMS calcd. for $C_{11}H_{17}NO_3$: 211.1208; found 211.1212.

(*R*)-2-(Methoxycarbonyloxy)-3-phenylpropanenitrile (7o):[2b,4d] Colorless oil. $[\alpha]_D^{25}$ = –2.3 (*c* = 1.0, $CHCl_3$) (34% *ee* by HPLC, Daicel Chiralpak AD, λ = 254 nm, *n*-hexane/propan-2-ol, 99:1, 1.0 mL min^{-1}, t_r = **20.5** and 21.5 min). TLC: R_f = 0.78 (*n*-hexane/ethyl acetate, 3:2). ^1H NMR: δ_H = 3.25 (d, *J* = 7 Hz, 2 H, CH_2CH), 3.86 (s, 3 H, OCH_3), 5.37 (t, *J* = 7.0 Hz, 1 H, CHCN), 7.28–7.42 (m, 5 H, ArH) ppm. ^{13}C NMR: δ_C = 38.5 (CH_2CH), 55.7 (OCH_3), 65.5 (*C*HCN), 115.9 (CN), 127.9, 128.8, 129.5, 132.8 (ArC), 154.0 (OCOO) ppm. IR (neat): $\tilde{\nu}$ = 2244, 1754 cm^{-1}. MS (EI): *m/z* (%) = 146 $[M - 59]^+$, 0.1, 129 (100), 103 (9), 91 (86). HRMS calcd. for $C_{11}H_{11}NO_3$: 205.0739; found 205.0734.

(*S*)-2-(Methoxycarbonyloxy)-4-phenylbutanenitrile (7p):[4c,31] Colorless oil. $[\alpha]_D^{25}$ = –14.9 (*c* = 4.1, $CHCl_3$) (58% *ee* from GC, WCOT γ-CD, FS-Lipodex-E stationary phase, $T_{injector}$ = 250 °C, $T_{detector}$ = 260 °C, T_{column} = 90 °C, 10 min and 180 °C final temperature, rate 10 °C min^{-1}, *P* = 100 kPa, t_r = 44.7 and **45.2** min.), {ref.[30] $[\alpha]_D^{25}$ = –7.0 (*c* = 1.465, $CHCl_3$)}. TLC: R_f = 0.71 (*n*-hexane/ethyl acetate, 3:2). ^1H NMR: δ_H = 2.27 (m, 2 H, CH_2CH), 2.85 (t, *J* = 7.7 Hz, 2 H, CH_2Ph), 3.87 (s, 1 H, OCH_3), 5.14 (t, *J* = 6.8 Hz, 1 H, CHCN), 7.17–7.32 (m, 5 H, ArH) ppm. ^{13}C NMR: δ_C = 30.5 (CH_2CH), 33.8 (CH_2Ph), 55.7 (OCH_3), 64.1 (*C*HCN), 116.2 (CN), 126.7, 128.3, 128.7, 138.7 (ArC), 154.1 (OCOO) ppm. IR (neat): $\tilde{\nu}$ = 2249, 1759 cm^{-1}. MS (EI): *m/z* (%) = 219 $[M]^+$ (0.02), 143 (100), 116 (32), 91 (42), 65 (11). HRMS calcd. for $C_{12}H_{13}NO_3$: 219.0973; found 119.0980.

(*S*)-2-(Methoxycarbonyloxy)octanenitrile (7q):[2b,4d] Colorless oil. $[\alpha]_D^{25}$ = –43.9 (*c* = 2.0, $CHCl_3$) [68% *ee* from GC, WCOT γ-CD stationary phase FS-Lipodex-E, $T_{injector}$ = 250 °C, $T_{detector}$ = 260 °C,- T_{column} = 90 °C (3 min), final temperature 180 °C, rate 3 °C min^{-1}, *P* = 70 kPa, t_r = 42.9 and **43.3** min]. TLC: R_f = 0.89 (*n*-hexane/ethyl acetate, 3:2). ^1H NMR: δ_H = 0.87 (t, *J* = 6.7 Hz, 3 H, CH_2CH_3), 1.29–1.38 (m, 6 H, 3×CH_2), 1.44–1.54 (m, 2 H, CH_2), 1.92 (dd, *J* = 15.5, 6.8 Hz, CH_2CH), 3.84 (s, 3 H, OCH_3), 5.18 (t, *J* = 6.8 Hz, 1 H, CHCN) ppm. ^{13}C NMR: δ_C = 13.8 (CH_3CH_2), 22.3 (CH_3CH_2), 24.2 ($CH_3CH_2CH_2$), 28.3 ($CH_3CH_2CH_2CH_2$), 31.3 ($CNCHCH_2CH_2$), 32.2 ($CNCHCH_2$), 55.6 ($COCH_3$), 64.8 (*C*HCN), 116.4 (CN), 154.2 (OCOO) ppm. IR (neat): $\tilde{\nu}$ = 2235, 1763 cm^{-1}. MS (EI): *m/z* (%) = 200 $[M + 1]^+$, (0.04), 140 (5), 115 (12), 108 (14), 95 (57), 81 (84), 55 (100). HRMS calcd. for $C_{10}H_{17}NO_3$: 199.1208; found 199.1203.

(*R*)-2-Cyclohexyl-2-(methoxycarbonyloxy)acetonitrile (7r):[4d,2c,29] Colorless oil. $[\alpha]_D^{25}$ = +32.1 (*c* = 1.0, $CHCl_3$) (56% *ee* from GC, WCOT γ-CD stationary phase FS-Lipodex-E, $T_{injector}$ = 250 °C, $T_{detector}$ = 260 °C, T_{column} = 90 °C, 3 min, final temperature 180 °C, rate 10 °C min^{-1}, *P* = 120 kPa, t_r = **21.2** and 21.5 min). TLC: R_f = 0.66 (*n*-hexane/ethyl acetate, 3:2). ^1H NMR: δ_H = 1.18–1.23 (m, 5 H, Cy), 1.80–1.94 (m, 6 H, Cy), 3.86 (s, 3 H, OCH_3), 5.04 (d, *J* = 5.7 Hz, 1 H, CHCN) ppm. ^{13}C NMR: δ_C = 25.1, 25.1, 25.5, 27.6, 27.8, 40.0 (Cy), 55.6 ($COCH_3$), 69.0 (*C*HCN), 115.6 (CN), 154.3 (OCOO) ppm. IR (neat): $\tilde{\nu}$ = 2247, 1762 cm^{-1}. MS (EI): *m/z* (%) = 197 $[M]^+$ (0.03), 115 (83), 83 (100), 55 (83). HRMS calcd. for $C_{10}H_{15}NO_3$: 197.1052; found 197.1060.

Synthesis of 7a from Enantioenriched Cyanohydrin 8: A mixture of commercially available mandelonitrile (>98% *ee*, 0.5 mmol, 59 μL), methyl cyanoformate (41 μL, 0.51 mmol), and triethylamine (71 μL, 0.51 mmol) in THF (2 mL) was stirred at room temperature for 1 h. Water (10 mL) and ethyl acetate (5 mL) were added and the resulting biphasic mixture was separated. The aqueous phase was extracted with ethyl acetate (2×5 mL), the combined organic layers were dried ($MgSO_4$) and concentrated under vacuum, and the residue was percolated through a silica gel column, thereby yielding enantiomerically enriched (>98% *ee*) compound **7a** in quantitative yield.

Hydrolysis of Cyanocarbonate (*R*)-7i. Synthesis of Ethyl (2*R*,3*E*)-2-Hydroxy-3-methyl-4-(2-methyl-1,3-thiazol-4-yl)-3-butenoate (9i): [17b] Compound **7i** (63 mg, 0.25 mmol) was dissolved in ethanol (3 mL) and concentrated HCl (3 mL) was added. The resulting mixture was stirred at 90 °C for 5 h. A saturated aqueous solution of $NaHCO_3$ (70 mL) was added and the ethanol was evaporated under vacuum. The aqueous phase was then extracted with ethyl acetate (3×50 mL), the organic phase was dried ($MgSO_4$), and the solvents were evaporated. The residue was purified by flash column chromatography, thereby affording pure compound **9i** as a colorless oil. $[\alpha]_D^{25}$ = –83.6 (*c* = 1.0, $CHCl_3$, 72% *ee*), {ref.[17b] $[\alpha]_D^{25}$ = –116 (*c* = 0.72, $CHCl_3$, 99% *ee*)}. ^1H NMR: δ_H = 1.29 (t, *J* = 7.0 Hz, 3 H, CH_2CH_3), 2.07 (s, 3 H, CH=CCH_3), 2.71 (s, 3 H, N=CCH_3), 4.26 (q, *J* = 7.0 Hz, 2 H, CH_2CH_3), 4.65 (s, 1 H, C*H*OH), 6.64 (s, 1 H, C*H*=CCH$_3$), 7.00 (s, 1 H, N=CCH$_3$) ppm. ^{13}C NMR: δ_C = 14.0, 14.1 (CH_2CH_3, CH=CCH_3), 19.1 (N=CCH_3), 62.2 (CH_2CH_3), 76.8 (*C*HOH), 116.7 (S*C*H=C), 122.6 (*C*H=CCH$_3$), 135.8 (CH=*C*CH$_3$), 152.3 (SCH=*C*), 164.7 (N=*C*CH$_3$), 173.3 (C=O) ppm. IR (neat): $\tilde{\nu}$ = 3039, 1510 cm^{-1}.

Synthesis of Compounds 10. General Procedure: Concentrated HCl (2 mL) was added at 0 °C to a methanol solution (2 mL) of a cyanocarbonate **7** (0.25 mmol). The mixture was then stirred at room temperature until the reaction was judged complete by GC. The methanol was then evaporated under vacuum and water (10 mL) was added. The aqueous phase was then extracted with ethyl acetate (2×10 mL), the organic phase being dried ($MgSO_4$) and concentrated under vacuum, thus affording the pure compounds **10**.

Methyl (*R*)-2-(Methoxycarbonyloxy)-2-phenylacetate (10a): Colorless oil. $[\alpha]_D^{25}$ = –85.1 (*c* = 1.0, $CHCl_3$) (77% *ee* from GC, WCOT γ-CD, stationary phase FS-Lipodex-E, $T_{injector}$ = 250 °C, $T_{detector}$ = 260 °C, T_{column} = 90 °C, 5 min, final temperature 180 °C, rate 10 °C min^{-1}, *P* = 100 kPa, t_r = 24.9 and **25.3** min). TLC: R_f = 0.66 (*n*-hexane/ethyl acetate, 3:2). ^1H NMR: δ_H = 3.73, 3.83 (2×s, 6 H, 2×OCH_3), 5.95 (s, 1 H, CHCN), 7.37–7.39 (m, 3 H, ArH), 7.45–7.47 (m, 2 H, ArH) ppm. ^{13}C NMR: δ_C = 52.7 (CCOO*C*H$_3$), 55.2 (OCOO*C*H$_3$), 77.0 (PhCH), 127.5, 128.7, 129.4, 133.1 (ArC), 154.9 (O*C*OOCH$_3$), 168.9 (C*C*OOCH$_3$) ppm. IR (neat): $\tilde{\nu}$ = 1750 cm^{-1}. MS (EI): *m/z* (%) = 224 $[M]^+$ (2), 192 (37), 165 (31), 121 (100), 105 (33), 91 (38), 77 (62), 59 (53). HRMS calcd. for $C_{11}H_{12}O_5$: 224.0689; found 224.0684.

Methyl (2*R*,3*E*)-2-(Methoxycarbonyloxy)non-3-enoate (10n): Colorless oil. $[\alpha]_D^{25}$ = –16.9 (*c* = 1.0, $CHCl_3$) (80% *ee* from GC, WCOT

γ-CD, stationary phase FS-Lipodex-E, $T_{injector}$ = 250 °C, $T_{detector}$ = 260 °C, T_{column} = 90 °C, 5 min, final temperature 180 °C, rate 5 °C min^{-1}, P = 75 kPa, t_r = 52.4 and **52.8** min). TLC: R_f = 0.78 (*n*-hexane/ethyl acetate, 3:2). ^{1}H NMR δ_H: 0.88 (t, J = 6.7 Hz, 3 H, CH_2CH_3), 1.26–1.44 (m, 6 H, 3×CH_2), 2.02–2.11 (m, 2 H, $CHCH_2$), 3.76, 3.80 (2×s, 6 H, 2×OCH_3), 5.32 (d, J = 12.5 Hz, 1 H, $CHCO_2CH_3$), 5.53 (dd, J = 15.2 and 7.2, 1 H, CH=CH), 5.92–5.97 (m, 1 H, CH=CH) ppm. ^{13}C NMR: δ_C = 13.9 (CH_2CH_3), 22.3, 28.0, 31.1, 32.1 (4×CH_2), 52.4, 55.0 (2×OCH_3), 75.9 ($CHCO_2CH_3$), 121.0, 138.6 (2×CH=CH), 154.8 ($OCOOCH_3$), 169.1 ($COOCH_3$) ppm. IR (neat): $\tilde{\nu}$ = 1752, 1669 cm^{-1}. MS (EI): *m*/*z* (%) = 244 [M]$^+$ (0.3), 111 (12), 81 (12), 71 (100), 67 (34), 59 (50), 41 (72). HRMS calcd. for $C_{12}H_{20}O_5$: 244.1308; found 244.1299.

Synthesis of (*R*)-2-(Methoxycarbonyloxy)-2-phenylacetic Acid (11a):[32] A suspension of compound (*R*)-**7a** (191 mg, 1 mmol) in concentrated HCl (3 mL) was stirred at room temperature for 19 h. The reaction was basified with sodium hydrogen carbonate and ethyl acetate was added (10 mL). The aqueous phase was acidified with hydrochloric acid (2 M) and extracted with ethyl acetate (2×10 mL). The collected organic phase was dried (Mg_2SO_4) and evaporated, thereby affording crude pure compound **11a** (201 mg, 96%) as colorless prisms. M.p. 122–124 °C (*n*-hexane/ethyl acetate). $[a]_D^{25}$ = –135.6 (c = 1.0, $CHCl_3$) (78% *ee*, see text). TLC: R_f 0.31 (ethyl acetate). ^{1}H NMR: δ_H = 3.82 (s, 3 H, OCH_3), 5.87 (s, 1 H, CHPh), 7.38–7.39 (m, 3 H, ArH), 7.46–7.47 (m, 2 H, ArH), 10.78 (s, 1 H, COOH) ppm. ^{13}C NMR: δ_C = 55.4 ($CO CH_3$), 76.6 ($CHCOOH$), 127.5, 128.8, 129.6, 132.4 (ArC), 154.9 (OCOO), 174.2 (COOH) ppm. IR (KBr): $\tilde{\nu}$ = 3064, 1751, 1717 cm^{-1}. MS (EI): *m*/*z* (%) = 166 [M – 44]$^+$ (2), 136 (27), 122 (14), 107 (100), 91 (80), 77 (93), 51 (29). Microanalysis required for $C_{10}H_{10}O_5$: C 57.1, H 4.8; found C 57.2, H 4.7.

Synthesis of (*R*)-Mandelic Acid (12a):[33] A suspension of compound (*R*)-**7a** (191 mg, 1 mmol) in concentrated hydrochloric acid (12 M, 3 mL) was heated at reflux for 19 h. The reaction was basified with sodium hydrogen carbonate and ethyl acetate was added (10 mL). The aqueous phase was acidified with hydrochloric acid (2 M) and then extracted with ethyl acetate (2×10 mL). The organic phase was dried (Mg_2SO_4) and evaporated, affording crude pure compound **12a** (142 mg, 95%) as colorless needles. $[a]_D^{25}$ = –122.6 (c = 1, $CHCl_3$) (78% *ee*), {ref.[31] $[a]_D^{25}$ = –157 (c = 1, $CHCl_3$, 99% *ee*)}. ^{1}H NMR: δ_H = 5.26 (s, 1 H, CH), 7.37–7.44 (m, 5 H, ArH) ppm.

Synthesis of Amides 13: Amides **13** were prepared by the procedure reported in the literature.[24]

(*R*)-2-(Methoxycarbonyloxy)-2-phenylacetamide (13a): Colorless prisms. M.p. 148–149 °C (ethyl acetate). $[a]_D^{25}$ = –104.0 (c = 1, $CHCl_3$) (78% *ee* by HPLC, Daicel Chiralcel OD-H, λ = 254 nm, *n*-hexane/propan-2-ol, 90:10, 1.0 mL min^{-1}, t_r = **27.7** and 30.7 min). TLC: R_f = 0.62 (ethyl acetate). ^{1}H NMR ([D$_6$]DMSO): δ_H = 2.48 (s, 2 H, NH_2), 2.94 (s, 3 H, OCH_3), 4.83 (s, 1 H, CHCN), 6.21–7.13 (m, 5 H, ArH) ppm. ^{13}C NMR ([D$_6$]DMSO): δ_C = 54.9 (OCH_3), 77.6 (CHO), 127.3, 128.4, 128.7, 135,3 (ArC), 154.3 (CO-OCH_3), 169.4 ($CONH_2$) ppm. IR (KBr): $\tilde{\nu}$ = 3439, 3179, 1760–1710 cm^{-1}. MS (EI): *m*/*z* (%) = 209 [M]$^+$ (0.7), 166 (43), 165 (31), 122 (15), 121 (71), 107 (18), 105 (22), 91 (34), 77 (68), 59 (34), 44 (100). Microanalysis required for $C_{10}H_{11}O_4N$: C 57.4, H 5.3, N 6.7; found C 57.1, H 5.2, N 6.5.

(*R*)-2-(Methoxycarbonyloxy)non-3-enamide (13n): Colorless prisms. M.p. 93–94 °C. $[a]_D^{25}$ = –60.5 (c = 1, $CHCl_3$) (81% *ee*, from HPLC, Daicel Chiralcel OD-H, λ = 254 nm, *n*-hexane/propan-2-ol, 90:10, 1.0 mL min^{-1}, t_r = **15.8** and 19.0 min.). TLC: R_f = 0.7 (ethyl acetate). ^{1}H NMR: δ_H = 0.88 (t, J = 6.6 Hz, 3 H, CH_2CH_3), 1.26–1.42 (m, 6 H, 3×CH_2), 2.04–2.09 (m, 2 H, $CHCH_2$), 3.82 (s, 3 H, $COCH_3$), 5.39 (d, J = 7.2 Hz, 1 H, $CHCONH_2$), 5.54 (dd, J = 15.3 and 7.2 Hz, 1 H, CH=CH), 5.93–6.03 (m, 1 H, CH=CH), 6.27, 6.66 (2×br. s, 2 H, NH_2) ppm. ^{13}C NMR: δ_C = 13.9 (CH_2CH_3), 22.3, 28.0, 31.2, 32.1 (4×CH_2), 55.2 (OCH_3), 77.5 ($CHCONH_2$), 122.2, 138.8 (2×CH=CH), 154.2 ($OCOOCH_3$), 171.3 ($CONH_2$) ppm. IR (KBr): $\tilde{\nu}$ = 3388, 3203, 1745–1715, 1668 cm^{-1}. MS (EI): *m*/*z* (%) = 229 [M]$^+$ (0.7), 166 (43), 165 (31), 122(15), 121 (71), 107 (18), 105 (22), 91 (34), 77 (68), 59 (34), 44 (100). Microanalysis required for $C_{10}H_{11}O_4N$: C 57.6, H 8.4, N 6.1; found C 57.7, H 8.2, N 6.0.

Synthesis of (*R*)-2-(*tert*-Butoxycarbonylamino)-1-phenylethanol (14a):[26] $LiAlH_4$ (190 mg, 5 mmol) was added in small portions at 0 °C to a stirred solution of compound (*R*)-**7a** (191 mg, 1 mmol) in anhydrous THF (6 mL). The reaction mixture was stirred at room temperature for 4 h, the reaction was quenched with water (1 mL), di-*tert*-butyl dicarbonate was added (262 mg, 1.2 mmol), and the stirring was continued overnight at room temperature. The THF was evaporated and the residue was extracted with ethyl acetate (2×10 mL). The collected organic phase was dried ($MgSO_4$) and concentrated to give a residue that was purified by flash chromatography, thereby affording pure **14a** as a colorless oil. $[a]_D^{25}$ = –4.4 (c = 1.5, EtOH) (78% *ee*). {ref.[26] $[a]_D^{25}$ = +3.5 (c = 1.0; EtOH, 99% *ee*)}. ^{1}H NMR: δ_H = 1.42 [s, 9 H, $C(CH_3)_3$], 3.14–3.26, 3.40–3.45 (2×m, 2 H, CH_2), 4.75–4.79 (m, 1 H, $CHOH$), 7.24–7.33 (m, 5 H, Ar) ppm.

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